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Aptamer-Based Approaches in Oncology

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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.

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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.

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