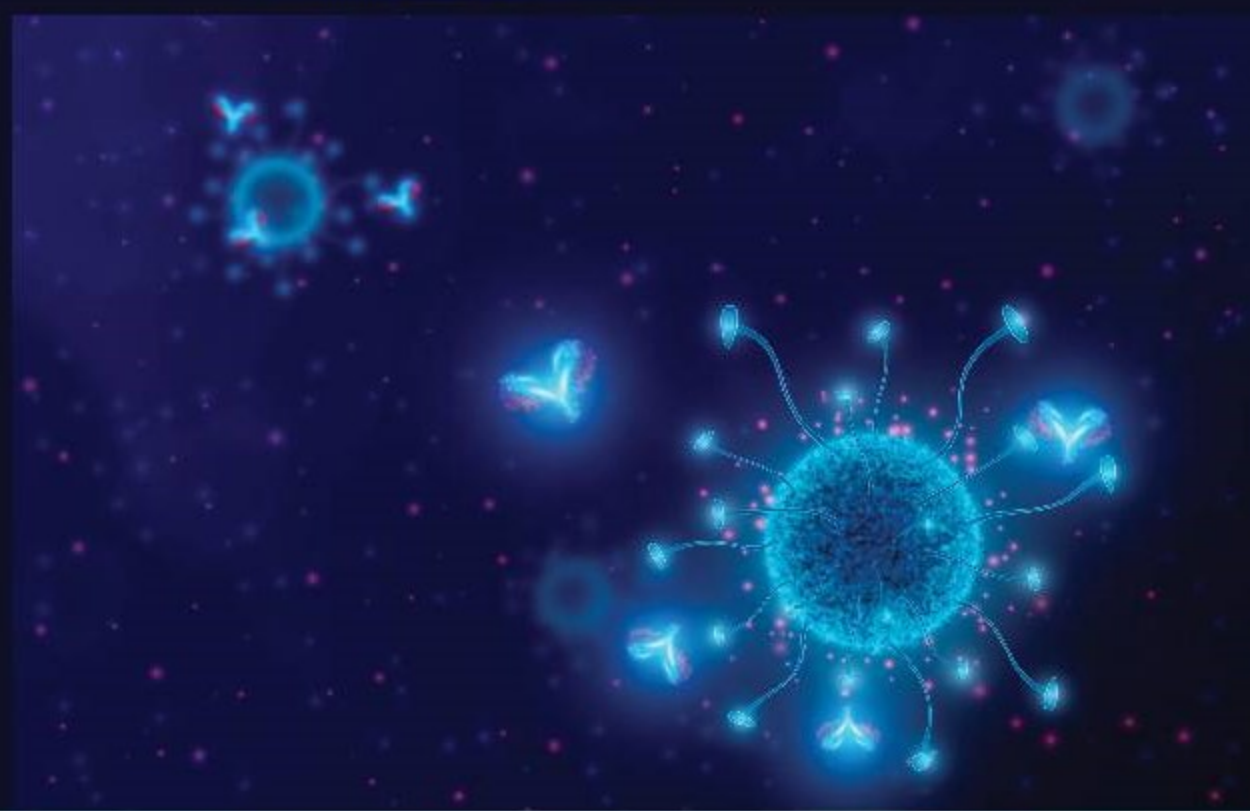
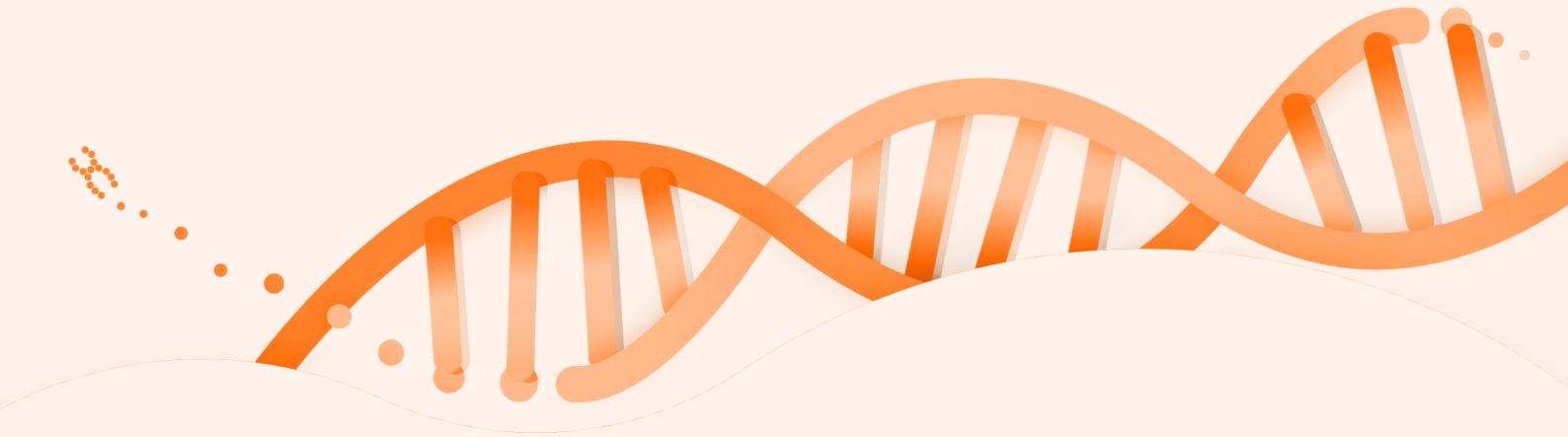
Medicine Personalized JOURNAL

Medical Journal/9 Year/No.34/500000 Rials/2024 Summer/ISSN 2717-3860



The Future of Medicine is Personalized

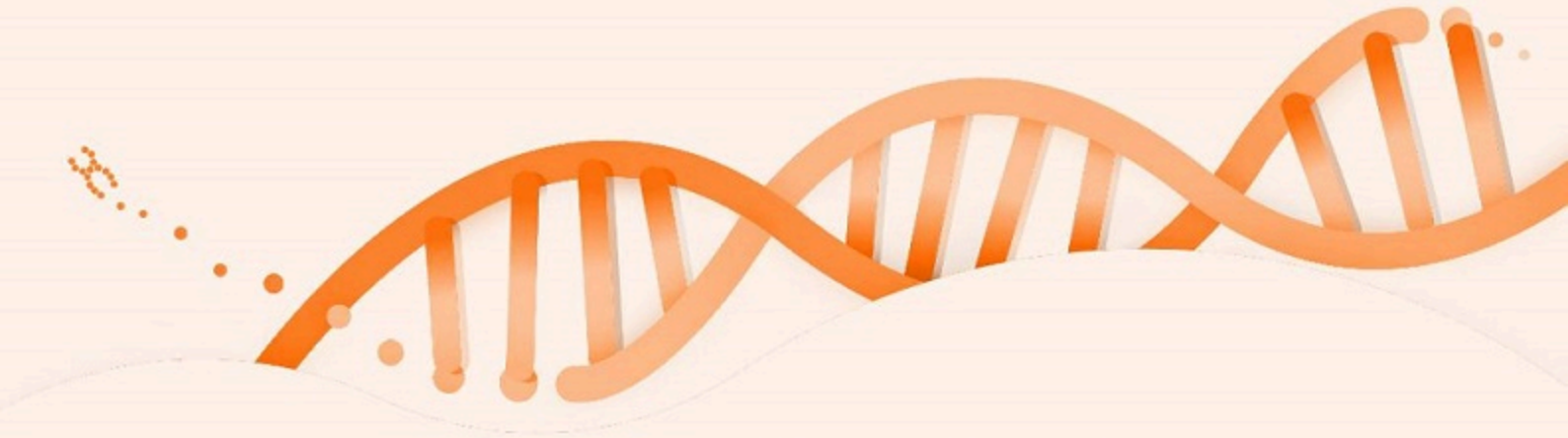


Journal Information

Name: Personalized Medicine Journal
Abbreviated Name: PMJ
Date of First Issue Published: February 2019
Concessionaire: AmitisGen TECH Dev Group
Release Period: Quarterly

Editorial Board Information

Contact Information
Tel: (98)2188985291-3
Fax: (98)2189775181
Email: Editor@pmjournal.ir
Address: No. 2, Italia Street, Tehran, Iran
Postal code : 1416673744



Personalized Medicine Journal
Summer 2024,Volume9,Issue 34
Table of Content

http://pmjournal.ir Reviwe Article

Summer 2024, Volume 9, Issue 34 (1- 8)

Recent Developments in RNA Therapeutics for Humans Disorders

Farnaz Roshan Mehr[1,*], Fatemeh Gabeleh[2], Roshanak Jazayeri[3]

[1]Department of Medical Biotechnology, Golestan University of Medical Sciences, Gorgan, Iran.
[2]Department of Medical Virology, Tarbiat Modares University, Tehran, Iran.
[3] Non-communiable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran.

DOI: 10.22034/pmj.2024.715088

**Corresponding author: Farnaz Roshan Mehr, Department of Medical Biotechnology, Golestan University of Medical Sciences, Gorgan, Iran. Email: Farnazroshanmehr@gmail.com.*

Submitted: 2024-05-02
Accepted: 2024-08-26

Keywords:
Antisense
RNA
Aptamer
RNA interference

How to Cite this Article:

F. Roshan Mehr, F. Gabeleh, R.jazayeri. "Recent Developments in RNA Therapeutics for Humans Disorders" Personalized Medicine Journal, Vol. 9, no. 34, pp. 1- 8.

Abstract:

Recent research has uncovered a wide range of RNAs, including noncoding RNAs, and have discovered their varied modes of action inside cells. These ribonucleic acids (RNAs) play a crucial role in controlling many cellular processes and are thus anticipated to be significant targets for the treatment of human disorders. In recent years, RNA-based medicinal approaches have made significant advancements alongside their comprehensive functional research. Following extensive study and experimentation, medications based on antisense RNAs and small interfering RNAs have been successfully created and are already being used in clinical settings. Furthermore, there is now ongoing research focused on the development of pharmaceuticals using RNA aptamers and messenger RNA. In addition to the advancement of RNA-based medications, many techniques have been devised to effectively deliver RNA drugs into cells. RNA treatment offers several benefits compared to current therapeutics based on small molecules or monoclonal antibodies, mostly due to its ability to selectively target all genes inside cells. The purpose of this article is to provide an overview of the introduction of various RNA-based technologies and the introduction of RNA-based drugs in the market. In addition, the future prospects of RNA therapy will be addressed.

INTRODUCTION

The use of antisense oligonucleotides (ASOs) to hinder protein synthesis in the early 1980s greatly facilitated the fast progress of RNA-based treatments. The idea of RNA interference (RNAi) and the use of small interfering RNA (siRNA) to suppress human genes resulted in a surge in financial support for RNA therapies throughout the 2000s (1). Additional RNA molecule regulators and associated processes have been thoroughly studied. Currently, many RNA-based drugs have been authorized and others undergoing phase III research. RNA-based treatments have promising potential in contrast to traditional protein-targeted and DNA-based medications, because of their unique physicochemical and physiological features. RNAs play a crucial role in three fundamental biological macromolecules: DNAs, RNAs, and proteins (2). RNA molecules, including ASOs, siRNAs, and miRNAs, can specifically bind to and target both mRNAs and ncRNAs via Watson-Crick base-pairing. Hence, RNA has the potential to selectively target any desired gene by precisely choosing the appropriate nucleotide sequence on the target RNA. In contrast, a mere 0.05% of the human genome has been affected by the presently authorized protein-targeted treatments, which include small-molecule drugs and antibodies (3). This is because the majority of DNA sequences in the human genome are translated into noncoding transcripts. In addition, about 85% of proteins do not possess particular clefts and pockets that may accommodate tiny molecules for binding. Furthermore, intracellular delivery of in vitro transcribed (IVT) mRNA may be

used for protein replacement therapy or vaccination purposes (3).

The majority of medications available today are either tiny molecules or proteins. Small molecule medications often act as competitive inhibitors of their target proteins, but protein-based drugs are often used to attach to target proteins, replace dysfunctional target proteins, or compensate for insufficient levels of a target protein. An inherent challenge associated with protein-based medications is their limited ability to penetrate target cells due to their huge size (4). Consequently, these treatments can only exert their therapeutic effects when the target molecule is located outside the cell or is expelled. Although small-molecule and protein-based medications have proven beneficial in several situations, there remains a multitude of disorders that cannot be addressed with either small molecules or proteins (5). For instance, a significant number of individuals with diabetes have insulin resistance, rendering the administration of more insulin ineffective in reducing their blood glucose levels. RNA-based medicines show promise as future therapies for disorders like diabetes, cancer, and Huntington's disease. RNA treatments provide improved therapy options for targeting the pathophysiological underpinnings of various illnesses, perhaps resulting in enhanced patient outcomes. Furthermore, the United States Food and Drug Administration (FDA) has previously approved several RNA treatments. Additionally, several other therapies are now undergoing clinical trials at different stages, providing further evidence of the effectiveness of RNA therapies in treating various disorders. This article offers a comprehensive summary of notable advancements in the field of RNA-based therapies. The categorization of RNA-based therapeutics and their mechanisms of action have been delineated. This study also addresses the key obstacles in implementing these RNA therapeutics and their remedies.

Different types of RNA-based therapies and mechanisms of action

Antisense oligonucleotides (ASOs)

In this review, antisense oligonucleotides (ASOs) refer to chemically manufactured oligonucleotides, typically 12-30 nucleotides long, which are specifically engineered to bind to RNA using Watson-Crick base pairing principles. The specificity of ASOs is partly determined by their length, since oligonucleotides that are 16–20 nucleotides in size may selectively attach to a single target RNA. After attaching to the specific RNA, the oligonucleotide alters RNA function in several ways (6). These processes may be roughly classified as either facilitating RNA breakage and destruction or as occupancy-only mechanisms, sometimes known as steric blocking. The modulation of RNA by the ASO is contingent upon the chemistry and design of the ASO, the specific location on the RNA where the ASO is intended to bind, and the role of the RNA. By considering the specific chemical and positional criteria for various pathways, it is feasible to deliberately create ASOs (antisense oligonucleotides) to regulate the target RNA. However, some screening is still necessary to get the most effective activity and tolerability (7).

During occupancy-mediated degradation, ASOs attach to and cut the target RNA at the ASO binding sites using natural enzymes, which increases the suppression of target transcripts. This process is sometimes referred to as enzymatic RNA breakdown due to its reliance on certain enzymes. The most well-defined mechanism for degradation is by RNase H1, which functions as a highly selective endonuclease to specifically break the RNA-DNA heteroduplex (8). RNase H1 efficiently and selectively targets both the cytoplasmic and nuclear transcripts owing to its widespread distribution. Ribozymes, along with other enzymes, may facilitate occupancy-mediated destruction. The ribozyme catalyzes the cleavage of target RNAs using either hammerhead or hairpin structures. Furthermore, the substrate recognition domain of the enzyme may be altered to enhance the cleavage at either the cis or trans site (9).

ASOs in occupancy-only methods regulate the up- or down-regulation of target transcripts by directly binding to them, independent of particular enzymes. Occasionally, this process is referred to as the steric block mechanism. The manipulation of RNA splicing is the most often-used approach (10). Splice-switching ASOs can modify the way genetic material is spliced by specifically targeting cis-elements that regulate splicing. Cis-acting elements exert their influence on nearby splice sites by attracting trans-splicing factors, which may either activate or stop the splicing process. They are composed of splicing enhancers and silencers. When ASOs form base pairs with a splicing enhancer sequence, they prevent the stimulatory splicing factor from binding to its specific enhancer-binding site. This inhibition of splicing leads to exon skipping. On the other hand, ASOs specifically aim at a splicing silencer sequence motif that prevents the inhibitory splicing factor from binding. The silencer element has a negative regulatory effect on splicing activation at the splice site, leading to the inclusion of the exon (11, 12).

Eteplirsen regulates the process of skipping exons, whereas nusinersen promotes the process of including exons. Regarding the applicability aspect, we analyze two splice-modulating ASO medicines, namely eteplirsen and nusinersen. The FDA approved to nusinersen in 2016 for the treatment of spinal muscular atrophy (SMA). This condition is the result of deletions or mutations in the survival motor neuron 1 (SMN1) gene. Insufficient production of SMN protein

results in the weakening and wasting away of skeletal and respiratory muscles (13). Nusinersen regulates the process of splicing in SMN2, which differs from SMN1 only in that it undergoes alternative splicing and excludes exon 7. This exclusion leads to the production of a truncated protein with a functionality that ranges from 5% to 10%. Nevertheless, nusinersen controls the process of alternative splicing in a manner that ensures the inclusion of exon 7. This inclusion leads to the production of fully functioning SMN, which ultimately improves motor function in individuals with SMA (14).

Eteplirsen received FDA approval in 2016 for the treatment of Duchenne muscular dystrophy (DMD). Alterations in the DMD gene, which encodes the dystrophin protein, result in the onset of DMD (15). The predominant mutation leading to DMD is situated in exon 51. Consequently, eteplirsen, a 30-mer ASO, specifically focuses on exon 51 of the DMD gene. This targeting results in the exclusion of exon 51 during the process of alternative splicing. This mechanism avoids the occurrence of frameshift mutations, which result in the synthesis of dysfunctional dystrophin. The resultant dystrophin protein is somewhat shorter than its wild-type cousin, however it retains its functioning (16).

Inotersen was granted FDA clearance in 2018 for the treatment of familial amyloid polyneuropathy. The etiology of this condition may be attributed to autosomal dominant mutations in the transthyretin (TTR) gene (17). These mutations cause the TTR tetramer to be disrupted, resulting in the aggregation of TTR monomers into amyloid deposits throughout the body. To counteract the accumulation of TTR, inotersen specifically acts on the 3′ UTR of the TTR mRNA, hence blocking the synthesis of TTR and impeding the advancement of the illness. Clinical investigations have shown that inotersen is effective and safe in reducing the levels of circulating TTR (18).

RNA interference (RNAi)

RNA interference (RNAi) is a regulatory mechanism found in most eukaryotic cells. It involves the use of tiny double-stranded RNA (dsRNA) molecules to limit gene activity via homology-dependent mechanisms. Small interfering RNAs (siRNA) are double-stranded RNA molecules that are around 21-22 base pairs long. They include distinct 2 nucleotide overhangs at the 3’ end, which enables them to be identified by the enzymatic machinery of RNAi (19). This recognition ultimately results in the targeted mRNA being broken down by a process that relies on homology. SiRNAs in mammalian cells are generated by the cleavage of longer dsRNA precursors by the RNase III endonuclease Dicer, or they may be created using chemical or biological techniques. Dicer forms complexes with RNA-binding proteins, including TAR-RNA-binding protein (TRBP), PACT, and Ago-2. These proteins play a role in transferring siRNAs to the RNA-induced silencing complex (RISC) (20). The fundamental elements of RISC consist of the members belonging to the Argonaute (Ago) family. Among humans, there are eight members in this family, but only Ago-2 exhibits a functional catalytic domain for cleavage action. When siRNAs are loaded into RISC, they exist as double-stranded molecules. However, Ago-2 enzyme cleaves and releases one of the strands, known as the “passenger” strand. This process results in an active version of RISC that contains a single-stranded molecule called the “guide” RNA. The guide RNA is responsible for directing the specificity of target identification via intermolecular base pairing. The selectivity of strand loading into RISC is determined by rules that rely on the differing thermodynamic stabilities of the ends of the siRNAs. The PIWI domain of Ago-2 prefers to bind to the less thermodynamically stable end (21).

MicroRNAs (miRNAs) play a crucial role in RNAi. These are naturally occurring double-stranded molecules that control gene expression after transcription by forming a complex with RISC and attaching to the 3’ untranslated regions (UTRs) of target sequences via small sections of similarity, known as “seed sequences”. The main mode of operation of miRNAs is to inhibit translation, however, this may also destroy the messenger RNA (22). The miRNA duplexes exhibit partial Watson-Crick base pairing, and unlike siRNAs, the antisense strand cannot be determined by cleaving the passenger strand. Consequently, another method must be used to choose the antisense strand. miRNAs serve as natural substrates for the RNAi machinery. The original transcripts of microRNAs (pri-miRNAs) are first produced as lengthy molecules. These pri-miRNAs are then processed in the nucleus by the Microprocessor complex, which is made up of Drosha and DGCR8. This processing results in the formation of hairpin structures that are around 60-70 base pairs in length, known as pre-miRNAs (23). The pre-miRNAs undergo further processing in the cytoplasm by an enzyme called Dicer. One of the two strands is then inserted into the RISC, likely by contact with one of the accessory proteins associated with Dicer. Crucially, it is feasible to use this inherent gene silencing process to control the expression of certain gene(s). When the siRNA effector is introduced into the cell, it will trigger the activation of RISC, leading to a powerful and focused suppression of the desired mRNA. Due to its high efficacy and specificity, RNAi has become the preferred approach for suppressing particular gene expression in mammalian cells (24).

RNA activation (RNAa) is a distinct mechanism from RNAi in which dsRNA stimulates gene expression by specifically targeting promoter regions. saRNAs, also

known as small activating RNAs, are produced by synthesizing homologous sequences that are located near or inside gene promoters. These saRNAs can induce RNAa, which is the process of activating gene expression. Like miRNA-like target recognition, the functions of saRNAs rely on the AGO2 protein (25). Within the nucleus, AGO2–saRNA utilizes the "seed" region to establish base pairing with sequences present in the chromatin-bound RNA transcripts or complementary DNA. In addition to saRNA and AGO2, new studies have shown that the RNA-induced transcriptional activation (RITA) complex also includes RHA and CTR9. saRNA has the potential to mitigate the decrease in expression of dormant tumor suppressors genes, such as p21, or other often disrupted genes, such as E-cadherin. Consequently, saRNA might facilitate the advancement of therapeutic approaches based on dsRNA for the treatment of cancer and other related conditions (26, 27).

Patisiran was the first siRNA therapeutic authorized for use by the FDA (28). In 2018, it received approval for treating polyneuropathy resulting from hereditary transthyretin-mediated (hATTR) amyloidosis (29). hATTR amyloidosis is an inherited condition characterized by the accumulation of aberrant TTR protein, mostly in the peripheral nervous system, leading to polyneuropathy. Patisiran is a small interfering RNA (siRNA) medication that specifically targets the mutant TTR mRNA, resulting in the breakdown of the mRNA and a reduction in the production of TTR protein. Studies have shown that this intervention significantly decreases the accumulation of TTR in individuals with polyneuropathy resulting from hATTR amyloidosis (28).

In 2020, the FDA approved lumasiran for the treatment of primary hyperoxaluria type 1 (PH1) (30). Different genetic alterations in the enzyme alanine-glyoxylate aminotransferase result in elevated levels of oxalate and the creation of calcium oxalate crystals, which ultimately leads to the development of PH1. Lumasiran specifically targets the mRNA responsible for encoding glycolate oxidase. This action results in a decrease in the availability of the substance needed for oxalate formation, thereby lowering the levels of oxalate (31).

The FDA approved inclisiran in December 2021 for the treatment of atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) (32). These disorders are distinguished by elevated levels of LDL-C. Inclisiran functions by specifically targeting the mRNA responsible for producing proprotein convertase subtilsin/kexin type 9 (PCSK9), a protein involved in lipid metabolism and the control of cholesterol levels (32). This action leads to a reduction in LDL-C levels. Inclisiran has shown efficacy in lowering LDL-C levels in individuals who have not achieved sufficient reduction with statin monotherapy. In addition, inclisiran has shown enhanced effectiveness in reducing LDL-C levels when used with statins in individuals who have only seen partial success with statins alone in decreasing LDL-C levels (32).

mRNAs and mRNA vaccine

mRNA is a kind of RNA that is synthesized by transcribing the genomic DNA and functions as a template for protein synthesis. Messenger RNAs (mRNAs) are generally around 2 kilobases (kb) long and are characterized by the presence of a 5′ cap, a 5′ untranslated region (UTR), a coding region, a 3′ UTR, and a poly(A) tail. Messenger RNAs (mRNAs) are very suitable options for addressing disorders that have a well-established genetic basis (33). Historically, messenger RNAs (mRNAs) have been used in replacement treatment to address disorders resulting from inadequate production of a certain protein. Furthermore, CRISPR–Cas-based mRNA treatments have the potential to rectify DNA mutations that result in non-functional downstream products. The mRNA vaccination is an innovative technique that combines principles from molecular biology and immunology (34). The technique is intricately linked to gene therapy. The exogenous mRNAs encoding antigens are delivered into somatic cells to facilitate the synthesis of antigens via the expression system. Synthetic antigens can elicit an immunological response. In 1990, scientists used mRNA expression vectors to directly introduce mRNAs into live mouse somatic cells to express luciferase, beta-galactosidase, and chloramphenicol acetyltransferase (35). In 1992, Jirikowski et al. discovered that the introduction of mRNAs encoding oxytocin and vasopressin into genetically mutated mice with diabetes insipidus resulted in a temporary reversal of the condition within a few hours after injection (36). Despite the great results that were revealed thereafter, we did not make any significant advancements in mRNA investigations. The problems included mRNA instability, heightened immunogenicity, and the absence of an efficient mRNA delivery method (37).

Over the course of these decades, more investigations and advancements in experimental methodologies have led to advancements in the safety, effectiveness, and industrial-scale manufacturing of mRNA vaccines. The benefits of mRNA-based vaccinations make them a top priority for treating cancers and viral illnesses. Initially, mRNA vaccines are safe in stimulating the production of antibodies during phase I clinical trials in humans (38). The rationale for this is that mRNA does not possess the ability to replicate itself. The mRNA vector does not possess any traits associated with antibiotic resistance, genomic integration, or

significant immunogenic reactions. In addition, nucleases efficiently break down single-stranded RNA. While the degraded mRNA components stimulate an overactive immune system response, the development of a modified mRNA delivery mechanism may improve effectiveness and prevent any adverse effects (39).

Furthermore, enhanced treatment effectiveness is achieved by the use of modified mRNAs and mRNA carriers. The nucleoside-modified mRNA vaccination for HSV-2 (herpes simplex virus 2) reduced the amount of virus present in viral illnesses. Mannose-functionalized liposomes were used for the intracellular delivery of mRNA. The vector safeguarded the mRNA from degradation and enhanced mRNA overexpression by increasing the expression of mannose receptor (CD206) on the surfaces of cells (40). Currently, much research has been conducted on several types of delivery vectors and modified mRNAs to assess their therapeutic effectiveness, particularly in the context of the COVID-19 pandemic. Manufacturing mRNA vaccines on a big scale is often industrialized. Mass manufacturing depends on translational research, which is crucial for increasing production speed. In laboratory settings, translational technology efficiently chooses formulations and structures in preclinical and clinical investigations (41, 42).

Presently, two mRNA vaccines have received approval from the FDA, while one is currently undergoing clinical testing. BNT162b2 was the first mRNA vaccination authorized by the FDA. The partnership between Pfizer and BioNTech resulted in the development of this vaccine, which aims to induce a strong immune response and production of antibodies against SARS-CoV-2, the virus responsible for causing COVID-19. This vaccine candidate underwent clinical trials in both Germany and the US, and the results showed a considerable reduction in the likelihood of developing COVID-19. BNT162b2 codes for the complete membrane-anchored spike (S) protein, which has two minor changes to enhance its conformational stability (43). The second mRNA vaccine authorized by the FDA is mRNA-1273. This vaccine contains the perfusion-stabilized S protein of SARS-CoV-2, together with the S1-S2 cleavage site. Like BNT162b2, the mRNA-1273 vaccination was produced by Moderna to prevent the acquisition of COVID-19. Both FDA-approved mRNA COVID-19 vaccines include 1-methyl-pseudouridine, which serves to inhibit the detection of the innate immune system, while simultaneously enhancing the capacity of the mRNA to be translated. Furthermore, both of them are enclosed by lipid nanoparticles. Moreover, both vaccines have shown substantial efficacy in preventing SARS-CoV-2 infection, while also upholding rigorous safety protocols. It is important to acknowledge the remarkable pace at which both vaccinations were produced. Thus far, no other vaccine has been created this quickly while yet preserving effectiveness. This emphasizes the therapeutic benefit of using RNA-based vaccinations in the treatment of life-threatening illnesses (44).

Aptamer

Nucleic acid aptamers are a unique group of synthetic polymers or oligomers made up of single-stranded ssDNA or RNA molecules. They possess the ability to attach to a particular target by creating secondary and/or tertiary structures. The term “aptamer” is derived from the Latin word “aptus”, which means “to fit”, and the Greek word “meros”, which means “particle”. It was selected to depict the “lock and key model” that characterizes the interaction between aptamers and their binding targets. Aptamers have strong binding affinity and selectivity towards a diverse array of targets, including proteins, peptides, small compounds, metal ions, bacteria, viruses, and even living cells. The development of aptamers originated in 1990 via an experiment conducted by Tuerk and Gold, using the systematic evolution of ligands in an exponential enrichment (SELEX) technique. The aptamer selection technique used the SELEX approach, which included using purified target molecules and starting with a vast library of random oligonucleotides. The oligonucleotides with high affinity for the target molecule were chosen from the original library using a process that included repeated cycles of binding to the target, selection, and amplification.

Aptamers are a potentially valuable group of molecules that serve as the chemical counterparts of antibodies. Monoclonal antibodies (mAbs) are widely acknowledged as very effective instruments in contemporary medicine for both therapeutic and diagnostic purposes. Aptamers have many advantages over typical antibodies, including exceptional chemical stability and efficient large-scale chemical synthesis. Furthermore, they may be manufactured in huge quantities at a minimal expense, while maintaining a high level of consistency and dependability. Aptamers may exert their effects via three primary mechanisms: (1) Aptamers with cell-type specificity can transport therapeutic agents to the desired tissue or cells; (2) Aptamers can function as agonists, activating their target molecules; (3) Aptamers can act as antagonists, inhibiting the association of molecules involved in disease processes.

Pegaptanib is the first aptamer to get FDA approval and is used in the treatment of neovascular age-related macular degeneration. This condition is distinguished by the deterioration of the retina, resulting in a loss of eyesight. This disorder has been linked to elevated levels of vascular endothelial growth factor (VEGF). Thus, anti-VEGF therapy was considered a very effective

approach for managing this condition. Pegaptanib had a strong attraction to VEGF and effectively sequestered it, hence inhibiting its ability to attach to its receptor. Following successful clinical studies demonstrating the efficacy of pegaptanib in improving or halting eyesight loss, the FDA approved its usage in 2004.

In 2020, the FDA approved Defibrotide for the treatment of hepatic veno-occlusive disease/ sinusoidal obstruction syndrome. This is a potentially fatal complication that may occur as a result of chemotherapy and hematopoietic stem cell transplant (HSCT) conditioning. Defibrotide has been shown to enhance the stability of endothelial cells by decreasing endothelial cell activation. This protects endothelial cells, preventing any more harm and thereby reversing this situation. Both FDA-approved medications have negligible side effects and underscore the potential of aptamer-based therapies.

Ribozymes

Ribozymes, which are RNA molecules with catalytic properties, may selectively break down certain target mRNAs. They are also considered a kind of RNA therapy. Catalytic RNAs were first discovered in the early 1980s, which led to a surge of research into gene expression inhibitors based on nucleic acids. In the late 1980s and early 1990s, researchers established simplified catalytic motifs. This breakthrough allowed for the chemical synthesis of ribozymes, which are molecules capable of inhibiting gene expression in a precise manner. Ribozymes function as catalysts that facilitate the cleavage or synthesis of covalent bonds, enhancing certain processes with or without the involvement of proteins. Over 10 ribozymes primarily catalyze generic acid-base reactions, however the specific mechanisms differ. The general base causes deprotonation at the 2′-OH position to activate the 2′-O− group, whereas the general acid protonates the 5′-O of the leaving group. After the reaction concludes, the 3,5-phosphodiester link at the cutting site is cleaved, resulting in the formation of covalent bonds between 2′-O− and 3′-phosphoric acid. Instead of the mRNA being divided into two fragments, this process occurs. Translation is hindered due to mRNA degradation, resulting in the inhibition of gene expression.

Ribozymes occur naturally but may also be purposefully designed to selectively recognize and bind to certain sequences either on the same nucleic acid strand (cis) or on a noncovalently linked nucleic acid (trans). The phrase “hammerhead” ribozyme refers to a collection of tiny ribozymes that can cleave themselves, and they are generated from single-stranded plant viroid RNAs. The hammerhead ribozyme consists of 30 nucleotides and its simple structure makes it a very suitable option for the creation of trans-acting ribozymes. Through the use of Watson-Crick base pairing, it is possible to manipulate it to specifically cleave any desired RNA target. The “hairpin” or “paperclip” ribozyme is a ribozyme that is derived from plants and is capable of self-cleavage. It has been found in the negative strand of tobacco satellite RNA.34 The hairpin ribozyme catalyzes a reversible process that cleaves RNA substrates, resulting in the formation of 2′,3′-cyclic phosphate and 5′-hydroxyl termini. Through the process of engineering, it is capable of cleaving and converting multiple copies of various targets in the trans form, which refers to a noncovalently linked nucleic acid. Furthermore, the hairpin ribozyme has been used to facilitate ligation processes.

Ribozymes are molecular entities that possess the ability to catalyze chemical reactions. Like protein enzymes, they need precise folding into a well-organized tertiary structure to carry out their tasks. The nucleophilic attack group and the reactive phosphorus atom of the nucleoside hydrolase ribozyme are situated inside the same nucleotide, facilitating the creation of their active structure. In the case of big ribozymes, the nucleophilic attack group and the sensitive phosphorus atom are either located at a significant distance from each other or exist in separate molecules. Consequently, the identification of the cleavage site and the correct placement of the substrate in the active site are more intricate, sometimes necessitating the involvement of metal ions or protein components. For instance, the presence of the magnesium ion plays a crucial role in the interaction between the RNase P ribozyme and the substrate, as well as in the stability of its active center. Nevertheless, the precise targeting of ribozyme activity is a significant obstacle that restricts the practical use of ribozymes. Ribozymes typically identify their cleavage sites by base pairing, however, certain ribozymes may tolerate minor mismatches.

Final thoughts and prospective developments

RNA molecules are very versatile and have a wide range of activities. The use of RNA therapies in clinical settings for the treatment and prevention of human illnesses has shown substantial promise in cutting-edge research. In addition, the process of developing RNA therapies is comparatively easier, faster, and more cost-effective than the creation of standard pharmaceuticals based on proteins and small molecules. How RNA treatment techniques target different clinical problems might vary. For example, siRNAs have a high degree of specificity and selectively target a single mRNA molecule. As a result, they are very efficient in treating diseases that result from mutations in a single gene. However, miRNAs are well-suited for treating disorders that include many pathologies and/or gene alterations since they may target different mRNAs. The field of RNA therapies is now faced with the

following challenges: (i) Cell specificity refers to the ideal characteristic of an RNA therapeutic molecule that selectively targets certain cells without causing unintended effects on other cells or undesirable effects on the intended target cells. (ii) One of the major obstacles in RNA treatments is effectively and consistently delivering the molecule to the exact kind of cell it is intended for while ensuring that the delivery agent remains functional and capable of carrying out its intended purpose.

Emphasizing early study design in clinical trials is crucial to mitigate potential bad outcomes, such as acute toxicity. In addition, this first research design needs to prioritize in vivo functional assays over just relying on in vitro functional tests. Moreover, a crucial aspect of RNA therapy development is to evaluate the clinical results about their efficacy in addressing the mechanistic factors. To achieve this objective, it is necessary to thoroughly assess the RNA therapeutic candidates, specifically in terms of their immunological tolerance, pharmacokinetics, and pharmacodynamics. RNA therapeutic compounds are often designed using the cellular and molecular pathways that cause illnesses. As a result, these molecules are well-positioned for future clinical trials. The existing gaps in knowledge need the adoption of a contemporary strategy to comprehensively comprehend the cellular and molecular mechanisms behind diseases. This understanding will facilitate the development of treatment strategies aimed at not only ameliorating symptoms but also addressing the precise etiology of the illness. Despite the existing barriers in RNA therapy development, the combination of innovative multidisciplinary methods, advancements in contemporary science, and enhanced early study design for clinical trials may ultimately overcome these problems shortly. This will provide significant optimism for the practical use of RNA therapies in many disease states and result in an improved standard of living for millions of patients.

Acknowledgements

We would like to express our heartfelt thanks and appreciation to all those who offered aid and support throughout the implementation of this research project.

Authors's Contribution

Farnaz Roshan Mehr: data curation; editing and review. Fatemeh Gabeleh and Roshanak Jazayeri: investigation and writing. All authors read and confirmed the final manuscript.

Funding

This study is the outcome of self-directed research carried out without any financial assistance.

Ethics approval and consent to participate

Not applicable

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable

REFERENCES

1.Zhu Y, Zhu L, Wang X, Jin H. RNA-based therapeutics: an overview and prospectus. Cell death & disease. 2022;13(7):644.
2.Wang F, Zuroske T, Watts JK. RNA therapeutics on the rise. Nat Rev Drug Discov. 2020;19(7):441-2.
3.Crooke ST, Witztum JL, Bennett CF, Baker BF. RNA-targeted therapeutics. Cell metabolism. 2018;27(4):714-39.
4.Zogg H, Singh R, Ro S. Current advances in RNA therapeutics for human diseases. International journal of molecular sciences. 2022;23(5):2736.
5.Hanna J, Hossain GS, Kocerha J. The potential for microRNA therapeutics and clinical research. Frontiers in genetics. 2019;10:478.
6.Bennett CF. Therapeutic antisense oligonucleotides are coming of age. Annual review of medicine. 2019;70(1):307-21.
7.Agrawal S. Remembering Paul C. Zamecnik, MD," father of antisense"(1912-2009). Oligonucleotides. 2010;20(1):47-50.
8.Crooke ST, Baker BF, Crooke RM, Liang X-h. Antisense technology: an overview and prospectus. Nature reviews Drug discovery. 2021;20(6):427-53.
9.Liang X-H, Sun H, Nichols JG, Crooke ST. RNase H1-dependent antisense oligonucleotides are robustly active in directing RNA cleavage in both the cytoplasm and the nucleus. Molecular therapy. 2017;25(9):2075-92.
10.Desterro J, Bak-Gordon P, Carmo-Fonseca M. Targeting mRNA processing as an anticancer strategy. Nature Reviews Drug Discovery. 2020;19(2):112-29.
11.Li D, Mastaglia FL, Fletcher S, Wilton SD. Precision medicine through antisense oligonucleotide-mediated exon skipping. Trends in Pharmacological Sciences. 2018;39(11):982-94.
12.Nakamura A, Takeda Si. Exon-skipping therapy for Duchenne muscular dystrophy. The Lancet. 2011;378(9791):546-7.
13.Aartsma-Rus A. FDA approval of nusinersen for spinal muscular atrophy makes 2016 the year of splice modulating oligonucleotides. Nucleic acid therapeutics. 2017;27(2):67-9.
14.Burr P, Reddivari AKR. Spinal muscle atrophy. 2020.
15.Chamberlain JR, Chamberlain JS. Progress toward gene therapy for Duchenne muscular dystrophy. Molecular Therapy. 2017;25(5):1125-31.
16.Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Annals of neurology. 2013;74(5):637-47.
17.Sekijima Y. Hereditary transthyretin amyloidosis. 2021.
18.Benson MD, Waddington-Cruz M, Berk JL, Polydefkis

M, Dyck PJ, Wang AK, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. New England Journal of Medicine. 2018;379(1):22-31.
19.Kim DH, Rossi JJ. RNAi mechanisms and applications. Biotechniques. 2008;44(5):613-6..
20.Agrawal N, Dasaradhi P, Mohmmed A, Malhotra P, Bhatnagar RK, Mukherjee SK. RNA interference: biology, mechanism, and applications. Microbiology and molecular biology reviews. 2003;67(4):657-85.
21.Chery J. RNA therapeutics: RNAi and antisense mechanisms and clinical applications. Postdoc journal: a journal of postdoctoral research and postdoctoral affairs. 2016;4(7):35.
22.Hill M, Tran N. miRNA interplay: mechanisms and consequences in cancer. Disease models & mechanisms. 2021;14(4):dmm047662.
23.Wahid F, Shehzad A, Khan T, Kim YY. MicroRNAs: synthesis, mechanism, function, and recent clinical trials. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2010;1803(11):1231-43.
24.O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Frontiers in endocrinology. 2018;9:402.
25.Li L-C, Okino ST, Zhao H, Pookot D, Place RF, Urakami S, et al. Small dsRNAs induce transcriptional activation in human cells. Proceedings of the National Academy of Sciences. 2006;103(46):17337-42.
26.Tan CP, Sinigaglia L, Gomez V, Nicholls J, Habib NA. RNA activation—a novel approach to therapeutically upregulate gene transcription. Molecules. 2021;26(21):6530.
27.Janowski BA, Younger ST, Hardy DB, Ram R, Huffman KE, Corey DR. Activating gene expression in mammalian cells with promoter-targeted duplex RNAs. Nature chemical biology. 2007;3(3):166-73.
28.Hoy SM. Patisiran: first global approval. Drugs. 2018;78:1625-31.
29.Kaku M, Berk JL, editors. Neuropathy associated with systemic amyloidosis. Seminars in Neurology; 2019: Thieme Medical Publishers.
30.Scott LJ, Keam SJ. Lumasiran: first approval. Drugs. 2021;81:277-82.
31.Liebow A, Li X, Racie T, Hettinger J, Bettencourt BR, Najafian N, et al. An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. Journal of the American Society of Nephrology. 2017;28(2):494-503.
32.Lamb YN. Inclisiran: first approval. Drugs. 2021;81:389-95.
33.Wang Y, Zhang Z, Luo J, Han X, Wei Y, Wei X. mRNA vaccine: a potential therapeutic strategy. Molecular cancer. 2021;20(1):33.
34.Pollard C, De Koker S, Saelens X, Vanham G, Grooten J. Challenges and advances towards the rational design of mRNA vaccines. Trends in molecular medicine. 2013;19(12):705-13.
35.Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, et al. Direct gene transfer into mouse muscle in vivo. Science. 1990;247(4949):1465-8.
36.Jirikowski GF, Sanna PP, Maciejewski-Lenoir D, Bloom FE. Reversal of diabetes insipidus in Brattleboro rats: intrahypothalamic injection of vasopressin mRNA. Science. 1992;255(5047):996-8.
37.Pardi N, Hogan MJ, Weissman D. Recent advances in mRNA vaccine technology. Current opinion in immunology. 2020;65:14-20.
38.Alberer M, Gnad-Vogt U, Hong HS, Mehr KT, Backert L, Finak G, et al. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. The Lancet. 2017;390(10101):1511-20.
39.Kaczmarek JC, Kowalski PS, Anderson DG. Advances in the delivery of RNA therapeutics: from concept to clinical reality. Genome medicine. 2017;9:1-16.
40.Egan KP, Hook LM, Naughton A, Pardi N, Awasthi S, Cohen GH, et al. An HSV-2 nucleoside-modified mRNA genital herpes vaccine containing glycoproteins gC, gD, and gE protects mice against HSV-1 genital lesions and latent infection. PLoS Pathogens. 2020;16(7):e1008795.
41.Wang F, Xiao W, Elbahnasawy MA, Bao X, Zheng Q, Gong L, et al. Optimization of the linker length of mannose-cholesterol conjugates for enhanced mRNA delivery to dendritic cells by liposomes. Frontiers in Pharmacology. 2018;9:980.
42.Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. New England Journal of Medicine. 2020;383(16):1544-55.
43.Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New England journal of medicine. 2020;383(27):2603-15.
44.Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. New England journal of medicine. 2021;384(5):403-16.

http://pmjournal.ir Reviwe Article

Summer 2024, Volume 9, Issue 34 (9- 13)

Aptamer-Based Approaches in Oncology

Behnoush Khasheii[1,*], **Parisa Haghpour**[2]

[1]Department of pathobiology, faculty of veterinary science, Bu Ali Sina university, Hamedan, Iran.
[2]Department of Biotechnology, Alzahra University, Tehran, Iran.

*Corresponding author: Behnoush Khasheii, Department of pathobiology, faculty of veterinary science, Bu Ali Sina university, Hamedan, Iran. Email: Bh-kh@yahoo.com.

DOI: 10.22034/pmj.2024.715089

Submitted: 2022-04-20
Accepted: 2022-08-16

Keywords:
Aptamer
Cancer
Therapy
SELEX

How to Cite this Article:
B. Khasheii, P. Haghpour. "Aptamer-Based Approaches in Oncology" Personalized Medicine Journal, Vol. 9, no. 34, pp. 9- 13.

Abstract:
Cancer is a significant global cause of mortality, and enhancing therapy is essential to save lives and minimise adverse consequences. Aptamers, composed of DNA or RNA, have the potential for cancer treatment by precise targeting of certain molecules. Aptamers, unlike conventional therapies such as chemotherapy, have the specific objective of delivering medications directly to cancer cells, while reducing injury to healthy cells. This paper examines the process of aptamer development and utilisation in cancer treatment, with a specific emphasis on their capacity to enhance therapy and surmount drug resistance. Additionally, it explores the obstacles and potential advancements in using aptamers to transform cancer therapy.

INTRODUCTION

Background

Cancer is a prevalent worldwide cause of death, impacting several nations where it is among the top causes of mortality before the age of 70 (1). This disease is characterized by various traits, including increased growth signaling, resistance to cell death, unlimited replication capacity, promotion of new blood vessel formation, and activation of invasion and metastasis. It involves the uncontrolled multiplication of abnormal cells, which can potentially spread to nearby or distant tissues (2). In recent years, there has been increasing study focus on the many genetic and molecular changes that occur in cancer, a complicated illness defined by abnormal cell growth and multiplication. The rising death rates from cancer are made worse by the inefficiencies in diagnosing and managing cancer therapy (3). For cancer patients, early identification and appropriate treatment are essential. Surgery, radiation, chemotherapy, targeted therapy, and immunotherapy are among the available treatments (4, 5).

SELEX (Systematic Evolution of Ligands by Exponential Enrichment), a technique for creating unique biomolecules known as aptamers, was invented by scientists in the 1990s (6, 7). Aptamers are solitary sequences of DNA or RNA that assemble in a 3D shape to bind to specific targets, like antibodies (8). This renders them highly effective in binding to their targets. Aptamers are generally less likely to induce immune responses than antibodies, rendering them appropriate for recurrent use with fewer adverse effects (9). For instance, the FDA-approved aptamer Macugen addresses age-related macular degeneration (AMD) by binding to and targeting a molecule known as VEGF (10).

Chemotherapy, radiation, and surgery, which are the current methods used to treat cancer, present various issues when administered to patients. Chemotherapy is a treatment that distributes chemicals throughout the body to eliminate cancer cells. However, it also damages healthy cells, resulting in significant toxicity and many adverse effects. Patients may develop resistance to these medications, resulting in a decrease in their effectiveness over time. Targeted therapy and immunotherapy, which are more recent forms of treatment, provide a certain degree of optimism. Targeted treatment employs pharmaceutical agents specifically tailored to target proteins that facilitate the growth of cancer cells. This approach allows for greater precision and minimizes the potential damage to healthy cells. Immunotherapy enhances the patient's immune system to combat the malignancy. Although these emerging therapies have potential,

they nevertheless encounter challenges such as the development of cancer cell resistance and the occurrence of adverse effects that restrict the dosage of the medicine, resulting in limited short-term advantages (11).

Given the increasing mortality rate associated with cancer, it is important to discover more effective methods for diagnosing, detecting in its early stages, and treating this disease. Although there are already available diagnostic technologies, the task of identifying cancer in its first stages remains challenging. Several innovative techniques are now being developed and demonstrating enhancements compared to the existing ones. A notable breakthrough in cancer therapy involves the use of aptamers. In recent studies, aptamers have shown superior efficacy compared to conventional treatments (12). This review examines the creation and selection of aptamers for targeted cancer therapy, aiming to address drug resistance and minimize the side effects associated with traditional treatments. It also offers an overview of the latest advancements and challenges in developing aptamers for cancer treatment.

Characteristics and Types of Aptamers

Aptamers are small strands of DNA or RNA that fold into specific shapes and tightly bind to their targets. Often likened to chemical antibodies, aptamers outperform traditional antibodies by being more efficient and avoiding issues such as size, instability, and immune activation (11). The term “aptamer” originates from Latin (“aptus,” meaning to fit) and Greek (“meros,” meaning particle). There are two main types: nucleic acid aptamers (NA-Apts) and peptide aptamers (P-Apts)(11, 12). Aptamers can encircle small molecules or fit into gaps in larger molecules, binding to peptides, proteins, small molecules, organic compounds, metal ions, and various biological targets like viruses and cells. This binding is driven by forces such as van der Waals interactions, hydrogen bonding, and complementary shapes, resulting in strong bonds (13, 14). NA-Apts are short, single-stranded DNA or RNA molecules (20–100 bps) that fold into specific 3D shapes, allowing them to bind precisely to their targets. RNA-based aptamers are more flexible than DNA-based ones but are also more susceptible to degradation and require more complex selection processes (15, 16). P-Apts, which followed NA-Apts in development, are polypeptides with a short amino acid loop embedded in a rigid protein structure, offering high binding affinity (17). Aptamers offer several advantages over antibodies for targeted cancer treatment. They are smaller, more stable, easier to produce, and have better tissue penetration. Unlike antibodies, aptamers do not require animals for production and can be synthesized chemically, allowing for economical, high-accuracy large-scale production with reduced batch-to-batch variability (18, 19). Additionally, aptamers can be chemically modified to enhance stability and binding affinity, and detection labels or conjugation linkers can be easily incorporated without compromising their function. This chemical synthesis enables the generation of aptamers against otherwise toxic compounds and allows for their reuse after denaturation (20, 21).

Bioinformatics for in-silico aptamer screening and design

The Systematic Evolution of Ligands by Exponential Enrichment (SELEX), which was first presented in 1990, is a method used to identify single-stranded DNAs or RNAs with a strong binding ability from a vast collection of random sequences (14, 15). Subsequently, this technique has been used to create a multitude of aptamers that specifically bind to various compounds, such as amino acids, proteins, metal ions, and cells (16).

SELEX consists of multiple stages: first, a random nucleic acid library is mixed with a target molecule and allowed to incubate. Then, the bound strands are separated from the unbound strands. Next, the bound strands are eluted and amplified. This entire process is repeated for 6-18 rounds, with each round being carried out under more strict conditions to guarantee a strong affinity and specificity. To enhance efficiency, SELEX may be integrated with high-throughput sequencing (HT-SELEX), which allows for the swift screening of many sequences within a short period (17). HT-SELEX has led to the creation of computational bioinformatics techniques for aptamer design. These techniques include sequence-based, motif-searching, multi-dimensional scoring, and machine-learning algorithms. These techniques may improve the process of identifying and optimising aptamers, hence lowering the time needed for design. Although there have been improvements, the use of computer-based approaches for designing aptamers has not been generally embraced owing to the limited number of citations received by computational tools (18).

Clinical studies that are registered to evaluate the effectiveness of aptamers in treating cancer

Aptamers are promising for treating diseases like Alzheimer’s and cancer because they are easy to make, stable, and target specific. Pegaptanib (Macugen) was approved by the FDA in 2004 for eye disease but newer drugs are now more popular. Avacincaptad pegol (Izervay) was approved in 2023 for a similar eye condition. AS1411 was the first aptamer tested in cancer trials. It targets nucleolin, a protein found more in cancer cells. Spiegelmers, another type of aptamer, are being tested for cancer

treatment to block substances in tumors. Research continues using aptamers to diagnose and treat cancer. Many trials are registered until 2023, showing interest despite challenges. Aptamers have been studied for 30 years to treat diseases like cancer, hepatitis, and HIV. Macugen, which targets VEGF, is used clinically, and other aptamers are in different trial stages to improve their use as treatments (11, 19).

Cancer chemotherapy using aptamers

Chemotherapy is still the mainstay of cancer treatment, but its efficacy varies and its non-specific drug delivery to healthy tissues may have serious adverse effects (21). When it comes to drug delivery, aptamers are superior to antibodies because they allow for quicker tissue penetration during targeted treatment. Drug transport to cancer cells is improved by aptamer-drug conjugates (AptDCs), which may improve therapy results.This strategy entails designing aptamers to intercalate medications, enhancing targeting and lowering toxicity. For the purpose of concurrently targeting numerous cell receptors, bispecific aptamers (bsApts) provide a more affordable option than bispecific antibodies (20).

Cancer radiation treatment based on aptamers

Radiotherapy, often known as radiation therapy (RT), is a widely used treatment for primary solid tumours, providing benefits to more than half of cancer patients every year. The objective is to reduce the size of tumours and eliminate cancer cells by using high-energy radiation. One of the main difficulties in radiotherapy is ensuring that the tumour receives an adequate amount of radiation while minimising damage to the surrounding healthy tissues.To tackle this issue, scientists are investigating radiosensitizers and tailored delivery techniques that amplify the efficacy of radiation on cancer cells while minimising any adverse consequences (22). Aptamers provide great potential as vehicles for the targeted delivery of radiosensitizers to tumours, owing to their unique and precise binding capabilities. They may be combined with other radiosensitizers, such as metal formulations and nucleoside analogues, to enhance their absorption by cancer cells and make them more sensitive to radiation. Research indicates that aptamers such as AS1411 and anti-MUC1 have the potential to augment radiation treatment by amplifying DNA damage in cancerous cells. Moreover, aptamers such as the U2 aptamer, which specifically target EGFRvIII in glioblastoma cells, have the potential to enhance radiosensitivity by blocking the mechanisms that respond to DNA damage (23).

Cancer immunotherapy based on aptamers

Cancer immunotherapy involves enhancing the immune system to target cancer cells, aiming to minimise damage to healthy tissues. In recent decades, cancer immunotherapy has become a major focus of research in cancer treatment. Various methods like immune checkpoint blockade (ICB) and adoptive T cell immunotherapy have been developed to slow down tumor growth. For instance, Gao et al. identified the anti-PD-1 aptamer PD4S using Cell-SELEX, which successfully reversed T-cell exhaustion caused by PD-1/PDL1. Du et al. created a durable aptamer that blocked CTLA-4/B7 and PD-1/PD-L1 pathways, boosting the immune response against liver tumors. Yang et al. proposed a logical strategy using aptamers modified on cell surfaces to improve treatment accuracy and reduce harmful side effects of ICB therapy. Adoptive T cell therapies like CAR T cell therapy, used for blood cancers, face challenges with complex engineering and systemic side effects. Yang et al. suggested a method where aptamers directly attract and activate naive T cells at the disease site, offering a cost-effective approach for cancer immunotherapy. Zhang et al. also proposed using aptamer-equipped NK cells to enhance adoptive immunotherapy in solid tumors, aiming to target specific cells and increase cytokine production to kill tumor cells (24).

Aptamer-based nanomaterials for targeted medication delivery

Aptamer-based nanomaterial systems represent a significant advancement in nanomedicine, particularly in targeted drug delivery. Nanomaterials, with their unique physicochemical properties such as ultra-small size, large surface area, and drug-loading capabilities, have revolutionized therapeutic approaches by leveraging the Enhanced Permeability and Retention (EPR) effect. This effect allows nanoparticles to accumulate preferentially in cancerous tissues, enhancing drug delivery while minimizing systemic toxicity. Aptamers, though promising for targeted therapy due to their high specificity, face challenges like nuclease degradation and rapid renal excretion in vivo. Strategies to enhance aptamer stability and binding affinity through modifications and nanocarrier encapsulation have been explored, aiming to optimize their pharmacokinetics and therapeutic efficacy. The integration of aptamers with nanocarriers, such as liposomes, DNA/RNA nanostructures, and inorganic nanomaterials like gold nanoparticles and silica nanoparticles, has significantly improved drug delivery efficiency. These nanocarriers not only enhance drug payload and control release kinetics but also enable targeted delivery to specific disease sites, exploiting the EPR effect for enhanced therapeutic outcomes.

Overall, aptamer-functionalized nanomaterials represent a promising strategy in nanomedicine, advancing targeted drug delivery systems that improve

therapeutic effectiveness while minimizing adverse effects associated with conventional treatments (25).

CONCLUSIONS

In conclusion, cancer is a serious global problem, driving intense research into new treatments. Aptamers, special molecules that can precisely find and attach to specific targets, offer clear advantages over traditional therapies like chemotherapy and radiation. They can be customized with various drugs, including chemotherapy, radiation enhancers, and immune system boosters, as well as nanoparticles and polymers. Despite challenges like a quick breakdown in the body, aptamers are gaining attention for personalized cancer treatment because of improvements in technology and screening methods. By improving how drugs are delivered and reducing side effects, aptamers have the potential to revolutionize cancer treatment, making it more effective and tailored to individual patients. Ongoing research is crucial to confirm these advancements and develop new therapies for future use in medicine.

Acknowledgements

The authors would like to thank the Department of Biotechnology, Alzahra Universit, Tehran, Iran for their support.

Authors's Contribution

Behnoush Khasheii, Parisa Haghpour involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

Funding

The author of this article has not received any financial support from private or government sources.

Ethics approval and consent to participate

Not applicable

Conflict of Interest

The authors declared no conflict of interest.

Consent for publication

Not Applicable

REFERENCES

1.Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 71(3), 209–249. 2.Soldevilla, M. M., Villanueva, H., & Pastor, F. (2016). Aptamers: A feasible technology in cancer immunotherapy. Journal of Immunology Research, 2016, 1083738.

3.Gillespie, M.-S., Ward, C.-M., & Davies, C.-C. (2023). DNA repair and therapeutic strategies in cancer stem cells. Cancers (Basel), 15(8), 1897.

4.Feng, J., Li, B., Ying, J., Pan, W., Liu, C., Luo, T., et al. (2020). Liquid biopsy: Application in early diagnosis and monitoring of cancer. Small Structures, 1(3), 2000063.

5.Wang, J. J., Lei, K. F., & Han, F. (2018). Tumor microenvironment: Recent advances in various cancer treatments. European Review for Medical and Pharmacological Sciences, 22(12), 3855–3864.

6.Tuerk, C., & Gold, L. (1990). Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. Science, 249, 505–510. doi: 10.1126/science.2200121.

7.Ellington, A. D., & Szostak, J. W. (1990). In vitro selection of RNA molecules that bind specific ligands. Nature, 346, 818–822.

8.Zhou, J., & Rossi, J. J. (2016). Aptamers as targeted therapeutics: Current potential and challenges. Nature Reviews Drug Discovery, 16, 181–202. doi: 10.1038/nrd.2016.199.

9.Nimjee, S. M., White, R. R., Becker, R. C., & Sullenger, B. A. (2017). Aptamers as therapeutics. Annual Review of Pharmacology and Toxicology, 57, 61–79. doi: 10.1146/annurev-pharmtox-010716-104558.

10.Stewart, M. W. (2018). Extended duration vascular endothelial growth factor inhibition in the eye: Failures, successes, and future possibilities. Pharmaceutics, 10(1), 21. doi: 10.3390/pharmaceutics10010021.

11.Mahmoudian, F., Ahmari, A., Shabani, S., et al. (2024). Aptamers as an approach to targeted cancer therapy. Cancer Cell International, 24(1), 108. doi: 10.1186/s12935-024-03295-4.

12.Venkatesan, S., Chanda, K., & Balamurali, M. M. (2023). Recent advancements of aptamers in cancer therapy. ACS Omega, 8(36), 32231-32243. doi: 10.1021/acsomega.3c04345.

13.He, J., Duan, Q., Ran, C., Fu, T., Liu, Y., & Tan, W. (2023). Recent progress of aptamer–drug conjugates in cancer therapy. Acta Pharmaceutica Sinica B, 13(7), 1358–1370. doi: 10.1016/j.apsb.2023.01.017.

14.Stoltenburg, R., Reinemann, C., & Strehlitz, B. (2007). SELEX—A (r)evolutionary method to generate high-affinity nucleic acid ligands. Biomolecular Engineering, 24(4), 381–403.

15.Liu, Q., Zhang, W., Chen, S., Zhuang, Z., Zhang, Y., Jiang, L., et al. (2020). SELEX tool: A novel and convenient gel-based diffusion method for monitoring of aptamer-target binding. Journal of Biological Engineering, 14, 1–13.

16.Zhuo, Z., Yu, Y., Wang, M., Li, J., Zhang, Z., Liu, J., et al. (2017). Recent advances in SELEX technology and aptamer applications in biomedicine. International Journal of Molecular Sciences, 18(10), 2142.

17.Buglak, A. A., Samokhvalov, A. V., Zherdev, A. V., & Dzantiev, B. B. (2020). Methods and applications of in silico aptamer design and modeling. International Journal of Molecular Sciences, 21(22), 8420.

18.Sun, D., Sun, M., Zhang, J., Lin, X., Zhang, Y., Lin, F., et al. (2022). Computational tools for aptamer identification and optimization. TrAC, Trends in Analytical Chemistry, 157, 116767.

19.Esawi, E., Nsairat, H., Mahmoud, I. S., Lafi, Z., Al-Kadash, A., Al-Ragheb, B. A., ... & Alhaer, W. (2023). Clinical use and future perspective of aptamers. In E. Esawi & B. A.

Al-Ragheb (Eds.), Aptamers Engineered Nanocarriers for Cancer Therapy (pp. 481-520). Woodhead Publishing.
20. Zhu, G., & Chen, X. (2018). Aptamer-based targeted therapy. Advanced Drug Delivery Reviews, 134, 65–78.
21. Kroschinsky, F., Stölzel, F., von Bonin, S., Beutel, G., Kochanek, M., Kiehl, M., et al. (2017). New drugs, new toxicities: Severe side effects of modern targeted and immunotherapy of cancer and their management. Critical Care, 21(1), 89.
22. Yazdian-Robati, R., Bayat, P., Oroojalian, F., Zargari, M., Ramezani, M., Taghdisi, S. M., et al. (2020). Therapeutic applications of AS1411 aptamer, an update review. International Journal of Biological Macromolecules, 155, 1420–1431.
23. Li, Q., Maier, S. H., Li, P., Peterhansl, J., Belka, C., Mayerle, J., et al. (2020). Aptamers: A novel targeted theranostic platform for pancreatic ductal adenocarcinoma. Radiation Oncology, 15(1), 189.
24. Wu, L., Zhang, Y., Wang, Z., Zhang, Y., Zou, J., & Qiu, L. (2022). Aptamer-based cancer cell analysis and treatment. ChemistryOpen, 11(10), e202200141.
25. Gao, F., Yin, J., Chen, Y., Guo, C., Hu, H., & Su, J. (2022). Recent advances in aptamer-based targeted drug delivery systems for cancer therapy. Frontiers in Bioengineering and Biotechnology, 10, 972933.

http://pmjournal.ir Reviwe Article

Summer 2024, Volume 9, Issue 34 (14- 19)

The Impact of Anesthesia on Cancer Outcomes

Mahtab Dolatabadi[1,*], Yasaman Vojgani[2]

[1]Kamali Hospital, Alborz University of Medical Science, Anesthesiology Department, Karaj, Iran.
[2]Department of Molecular Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran.

**Corresponding author: Mahtab Dolatabadi, Kamali Hospital, Alborz University of Medical Science, Anesthesiology Department. Email: Mahtab.Dolatabadi@gmail.com*

DOI: 10.22034/pmj.2024.715090

Submitted: 2024-05-03
Accepted: 2024-08-27

Keywords:
Anesthesia
Cancer
Radiation therapy
Chemotherapy
Personalized Medicine

How to Cite this Article:

M. Dolatabadi, Y. Vojgani. "AThe Impact of Anesthesia on Cancer Outcomes" Personalized Medicine Journal, Vol. 9, no. 34, pp. 14- 19.

Abstract:
In cancer treatment, anesthesia is commonly used during surgery to remove tumors, as well as for other procedures like biopsies, radiation therapy, and chemotherapy administration. Some research suggests that the choice of specific anesthetic drugs and nerve-sparing techniques can have a significant impact on cancer recurrence rates and overall patient survival. It is well-established that a patient's immune system plays a direct role in postoperative complications and long-term outcomes, highlighting the importance of optimizing anesthesia to minimize potential immune system suppression and improve immune function during cancer surgery. Recent studies have revealed a strong connection between the type of anesthesia used during surgery and the likelihood of cancer relapse and related mortality. Therefore, it is crucial to select the appropriate anesthesia technique for cancer resection, focusing on reversible effects, rapid recovery, and resistance to feedback. The specific anesthetic agents used during surgery have a significant impact on survival rates and the risk of cancer-related mortality. Genetic influences on anesthesia response are significant for improving patient care and achieving better results. Additionally, personalized medicine, which combines diagnostic testing and treatment, is now a clinical reality. Anesthesia's effects on depth, pain signals, vital signs, and the motor system are complex and not fully understood, and many researchers believe that anesthesia is regulated by multiple genes, although further research is needed to identify them and understand how they are regulated. The relationship between anesthesia and cancer is complex and evolving with implications for medical treatment. Limited evidence suggests that anesthesia and surgery-related factors can affect cancer biology and outcomes. Further research is needed to understand these interactions and develop strategies for improving cancer care during surgery. Better understanding can lead to safer and more effective cancer treatment, benefitting patients.

INTRODUCTION

Anesthesia is a medical intervention that induces a reversible loss of sensation and consciousness, allowing for invasive procedures to be performed without causing pain or discomfort to the patient. In the context of cancer treatment, anesthesia is commonly used during the surgical resection of tumors, as well as for other procedures such as biopsies, radiation therapy, and chemotherapy administration (1). While the primary goal of anesthesia is to ensure patient comfort and safety during these procedures, there is growing evidence to suggest that certain anesthetic agents and perioperative factors may have the potential to influence the biological behavior of cancer cells and impact long-term oncological outcomes (2).

The role of anesthesia in cancer surgery is widely acknowledged as life-saving and not linked to cancer recurrence or progression. However, the question remains: can the choice of anesthetic agents and methods impact the perioperative period and tumor microenvironment to influence cancer progression? Cancer is a complex process, with the immune system playing a crucial role. As cancer progresses, the delicate balance between the body's immune defenses and the developing tumor is disrupted, leading to a tolerogenic environment known as cancer immune editing. Anesthesia and surgery can also have a profound impact on the body's immune response, potentially leading to a less effective defense against the tumor and impacting patient outcomes (3). Some studies

suggest that the selection of specific anesthetic drugs and nerve-sparing techniques can exert a significant influence on cancer recurrence rates and overall patient survival. It is now well-established that the immune competence of the patient is directly connected to postoperative complications and long-term therapeutic outcomes, underscoring the importance of optimizing anesthesia protocols to mitigate potential immunosuppressive effects and enhance immune function in the context of cancer surgery. By carefully considering the immunological implications of anesthetic choices and implementing strategies to minimize immunosuppression, healthcare providers may be able to improve patient outcomes and reduce the risk of cancer progression during the perioperative period. The potential interactions between anesthesia and cancer have been a topic of increasing interest and concern in the medical community (4). As anesthesia is a crucial component of cancer surgery and other cancer-related procedures, understanding its potential effects on cancer progression and recurrence is of paramount importance. This paper aims to provide a comprehensive overview of the current understanding of the interactions between anesthesia and cancer, covering various aspects including the impact of different anesthetic agents, perioperative factors, and potential mechanisms underlying these interactions (5).

Overview of Anesthesia in Cancer Surgery

Anesthesia plays a critical and indispensable role in the field of cancer surgery, as it provides an enabling environment for physicians to conduct intricate procedures such as tumor excision and preventing metastasis. Recent retrospective studies, which have charted the course of medical exploration, have illuminated a remarkable link between the type of anesthesia employed during surgical interventions and the long-term likelihood of cancer relapse and related mortality (5). Expanding the boundaries of medical knowledge, researchers have embarked upon a series of animal and cell experiments to unravel the intricate connections between anesthesia, surgical techniques, and postoperative cancer outcomes, thereby opening new frontiers of inquiry within the medical sphere (6, 7). However, it is essential to approach the results of retrospective studies with caution, as inherent biases may be involved. Hence, to corroborate the intricate relationship between anesthesia and cancer, further prospective and randomized controlled experiments are indispensable. The realm of cancer patient management during surgery encompasses a wide array of modern anesthetic agents, each wielding invaluable potential. These agents, including hypnotics, opioids, and local anesthetics, have proven instrumental in effectively managing cancer patients undergoing surgery (8). Beyond their primary purpose, these avant-garde anesthetic agents possess diverse biological effects, which may potentially impact the trajectory of cancer progression. As medical practitioners, it is paramount to strike a delicate balance between the potential risks and benefits of anesthesia to ensure that cancer patients undergoing surgical interventions receive the most efficacious and safe treatment available (9). Against this backdrop, the present review embarks on a comprehensive analysis, primarily focusing on the profound impact of different anesthetic agents and drugs utilized in the realm of cancer surgery. The overarching objective of this exploration is to deepen our understanding of the multifaceted effects these agents exert on cancer operations, thereby providing practical recommendations to guide their appropriate and judicious usage (10).

Types of Anesthesia Used in Cancer Surgery

Cancer surgery involves the utilization of various treatments, such as local ablative therapy and surgical resection, to prevent postoperative metastasis. The growth of malignant tumors requires chronic inflammation and wound repair by different cells in the body. However, the inflammatory response to surgery can interfere with the body's defense against cancer cells(10). Managing postoperative pain is crucial, and non-opioid relief methods are being explored. Anesthesia techniques for cancer surgery are also being revised, with some drugs showing potential for suppressing tumor growth in preclinical trials (11).

Advanced soft tissue surgeries, such as open cholecystectomy and pelvic organ operations, are effective in providing extensive pain relief for postoperative patients. These same surgeries, along with procedures for kidney deformities, are also utilized in the surgical management of solid tumors. It has been observed that the use of general anesthesia is on the rise, but it is associated with poor outcomes for cancer patients, including recurrence and overall perioperative adverse effects. This can be attributed to a combination of factors such as anesthesia, endomorphin, tumor growth factors, and neuroendocrine responses (11, 12). Therefore, selecting the appropriate general anesthesia technique is crucial for cancer resection, with a focus on reversible effects, rapid postoperative recovery, and resistance to feedback. Factors that should be considered in choosing the appropriate anesthesia for cancer patients include endocrine tumor markers, chronic drug use, previous responses to anesthesia, and allergy information. Collaboration between anesthesiologists and attending physicians and surgeons is essential, with medical advice tailored to individual patient needs and professional tolerances (12, 13).

Impact of Anesthetic Agents on Cancer

The relationship between anesthetics, surgery, and

cancer outcomes is currently being explored by a wide range of medical professionals, including surgeons and anesthesiologists. They are investigating how anesthetics interact with the body's inflammatory, immunological, and wound repair processes, all of which play a role in cancer. There is a curiosity about whether anesthesia could help promote beneficial inflammation or reduce harmful inflammation to improve cancer treatment results (12). This could potentially reduce the need for other expensive drugs and treatments that often come with significant side effects. By examining evidence of how anesthesia affects surgical outcomes and identifying potential molecular targets, researchers hope to develop more effective drug regimens for cancer treatment. It is important to look at how cancer and anesthetics interact with inflammation to gain a better understanding of how anesthesia impacts cancer development and progression. Researchers have theorized that cancer utilizes the body's inflammatory system to aid in tumor growth and the spread of cancerous cells to other parts of the body (14).

One of the key areas of research in the field of anesthesia and cancer relates to the impact of different anesthetic agents on cancer progression and recurrence. Studies have investigated the potential effects of volatile anesthetics (such as sevoflurane and desflurane) and intravenous anesthetics (such as propofol) on various aspects of cancer biology, including tumor cell proliferation, migration, and metastasis. While the evidence remains inconclusive, some preclinical and clinical studies have suggested that certain anesthetic agents may exhibit pro- or anti-tumorigenic properties, potentially influencing the behavior of residual cancer cells following surgical resection (14).

Anesthetic Agents and Their Importance in Surgery

The immune-modulatory effects of different types of anesthetic agents and their impact on cancer cell biology are crucial considerations for healthcare practitioners in perioperative periods. These agents, including general and regional anesthetics, are commonly employed to alleviate pain and immobilize patients during surgery (15). Recent research has revealed that specific anesthetic agents, administered at specific times during surgery, hold the potential to influence the growth and persistence of cancer cells. The long-term patient outcomes from various surgical models further implicate the specific anesthetic agents in determining both survival rates and the risk of cancer-related mortality. One potential mechanism through which these effects occur is the impact of anesthetic agents on immune function (15). By recognizing and proactively addressing postoperative immune function lapses caused by sedating anesthetic agents, medical professionals may significantly enhance the outcomes for cancer patients. As approximately 80% of cancer surgeries currently employ general anesthesia, a comprehensive evaluation of the effects of different anesthetic agents on immune function becomes imperative. This evaluation should include an exploration of their correlation with overall survival rates and cancer-related deaths (16).

Perioperative Factors and Cancer Outcomes

In addition to the specific choice of anesthetic agent, various perioperative factors have been implicated in potentially modulating the interaction between anesthesia and cancer. These factors include the use of regional anesthesia techniques, perioperative pain management strategies, intraoperative blood transfusions, and the perioperative stress response (17). For example, regional anesthesia techniques such as epidural analgesia have been proposed to attenuate the neuroendocrine stress response to surgery, which in turn may have implications for cancer progression and recurrence. Furthermore, the perioperative period is characterized by complex immunological and inflammatory changes, which could potentially impact the host-tumor interaction and influence long-term cancer outcomes (18).

Potential Mechanisms Underlying Anesthesia-Cancer Interactions

The role of anesthesia in cancer progression is receiving increasing attention and raising concerns in both the scientific community and the general public. Many factors, including the type of anesthesia used, methods for pain relief, potential complications, and duration of surgery and recovery, are causing apprehension in the context of cancer surgery. Numerous studies have focused on the short-term effects of perioperative care on cancer outcomes, analyzing each stage from pre-surgery to post-surgery (12). However, there are still many unanswered questions in clinical oncology, highlighting the need for fundamental research in perioperative oncology. Researchers must shift from observational studies to detailed mechanistic analyses and broaden the focus to encompass a comprehensive perioperative approach (19).

While current clinical research provides solid evidence, it is crucial to establish the connection between mechanisms and clinical trials while considering the complex nature of clinical oncology. In doing so, we can begin to unravel the complex relationship between anesthesia and cancer progression, leading to improved patient care, better outcomes, and potentially groundbreaking discoveries in perioperative oncology. Understanding the potential mechanisms underlying the interactions between anesthesia and cancer is

essential for elucidating the biological basis of any observed effects. Several mechanistic hypotheses have been proposed, including the modulation of immune function, effects on angiogenesis and tumor microenvironment, and the influence of anesthetic-induced stress responses on cancer cell behavior (19). For instance, some studies have suggested that certain anesthetic agents may exert immunomodulatory effects, potentially affecting the body's ability to mount an effective anti-tumor immune response. Similarly, anesthesia-induced changes in the perioperative stress response and neuroendocrine signaling pathways may impact tumor biology through mechanisms such as altered gene expression, cell signaling, and metastatic potential (20).

Clinical Implications and Future Directions

Anesthesia is often necessary for cancer patients undergoing surgery, biopsies, or airway evaluations. To ensure optimal patient care, it is important to have a trained anesthesiologist or CRNA administer the anesthesia, as they are best equipped to anticipate and manage any changes in the patient's circulatory and respiratory system (21). This helps reduce the risk of complications from chronic diseases and ensures the patient remains appropriately anesthetized and pain-free during surgery, ultimately leading to a better surgical outcome. Surprisingly, research has shown that anesthetics can also have a significant impact on the primary tumor and its metastases, as well as affecting the long-term outcome for cancer patients. Both positive and negative effects on various aspects of cancer treatment have been observed, along with interference with the antitumor immune response, as demonstrated in animal studies and initial clinical work (22).

The potential interactions between anesthesia and cancer have significant clinical implications for the perioperative management of cancer patients. While the current evidence is largely derived from preclinical studies and retrospective clinical analyses, the findings suggest the need for further research to elucidate the precise nature of these interactions and their impact on long-term cancer outcomes. Future studies should aim to address key knowledge gaps, such as the comparative effects of different anesthetic agents, the influence of perioperative factors, and the underlying mechanistic pathways. Additionally, prospective clinical trials and translational research efforts are warranted to validate the findings from observational studies and to inform evidence-based clinical practice guidelines for the perioperative care of cancer patients (5).

Genetic Factors in Anesthetic Response

The response to anesthesia is a complex concern in toxicology that is influenced by genetics. Genetic variation greatly impacts how an individual metabolizes and reacts to anesthesia. The study of genetic influences on anesthesia response is of utmost significance for optimizing patient care and achieving better outcomes (18). This in-depth chapter specifically emphasizes the crucial role of genetic influences on propofol response, shedding light on the intricate interplay between an individual's genetic makeup and their response to this widely used anesthetic. Furthermore, it delves into the realm of nano-poisons and prion-controlled drugs, exploring the genetic factors associated with these substances and their impact on anesthesia response (23). It is essential to recognize that environmental factors also contribute to anesthesia response, thus warranting thorough consideration. By comprehending and intricately studying these genetic influences in the field of anesthesia, healthcare professionals can enhance patient outcomes and provide truly personalized care that takes into account each individual's unique genetic profile (24).

The Impact of Molecular Medicine on Cancer Treatment

The utilization of cutting-edge advancements in molecular medicine plays a crucial role in the anesthesia management of cancer patients. Molecular medicine focuses on personalized treatment, targeted therapeutics, and early detection of various diseases, including cancer, cardiovascular issues, genitourinary conditions, and laparoscopy. Anesthesiologists must adapt to the evolving field of molecular diagnostics, effectively implementing and controlling molecular-level therapies (25). Additionally, theranostics, a subset of molecular medicine and personalized treatment, combines diagnostic testing and treatment in a unified approach. Personalized medicine is now a clinical reality. It has led to improvements in drugs and therapies, resulting in better outcomes and safety for patients. It also holds promise for less toxic interventions in cancer treatment (26). Molecular medicine is connecting genomics and pharmacology with clinical results. Anesthesiologists recognize the need for unique approaches to cancer patients receiving anesthesia. These approaches help avoid complications and improve surgical and anesthetic procedures for patients with different types of cancer (27).

Personalized Anesthesia

Anesthetic drugs can have various effects, both helpful and harmful, such as pain relief, immobility, and potentially negative impacts on cardiac and skeletal muscle function and breathing. These effects depend on factors like drug dosage, duration of action, protein binding, and distribution in the body. Patient-specific factors such as age, sex, body mass, blood volume, and existing conditions also play a role (20). While there

is a good amount of knowledge about anesthetic drugs and potential patient-specific variables, it has been challenging to develop and utilize unified analyses of individual patients. However, a combination of systems biology and pharmacology can be used to predict patient-specific responses to anesthetic drugs, helping to enhance our understanding of how different combinations of drugs cause different reactions (20, 28). By applying network-based approaches and utilizing system pharmacology models, machine learning, and Bayesian methods, it is possible to collect and analyze patient-specific response data and develop personalized strategies for anesthetic drug prescription. This approach is demonstrated through the creation of a simplified patient-specific response network, pointing the way towards a better understanding of anesthetic drug response biology and the potential for developing personalized treatments (20).

Personalized anesthesiology intends to realize a targeted and efficient approach to drug therapy to collectively achieve the aims of anesthesia: unconsciousness (pain suppression), amnesia (short-term memory deactivation), and surgical skeletal muscle paralysis. Tailoring anesthetic protocols according to individual patient needs is not achievable. A "one size fits all" or "magic bullet" approach is commonly used in clinical anesthesia, despite significant between-patient variability and uncertainty concerning the detailed processes that may underpin physiologic changes in response to anesthetics, and also between individuals. The additional fact that anesthetic drugs have many non-specific effects reduces the strength of this strategy (29).

While personalized medicine has the potential to improve the precision and optimization of clinical procedures, personalized anesthesia has the potential to improve patient safety because the principles of precision mechanistic approaches and systems biology, including the involvement with genome-wide association and pharmacogenomic approaches, may reveal the reasons for such unpredictability, showing the patient's vulnerability to possible unwanted complications (30). Providing anesthetics using a personalized approach, utilizing the principles of precision medicine, takes into account each patient's specific variables that may contribute to their unique vulnerabilities, offering an alternative approach to the standard dosing strategy, based on the use of age and/or weight as dimensions in pharmacokinetic and pharmacodynamic models (31).

Key Genes and Pathways Involved in Anesthesia

Revealing the underlying key genes and pathways of mechanisms in the administration of anesthesia has potential importance in medical science by detecting changes inherent in the body during anesthesia and elucidating how the brain generates consciousness. It is also essential to uncover potential molecular targets for optimizing the clinical outcome of the methods. These methods can be performed by preferred functional strategies involving sophisticated statistical tests for RNA expression studies, and available hubs can be identified for experimental validation (32). The effects of various general anesthetic drugs on anesthesia depth, pain signals, vital signs, and motor system are complex and not fully understood. Many researchers believe anesthesia is regulated by multiple genes, but we have yet to identify which genes and how they are regulated. To address these questions, researchers have analyzed gene expression data from the GEO database and conducted experiments at the molecular and functional levels. This has led to the identification of differentially expressed genes and significant pathways (33).

CONCLUSION

In conclusion, the potential interactions between anesthesia and cancer represent a complex and evolving area of research with important implications for clinical practice. While the current understanding of these interactions is still incomplete, the available evidence suggests that anesthesia and perioperative factors may have the capacity to influence cancer biology and long-term oncological outcomes. As such, further research is needed to elucidate the mechanistic underpinnings of these interactions and to inform evidence-based perioperative strategies for optimizing cancer care. By advancing our understanding of the interplay between anesthesia and cancer, we can strive to improve the safety and efficacy of cancer treatment and ultimately enhance patient outcomes.

Acknowledgements

The authors would like to thank the Anesthesiology Department, Kamali Hospital, Alborz University of Medical Science, Alborz, Iran.

Authors' Contribution

Mahtab Dolatabadi and Yasaman Vojgani were involved in the conceptualization, design and writing of the manuscript draft. All authors read and confirmed the final manuscript.

Funding

Not applicable.

Availability of data and materials

All data are obtainable after an appeal from the corresponding author.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1.Efremidou E, Zachou M-E, Kaprana A, Koukourakis M, Chloropoulou PJJoS, Research S. The effects of anesthesia on cancer progression and anti-tumor immunity. A review. 2024;10(1):014-21.

2.Dodds C. General anaesthesia: practical recommendations and recent advances. Drugs. 1999;58(3):453-67.

3.Allan N, Siller C, Breen A. Anaesthetic implications of chemotherapy. Continuing Education in Anaesthesia Critical Care & Pain. 2011;12(2):52-6.

4.Kurdi MS, Agrawal P, Thakkar P, Arora D, Barde SM, Eswaran K. Recent advancements in regional anaesthesia. Indian journal of anaesthesia. 2023;67(1):63-70.

5.Xia SH, Zhou D, Ge F, Sun M, Chen X, Zhang H, et al. Influence of Perioperative Anesthesia on Cancer Recurrence: from Basic Science to Clinical Practice. Current oncology reports. 2023;25(2):63-81.

6.Ødemark J, Engebretsen E. Challenging medical knowledge translation: convergence and divergence of translation across epistemic and cultural boundaries. Humanities and Social Sciences Communications. 2022;9(1):71.

7.Broniatowski DA, Magee CL. The Emergence and Collapse of Knowledge Boundaries. IEEE transactions on engineering management. 2017;64(3):337-50.

8.De Sanctis V, Soliman AT, Daar S, Tzoulis P, Fiscina B, Kattamis C, et al. Retrospective observational studies: Lights and shadows for medical writers. Acta bio-medica : Atenei Parmensis. 2022;93(5):e2022319.

9.Varkey B. Principles of Clinical Ethics and Their Application to Practice. Medical principles and practice : international journal of the Kuwait University, Health Science Centre. 2021;30(1):17-28.

10.Cave E. Protecting Patients from their Bad Decisions: Rebalancing Rights, Relationships, and Risk. Medical law review. 2017;25(4):527-53.

11.Wyld L, Audisio RA, Poston GJ. The evolution of cancer surgery and future perspectives. Nature Reviews Clinical Oncology. 2015;12(2):115-24.

12.Alam A, Rampes S, Patel S, Hana Z, Ma D. Anesthetics or anesthetic techniques and cancer surgical outcomes: a possible link. Korean journal of anesthesiology. 2021;74(3):191-203.

13.Liu X, Wang Q. Application of Anesthetics in Cancer Patients: Reviewing Current Existing Link With Tumor Recurrence. Frontiers in oncology. 2022;12:759057.

14.Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, et al. New approaches and procedures for cancer treatment: Current perspectives. SAGE open medicine. 2021;9:20503121211034366.

15.Boavista Barros Heil L, Leme Silva P, Ferreira Cruz F, Pelosi P, Rieken Macedo Rocco P. Immunomodulatory effects of anesthetic agents in perioperative medicine. Minerva anestesiologica. 2020;86(2):181-95.

16.Zhang Y, Lu J, Qin M, Xu M, Luo W, Li B, et al. Effects of different anesthesia methods on postoperative immune function in patients undergoing gastrointestinal tumor resection. Scientific Reports. 2023;13(1):243.

17.Hyland SJ, Brockhaus KK, Vincent WR, Spence NZ, Lucki MM, Howkins MJ, et al. Perioperative Pain Management and Opioid Stewardship: A Practical Guide. Healthcare (Basel, Switzerland). 2021;9(3).

18.Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA education. 2020;20(9):321-8.

19.Amend SR, de Groot AE, Torga G, Axelrod HD, Reyes DK, Valkenburg KC, et al. Ten unanswered questions in cancer: "If this is true, what does it imply"? American journal of clinical and experimental urology. 2018;6(2):26-31.

20.Ackerman RS, Luddy KA, Icard BE, Piñeiro Fernández J, Gatenby RA, Muncey AR. The Effects of Anesthetics and Perioperative Medications on Immune Function: A Narrative Review. 2021;133(3):676-89.

21.Montejano J, Jevtovic-Todorovic V. Anesthesia and Cancer, Friend or Foe? A Narrative Review. Frontiers in oncology. 2021;11:803266.

22.AbdulRaheem Y. Unveiling the Significance and Challenges of Integrating Prevention Levels in Healthcare Practice. Journal of primary care & community health. 2023;14:21501319231186500.

23.Virolainen SJ, VonHandorf A, Viel K, Weirauch MT, Kottyan LC. Gene-environment interactions and their impact on human health. Genes and immunity. 2023;24(1):1-11.

24.Gasciauskaite G, Lunkiewicz J, Spahn DR, Von Deschwanden C, Nöthiger CB, Tscholl DW. Environmental sustainability from anesthesia providers' perspective: a qualitative study. BMC Anesthesiology. 2023;23(1):377.

25.Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, et al. Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Molecular Cancer. 2023;22(1):169.

26.Belge Bilgin G, Bilgin C, Burkett BJ, Orme JJ, Childs DS, Thorpe MP, et al. Theranostics and artificial intelligence: new frontiers in personalized medicine. Theranostics. 2024;14(6):2367-78.

27.Min H-Y, Lee H-Y. Molecular targeted therapy for anticancer treatment. Experimental & Molecular Medicine. 2022;54(10):1670-94.

28.Rong LQ, Audisio K, O'Shaughnessy SM. Guidelines and evidence-based recommendations in anaesthesia: where do we stand? British journal of anaesthesia. 2022;128(6):903-8.

29.Puccetti M, Pariano M, Schoubben A, Giovagnoli S, Ricci M. Biologics, theranostics, and personalized medicine in drug delivery systems. Pharmacological Research. 2024;201:107086.

30.Krzyszczyk P, Acevedo A, Davidoff EJ, Timmins LM, Marrero-Berrios I, Patel M, et al. The growing role of precision and personalized medicine for cancer treatment. Technology. 2018;6(3-4):79-100.

31.Akhoon N. Precision Medicine: A New Paradigm in Therapeutics. International journal of preventive medicine. 2021;12:12.

32.Horta MAC, Pimenta RJG, Almeida DA, Rosolen RR, Aono AH, Filho JF, et al. Chapter 1 - Transcriptomic analysis of genes: expression and regulation. In: Ajmal Ali M, Lee J, editors. Transcriptome Profiling: Academic Press; 2023. p. 1-41.

33.Shin TJ, Kim PJ, Choi B. How general anesthetics work: from the perspective of reorganized connections within the brain. Korean journal of anesthesiology. 2022;75(2):124-38.

http://pmjournal.ir Reviwe Article

Summer 2024, Volume 9, Issue 34 (20- 26)

An Overview of the Role of Microbiomes in the Severity of Colorectal Cancer

Ramesh Ranjbar[1,*]

[1]Department of Genetics, Faculty of Basic Sciences, Shahrekord Islamic Azad University, Shahrekord, Iran.

**Corresponding author: Ramesh Ranjbar, Department of Genetics, Faculty of Basic Sciences, Shahrekord Islamic Azad University, Shahrekord, Iran. Email:Ranjbar.Ramesh@gmail.com.*

DOI: 10.22034/pmj.2024.715091

Submitted: 2024-04-21
Accepted: 2024-08-29

Keywords:
Microbiome
colorectal cancer
Genetics
Environmental factors

How to Cite this Article:

R. Ranjbar. "An Overview of the Role of Microbiomes in the Severity and Severity of Colorectal Cancer" Personalized Medicine Journal, Vol. 9, no. 34, pp. 20- 26.

Abstract:

Microbiome means microbes coexisting with the host, regardless of the species, in a part of the body of an organism called microbiome. Nowadays, changes in gut microbiota are considered as a potential therapeutic approach for the prevention or treatment of colorectal cancer (CRC).
Studies have shown that dietary habits and lifestyle play a role in modulating the gut microbiota.
Intestinal microbiota plays a role in converting food components into oncometabolites. Some studies showed that Shigella, Citrobacter and Salmonella bacteria are more abundant in the early stages of cancer compared to healthy people. The aim of this study is to review the role of microbiomes in the development of colorectal cancer and the metabolites produced by microbiomes in the development of colorectal cancer.

INTRODUCTION

During the past few decades, the importance of the microbiome on human health and disease has been increasing. Microbes, which are even more numerous than our own cells, live on the surface and inside our bodies and can protect humans from pathogens and on the other hand regulate immunity and tolerance. The immune system also plays a role (1).

It also helps in digesting many foods that we cannot digest ourselves. However, if their balance is disrupted by antibiotics, immune system disorders or other disorders. They can lead to disease. The focus of microbiomes has largely been on the bacterial diversity of the microbiome.

Because they constitute the largest proportion of living organisms and lead to microbiota. Bacteria exist alongside a variety of microorganisms such as fungi, single eukaryotes and some worms, as well as different families of viruses. All components can affect health and disease with each other and the host.

The clearest interaction occurs between the bacterial and archaeal microbiota and the eukaryotic host.

Studies on animals without microbiota have shown that the lack of microbiota leads to metabolic and immune differences compared to normal animals. In general, the impact of the microbiome on humans can be summarized in two areas. releasing energy and nutrients from food and activating the immune system to promote the host; Due to the fact that bacteria are part of the microbiome, it has attracted the most attention.

The quantity and diversity of microbial species in the intestine increases longitudinally from the stomach to the colon, and the colon microbiota is the most dense and metabolically active community (2).

Although microbiota composition is influenced by genetics (3). Although microbiota composition is influenced by genetics and may be considered relatively stable over time in healthy adults, there is great variability in microbiota composition among individuals. This change is caused by various external environmental factors such as diet, exposure to chemicals and antibiotic/drug use (4).

Alterations of gut microbiota may be used as potential therapeutic approaches to prevent or treat CRC(5). Probiotics such as Lactobacillus and Bifidobacterium inhibit the development of CRC by inhibiting inflammation and angiogenesis and increasing intestinal barrier function through the secretion of short-chain fatty acids (SCFAs) (6). The interplay between lifestyle, host genetics, and gut microbiota is well documented in the prevention and treatment of CRC. Future studies are needed to understand the

interaction between the gut microbiota and the host to influence and prevent CRC (7).

The clinical benefits of probiotics in CRC are still unclear. Metagenomic approaches combined with metabolomics and immunology will soon open a new way to treat CRC. Dietary interventions may be suitable for modulating the growth of beneficial microbiota in the gut(7) (Figure 1)

The intestinal microbiome consists of different species of bacteria, fungi, protozoa and viruses (8). Bacteria belonging to Firmicutes and Bacteroidetes predominate in the gut (9).

Gut microbiota plays a role in host physiology such as nutrition, metabolism and immunity (10).

Dysbiosis of the intestinal microbiome plays a role in various human diseases (11).

The gut microbiome is involved in inflammation and biosynthesis of chemical carcinogens such as N-nitroso compounds that cause cancer (12). It is estimated that about 70% of the human microbiome resides in the large intestine (13).

Dietary habits and lifestyle play a role in modulating the intestinal microbiota (14).

People exposed to antibiotics early in life may develop colorectal adenomas later in life (15). Gut microbiome dysbiosis is associated with the development of colorectal cancer (CRC). Gut microbiota plays a role in the metabolic conversion of dietary components into oncometabolites and tumor suppressor metabolites, which in turn affect CRC development (16).

Colorectal cancer (CRC) is classified into two categories: colitis-associated colorectal cancer (CAC) and diffuse colorectal cancer (SCC) (17). Subjects with inflammatory bowel disease converted to CAC. Gut microbiota may contribute to the initiation and development of CRC (17). Ninety-nine percent of gut bacteria cannot be cultured. Ribosomal RNA sequencing from stool or tissue of CRC patients can be used for taxonomic classification of bacteria by DNA isolation from stool samples or tumor tissue samples of CRC patients. 16S rRNA sequencing is able to identify bacterial species at the genus level (18).

The role of the gut microbiome in host cell physiology

Human microbiota colonization has been reported

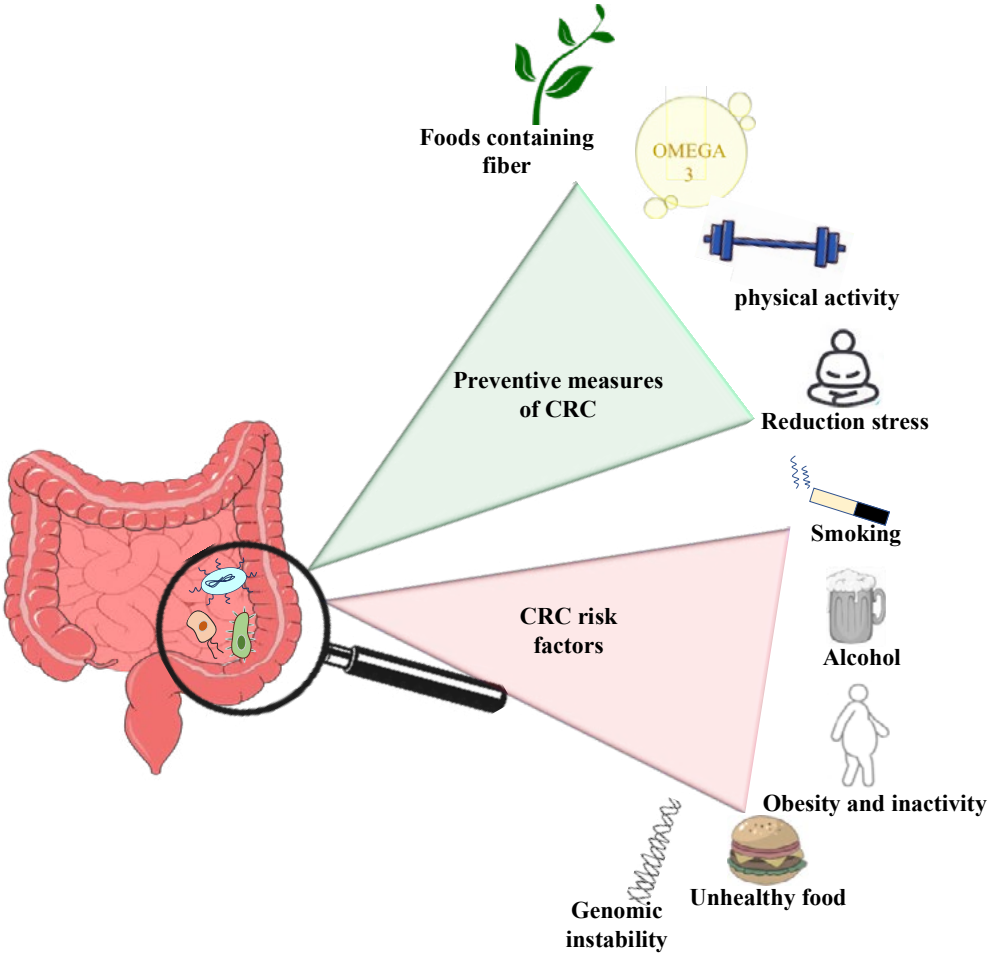


Fig1. Risk factors for CRC and preventive factors for CRC. The type of lifestyle, food pattern can affect the microbial diversity of the gut microbiome as well as the increase and decrease of CRC factors.

in the gastrointestinal tract, oronasopharyngeal cavity, skin, and genitourinary tract. The human body has 10^{14} bacterial cells, which is 10 times more than the number of cells in the body (19). In humans, the colon showed the highest microbial density and species diversity (10^{11} cells per gram of feces). Facultative anaerobes reside in the mucosa of the large intestine, while strict anaerobes reside in the lumen of the colon due to different oxygen tensions (20). A decrease in oxygen tension in the large intestine favors the growth of more bacteria and Firmicutes, followed by Actinobacteria and Veromicrobia(21).

The large intestine is considered a suitable place for bacterial growth due to its high pH, nutrients and low concentration of bile salts and pancreatic secretions (22). Lipopolysaccharide (LPS) of Gram-negative bacteria induces an innate immune function that prevents inflammation (23). Anaerobes such as Bacteroides, Eubacterium, Bifidobacterium, Fusobacterium, Peptostreptococcus, and Atopobium are abundant in the gut, while facultative anaerobes such as Lactobacilli, Enterococci, Streptococcus, and Enterobacteriaceae represent a microbiome of the gut.

Intestinal microbiota plays an important role in host mucosal homeostasis and regulation of epithelial barrier function in the intestine (24, 25). The composition of the host microbiome in the gut is regulated by diet, medications, and other lifestyle factors such as smoking, alcohol drinking, and physical activity (18). The normal intestinal microbiota plays a role in the degradation of nutrients, prevention of colonization of pathogenic bacteria, differentiation of epithelial cells and development of immune cells in the intestine (26). Gram-negative bacteria and Gram-positive Firmicutes predominate in the gut.

Short chain fatty acids (SCFAs) such as acetate, propionate and butyrate are produced by Bacteroidetes, Bifidobacterium, Clostridium, Lactobacillus, Provetella and Propionibacterium. Butyrate induces the anti-inflammatory activity of macrophages and dendritic cells. It also causes the release of anti-inflammatory cytokine IL-10 from the differentiation of Tregs and T cells. Foods rich in probiotics and prebiotics increase the levels of bifidobacterium and butyrate-producing bacteria that play a role in gut homeostasis (9).

IL-33 and TGF-β induce IgA secretion from B cells. Intestinal IgA protects against intestinal microorganisms and toxins. IL-33 blocks IL-1α-dependent CAC development through activation of the IgA-microbiota axis. Antimicrobial siderophore-binding protein lipocalin 2 (LCN2) inhibits the growth of colitogenic microbiota in the intestine (27). Gut microbes have NAD(P)H dehydrogenase (azoreductase), nitroreductase, β-glucuronidase, β-glucosidase, and 7-α-dehydroxylase, which cause cancer (28). In a healthy colon, the majority of microbial metabolism is via saccharolytic fermentation pathways. Bacteria are mainly involved in propionate production while Firmicutes are mainly involved in butyrate production (29). Butyrate showed anti-inflammatory effects by inhibiting the activity of histone deacetylase, reducing the secretion of pro-inflammatory cytokines and activating regulatory T cells expressing FOXP3 (30) . Proteolytic fermentation by Firmicutes and Bacteroides spp are involved in the production of phenols, indoles, amines and ammonia; Proteobacteria are involved in the production of N-nitroso compounds from dietary proteins in the large intestine (31, 32) .Butyrate, mainly produced in the gut by Faecalibacterium prausnitzii and Eubacterium rectale, is involved in cell proliferation, differentiation and programmed cell death in colonic cells (33).

Clostridium species are responsible for the secretion of the anti-inflammatory cytokine interleukin-10 (IL-10) in the intestine through increasing the activity of Treg cells (34). Ursodeoxycholic acid (UDCA, ursodiol), which is a metabolic byproduct of intestinal bacteria, inhibits the expression of cyclooxygenase-2 (COX-2) in CRC cells. It also inhibits deoxycholic acid (DCA) regulation of epidermal growth factor receptor (EGFR) and Raf-1 kinase activity in colon cells (35). The epithelium of the colon is covered by mucin, which prevents the entry of pathogenic bacteria. Akkermansia muciniphila, which showed an inverse association with obesity and metabolic disorders, resides in the nutrient-rich environment of human mucin (36).

Gut microbiome changes associated with colorectal cancer

One hypothesis proposes that oncogenic bacteria such as enterotoxigenic Bacteroides fragilis (ETBF) cause CRC through direct interaction with colonic epithelial cells and changes in microbiota composition at the colorectal site. Enterotoxigenic Bacteroides fragilis (ETBF) is considered to be protumorogenic (37).

Another hypothesis states that some bacteria cause changes in the local environment of the tumor and allow the establishment of bacteria such as Fusobacterium nucleatum in the tumor microenvironment (38).

Sulfidogenic bacteria such as Fusobacterium, Desulfovibrio, and Bilophila wadsworthia have been shown to be associated with the development of CRC through the production of hydrogen sulfide, leading to the induction of genomic instability (39).

In the stool samples of CRC patients, the microbial changes in the mucosal layers are different (40). Shigella, Citrobacter and Salmonella bacteria were more frequent in the early stages of colorectal cancer compared to healthy people (41). E. coli showed a higher prevalence in CRC mucosa tissue (42). F. F. nucleatum, Bacteroides clarus, Roseburia intestinalis

and Clostridium hathewayi are usually common and identified in CRC (43). Peptostreptococcus anaerobius showed higher frequency in CRC (44). Bacterial biofilms play an important role in the development of CRC (45). In table 1 lists some bacteria that have antitumor activity and some bacteria that cause CRC.

The role of dietary pattern containing fiber and unsaturated fatty acids on CRC

Studies have shown that foods containing fiber have a positive effect on the metabolic activity of the digestive system (57).

In another study, it was found that dietary fiber has an inverse relationship with the incidence of colon cancer. No difference was observed among different sources of dietary fiber intake against CRC prevention (58). In a cohort study, consumption of whole grains was associated with a slight reduction in the risk of CRC. Recently, it has been found that the fermentation of soluble fibers such as lignan and B-glucan to SCFA (short chain acids) by intestinal microbiota plays an important role in cancer prevention. Dietary fiber intake is also associated with the presence of butyrate-producing bacteria in feces (59, 60). Lower amounts of SCFA in feces as a result of lower consumption of fibrous foods and lower amounts of Clostridium, Eubacterium species were found in subjects at risk of CRC compared to healthy subjects (60).

A possible mechanism that could explain dietary fiber in the prevention of CRC could be that fiber reduces carcinogenic substances due to decreased transit time and increased stool volume, which can reduce the interaction of fecal mutagens with the colon mucosa (61). In general, the dietary pattern containing high fiber not only prevents the disorders and adverse function of the intestinal microbiota, but can also stimulate the production of bacterial metabolites with anti-CRC activity, such as butyrate. In addition, in patients with CRC, receiving a dietary pattern with fiber was associated with better survival. However, more clinical and preclinical studies are necessary for these dietary interventions including high fiber intake to prevent CRC.

Various studies have defined the effect of omega-3 unsaturated fatty acids in the diet on the intestinal microbiota. Unsaturated fatty acids are able to increase the ratio of beneficial bacteria to pathogenic bacteria in the digestive system (62). This category of fatty acids has been widely studied due to their role in the protective effect of CRC carcinogenesis mainly through the mechanisms that regulate the apoptosis of colonocytes. It can also change cell cycle components and affect the immune system and modulate the expression of CRC-related genes.

DISCUSSION

Colorectal cancer is the third most common cancer in men and the second most common cancer in women.

Table 1. Microbiomes with antitumor activity against CRC and the microbiome that can lead to CRC.

Microbiomes with antitumor activity against CRC	Ref	Microbiome that can lead to CRC.	Ref
prausnitzii	(33)	Bacteroides fragilis	(37)
Lactobacillus reuteri	(33)	Helicobacter pylori	(46)
Saccharomyces boulardii	(47)	Streptococcus gallolyticus	(48)
Bacillus polyfermenticus	(47)	Escherichia coli (E. coli)	(42)
Clostridium leptum	(50)	S. bovis	(51)
Propionibacterium spp.	(52)	Fusobacterium nucleatom	(53)
Bifidobacterium longum	(54)	Desulfovibrio	(55)
Propionibacterium freudenreichii	(50)	Bilophila wadsworthia	(55)
Lactobacillus plantarum	(50)	Bacteroides clarus	(43)
Eubacterium rectale	(33)	Roseburia intestinalis	(43)
Lactobacillus/ Bifidobactrium	(56)	Peptostreptococcus anaerobius	(44)

It is the fourth leading cause of death in the world (63). CRC is a multifactorial disease in which genetic and environmental risk factors are involved. Smoking, alcohol consumption, obesity and diabetes, and dietary factors such as a diet high in processed foods, animal fat, and red meat are known risk factors for CRC. Genetic and epigenetic changes of tumor suppressor genes, proto-oncogenes and DNA repair genes cause the transformation of normal colonic epithelium to CRC (64). In addition to the effect of genetic factors, environmental factors can also be effective in causing colorectal cancer, such as the dietary pattern containing animal fatty acids, animal fatty acids cause the growth of bacteria that produce carcinogenic products such as polyamine hydrogen sulfide, DCA, lithocholic acid (LCA) and reactive oxygen species (ROS) are active, and diets rich in sugar also play a role in the growth of these bacteria (55, 65, 66).

Butyrate of intestinal microbes causes the secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), which damage intestinal epithelial cells and can be known as risk factors for CRC (67). fragilis and Enterococcus faecalis are responsible for the production of enterotoxins (eg, fragilisin) and reactive oxygen species that cause oxidative DNA damage and inflammation in intestinal epithelial cells (68).

CONCLUSION

During the last few decades, the importance of microbiomes on human health has been investigated. These microbes play a role in the regulation and tolerance of the immune system, most studies on microbiomes have been conducted on intestinal microbes because the highest concentration of bacterial population is located in the large intestine.

The diversity of intestinal microbiota is genetic, but external environmental factors such as diet, exposure to chemicals and other environmental factors, and the use of antibiotics are effective in changing intestinal microbiota.

Also, consuming foods containing saturated fatty acids and sugar leads to the proliferation of bacteria that produce carcinogenic products.

In total, the studies show that the separation of genetic factors and genes involved in the development of this disease and especially familial CRC; The type of intestinal microbiota and the food pattern and lifestyle of a person play a role in causing this condition. It should be noted that dietary pattern plays a role in the proliferation of microbiota that produce carcinogenic products.

Acknowledgements

The authors would like to thank the staff members of the Biotechnology Research Center of the Islamic Azad University of Shahrekord Branch in Iran for their help and support.

Author contributions

Conceptualization, R.R.; All authors reviewed the manuscript.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of Data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1.Sánchez-Alcoholado, L., et al., The role of the gut microbiome in colorectal cancer development and therapy response. Cancers, 2020. 12(6): p. 1406.
2.Rooks, M.G. and W.S. Garrett, Gut microbiota, metabolites and host immunity. Nature reviews immunology, 2016. 16(6): p. 341-352.
3.Benson, A.K., et al., Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. Proceedings of the National Academy of Sciences, 2010. 107(44): p. 18933-18938.
4.Costello, E.K., et al., Bacterial community variation in human body habitats across space and time. science, 2009. 326(5960): p. 1694-1697.
5.Piri Gharaghie T, Doosti A, Mirzaei SA. Prevalence and antibiotic resistance pattern of Acinetobacter spp. infections in Shahrekord medical centers. Developmental Biology. 2021 Nov 22;13(4):35-46.
6.Bhat, M.I. and R. Kapila, Dietary metabolites derived from gut microbiota: critical modulators of epigenetic changes in mammals. Nutrition reviews, 2017. 75(5): p. 374-389.
7.Chattopadhyay, I., et al., Exploring the role of gut microbiome in colon cancer. Applied biochemistry and biotechnology, 2021. 193: p. 1780-1799.
8.Costello, E.K., et al., The application of ecological theory toward an understanding of the human microbiome. Science, 2012. 336(6086): p. 1255-1262.
9.Wieczorska, K., M. Stolarek, and R. Stec, The role of the gut microbiome in colorectal cancer: where are we? Where are we going? Clinical Colorectal Cancer, 2020. 19(1): p. 5-12.
10.Dzutsev, A., et al., The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. European journal of immunology, 2015. 45(1): p. 17-31.
11.Piri Gharaghie T, Hajimohammadi S. Comparison of anti-candida effects of aqueous, ethanolic extracts and essential

oil of E. angustifolia with fluconazole on the growth of clinical strains of Candida. New Cellular and Molecular Biotechnology Journal. 2021 Jul 10;11(43):25-38.
12.Rubinstein, M.R., et al., Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell host & microbe, 2013. 14(2): p. 195-206.
13.Taghiloo S, Ghajari G, Zand Z, Kabiri-Samani S, Kabiri H, Rajaei N, Piri-Gharaghie T. Designing alginate/chitosan nanoparticles containing echinacea angustifolia: a novel candidate for combating multidrug-resistant staphylococcus aureus. Chemistry & Biodiversity. 2023 Jul;20(7):e202201008.
14.Moskal, A., et al., Main nutrient patterns and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study. British journal of cancer, 2016. 115(11): p. 1430-1440.
15.Piri Gharaghie Tohid, DOOSTI ABBAS, MIRZAEI SEYED ABBAS. Detection of T6SS secretory system and membrane purine involved in antibiotic resistance in multidrug-resistant Acinetobacter baumannii isolates. JOURNAL OF MICROBIAL WORLD(Internet). 2021;14(1 (46)):47-58. Available from: https://sid.ir/paper/999438/en
16.Gharaghie TP, Beiranvand S, Abbas Doosti AH, Ghadiri SH. A review of the epidemiology and clinical signs of SARS-COV-2. NCMB J. 2020;11(41):103-20.
17.Gao, R., et al., Gut microbiota and colorectal cancer. European Journal of Clinical Microbiology & Infectious Diseases, 2017. 36: p. 757-769.
18.Saus, E., et al., Microbiome and colorectal cancer: Roles in carcinogenesis and clinical potential. Molecular aspects of medicine, 2019. 69: p. 93-106.
19.Ambalam, P., et al., Probiotics, prebiotics and colorectal cancer prevention. Best practice & research Clinical gastroenterology, 2016. 30(1): p. 119-131.
20.Albenberg, L., et al., Correlation between intraluminal oxygen gradient and radial partitioning of intestinal microbiota. Gastroenterology, 2014. 147(5): p. 1055-1063. e8.
21.Ghourchian H, Pecho RD, Karimi-Dehkordi M, Mazandarani A, Ghajari G, Piri-Gharaghie T. Novel niosome-encapsulated 2, 5-diketopiperazine (BHPPD): Synthesis, formulation, and anti-breast cancer activity. Applied Biochemistry and Biotechnology. 2024 Jun;196(6):3126-47.
22.Kahouli, I., C. Tomaro-Duchesneau, and S. Prakash, Probiotics in colorectal cancer (CRC) with emphasis on mechanisms of action and current perspectives. Journal of medical microbiology, 2013. 62(8): p. 1107-1123.
23.Zarinnezhad A, Shahhoseini MH, Piri Gharaghie T. Evaluating the relative frequency of fungal infections in the serum of patients with multiple sclerosis and healthy subjects using PCR. Journal of Microbial Biology. 2021 Mar 21;10(37):37-50.
24.Peterson, D.A., et al., Metagenomic approaches for defining the pathogenesis of inflammatory bowel diseases. Cell host & microbe, 2008. 3(6): p. 417-427.
25.Owyang, C. and G.D. Wu, The gut microbiome in health and disease. Gastroenterology, 2014. 146(6): p. 1433-1436.
26.Goubet, A.-G., et al., The impact of the intestinal microbiota in therapeutic responses against cancer. Comptes rendus biologies, 2018. 341(5): p. 284-289.
27.Yang, Y. and C. Jobin, Novel insights into microbiome in colitis and colorectal cancer. Current opinion in gastroenterology, 2017. 33(6): p. 422-427.
28.Plotnikoff, G.A., Three measurable and modifiable enteric microbial biotransformations relevant to cancer prevention and treatment. Global Advances in Health and Medicine, 2014. 3(3): p. 33-43.
29.Raay, T.V. and E. Allen-Vercoe, Microbial interactions and interventions in colorectal cancer. Bugs as Drugs: Therapeutic Microbes for the Prevention and Treatment of Disease, 2018: p. 99-130.
30.Chang, P.V., et al., The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proceedings of the National Academy of Sciences, 2014. 111(6): p. 2247-2252.
31.Macfarlane, G.T. and S. Macfarlane, Bacteria, colonic fermentation, and gastrointestinal health. Journal of AOAC International, 2012. 95(1): p. 50-60.
32.Calmels, S., et al., Screening of microorganisms for nitrosation catalysis at pH 7 and kinetic studies on nitrosamine formation from secondary amines by E. coli strains. Carcinogenesis, 1985. 6(6): p. 911-915.
33.Sabit, H., E. Cevik, and H. Tombuloglu, Colorectal cancer: The epigenetic role of microbiome. World journal of clinical cases, 2019. 7(22): p. 3683.
34.Cui, H., et al., Berberine regulates Treg/Th17 balance to treat ulcerative colitis through modulating the gut microbiota in the colon. Frontiers in pharmacology, 2018. 9: p. 370842.
35.Khare, S., et al., Ursodeoxycholic acid inhibits Ras mutations, wild-type Ras activation, and cyclooxygenase-2 expression in colon cancer. Cancer research, 2003. 63(13): p. 3517-3523.
36.Everard, A., et al., Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proceedings of the national academy of sciences, 2013. 110(22): p. 9066-9071.
37.Sears, C.L. and D.M. Pardoll, Perspective: alpha-bugs, their microbial partners, and the link to colon cancer. Journal of Infectious Diseases, 2011. 203(3): p. 306-311.
38.Tjalsma, H., et al., A bacterial driver–passenger model for colorectal cancer: beyond the usual suspects. Nature Reviews Microbiology, 2012. 10(8): p. 575-582.
39.Attene-Ramos, M.S., et al., Evidence that hydrogen sulfide is a genotoxic agent. Molecular Cancer Research, 2006. 4(1): p. 9-14.
40.Gao, R., et al., Mucosa-associated microbiota signature in colorectal cancer. European journal of clinical microbiology & infectious diseases, 2017. 36(11): p. 2073-2083.
41.DuPont, H.L., Bacterial diarrhea. New England Journal of Medicine, 2009. 361(16): p. 1560-1569.
42.Buc, E., et al., High prevalence of mucosa-associated E. coli producing cyclomodulin and genotoxin in colon cancer. PloS one, 2013. 8(2): p. e56964.
43.Liang, Q., et al., Fecal bacteria act as novel biomarkers for noninvasive diagnosis of colorectal cancer. Clinical Cancer Research, 2017. 23(8): p. 2061-2070.
44. Tsoi, H., et al., Peptostreptococcus anaerobius induces intracellular cholesterol biosynthesis in colon

cells to induce proliferation and causes dysplasia in mice. Gastroenterology, 2017. 152(6): p. 1419-1433. e5.
45.Dejea, C.M. and C.L. Sears, Do biofilms confer a pro-carcinogenic state? Gut microbes, 2016. 7(1): p. 54-57.
46.Papastergiou, V., S. Karatapanis, and S.D. Georgopoulos, Helicobacter pylori and colorectal neoplasia: Is there a causal link? World journal of gastroenterology, 2016. 22(2): p. 649.
47.Zhang, J.-W., et al., Preoperative probiotics decrease postoperative infectious complications of colorectal cancer. The American journal of the medical sciences, 2012. 343(3): p. 199-205.
48.Boleij, A., et al., Bacterial responses to a simulated colon tumor microenvironment. Molecular & Cellular Proteomics, 2012. 11(10): p. 851-862.
49.Liu, Z., et al., Positive regulatory effects of perioperative probiotic treatment on postoperative liver complications after colorectal liver metastases surgery: a double-center and double-blind randomized clinical trial. BMC gastroenterology, 2015. 15: p. 1-14.
50.Molska, M. and J. Reguła, Potential mechanisms of probiotics action in the prevention and treatment of colorectal cancer. Nutrients, 2019. 11(10): p. 2453.
51.Dahmus, J.D., et al., The gut microbiome and colorectal cancer: a review of bacterial pathogenesis. Journal of gastrointestinal oncology, 2018. 9(4): p. 769.
52.Whitehead, R., G. Young, and P. Bhathal, Effects of short chain fatty acids on a new human colon carcinoma cell line (LIM1215). Gut, 1986. 27(12): p. 1457-1463.
53.Bashir, A., et al., Fusobacterium nucleatum: an emerging bug in colorectal tumorigenesis. European Journal of Cancer Prevention, 2015. 24(5): p. 373-385.
54.Bozkurt, H.S., E.M. Quigley, and B. Kara, Bifidobacterium animalis subspecies lactis engineered to produce mycosporin-like amino acids in colorectal cancer prevention. SAGE open medicine, 2019. 7: p. 2050312119825784.
55.Attene-Ramos, M.S., et al., Hydrogen sulfide induces direct radical-associated DNA damage. Molecular cancer research, 2007. 5(5): p. 455-459.
56.Pithva, S.P., et al., Antigenotoxic and antimutagenic activities of probiotic Lactobacillus rhamnosus Vc against N-methyl-N′-nitro-N-nitrosoguanidine. Nutrition and cancer, 2015. 67(7): p. 1142-1150.
57.Lattimer, J.M. and M.D. Haub, Effects of dietary fiber and its components on metabolic health. Nutrients, 2010. 2(12): p. 1266-1289.
58.Bingham, S.A., et al., Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. The lancet, 2003. 361(9368): p. 1496-1501.
59.Deehan, E.C., et al., Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. Cell host & microbe, 2020. 27(3): p. 389-404. e6.
60.Chen, H.-M., et al., Decreased dietary fiber intake and structural alteration of gut microbiota in patients with advanced colorectal adenoma. The American journal of clinical nutrition, 2013. 97(5): p. 1044-1052.
61.Gensollen, T., et al., How colonization by microbiota in early life shapes the immune system. Science, 2016. 352(6285): p. 539-544.
62.Watson, H., et al., A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. Gut, 2018. 67(11): p. 1974-1983.
63.Torre, L.A., et al., Global cancer statistics, 2012. CA: a cancer journal for clinicians, 2015. 65(2): p. 87-108.
64.Fleming, M., et al., Colorectal carcinoma: Pathologic aspects. Journal of gastrointestinal oncology, 2012. 3(3): p. 153.
65.Merchant, N.B., et al., Ligand-dependent activation of the epidermal growth factor receptor by secondary bile acids in polarizing colon cancer cells. Surgery, 2005. 138(3): p. 415-421.
66.Culpepper, T., et al., Associations between diet, gut microbiota and markers of CRC risk. Cancer & Metabolism, 2014. 2: p. 1-1.
67.Wu, S., et al., A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nature medicine, 2009. 15(9): p. 1016-1022.
68.Goodwin, A.C., et al., Polyamine catabolism contributes to enterotoxigenic Bacteroides fragilis-induced colon tumorigenesis. Proceedings of the National Academy of Sciences, 2011. 108(37): p. 15354-15359.

http://pmjournal.ir Original Article

Summer 2024, Volume 9, Issue 34 (27- 34)

Antibacterial Toxin-Derived Immunotoxins: Innovative Constructs for Targeted Breast Cancer Treatment

Mona Maleknezhad -Yazdi[1*], Ali Akbar Haddad-Mashadrizeh[2]

[1]Advanced Computational Center, Khayyam Innovation Ecosystem, Mashhad, Iran
[2]Department of Molecular and Cell Biology, Institute of Biotechnology, and Department of Ferdowsi University of Mashhad, Iran.

**Corresponding author:Mona Maleknezhad -Yazdi, Advanced Computational Center, Khayyam Innovation Ecosystem, Mashhad, Iran. Email: farabilaboratory@yahoo.com*

DOI: 10.22034/pmj.2024.2031780.1040

Submitted: 2024-05-04
Accepted: 2024-08-25

Keywords:
Breast Cancer
Immunotoxins
Antibacterial Toxins
Targeted Therapy
Binding Affinity

How to Cite this Article:
M. Maleknezhad-Yazdi, A.Akbar Haddad-Mashadrizeh "Antibacterial Toxin-Derived Immunotoxins: Innovative Constructs for Targeted Breast Cancer Treatment" Personalized Medicine Journal, Vol. 9, no. 34, pp. 27- 34.

Abstract:

Cancer remains one of humanity's leading causes of both illness and death globally. In women worldwide, breast cancer remains the most widespread malignant condition. The new possibilities for direct treatment offered by the advances made thereby were the subject of the recent study undertaken as it sought to unravel tumorigenesis through genetics and molecular appreciation of cancer. Specifically, this research centers on devising and testing immunotoxins as anti-bacterial toxin-based constructs to treat breast cancer. These immunotoxins can kill cancer cells selectively while leaving normal tissues unharmed as they bind only to cancer cell antigens by using both the specificity of antibodies and bacterial toxins' cytotoxicity power. We assessed immunotoxins' binding affinities to their respective antigens based on computational dockings like HADDOCK explaining encouraging results characterized by good docking scores accompanied by low RMSDs—also, dual targeting approaches combined with structure-based. Challenges such as immunogenicity and non-specific toxicity have been tackled by developing humanized antibodies and novel targeting moieties. Our findings suggest that optimized immunotoxins have great potential to enhance therapeutic window as well as efficacy in cancer treatments.

INTRODUCTION

Cancer grows uncontrollably and spreads sometimes in the body too. However, it is also caused by genetic mutations and other factors. Given the recent research findings, this integration is intended to offer a lucid view of what is currently known about this disease as well as its therapies, especially breast cancer (1).

Genetic Basis of Cancer

In essence, cancer stems from errors in genes, which must occur in multiples before a tumor may develop and spread in the body (2-4). Ground-breaking discoveries have been made in the areas of cancer genetics, which have unveiled principal transformations and routes connected to several types of cancer, thus opening doors to fresh treatment options (4).

Physical Traits of Tumors

Tumors possess specific physical characteristics including heightened solid stress, greater interstitial fluid pressure, rigidity, and changes in microstructure that lead to tumor progression and resistance to treatment.

Breast Cancer Specifics

The most frequent cancer in women globally is cancer affecting their breasts which, if discovered before it advances further are curable, but sometimes remain incurable when detected at later stages (5-7). Treatment strategies depend heavily on molecular subtypes. The molecular subtypes include the hormone receptor status and HER2 expression. Involving is a combination of surgery, radiation, endocrinal therapy as well as chemotherapeutics targeted at controlling cancer cells within breast tissues (7). The standard strategy has changed for treating breast cancer, particularly HER2-positive and triple-negative breast cancer using first-line treatment (5, 7).

Cancer Incidence and Mortality Trends

The rate of cancer occurrence and death is different depending on what type of cancer it is and some basic demographic characteristics. Breast cancer incidence is still escalating, whereas vaccination against HPVhas led to a drastic reduction in cervical cancer incidences (8, 9). Advances in treatment and early detection of cancer have led to reductions in its mortality despite

increasing incidences of some cancer types (8).

Tumor Microenvironment and Immunology

Cancer progression and response to treatment are greatly influenced by the tumor microenvironment, which comprises immune cells and physical conditions (8, 10). Incorporating immune parameters into clinical stratification schemes can improve prognostic and predictive information, guiding better clinical decisions (11). The cancer research field has made some noticeable advances in comprehending the genetic and physical bases of this ailment. Such discoveries result in better and more precise treatment methods being developed. Breast cancer for example is the best representation of this complexity seen in cancers where different types are responsive to different therapeutic agents at specific stages of one's life. This means that when you look at someone's blood samples under those circumstances they have molecular subtypes which have no resemblance with each other just like any other disease out there would be different within them. Advances made in immunology enable us to appreciate the contribution made by the tumor microenvironment towards personalizing patient-centered oncology.

Even with these new possibilities, we must address some serious issues in the future. For example, there's an increasing number of breast cancer cases that need specific treatment options. Antibiotics that release toxic substances ii immunotoxins are a new idea for fighting breast cancer. The antibody that identifies cancer cells combined with toxic substances from bacteria is the basis for immunotoxins meant to destroy these malignant cells without affecting other parts of the body.

Targeted Therapy with Immunotoxins

Immunotoxins are designed to target cancer cells by binding to certain antigens or receptors on the surface of these cells that have been overexpressed, bringing along a powerful toxin inside them to kill in destiny (12, 13). These constructs commonly contain toxins from bacteria, such as Pseudomonas exotoxin (PE) and diphtheria toxin (DT) (14, 15).

Clinical Efficacy and Trials

Some immunotoxins have indicated hopeful outcomes in clinical tests as they suggest potent anti-cancer impacts with chances of curing cancers that do not respond to standard therapies (13, 15-17). Denileukin diftitox was the first FDA-approved immunotoxin, followed by tagraxofusp and moxetumomab pasudotox. These drugs exploit bacterial toxins to kill cells (17).

Dual Targeting Strategies

When studying breast cancer models, the combination of HER2 and EpCAM toxins that target both primary tumors and metastases would be more effective, according to dual targeting strategies.

Challenges and Improvements

Immunogenicity and non-specific toxicity are major challenges that cause serious problems, resulting in conditions such as vascular leak syndrome(18). To minimize immunogenicity different approaches are used such as using humanized or less immunogenic forms of bacterial toxins and creating new homing devices (15, 18).

Mechanisms of Action

Some Immunotoxins act by joining when cancer cell receptors, are internalized plus eventually deliver poison in cytosol that will inhibit protein synthesis leading to the death of cells. Other modifications exist in triterpenoid saponins or the like which can lead to valuable increases in tumorcidal potentiality of immunotoxins (19). Specific targeted toxins derived from antibacterial materials could be a more effective strategy in treating breast cancer. Combining the specificity of antibodies with cytotoxicity from bacterial-derived toxins ensures complete eradication of cancerous cells with minimal harm on normal ones. Despite obstacles such as immune response stimulation or high levels of unspecific toxicity, improved outcomes are anticipated as research continues in this area including dual targeting approaches to enhance therapeutic outcomes without harming healthy tissues (1).

Evaluation of Antigen and Immunotoxin Docking Capability

Docks between antigens and immunotoxins are an area of research that is very important and has great implications for developing drugs, especially in terms of cancer therapy and immune system control processes. The focus of this review is to provide an overview based on diverse computational as well as experimental investigations about what current limits exist about antigen or immunotoxin docking procedures (20).

Antigen Docking

Forecasting the interaction of such immunity agents through simulation (antigen docking) can help predict immune response and aid in the production of healing antibodies. There have been various computer-based methods aimed at improving the correctness as well as speed of their projections.

Information-Driven Docking

For example, HADDOCK, a software for docking, has been combined with information regarding the complementarity-determining regions and binding

epitopes, and has been established to perform far better than other software suites like ClusPro, LightDock, and ZDOCK, both in terms of success rate and model quality.

Surface Complementarity

An innovation in positive superposition, which uses rough energy of the steric interactions in the interface region as a scoring function, has been used with antibody-antigen docking. The protocol is shown to be sufficiently accurate to recover near-native structures and recognize feasible docking orientations with root-mean-square deviations (r.m.s.d.) from 1.9 to 4.8 A (21).

Epitope Mapping

PIPER-Map, a protocol that combines template-based modeling and docking, has improved epitope prediction accuracy, showing that starting from antibody sequence alone can yield results comparable to those starting from unbound antibody structures.

Soft Docking Algorithms

Soft-docking techniques demonstrating potential in forecasting binding sites of antibody-antigen interactions, have been developed for camelid VHH antibody variable domains using side-chain flexibility and combined filtering approaches (22).

Immunotoxin Docking

Immunotoxins are molecules constructed by two persons that bring together the specificity shown by the monoclonal antibodies and toxicity of poisons; their action is pointed at killing cancer-preceding antigens. The therapeutic efficiency of such immunotoxins is pegged on how they attach and get into the cells.

Trimeric Immunotoxins

An innovative form of the trimeric immunotoxin, which aims at CEA, managed to kill more cells in xenografts of human colorectal cancer than its monomeric analog did, implying that immunotoxin design should be carefully considered as regards docking effects (23).

Internalization Efficiency

A recent study investigated how immune toxins against CD19 and CD22 are internalized differently. This study shows that the toxins targeting CD22 are internalized quickly, leading to more killing effects on a cell, thus making it more suitable for treatment than other diseases whose immune toxins do not work well inside. We can conclude based on the data presented here that different degrees of intercalation lead to various levels of toxicity for cancer cells using CD_19-based antigen ligand conjugated to recombinant diphtheria toxin (some of which kill rapidly while some don't kill any target cells at all) which implies that there is significant difference in activity between the conjugate single chain fragments with recombinant diphtheria toxin based on their rate and capacity for internalization (24). In antigen evaluation, it is generally accepted that there have been significant improvements in computational methods for information-driven docking, surface complementarity, and soft-docking algorithms. These methods greatly advanced the modeling of antibody-antigen interactions and supported the design of the most effective immunotoxins. Moreover, future research should be aimed at advancing these techniques and exploring their development in a therapeutic sense.

1.Modeling Antibody-Antigen Complexes by Information-Driven Docking (20).
2.New policy to mimic protein interaction based on surface complementarity application on antibody-antigen docking (21).
3.Epitopes of antibodies could be mapped out using homology modeling and docking (25).
4.Antibody-antigen complex structure can be predicted using an elastic docking algorithm (22).
5.Antitumor activity of human colorectal cancer xenografts is significantly enhanced by a novel CEA-Targeted Trimeric Immunotoxin that targets CEA (23).
6.Differential cellular internalization of anti-CD19, CD34 and -CD22 immunotoxins results in different cytotoxic activity

Materials and methods

Effective therapies in the sphere of immunology and cancer research typically hinge on accurate targeting and transportation of therapeutic agents to specific cell targets. For example, the cell-surface proteoglycan CD44 is one such target that has been highly investigated because of its involvement during cancer progression and metastasis However, predicting an antigen and its receptor is a problem characterized by borderline energy levels when analyzing the binding affinities of immunotoxins including energy computations—we also consider the energy levels instead of just focusing on these computations. (Figure 1).

The evaluation of the binding affinity of an immunotoxin to its antigen was very important to determine its effectiveness and specificity (Table 1).

Evaluation of binding affinity of immunotoxin to control antigens

Bispecific Antibody-Toxin Conjugates for T Cell Subset Depletion A bispecific antibody recognizing CD34 and CD22 was created to find CD22+CD34 bright T cells. It showed that binding bidirectionally to these both antigens enhanced toxins intracellular entrance and release, which resulted in the killing of just a few cells. Two studies reviewed in this paper provide

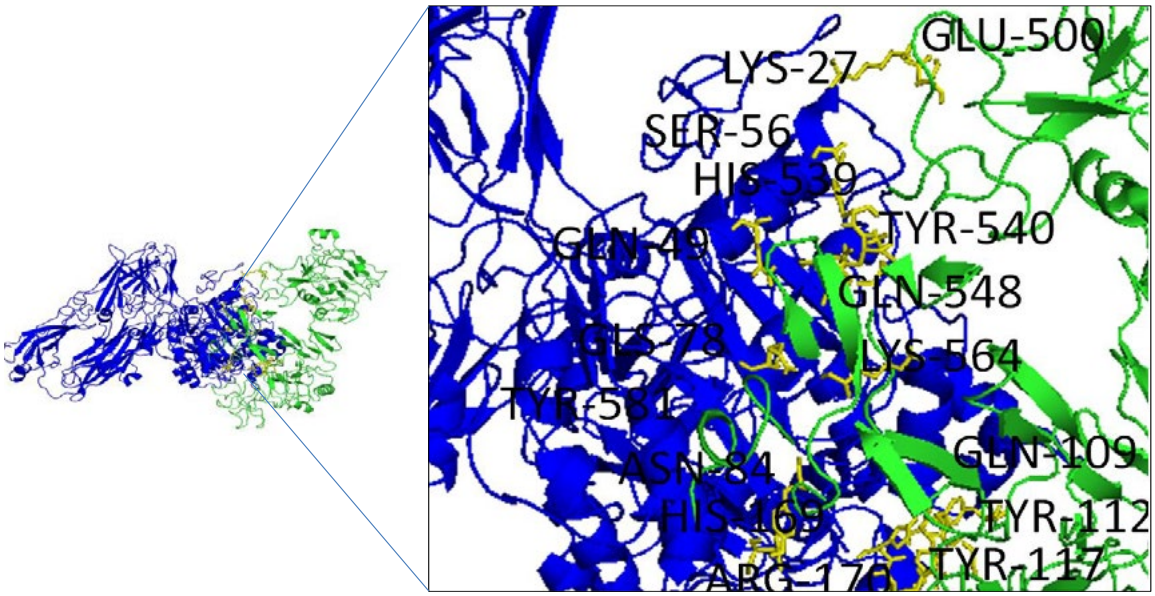


Fig1. Evaluation of binding affinity of immunotoxin and antigen

Table 1. Immunotoxin and antigen binding affinity evaluation table

HADDOCK Score	-16,3
RMSD	2,2
Z-Score	-2,4

useful insights into the development and optimization of immunotoxins for therapeutic purposes, thus revealing the importance of dual binding in boosting immunotoxin internalization and cytotoxicity; it is still unclear whether these cells use intracellular pathways to induce receptor-mediated endocytosis. Their binding abilities do not just determine the interaction between immunotoxins and normal antigens; rather, it is a composite process involving specificity, internalization, and serum half-life (Figure 2,3)2

The comparison of the binding affinity of antigens with immunotoxins reveals significant insights into the relationship between antigen binding and immunotoxin efficacy (Figure 4).

RESULTS

To determine their effectiveness and specificity in targeting cancer cells, we must assess the ability of different immunotoxins (IT) to bind to various antigens. Here, we employed HADDOCK (High Ambiguity Driven protein-protein DOCKing) software, which also happens to be very common in the docking field to study how these two agents interact with each other.

The HADDOCK score indicates the predicted quality of protein-protein interaction. By a docking energy measure. The worse the outcome, the lower the score: 16.3, RMSD Root mean square deviation on scores about 16 marks approximately average distance among atoms weighted upon one another protein superposition. It shows how closely the docked conformation reflects the native conformation. RMSD: 2.2 Å. Z-Score: The Z-score judges the HADDOCK score against several random scores to determine whether the docking result is significant. Z-Score: 2.4 Binding Affinity to Control Antigens to validate the specificity and efficacy of the immunotoxins, we compared their binding affinities against control antigens, CD22 and CD34. (Figures 2 and 3 show the schematic binding interactions of the designed drugs to these antigens. CD22 Bindin. The researchers found that CD22 is a good target for therapy because it is taken up quickly into the cell with the investigational agents which resulted in increased uptake and cytotoxic activity. Moreover, there is a greater affinity as shown by improved docked scores for this ligand. It binds specifically to CD34+ T cells that are bright making it efficient choosing this molecule to carry toxins to those that bear them. When looking at different antigens it can be concluded that this one has more significant binding characteristics Variants that had intermediate affinity for EGFR had a wider

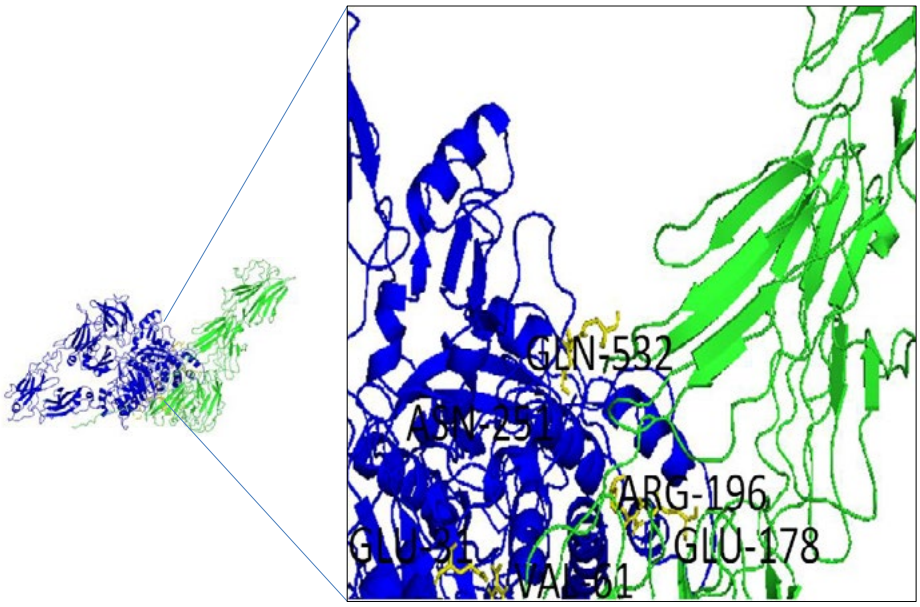


Fig 2. Schematic figure of binding of the designed drug to CD22 antigen

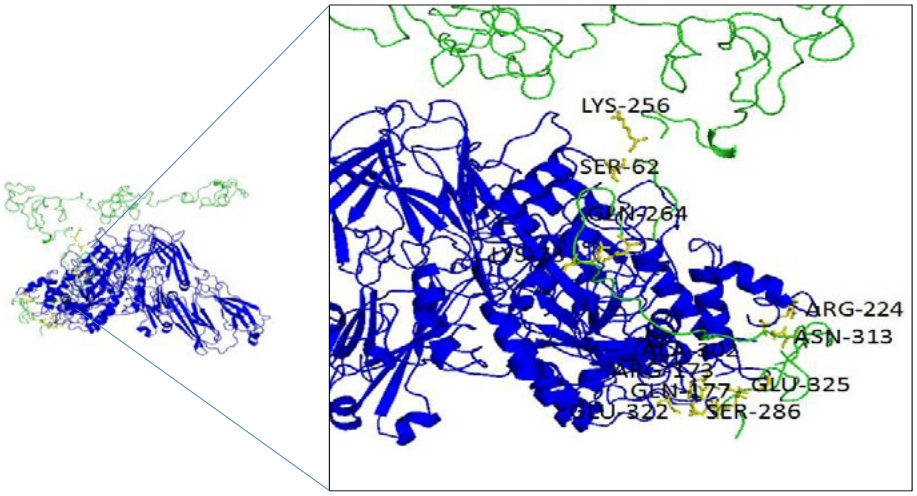


Fig 3. Schematic figure of binding of the designed drug to CD34 antigen

therapeutic window and could sustain higher maximum tolerated doses. The binding affinity: Optimal binding affinities are related to increased strength as well as higher cure rates. Trimeric Immunotoxin Targeting CEA: Its antitumor effects were significantly enhanced in human colorectal cancer xenografts compared to monomeric forms; thus, it underscores the significance of docking in immunotoxin optimization. Highly active trimeric forms have higher antitumor propensity; as detected by increased attachment affinity and cell killing. Several ways to use the computer for attaching antigen and protein toxins had been tried out to see if they might be effectively used together. Information Driven Docking (HADDOCK): Outperforms other programs because it uses CDRs and binding epitopes databases and other software in terms of performance and quality of the model. Complementarity between components of the interface; they can compute feasible starting attitudes (within 4.8 Å) displaying precise docking predictions thanks to their performance similar to that of known algorithms such as GSLIDE (5). The importance of optimizing affinity constants for a better therapeutic index in the efficacy and safety of immunotoxins became more apparent with these recent findings. This interpretation further highlights the significance of optimizing binding constants to improve the therapeutic, index, and margin of safety as well as decreasing immunogenicity levels. Based on the findings, immunotoxins hold great promise for the treatment of many types of cancer, including breast tumors, if they have optimal binding interactions. For the development of the targeted cancer therapy industry, such technologies must continue to evolve. By adjusting EGFR's bond ability, the therapeutic

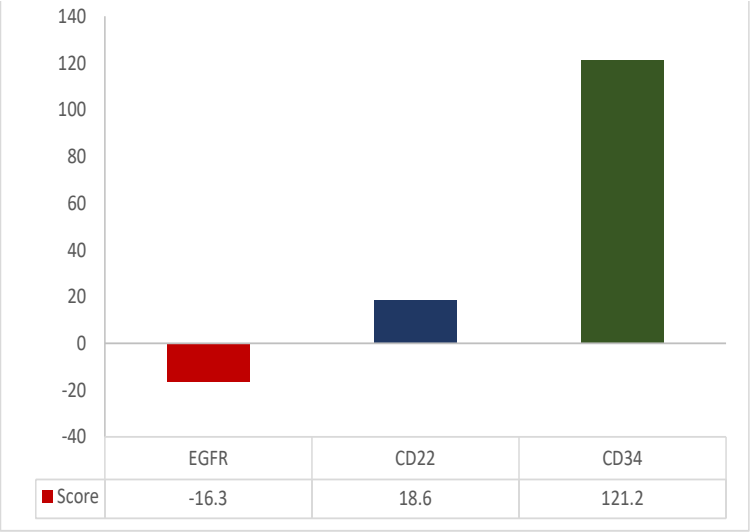


Fig4. Comparison of binding affinity of antigens with immunotoxin

interval of PE24 immunotoxin aimed toward EGFR-boosted cancers is extended. This research was about improving the therapeutic window by changing the bonding capability of anti-EGFR immunotoxins. The researchers produced numerous mutants that had varying reproducibility for EGFR and realized that some of these had better ranges of medication to toxicity than others in tumor models Intermediate affinity for example was associated with wider therapeutic windows and higher maximum doses than high-affinity tumors Therefore; it is known from the results that effectiveness of immunotoxins depends on an optimal binding strength this antigen. Immunoglobulin toxins' response rates will not be determined by anything but how they bond with respective antigens which are their targets. Immunotoxin effectiveness hinges mainly on the way it binds with an associated antigen, and it is in this context that a collection of analyses has been done. The more firmly immunotoxins are bound to cells' antigens, the greater their ability to kill these cells; nevertheless, sometimes exceptions do occur as a result of changes in bond strength between the particular toxin domains. Modifying affinity for binding can help to bring out these improvements thus enhancing immunotoxin efficacy which might reduce its side effects during its use in hospitals.

DISCUSSION & CONCLUSION

Cancer, which is a group of diseases characterized by abnormal cell proliferation, is second only to cardiovascular diseases as the leading cause of death among developed countries and third in developing ones. Over 25 million people worldwide are currently battling the condition, which adds up to more than 11 million fresh cases each year. Such dreadful statistics illustrate how dreadful this illness is: it can be described as an unnatural growth of body cells that tends to spread across different organs or tissues within an organism. Unlike harmless cancers, malignant tumors spread to other parts of the body. Humans have more than a hundred types of cancer which are associated with them. Cancerous cells grow within normal cells as either malignant or benign tumors. These growths are non-cancerous but typically benign and can be slow-growing like normal cells, however, their rapid division may lead to problems like swelling (which causes discomfort) or constricting pressure on adjacent organs as they grow too big for the space. Fast-growing cancerous growths, on the other hand, tend to spread to other parts of the body either through blood or lymphatic vessels where they form secondary tumors called metastases. Cancers are categorized according to the specific body tissues they affect; they are usually carcinoma of epithelial cells which account for a large proportion among elderly people about all types of cancers and we can also mention such ones as cancers of the lungs, prostate gland, or mammary gland. A malignant tumor is characterized by rapid multiplication without regulation and moving away from the place where it started. Human-like classifications include lymphatics, sarcomas are connected tissues or originate from mesenchyme outside of BM like nerves and muscle, and are the most widespread forms of cancer in children. The germ cells give rise to cancers such as those of testes and ovaries while embryonic cells account for pluripotent tumors found in different parts of the body. Blastomas arise from immature precursor cells (15-20), or embryonic tissue but without detailed sampling. Latin or Greek root combined with the suffixes carcinoma, sarcoma, or blastoma is typically used to label most cancers. For instance, though liver cancer could more accurately be referred to as hepatoblastoma, it is generally called hepatocellular carcinoma because it occurs in the liver;

similarly, while there are other names for adipose tissue tumors (cosmetic liposarcoma), people commonly say lipoma when speaking about fat cell tumors. Approximately 40,000 individuals perish yearly due to breast cancer which rates as one of the most frequently diagnosed malignancies in American women folk. Age-related death tolls differ depending on where individuals live – for instance, those who come from the North-Eastern part of the United States are more prone to dying from breast cancer than their Southern counterparts. It is estimated by analysts that before 2030 more than two million new cases of breast cancer will emerge every year mainly in underdeveloped areas, Immunohistochemistry and molecular approaches are employed in diagnosing breast cancer while the therapy involves traditional modes of treatment among others. Radiation, surgery, and chemotherapy are involved in traditional treatments, whereas hormone therapy, bacteriotherapy, and targeted treatments like cytotoxic, gene therapy, and immunotoxins are included in modern treatments. Nonetheless, traditional and new treatments still come with side effects such as nausea, immune suppression, and tissue damage. Diagnosing and treating cancer remains a significant challenge so The creation of new diagnostic and targeted therapeutic techniques is needed from bacteriotherapy, particularly with concern to the development of immunotoxins based on bacterial products gained prominence. Immunotoxins are hybrid proteins that contain a binding region, typically an antibody or any of its derivatives. The proteins also have a potent toxic part, which is usually an enzyme from plants or vegetables that binds specifically to an antigen on the surface of a cancer cell, killing it. Designing efficient immunotoxins has benefited significantly from intensive studies on bacterial poisons. We want to find out about new things that come from poison and harm cells but can be used as medicine to kill cancer cells. For this purpose, we are studying bacterial toxins made by dangerous germs and investigating how they are put together genetically and chemically for possible use as part of more suitable types of DNA that would destroy breast cancer cells when activated inside these dangerous organisms.

Acknowledgments

I want to thank Professor Massoud Houshmand who helped with this research.

Suggestions for further research

Optimizing Immunotoxin Design
Reducing Immunogenicity
Enhancing Internalization and Cytotoxicity
Exploring Novel Toxins
Clinical Trials and Translational Research
Tumor Microenvironment and Immune Modulation
Advanced Docking and Computational Methods
Patient-Specific Therapies.

Consent for publication

Not applicable.

Funding

Not applicable.

Conflict of interest

No conflict of interest.

Acknowledgements

Declared none.

REFERENCES

1.Maleknejadyazdi, M. and A.A. Haddad-Mashadrizeh, Designing and Simulating the Structure of an Effective Immunotoxin in Breast Cancer. Personalized Medicine Journal, 2023. 8(31): p. 10-25.
2.Vogelstein, B. and K.W. Kinzler, The multistep nature of cancer. Trends in genetics, 1993. 9(4): p. 138-141.
3.Vogelstein, B. and K.W. Kinzler, Cancer genes and the pathways they control. Nature medicine, 2004. 10(8): p. 789-799.
4.Stratton, M.R., P.J. Campbell, and P.A. Futreal, The cancer genome. Nature, 2009. 458(7239): p. 719-724.
5.Harbeck, N., et al., Breast cancer. Nature reviews Disease primers 5: 66. 2019.
6.Murali, B., et al., Treatment of HR+/HER2− breast cancer in urban mainland China: Results from the CancerMPact Survey 2019. Breast Cancer Research and Treatment, 2022. 195(3): p. 441-451.
7.Loibl, S., et al., Epidemiology and risk factors. Breast Cancer. Lancet, 2021. 397: p. 1750-1769.
8.Clancy, E., ACS Report Shows Prostate Cancer on the Rise, Cervical Cancer on the Decline. Renal & Urology News, 2023: p. NA-NA.
9.Ferlay, J., et al., Cancer statistics for the year 2020: An overview. International journal of cancer, 2021. 149(4): p. 778-789.
10.Nia, H.T., L.L. Munn, and R.K. Jain, Physical traits of cancer. Science, 2020. 370(6516): p. eaaz0868.
11.Galon, J. and D. Bruni, Tumor immunology and tumor evolution: intertwined histories. Immunity, 2020. 52(1): p. 55-81.
12.Mathew, M. and R.S. Verma, Humanized immunotoxins: a new generation of immunotoxins for targeted cancer therapy. Cancer science, 2009. 100(8): p. 1359-1365.
13.Kreitman, R.J. and I. Pastan, Immunotoxins for targeted cancer therapy. Advanced drug delivery reviews, 1998. 31(1-2): p. 53-88.
14.Amoozadeh, S., et al., Preparation of diphtheria and pseudomonas exotoxin a immunotoxins and evaluation of their cytotoxicity effect on SK-BR-3, BT-474, and MDA-MB-231 breast cancer cell lines. Cancer investigation, 2019. 37(10): p. 546-557.

15.Akbari, B., et al., Immunotoxins in cancer therapy: Review and update. International reviews of immunology, 2017. 36(4): p. 207-219.
16.Havaei, S.M., M.G. Aucoin, and A. Jahanian-Najafabadi, Pseudomonas exotoxin-based immunotoxins: over three decades of efforts on targeting cancer cells with the toxin. Frontiers in Oncology, 2021. 11: p. 781800.
17.Reiter, Y., Recombinant immunotoxins in targeted cancer cell therapy. 2001.
18.Li, Y.M. and W.A. Hall, Targeted toxins in brain tumor therapy. Toxins, 2010. 2(11): p. 2645-2662.
19.Dieffenbach, M. and I. Pastan, Mechanisms of resistance to immunotoxins containing pseudomonas exotoxin a in cancer therapy. Biomolecules, 2020. 10(7): p. 979.
20.Ambrosetti, F., et al., Modeling antibody-antigen complexes by information-driven docking. Structure, 2020. 28(1): p. 119-129. e2.
21.Walls, P.H. and M.J. Sternberg, New algorithm to model protein-protein recognition based on surface complementarity: Applications to antibody-antigen docking. Journal of molecular biology, 1992. 228(1): p. 277-297.
22.Li, C.H., et al., A soft docking algorithm for predicting the structure of antibody-antigen complexes. Proteins: Structure, Function, and Bioinformatics, 2003. 52(1): p. 47-50.
23.Lázaro-Gorines, R., et al., A novel carcinoembryonic antigen (CEA)-targeted trimeric immunotoxin shows significantly enhanced antitumor activity in human colorectal cancer xenografts. Scientific Reports, 2019. 9(1): p. 11680.
24.Du, X., et al., Differential cellular internalization of anti-CD19 and-CD22 immunotoxins results in different cytotoxic activity. Cancer research, 2008. 68(15): p. 6300-6305.
25.Desta, I.T., et al., Mapping of antibody epitopes based on docking and homology modeling. Proteins: Structure, Function, and Bioinformatics, 2023. 91(2): p. 171-182.

http://pmjournal.ir Reviwe Article

Summer 2024, Volume 9, Issue 34 (35- 44)

An Update on Kidney Diseases and Cancer

Zahra Taheri[1*]

[1]Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran.

**Corresponding author: Zahra Taheri, Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran· Email: Zahra_Taheri_2005@yahoo.com.*

DOI: 10.22034/pmj.2024.2030994.1038

Submitted: 2024-04-27
Accepted: 2024-08-13

Keywords:
Kidney diseases
Cancer
Chemotherapy
CKD
AKI

How to Cite this Article:

Z. Taheri, "An Update on Kidney Diseases and Cancer" Personalized Medicine Journal, Vol. 9, no. 34, pp. 35- 44.

Abstract:
Numerous individuals worldwide are grappling with kidney disease or malignancy. Renal cell carcinoma (RCC) and chronic kidney disease (CKD) are directionally associated and share risk factors. The investigation of the correlation between cancer chemotherapy and renal disorders is of importance due to the kidneys' involvement in detoxification. The current disparity between the occurrence of cancer and kidney problems is addressed by this investigation. CKD can induce RCC via a cystic disorder or oxidative stress. RCC promotes CKD in terms of tumor interactions, physical removal of a kidney mass, and perioperative acute renal disease. Kidney failure leads to renal cancer-specific pathways. For example, renal progenitors are converted to tumor-initiating cells via HIF, Notch, mTOR, and Hippo pathways. Furthermore, progress in cancer treatment during recent years increased the overall survival of patients with advanced malignancies faced with early and late adverse effects from therapeutics. There are conflicting findings about the dosing of typical chemotherapeutics because of loss of kidney function. Recommended doses are usually based on expert opinion, not scientific evidence. This investigation evaluated the issues in cancer patients with kidney problems that can help patients by informing physicians about GFR loss and its effect on chemotherapy.

INTRODUCTION

Worldwide, a large number of individuals are afflicted with cancer or kidney illness. Renal tumors and kidney disease are associated with similar risk factors. Renal cancer may result from risk factors for kidney illnesses such as obesity, diabetes, age, hypertension, smoking, nephrotoxic medications, and heavy metals, according to epidemiologic study (1-4). On the other hand, smoking, diabetes, and obesity are linked to nephron loss as a result of glomerular hyperfiltration and CKD linked to glomerulosclerosis (4). After all, renal damage ultimately results in hypertension and, less often, hypertension causes kidney injury. Another sensitive indicator of early CKD is hypertension (2). Nephrotoxic medicines and heavy metals stimulate necroinflammation and oxidative stress associated with toxic acute kidney injury (AKI) (3). Site-specific kidney diseases lead to determined kinds of kidney cancer. Moreover, different kidney cancer types are associated with specific kidney diseases (5). Because of the role of kidneys in detoxification, studying the relationship between cancer chemotherapy, and kidney disorders is significant. This study fills the current gap between cancer occurrence and the treatment of kidney problems.

From Renal Failure to Renal Tumor: Pathways and Mechanisms

The proliferation of long-lived renal progenitor cells during kidney repair is the cause of cancerogenesis (6). These cells are the source of epithelial cells in the glomerulus, the nephron, and the collecting duct (7). Kidney progenitors frequently exhibit delayed, spontaneous proliferation to compensate for the loss of ductal epithelial cells and podocytes (7, 8). The majority of ductal epithelial cells are proliferative and dedifferentiated in response to injury (9). However, the population of putative renal progenitors compensates for epithelial cell loss by the detachment of podocytes and necrosis of tubular epithelial cells through clonal proliferation (8, 10). Based on Lindgren et al. reports, transcriptomics and protein profiles of renal progenitors are similar to Papillary renal cell carcinomas (pRCCs), and papillary adenomas (11). The upregulation of the Notch1 pathway increases renal progenitor proliferation in AKI, papillary adenomas, and pRCC in transgenic animals (12). Renal progenitors of collecting

ducts can lead to oncocytoma, and carcinoma renal cell carcinoma (RCC) in this site (13).

According to estimation, 22%-36% of RCC patients who underwent partial or complete nephrectomy had an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m2 before surgery. Up to 45% of CKD patients with proteinuria may have background CKD (14, 15). Kidney failure leads to renal cancer-specific pathways. Through pathways like HIF, Notch, mTOR, and Hippo, renal progenitors transformed into tumor-initiating cells (12). HIF pathway plays a role in the hypoxic condition of AKI, CKD (16), and clear cell renal cell carcinoma (ccRCC) (17).

HIF pathway

In hypertensive individuals and those with the HIF pathway, the renin-angiotensin system, prostaglandins, and endothelin can induce vessel constriction, which may lead to kidney cancer and CKD (17).

mTOR pathway

The protein kinase B/mTOR pathway, in conjunction with hyperglycemia and hyperinsulinemia, is responsible for the development of RCC and diabetic renal disease in diabetes mellitus (17, 18). RCC was frequently associated with alterations in the phosphoinositide 3-kinase–protein kinase B–mTOR pathway, including PTEN, MTOR, and PIK3CA (19).

Notch pathway

The orientation and polarity of the mitotic spindle are regulated by Notch (20). In renal progenitor cells, aberrant notch expression results in atypical mitoses via the disruption of cell cycle checkpoints and/or mitotic spindle adjustment (12). Renal progenitor cells, papillary adenomas, and RCC are more likely to become malignant when the notch pathway is active, which is linked to renal failure (21).

Hippo pathway

The Hippo pathway, which is influenced by the yes-associated protein 1/transcriptional coactivator with PDZ-binding motif [YAP/TAZ] protein, is disrupted in cystic renal disease, acute kidney injury (AKI), and certain sporadic cancers. Thus, there is a potential correlation between RCC and cell growth in cysts (24). Salvador homolog-1 (SAV1) is a constituent of the Hippo pathway. The Hippo-YAP1 signaling pathway causes a loss of copy number and leads to the development of high-grade ccRCC (25). Furthermore, spontaneous pRCC is caused by the loss of chromosome 22. The tumor suppressor genes for Neurofibromatosis type 2 (NF2) are located on this chromosome. NF2 produces SAV1, a regulator of the Hippo pathway, and SMARCB1, a matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1 (SWI/SNF related, actin-dependent regulator of chromatin) that codes for a part of the lactate nonfermentable complex/chromatin-altering switch (26).

c-Met–hepatocyte growth factor pathway

Human oncogenesis is associated with iron overload (27). RCC is ultimately brought on by the generation of reactive oxygen species (a Fenton reaction) in the renal proximal tubules of mice after repeated iron treatment. Numerous genomic alterations were seen in these mice. The most often altered locus were a CDKN2a/2b deletion and a MET amplification. Tumor diameters are also correlated with met amplification and/or expression (28).

Chromatin remodeling pathways

Aberrant chromosomal arm 3p genes polybromo 1 (PBRM1), SET domain-containing protein 2 (SETD2), BRCA-associated protein-1 (BAP1), or SMARCB1 are among the chromatin remodelling pathways linked to ccRCC. Moreover, ccRCC is often linked to TP53 alterations and loss of CDKN2A as a result of deletions, mutations, or promoter hypermethylation (5).

Chronic Kidney Disease and Tumor Associations

CKD and tumors correlated via inter-relationships, such as chronic inflammation, collection of carcinogenic compounds, oxidative stress, and excessive parathyroid hormone.

Chronic Inflammation

In CKD, inflammation is complicated. Dialysis, oxidative stress, acidosis, metabolic abnormalities in adipose tissue, and intestinal problems are all risk factors for infection (29). Reduced renal excretion activity leads to increased plasma half-lives of IL-1β, IL-6, and TNF-α (30). The research found that infections afflicted 23.6% (95% CI: 22.8-24.6) of CKD patients, and hospitalization rates were greater for both groups (31).

Accumulation of Carcinogenic Compounds

Patients with end-stage kidney disease (ESKD) develop uremic as a result of high circulating nitrogen levels, which are impacted by carcinogens and agents. For example, uremic patients on dialysis have higher levels of circulating carcinogens such as 2-amino-6-methyldipyrido [1,2-a:3′,2′-d]imidazole (Glu-P-1) and 2-aminodipyrido [1,2-a:3′,2′-d]imidazole (Glu-P-2) than healthy people. These two substances' concentrations may stay increased in uremic individuals for a lengthy period, as they did after 30 days of dialysis (32).

Oxidative Stress

When the equilibrium between oxidation and

antioxidant activity in the body is disrupted, oxidative stress ensues. In CKD, oxidative activity increases while the antioxidant system decreases. For example, in early CKD, neutrophils, monocytes, and macrophages may be produced. This resulted in the synergistic production of reactive oxygen species (ROS) (33). In a study of 87 CKD patients, the plasma oxidative stress indicator 8-epiPGF2a demonstrated a substantial direct connection with CKD development (34). Simultaneously, increasing ROS impeded pro-oxidant clearance in CKD patients, creating a prooxidant environment. The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) responded to antioxidant reagents through the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway (35). During oxidative stress, the cytoplasmic covalent bond between Nrf2-keap1 and Nrf2 was disrupted, enabling Nrf2 to enter the nucleus. The Nrf2/Maf complex is subsequently formed by heterodimerization with Maf (musculoaponeurotic fibrosarcoma oncogene homolog) proteins. This complex transcribes the ARE-dependent gene of antioxidant and cytoprotective factors (36). In mononuclear cells of peripheral blood from uremic and hemodialysis patients, Nrf2-dependent antioxidant genes including heme oxygenase-1 (HO-1), glutamate-cysteine ligase modifier subunit (GCLM), and catalase were downregulated. Oxidant genes were overexpressed and NF-κB was increased at the same time (37). NF-κB may be stimulated by certain T cell types (38). DNA fixation of lymphocytes in chronic renal failure (CRF) individuals on dialysis was similar to that of healthy people. Still, it significantly decreased following UV or gamma exposure in the CRF people. So, CRF patients might have less ability to repair DNA and obtain this ability via dialysis. Unrepaired or improperly fixed DNA would cause mutations, aberrations in the chromosome, and even cancer (39). The lymphocytes of dialysis patients displayed indications of permanent genomic damage, such as aberrant dispersion of whole chromosomes, chromosomal breakage, and sister chromatid swaps. These anomalies raised the risk of uterine tumors, lymphoma, and cancers of the kidney, prostate, and liver (40). Variations in the DNA fixation enzyme genes of Xeroderma pigmentosum complementation group D (XPD) and X-ray cross-complementing group 1 (XRCC1) were reported to have significant relationships with ESKD (41).

Excessive Parathyroid Hormone

Lower phosphorus excretion from the slow renal failure results in higher circulating phosphorous and a mix of phosphorous and calcium phosphate lowered circulation calcium. Reduced active vitamin D, low blood calcium, and high serum phosphorous were the main causes of secondary hyperparathyroidism (SHPT) (42). Renal carcinoma (32) is caused by parathyroid hormone (PTH) and its receptors In late CKD, PTH also overexpressed Fibroblast growth factor-23 (FGF23) to balance the increased phosphate outflow from additional bone turnover (43). FGF23 is a hormone that originates from bone and inhibits the production of vitamin D hormone and phosphate reabsorption in the kidneys (44). The upregulation of FGF-23 in individuals with CKD may be associated with the adjustment of FGF-23 through bone remodelling, which is facilitated by the diffusion of low molecular weight FGFs. Prostate cancer, paraneoplastic malfunctions, and hypophosphatemia are the results of FGF23 overactivation through FGF/FGFR signal transduction. Consequently, FGF-23 may be linked to the development of cancer (45).

Chronic Kidney Disease in Tumor Survivors

The overall survival rate for those with advanced cancers has risen recently due to advancements in cancer therapy. Adverse consequences from therapies, including cardiac difficulties, neuropathy, bone loss, recurring malignancies, and renal failure, were seen by tumor survivors both early and late. One of the most prevalent kidney failures in these people is CDK, which manifests in a variety of ways in different survivors (46, 47).

CKD in Childhood Tumor Survivors

Childhood tumor survivors are at high risk for both acute and chronic renal failure. Nephrotoxic chemotherapy therapies such as ifosfamide, cisplatin, methotrexate, and high-dose cyclophosphamide may cause CKD and nephron loss. Furthermore, progressive chronic kidney disease (CKD) may develop in adolescence or adulthood in these children who have a higher risk of AKI because to volume depletion, sepsis-related acute tubular necrosis, tumor lysis syndrome, and loss of juvenile nephrons (48).

CKD in Patients Who Have Survived Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplant patients often have chronic kidney disease (CKD) (HSCT). Due to various types of autologous vs. allogenic and transplant times, as well as the absence of a consensus definition, the prevalence of CKD in these individuals ranges from 0 to 60% (49). Three kinds of chronic kidney disease (CKD) may be distinguished based on the specific causes of the condition: thrombotic microangiopathy, nephrotic syndrome, and chronic calcineurin inhibitor toxicity. On the other hand, the etiology of CKD in some individuals remains unknown (48).

CKD in Cancer Survivors Exposed to Immunotherapy

To enhance the anticancer capabilities of the host, tumor immune-therapeutics orchestrate the immune response. Cytotoxic Tlymphocyte-associated protein 4, programmed death protein 1, and programmed-death ligand 1 are the targets of monoclonal antibodies known as immune checkpoint inhibitors (ICIs). ICIs have the potential to eradicate critical negative regulators of T-cells. Despite the promising activity of ICIs, they are unsuccessful in 60%-80% of cases as a result of autoimmune adverse effects that affect nearly every human organ system. Allergic interstitial nephritis (AIN) is the most frequent kidney immune-linked adverse event. An ICI-related AIN affects 3%-5% of the individuals treated with ICIs (50, 51). Glomerular disorders are significantly less usual than AIN (52).

Chronic Kidney Disease and Cancer-Associated Mortality

CKD is linked with cancer mortality. In retrospective observational research on 961 stage IV tumor people having an average age of 69 years and 48.2% women, 15.6% had CKD. During the mean of 9.8 months, 66.4% of people died, of whom 82.44% died due to tumors. Whole death and cancer-associated mortality were significantly more prevalent in CKD individuals than in non-CKD individuals after adjusting for prognostic variables, including ECOG PS and tumor therapy (HR 1.41, 95% CI 1.13–1.77 vs. HR 1.43, 95% CI 1.12–1.83, respectively). A substantially increased mortality risk was associated with CKD in individuals with breast, kidney, and urinary tract malignancies. Additionally, for kidney and urinary tract cancer (HR 3.33, 95% CI 1.42–7.78) as well as breast cancers (HR 7.01, 95% CI 1.47–33.4), the association between CKD and cancer-associated mortality was site-dependent (53). Compared to those without CKD, the CKD patients were older, had more advanced ECOG PS, and had less anticancer therapy. Inadequate performance is linked to a worse survival rate in individuals with advanced cancer (54). Canadian research found that patients with ECOG PS 4 with advanced malignancies had an average life of 25 days, whereas those with ECOG PS 3 had an average survival of 50 days (55). Additionally, ECOG PS was lower in CKD patients than in healthy persons, and frailty is more frequent in CKD patients than in healthy individuals (56). For patients with stage IV malignancies, palliative chemotherapy is the recommended course of action to prolong survival, lessen symptoms, and enhance quality of life (57). However, because of more frequent side effects in cancer people with CKD, it is less common to prescribe antitumor medication than those without CKD (58). Therefore, the correlation between CKD, and tumor mortality could be a result of the lack of cancer treatment in CKD patients (53).

Cancer Drug Dosing in CKD

Kidneys eliminated a lot of anti-tumor drugs. To determine an appropriate equilibrate between drug impression and toxicity, medicine doses should be regulated based on renal activity. As most anti-tumor therapeutics cannot be monitored, adjustment is performed based on the evaluation of renal activity(59).

According to a study by Launay-Vacher et al., 50–60% of patients with tumors had a renal activity that is below normal or an eGFR of less than 90 mL/minute per 1.73 m2 (60). Furthermore, during anti-tumor treatment, patients with tumors often have a steady deterioration in renal function. A median decrease in GFR of 7 ml/min per 1.73 m2 was seen 24 months after diagnosis in a retrospective study of French cancer patients (59). The overestimation of renal activity causes overdosing or improper drug choice and likely elevated toxicity. However, its undervalue leads to underdosing or unsuitable element elimination and likely suboptimal tumor resultants (61). During drug development, most of the time, merely individuals with normal or mild renal failure are considered in clinical trials (62). As a result, data from persons with severe kidney failure and ESKD necessary kidney renewal are few, and only a few innovative therapy submissions to the FDA include data from them (63). The frequent exclusion of CKD patients from cancer clinical trials is a problem and a barrier to adequate dosing of cancer patients with CKD. As a result, it promotes a lack of adequate clinical treatment for this group (64).

CHANGES OF PHARMACOKINETICS AND PHARMACODYNAMICS IN CKD PATIENTS

The efficacy of a medication is contingent upon its pharmacokinetic and pharmacodynamic properties. The pharmacodynamic properties of a medication are determined by its receptor/cellular targets, downstream signal transduction pathways, and interactions. The absorption, distribution, metabolism, and excretion of a medication are all examples of its pharmacokinetic properties. In individuals with kidney failure, a drug's pharmacokinetic and pharmacodynamic characteristics can be altered. Some therapeutics are not omitted by the renal activity, but their metabolites are detoxified by the kidneys (65).

Chemotherapeutics And Kidney Injuries

Since there have been some contradictory reports regarding the dosage of common chemotherapeutics, we have examined some of the most often used drugs to treat cancer in this section, including methotrexate/pemetrexed, 5-fluorouracil/capecitabine, cyclophosphamide, ifosfamide, and cisplatin. Cisplatin

Cisplatin is a common drug against a wide range

of cancers. Cisplatin therapy as platinum-based chemotherapy leads to AKI in 6% to 30% of people who have testicular cancer depending on the population (66). Cisplatin induces AKI and urinary magnesium wasting by disrupting the S3 sector of the proximal tubule and distal nephron. Carboplatin and oxaliplatin do not cause severe renal damage, however, there have been cases of AKI and acute interstitial nephritis (AIN) after carboplatin treatment (67). The most common cisplatin-related side effects were nausea/vomiting, nephrotoxicity, and bone marrow suppression. Cisplatin is not an acceptable choice for persons with severe renal failure due to its nephrotoxicity influence on CKD progression and non-kidney side effects. The second constraint is more severe in ESKD patients who have decreased renal function (68). On non-dialysis days, they may get lesser dosages of cisplatin since it is strongly and permanently bound. The unbound cisplatin is dialyzed, and the bound moiety does not replace it (69).

Carboplatin

Carboplatin is usually administered therapeutically against different cancers. Carboplatin dose calculated with the Calvert Formula. Carboplatin-based multichemotherapy was efficacious in individuals undergoing hemodialysis and peritoneal dialysis, without enhancing toxicity or diminishing efficacy (70, 71). In hemodialysis patients, the Calvert formula is considered to have a GFR of zero, as are other formulae that are used for peritoneal dialysis (Table 1) (72). Carboplatin is frequently dialyzable, as it does not bind to protein rapidly after injection, in contrast to cisplatin. However, dialysis becomes ineffective as a result of its binding to plasma components after 24 hours. Therefore, hemodialysis should be performed within 24 hours of carboplatin administration, but not right following administration (69).

Cyclophosphamide

Cyclophosphamide is employed to manage a variety of solid and liquid malignancies. Hemodialysis is required for 12 hours following treatment, as cyclophosphamide and its metabolites are eliminated through this process. The dosage of cyclophosphamide was decreased to one-fourth in patients undergoing peritoneal dialysis (69).

Ifosfamide

Cyclophosphamide-associated agents like ifosfamide, as well as chloracetaldehyde metabolites, are their accumulation cause AKI and progressive CKD nephrotoxic via myelosuppressive, neurotoxicity, and tubular injury (73, 74).

A mitochondrial toxicity, chloroacetaldehyde is a metabolite of ifosfamide, another treatment for testicular sarcomas (48). Ifosfamide toxicity was comparable to that of other Fanconi-like

Table 1. Usual formulas to estimate GFR based on serum creatinine

Equation	Advantage	Disadvantage	Reference
Calvert Formula (81): dose (mg) = AUC (mg/mL x min) x [GFR (mL/min) + 25 (mL/min)].	Accurate	The GFR must be measured, containing invasive and inconvenient methods	(82, 83)
Cockcroft-Gault (84) **(((140-age) x weight)/(72xsCr))x0.85 (only for women)**	Accurate Widely apply in cancer sufferers	Imprecise in the elderly Biased in BMI ≥30 and BMI <18.5	(85)
MDRD (86) **186 × (SCr)$^{-1.154}$ × (age)$^{-0.203}$ × 1.212 (only for blacks) × 0.742 (only for women)**	More precise Accurate in elderly Accurate BMI ≥30	Biased in BMI <18.5 Not widely used in cancer sufferers	(87, 88)
CKD-EPI **Women with SCr ≤ 0.7: 144 × (0.993)^{age} × (SCr/0.7)$^{-0.329}$** **Women with SCr > 0.7: 144 × (0.993)^{age} × (SCr/0.7)$^{-1.209}$** **Men with SCr ≤ 0.9: 141 × (0.993)^{age} × (SCr/0.9)$^{-0.411}$** **Men with SCr > 0.9: 141 × (0.993)^{age} × (SCr/0.9)$^{-1.209}$**	More precise Accurate in elderly Accurate BMI ≥30	Biased in BMI <18.5 Not widely applied in cancer sufferers	(89)

Abbreviations: SCr, serum creatinine; BMI, body mass index

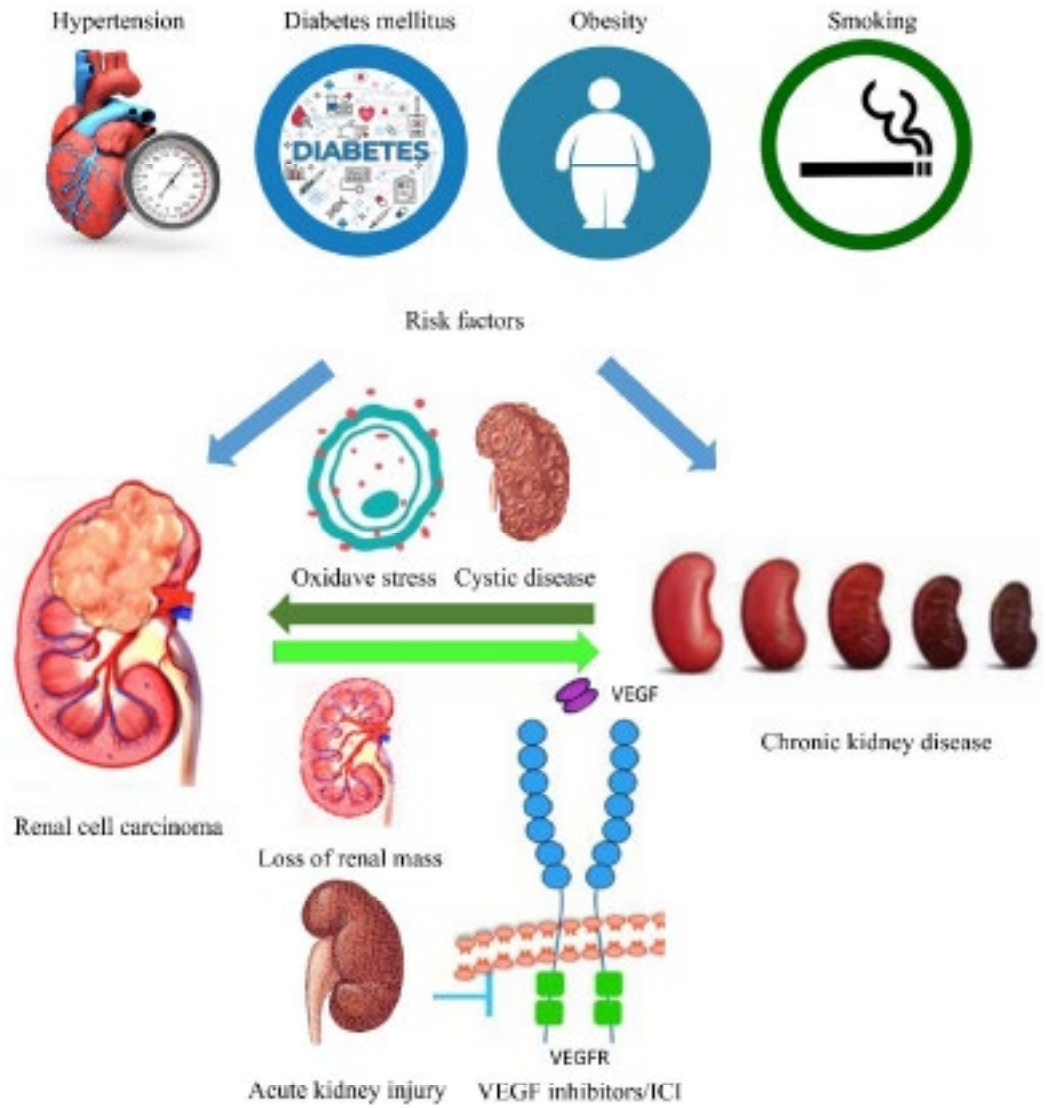


Fig 1. Inter-relationships between various host risk factors, chronic kidney disease, and renal cell carcinoma

syndromes, such as hypophosphatemia, metabolic acidosis, hypokalemia, and tubular proteinuria. It has the potential to result in lower eGFR and progressive tubular failure (75). Additionally, Ifosfamide may induce frequent episodes of nephrogenic diabetes insipidus. The following are risk factors for ifosfamide nephrotoxicity: stored cumulative dose, previous nephrectomy, basis CKD, and previous or simultaneous cisplatin subjection. Mesna coadministration can mitigate the risk of hemorrhagic cystitis caused by the other ifosfamide metabolite, acrolein; however, its impact on nephrotoxicity remains uncertain (76). Children who received an average stored ifosfamide dosage of 54 g/m2 showed encouraging long-term renal function after 10 years; 90% of the children had regular tubular activity and 79% showed eGFR. 90 milliliters per minute for 77 square meters. There is little information available on individuals using ifosfamide and long-term renal follow-up. Over the course of five years, the average eGFR dropped from 82 to 67 mL/min/1.73 m2 in a retrospective cohort of 259 people, and none of them had ESKD (78).

Methotrexate/Pemetrexed

Both methotrexate (MTX) and its derivative pemetrexed inhibit the cellular division pathways linked to folate. It first experiences renal excretion, precipitation of MTX high dosage in renal tubules, and temporary acute kidney injury. AKI causes an increase in serum MTX, which is quickly decreased by hemodialysis to avoid extra-renal damage. Since it usually reverses, more dialysis or the recombinant enzyme glucarpidase (GPDG2) of metabolites for hydrolysis is strongly advised (79).

Fluorouracil/Capecitabine

5-Fluorouracil and the oral pro-drug form of it,

capecitabine, do not have nephrotoxicity. However, as 5-FU metabolites accumulate in CKD people, they are not administered to individuals suffering from advanced CKD (69). Despite this, in some studies, capecitabine was successfully administered to CKD V patients or those on hemodialysis (69, 80).

CONCLUSION

There is a bidirectional relationship and shared risk factors between renal cell carcinoma and chronic kidney disorders. Cystic abnormalities or oxidative stress in people with chronic kidney disease may cause RCC. RCC may also make chronic kidney disease (CKD) worse due to tumor interactions, nephrectomy or partial kidneyectomy, and post-operative acute renal sickness. Furthermore, renal damage with vascular endothelial growth factor blockers and immune checkpoint inhibitors may result in chronic kidney disease. On the other hand, according to the once-nephrology reports, cancer morbidity in CKD patients and paraneoplastic renal diseases is high. Elevated tumor risk in CKD might be a result of chronic inflammation, carcinogen accumulation, oxidative stress, failure of DNA repair, as well as increased parathyroid hormone. The paraneoplastic renal failure was associated with hematologic malignancies, carcinoma, and anti- tumor treatments. Regarding the high risk of tumor in CKD, regular tumor screening, such as marker assessment monitoring, imaging evaluation, and endoscopy is highly recommended for early diagnosis and a more successful prognosis.

It is essential to investigate the long-term renal consequences of recently synthesized anticancer targets. By understanding the risks of chronic kidney disease (CKD) and its causes, we may prevent renal side effects by limiting the prescription or dosage of anticancer medications and the eligibility for clinical trial participation in cancer patients. Tumor death is associated with chronic kidney disease (CKD). Consequently, strategies to prevent AKI and the shift from AKI to CKD are needed to improve outcomes for tumor survivors. Since renin-angiotensin-aldosterone blockade, sodium-glucose cotransporter 2 suppressors, and selective mineralocorticoid receptor antagonists are renal therapies, their effectiveness in treating chronic kidney disease (CKD) or lowering eGFR elimination in tumor survivors will be highlighted. The interaction of renal disorders with tumors influences anti-cancer therapy. Control of this situation is tough. The pitfalls of circulating creatinine as a GFR biomarker are problematic. However, physicians should know about GFR loss and its effect on chemotherapy.

Consent for publication

Not applicable.

Funding

Not applicable.

Conflict of interest

No conflict of interest.

Acknowledgements

Declared none.

REFERENCES

1.Lee M, Wang Q, Wanchoo R, Eswarappa M, Deshpande P, Sise ME. Chronic Kidney Disease in Cancer Survivors. Advances in Chronic Kidney Disease.2021;28(5):469-76. e1.
2.Carriazo S, Vanessa Perez-Gomez M, Ortiz A. Hypertensive nephropathy: a major roadblock hindering the advance of precision nephrology. Oxford University Press; 2020. p. 504-9.
3.Mulay SR, Linkermann A, Anders H-J. Necroinflammation in kidney disease. Journal of the American Society of Nephrology: JASN. 2016;27(1):27.
4.Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. The Lancet. 2017;389(10075):1238-52.
5.Peired AJ, Lazzeri E, Guzzi F, Anders H-J, Romagnani P. From kidney injury to kidney cancer. Kidney International. 2021;100(1):55-66.
6.Young MD, Mitchell TJ, Vieira Braga FA, Tran MG, Stewart BJ, Ferdinand JR, et al. Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors. Science. 2018;361(6402):594-9.
7.Lazzeri E, Angelotti ML, Peired A, Conte C, Marschner JA, Maggi L, et al. Endocycle-related tubular cell hypertrophy and progenitor proliferation recover renal function after acute kidney injury. Nature communications. 2018;9(1):1344.
8.Lasagni L, Angelotti ML, Ronconi E, Lombardi D, Nardi S, Peired A, et al. Podocyte regeneration driven by renal progenitors determines glomerular disease remission and can be pharmacologically enhanced. Stem cell reports. 2015;5(2):248-63.
9.Kusaba T, Lalli M, Kramann R, Kobayashi A, Humphreys BD. Differentiated kidney epithelial cells repair injured proximal tubule. Proceedings of the National Academy of Sciences. 2014;111(4):1527-32.
10.Kang HM, Huang S, Reidy K, Han SH, Chinga F, Susztak K. Sox9-positive progenitor cells play a key role in renal tubule epithelial regeneration in mice. Cell reports. 2016;14(4):861-71.
11.Lindgren D, Boström A-K, Nilsson K, Hansson J, Sjölund J, Möller C, et al. Isolation and characterization of progenitor-like cells from human renal proximal tubules. The American journal of pathology. 2011;178(2):828-37.
12.Peired AJ, Antonelli G, Angelotti ML, Allinovi M, Guzzi F, Sisti A, et al. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. Science translational medicine. 2020;12(536):eaaw6003.
13.Christensen BM, Kim Y-H, Kwon T-H, Nielsen S. Lithium treatment induces a marked proliferation of primarily principal cells in rat kidney inner medullary collecting duct. American Journal of Physiology-Renal Physiology. 2006;291(1):F39-F48.
14.Dey S, Hamilton Z, Noyes SL, Tobert CM, Keeley J, Derweesh IH, et al. Chronic kidney disease is more common in locally advanced renal cell carcinoma.

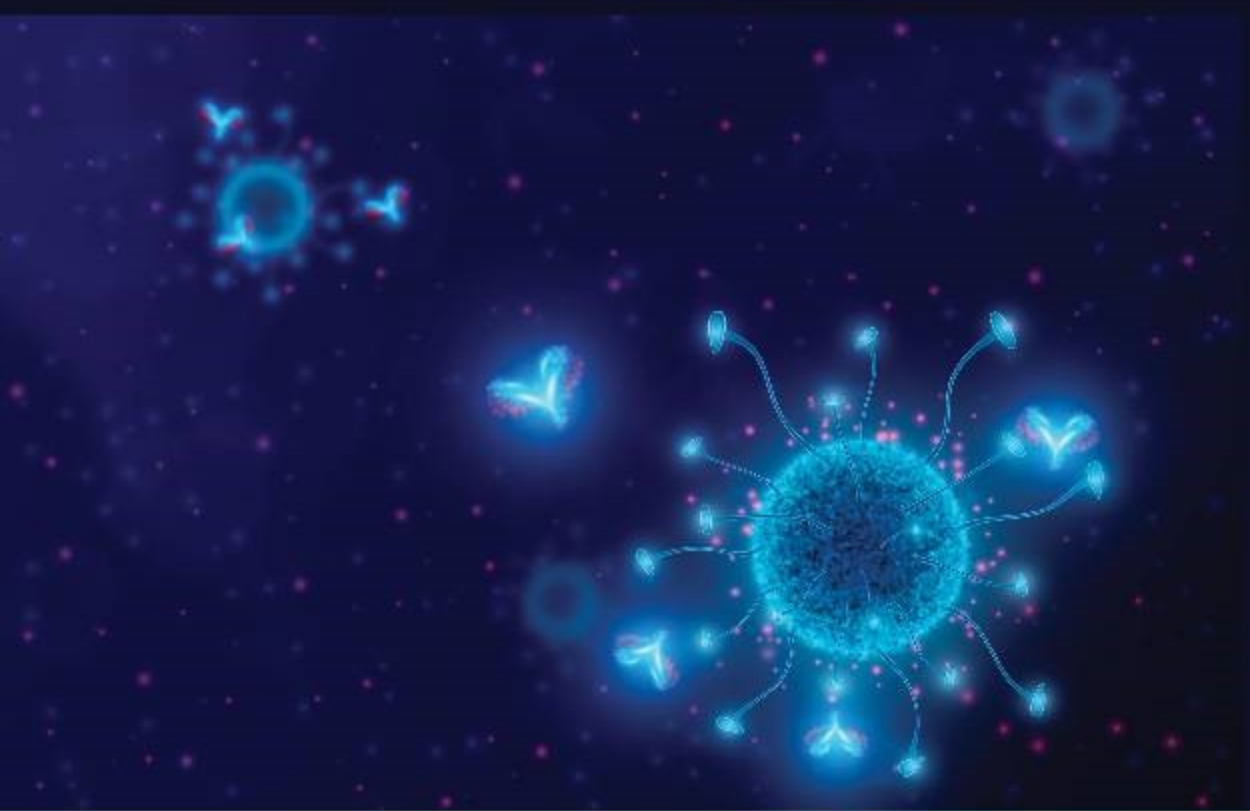
Urology.2017;105:101-7.
15.O'Donnell K, Tourojman M, Tobert CM, Kirmiz SW, Riedinger CB, Demirjian S, et al. Proteinuria is a predictor of renal functional decline in patients with kidney cancer. The Journal of Urology. 2016;196(3):658-63.
16.Shu S, Wang Y, Zheng M, Liu Z, Cai J, Tang C, et al. Hypoxia and hypoxia-inducible factors in kidney injury and repair. Cells. 2019;8(3):207.
17.Chappell JC, Payne LB, Rathmell WK. Hypoxia, angiogenesis, and metabolism in the hereditary kidney cancers. The Journal of clinical investigation. 2019;129(2):442-51.
18.Anders H-J, Huber TB, Isermann B, Schiffer M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. Nature Reviews Nephrology. 2018;14(6):361-77.
19.Guo H, German P, Bai S, Barnes S, Guo W, Qi X, et al. The PI3K/AKT pathway and renal cell carcinoma. Journal of genetics and genomics. 2015;42(7):343-53.
20.Charnley M, Ludford-Menting M, Pham K, Russell SM. A new role for Notch in the control of polarity and asymmetric cell division of developing T cells. Journal of Cell Science. 2020;133(5):jcs235358.
21.Lasagni L, Ballerini L, Angelotti ML, Parente E, Sagrinati C, Mazzinghi B, et al. Notch activation differentially regulates renal progenitors proliferation and differentiation toward the podocyte lineage in glomerular disorders. Stem cells. 2010;28(9):1674-85.
22.Seeger-Nukpezah T, Geynisman DM, Nikonova AS, Benzing T, Golemis EA. The hallmarks of cancer: relevance to the pathogenesis of polycystic kidney disease. Nature Reviews Nephrology. 2015;11(9):515-34.
23.Anorga S, Overstreet JM, Falke LL, Tang J, Goldschmeding RG, Higgins PJ, et al. Deregulation of Hippo–TAZ pathway during renal injury confers a fibrotic maladaptive phenotype. The FASEB Journal. 2018;32(5):2644.
24.Xie J, Wang X, Proud CG. mTOR inhibitors in cancer therapy. F1000Research. 2016;5.
25.Matsuura K, Nakada C, Mashio M, Narimatsu T, Yoshimoto T, Tanigawa M, et al. Downregulation of SAV1 plays a role in pathogenesis of high-grade clear cell renal cell carcinoma. BMC cancer. 2011;11(1):1-10.
26.Lee S, Karas PJ, Hadley CC, Bayley V JC, Khan AB, Jalali A, et al. The role of merlin/NF2 loss in meningioma biology. Cancers. 2019;11(11):1633.
27.Boffetta P, Fontana L, Stewart P, Zaridze D, Szeszenia-Dabrowska N, Janout V, et al. Occupational exposure to arsenic, cadmium, chromium, lead and nickel, and renal cell carcinoma: a case–control study from Central and Eastern Europe. Occupational and environmental medicine. 2011;68(10):723-8.
28.Akatsuka S, Yamashita Y, Ohara H, Liu Y-T, Izumiya M, Abe K, et al. Fenton reaction induced cancer in wild type rats recapitulates genomic alterations observed in human cancer. 2012.
29.Ebert T, Pawelzik S-C, Witasp A, Arefin S, Hobson S, Kublickiene K, et al. Inflammation and premature ageing in chronic kidney disease. Toxins. 2020;12(4):227.
30. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clinical journal of the American Society of Nephrology: CJASN. 2012;7(12):1938.
31.Ishigami J, Grams ME, Chang AR, Carrero JJ, Coresh J, Matsushita K. CKD and risk for hospitalization with infection: the atherosclerosis risk in communities (ARIC) study. American Journal of Kidney Diseases. 2017;69(6):752-61.
32.Hu M, Wang Q, Liu B, Ma Q, Zhang T, Huang T, et al. Chronic Kidney Disease and Cancer: Inter-Relationships and Mechanisms. Frontiers in Cell and Developmental Biology. 2022;10:868715-.
33.Putri AY, Thaha M. Role of oxidative stress on chronic kidney disease progression. Acta Medica Indonesiana. 2014;46(3):244-52.
34.Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, et al. Oxidative stress is progressively enhanced with advancing stages of CKD. American Journal of Kidney Diseases. 2006;48(5):752-60.
35.Shaw P, Chattopadhyay A. Nrf2–ARE signaling in cellular protection: Mechanism of action and the regulatory mechanisms. Journal of Cellular Physiology. 2020;235(4):3119-30.
36.Tu W, Wang H, Li S, Liu Q, Sha H. The anti-inflammatory and anti-oxidant mechanisms of the Keap1/Nrf2/ARE signaling pathway in chronic diseases. Aging and disease. 2019;10(3):637.
37.Feng Y-L, Chen H, Chen D-Q, Vaziri ND, Su W, Ma S-X, et al. Activated NF-κB/Nrf2 and Wnt/β-catenin pathways are associated with lipid metabolism in CKD patients with microalbuminuria and macroalbuminuria. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2019;1865(9):2317-32.
38.Giri DK, Aggarwal BB. Constitutive activation of NF-κB causes resistance to apoptosis in human cutaneous T cell lymphoma HuT-78 cells: autocrine role of tumor necrosis factor and reactive oxygen intermediates. Journal of Biological Chemistry. 1998;273(22):14008-14.
39.Helena JM, Joubert AM, Grobbelaar S, Nolte EM, Nel M, Pepper MS, et al. Deoxyribonucleic acid damage and repair: Capitalizing on our understanding of the mechanisms of maintaining genomic integrity for therapeutic purposes. International Journal of Molecular Sciences. 2018;19(4):1148.
40.Buemi M, Floccari F, Costa C, Caccamo C, Belghity N, Campo S, et al. Dialysis-Related Genotoxicity: Sister Chromatid Exchanges and DNA Lesions in T and B Lymphocytes of Uremic Patients. Genomic Damage in Patients on Hemodiafiltration: Genomic Damage in Patients on Hemodiafiltration. Blood purification. 2006;24(5-6):569-74.
41.Trabulus S, Guven GS, Altiparmak MR, Batar B, Tun O, Yalin AS, et al. DNA repair XRCC1 Arg399Gln polymorphism is associated with the risk of development of end-stage renal disease. Molecular biology reports. 2012;39:6995-7001.
42.Lau WL, Obi Y, Kalantar-Zadeh K. Parathyroidectomy in the management of secondary hyperparathyroidism. Clinical journal of the American Society of Nephrology: CJASN. 2018;13(6):952.
43.Quarles LD. Role of FGF23 in vitamin D and phosphate metabolism: implications in chronic kidney disease. Experimental cell research. 2012;318(9):1040-8.
44.Erben RG. Physiological actions of fibroblast growth factor-23. Frontiers in endocrinology. 2018:267.
45.Lee EK, Martinez MCR, Blakely K, Santos KD, Hoang VC, Chow A, et al. FGF23: mediator of poor prognosis in a sizeable subgroup of patients with castration-resistant prostate cancer presenting with severe hypophosphatemia? Medical hypotheses. 2014;83(4):482-7.
46.Clemens E, van den Heuvel-Eibrink MM, Mulder RL, Kremer LC, Hudson MM, Skinner R, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood

Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. The Lancet Oncology. 2019;20(1):e29-e41.
47.Schaapveld M, Aleman BM, van Eggermond AM, Janus CP, Krol AD, van der Maazen RW, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. New England Journal of Medicine. 2015;373(26):2499-511.
48.Lee M, Wang Q, Wanchoo R, Eswarappa M, Deshpande P, Sise ME. Chronic kidney disease in cancer survivors. Advances in Chronic Kidney Disease. 2021;28(5):469-76. e1.
49.Ellis MJ, Parikh CR, Inrig JK, Kambay M, Patel UD. Chronic kidney disease after hematopoietic cell transplantation: a systematic review. American Journal of Transplantation. 2008;8(11):2378-90.
50.Seethapathy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehn I, et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clinical Journal of the American Society of Nephrology: CJASN. 2019;14(12):1692.
51.Seethapathy H, Zhao S, Strohbehn IA, Lee M, Chute DF, Bates H, et al. Incidence and clinical features of immune-related acute kidney injury in patients receiving programmed cell death ligand-1 inhibitors. Kidney international reports. 2020;5(10):1700-5.
52.Mamlouk O, Selamet U, Machado S, Abdelrahim M, Glass WF, Tchakarov A, et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. Journal for immunotherapy of cancer. 2019;7(1):1-13.
53.Ishii T, Fujimaru T, Nakano E, Takahashi O, Nakayama M, Yamauchi T, et al. Association between chronic kidney disease and mortality in stage IV cancer. International Journal of Clinical Oncology. 2020;25(9):1587-95. [DOI: 10.1007/s10147-020-01715-9].
54.Maltoni M, Scarpi E, Pittureri C, Martini F, Montanari L, Amaducci E, et al. Prospective comparison of prognostic scores in palliative care cancer populations. The oncologist. 2012;17(3):446-54.
55.Jang RW, Caraiscos VB, Swami N, Banerjee S, Mak E, Kaya E, et al. Simple prognostic model for patients with advanced cancer based on performance status. Journal of oncology practice. 2014;10(5):e335-e41.
56.Shlipak MG, Stehman-Breen C, Fried LF, Song X, Siscovick D, Fried LP, et al. The presence of frailty in elderly persons with chronic renal insufficiency. American journal of kidney diseases. 2004;43(5):861-7.
57.Caires-Lima R, Cayres K, Protásio B, Caires I, Andrade J, Rocha L, et al. Palliative chemotherapy outcomes in patients with ECOG-PS higher than 1. Ecancermedicalscience. 2018;12.
58.Wei Y-F, Chen J-Y, Lee H-S, Wu J-T, Hsu C-K, Hsu Y-C. Association of chronic kidney disease with mortality risk in patients with lung cancer: a nationwide Taiwan population-based cohort study. BMJ open. 2018;8(1):e019661.
59.Launay-Vacher V, Spano J-P, Janus N, Gligorov J, Ray-Coquard I, Oudard S, et al. Renal insufficiency and anticancer drugs in elderly cancer patients: a subgroup analysis of the IRMA study. Critical reviews in oncology/hematology. 2009;70(2):124-33.
60.Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X, Rixe O, et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer. 2007;110(6):1376-84.
61.Launay-Vacher V, Aapro M, De Castro Jr G, Cohen E, Deray G, Dooley M, et al. Renal effects of molecular targeted therapies in oncology: a review by the Cancer and the Kidney International Network (C-KIN). Annals of Oncology. 2015;26(8):1677-84.
62.Kitchlu A, Shapiro J, Amir E, Garg AX, Kim SJ, Wald R, et al. Representation of patients with chronic kidney disease in trials of cancer therapy. Jama. 2018;319(23):2437-9.
63.Zhang Y, Zhang L, Abraham S, Apparaju S, Wu TC, Strong J, et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. Clinical Pharmacology & Therapeutics. 2009;85(3):305-11.
64.Sprangers B, Jhaveri KD, Perazella MA. Improving cancer care for patients with chronic kidney disease. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2020;38(3):188-92.
65.Latcha S. Pharmacokinetics of chemotherapeutic agents in kidney disease. Onco-nephrology curriculum. 2016:1-9.
66.Motwani SS, McMahon GM, Humphreys BD, Partridge AH, Waikar SS, Curhan GC. Development and validation of a risk prediction model for acute kidney injury after the first course of cisplatin. Journal of Clinical Oncology. 2018;36(7):682.
67.Asai A, Katsuno T, Yamaguchi M, Iwagaitsu S, Nobata H, Kinashi H, et al. Carboplatin-related acute interstitial nephritis in a patient with pancreatic neuroendocrine tumor. CEN case reports. 2020;9:114-21.
68.Watanabe R, Takiguchi Y, Moriya T, Oda S, Kurosu K, Tanabe N, et al. Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. British journal of cancer. 2003;88(1):25-30.
69.Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Annals of Oncology. 2010;21(7):1395-403.
70.Inoue A, Saijo Y, Kikuchi T, Gomi K, Suzuki T, Maemondo M, et al. Pharmacokinetic analysis of combination chemotherapy with carboplatin and etoposide in small-cell lung cancer patients undergoing hemodialysis. Annals of oncology. 2004;15(1):51-4.
71.Veal GJ, English MW, Grundy RG, Shakespeare C, Glaser A, Waters F, et al. Pharmacokinetically guided dosing of carboplatin in paediatric cancer patients with bilateral nephrectomy. Cancer chemotherapy and pharmacology. 2004;54:295-300.
72.Guddati AK, Joy PS, Marak CP. Dose adjustment of carboplatin in patients on peritoneal dialysis. Medical oncology (Northwood, London, England). 2014;31(5):946. [DOI: 10.1007/s12032-014-0946-z].
73.Ensergueix G, Pallet N, Joly D, Levi C, Chauvet S, Trivin C, et al. Ifosfamide nephrotoxicity in adult patients. Clinical kidney journal. 2020;13(4):660-5.
74.Kaijser G, Beijnen J, Bult A, Underberg W. Ifosfamide metabolism and pharmacokinetics. Anticancer research. 1994;14(2A):517-31.
75.Stöhr W, Paulides M, Bielack S, Jürgens H, Treuner J, Rossi R, et al. Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: a report from the Late Effects Surveillance System. Pediatric blood & cancer. 2007;48(4):447-52.
76.Skinner R, Cotterill S, Stevens M. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. British journal of cancer. 2000;82(10):1636-45.
77.Oberlin O, Fawaz O, Rey A, Niaudet P, Ridola V, Orbach D, et al. Long-term evaluation of Ifosfamide-related nephrotoxicity in children. Journal of clinical oncology.

2009;27(32):5350-5.
78.Farry JK, Flombaum CD, Latcha S. Long term renal toxicity of ifosfamide in adult patients–5 year data. European Journal of Cancer. 2012;48(9):1326-31.
79.Kumar N, Shirali AC, editors. What is the best therapy for toxicity in the setting of methotrexate-associated acute kidney injury: high-flux hemodialysis or carboxypeptidase G2? Seminars in dialysis; 2014.
80.Jhaveri KD, Flombaum C, Shah M, Latcha S. A retrospective observational study on the use of capecitabine in patients with severe renal impairment (GFR< 30 mL/min) and end stage renal disease on hemodialysis. Journal of Oncology Pharmacy Practice. 2012;18(1):140-7.
81.Van Warmerdam L, Rodenhuis S, ten Bokkel Huinink W, Maes Rt, Beijnen J. The use of the Calvert formula to determine the optimal carboplatin dosage. Journal of cancer research and clinical oncology. 1995;121:478-86.
82.Shepherd ST, Gillen G, Morrison P, Forte C, Macpherson IR, White JD, et al. Performance of formulae based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma. European Journal of Cancer. 2014;50(5):944-52.
83.Mazloom AL. Tolerability of Carboplatin When Using Rounded Serum Creatinine Values. 2012.
84.Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
85.Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clinical journal of the American Society of Nephrology: CJASN. 2010;5(6):1003.
86.Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals of internal medicine. 2006;145(4):247-54.
87.Rhee J, Kwon JM, Han SH, Kim SH, Park CH, Jeon JH, et al. Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration equations for estimating glomerular filtration rates in cancer patients receiving cisplatin-based chemotherapy. Kidney Research and Clinical Practice. 2017;36(4):342.
88.Séronie-Vivien S, Toullec S, Malard L, Thomas F, Durrand V, Chatelut E. Contribution of the MDRD equation and of cystatin C for renal function estimates in cancer patients. Medical Oncology. 2006;23:63-73.
89.Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12.

نشریه پزشکی شخصی

فصلنامه پزشکی/ سال نهم/ شماره ۳۴/ قیمت: ۵۰۰۰۰۰ ریال/ تابستان ۱۴۰۳/ شماره شاپا ۳۸۶۰-۲۷۱۷



آینده علم پزشکی، شخصی محور است