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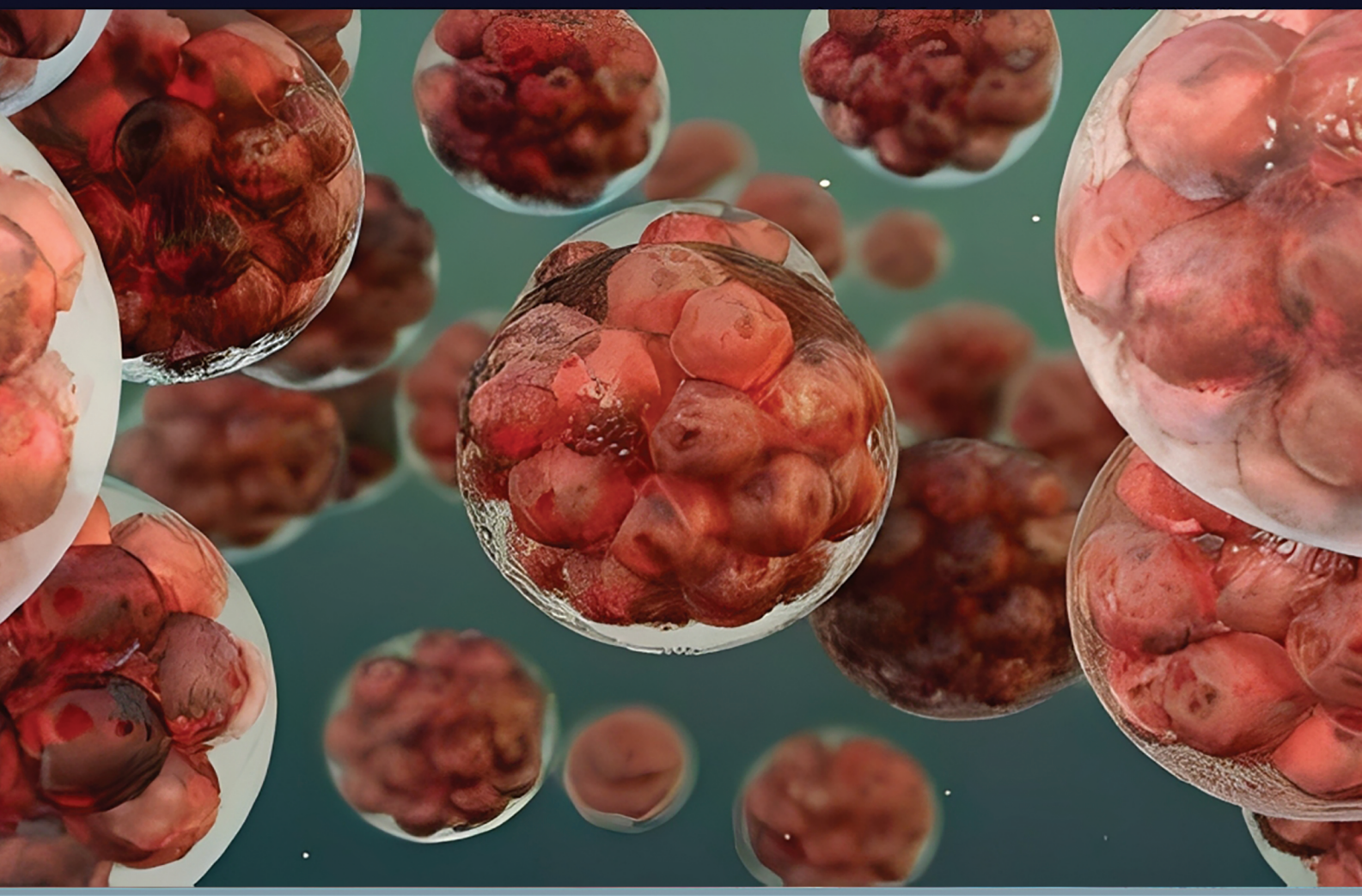

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Advancing Remyelination Therapies in Multiple Sclerosis: Beyond Inflammation Control

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ABSTRACT

Multiple sclerosis (MS) is a long-term disease that is frequently progressive and affects the central nervous system (CNS). This in turn breaks down the myelin sheath the protective covering around nerve fibers. Damage to myelin leads to a breakdown in nerve communication and can cause a number of neurological conditions. This study examines recent approaches towards increasing remyelination in the multiple sclerosis (MS) population as the protection of oligodendrocytes and promotion of remyelination are essential therapeutic goals. Materials and methods: A search was performed in national and international databases with the use of specific keywords. This search resulted in the identification of 235 articles, on "remyelination" and "multiple sclerosis". Seventy articles were included in this review from 2000 up to 2020. These findings lead to the conclusion that already established immunomodulatory therapies have some benefits for reduction of myelin breakdown, but are rather poor at promoting remyelination, most notably in progressive MS.Controversially during the last years a change has been made towards compounds targeting (symptomatic) inflammation as well as remyelination. These interventions may optimize function and may promote axonal conduction. These strategies, including stem cell therapy, growth factors, small molecules and gene therapies hold promise in future treatment of MS. Not only are they trying to stop further loss of myelin, but also attempt to repair what damage has already been done.

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INTRODUCTION

Multiple sclerosis is an inflammatory disorder that induces chronic inflammation of the central nervous system (CNS)(1). This inflammation results in demyelination and axonal damage. The degeneration of myelin, the protective covering encasing nerve fibers, is the primary pathogenic characteristic of multiple sclerosis (2). This deficit results in diminished neuronal transmission (3). This process disrupts neuronal connectivity and may lead to a progressive deterioration in neurological function. Multiple sclerosis predominantly impacts young adults aged 20 to 40, with a higher prevalence in women (4). The disease manifests in two principal forms: relapsing-remitting multiple sclerosis (RRMS) and progressive multiple sclerosis

(PPMS). Relapsing forms are defined by episodes of aggravation succeeded by partial recovery, whereas progressive forms exhibit a continuous decline in function with limited recovery (5).

Remyelination, the restoration of damaged myelin, is an essential phase in alleviating the impacts of multiple sclerosis (2). OPCs are crucial for generating new oligodendrocytes, which in turn produce myelin. However, in multiple sclerosis, chronic inflammation and other factors impede this repair process, particularly in the advanced stages of the disease (6). Accordingly, remyelination has emerged as a key objective in the research and treatment of MS. Interferons and glatiramer acetate Interferons and glatiramer acetate are pharmaceutical agents used in the treatment (2). These drugs reduce inflammation and regulate the immune system; however, they are primarily directed at the inflammatory part of the disease process and are not directly involved in myelin repair. (7).

Novel therapies that promote remyelination are designed to boost the recovery of remaining myelin and prevent further neurological decline. These include stem cell therapy, growth factors, drugs in form of small molecules and gene therapy (8).

While numerous techniques remain under evaluation, current research has demonstrated promising results in preclinical models and early-phase clinical trials. This paper summarizes current therapeutic options for remyelination in multiple sclerosis (2), highlights the limitations of existing drugs, and explores novel treatment strategies (9).

METHODS

No one method, or assessment tool should be used in isolation whilst managing pain (either acute or chronic) as it can be complex and multifaceted. For the multidimensional nature of pain, pharmacological treatments, interventional procedures, rehabilitation, psychological therapies and complementary modalities can be integrated. Multimodal approaches optimize analgesic effectiveness, functional recovery and quality of life while minimizing dependence on and side effects of opioids. And advances in neuroscience, precision medicine and digital health might be widening the avenues to treatment. Mechanism-based pharmacology, regenerative treatments, and AI-driven personalized interventions promise to shift from symptom-centric care towards the restoration of function and health over the long-term.

the future of pain management demands an integrated, evidence-based and personalized treatment that responds effectively to the multifaceted biological, psychological and social factors behind pain expression in order to “re-imagine” relief, empowerment and functional recovery based on the integration of clinical knowledge, technology and active patient involvement.”

RESULTS

Immunomodulatory Drugs and Their Impact on Remyelination

Immunomodulatory Drugs Are The Hallmark Of Modern Multiple Sclerosis Treatment. These drugs, such as interferon beta (IFN-β), glatiramer acetate, and monoclonal antibodies (mAbs) including natalizumab and ocrelizumab, largely intend to manipulate the immune response and alleviate inflammation in CNS (10). These medications help reduce the frequency of relapses and slow the progression of disease by suppressing productiaon of autoreactive T-cells and other immune cells that target mylein. But their participation in the promotion of remyelination is poor (11).

Studies suggest that immunomodulators might cause a secondary effect of enhancing remyelination by reducing inflammation. This reduction in inflammation could then allow a more permissive environment for the OPC to generate new myelin. Studies have shown that IFN-β promotes the survival of OPCs and dcevelopment into adult oligodendrocytes

(12). However, the effect of these drugs is restricted since they are more efficient during the early stage of MS (2). They lose their effectiveness with the progress of the disease. Therefore, new targeted therapy to provide remyelination to enhance immune-modulation and treat the progressive aspects of the disease is needed (13).

Experimental Therapies for Promoting Remyelination

A number of novel pharmaceuticals have shown promise in studies and early-phase clinical trials. These treatments aim at promoting recovery of damaged myelin and restoration of normal axonal conduction.

Stem Cell Therapy: OPC stem cells in particular have attracted much attention for their ability to remyelinate. The adult CNS hosts OPCs, which are able to differentiate into the mature cells responsible for myelination, oligodendrocytes (14). In the case of multiple sclerosis, an inflamed environment and other factors that limit regeneration suppress the regenerative ability of OPCs (2).

A number of stem cell treatments aimed to promote remyelination are under investigation. These include the engraftment of NSCs, mesenchymal stem cells MSCs and induced pluripotent stem cells (15).

Animal experiments clearly demonstrate that transplantation of stem cells can stimulate generation of OPC and improve remyelination. Indeed, transplantation of NPCs has been demonstrated to increase myelination and promote functional recovery in murine EAE models (16).

Stem cell transplantation in people with MS has been the subject of clinical trials, and some studies suggest it potentially enhances neurological functioning and quality of life (17). However, there are several challenges that still need to be addressed, including immunorejection of the cells, survival and integration of these transplantated cells as well as ethical problems. And furthermore, the delivery of enough viable stem cells into affected areas in CNS is a technical challenge because the regenerative potential is constrained by BBB(18).

Growth Factors and Small Molecules

Several growth factors and small molecules which might promote remyelination have been found. Insulin-like growth factor 1 (IGF-1) and fibroblast growth factor 2 (FGF-2) have been demonstrated to enhance the survival, proliferation and differentiation of OPCs to adult oligodendrocytes (Wang et al., 2012). These are of particular interest in that they could potentially augment the endogenous repair processes which occur in MS (19).

Clemastine fumarate is a small molecule that shows some promise. It is an antihistamine that has also been demonstrated to improve oligodendrocyte progenitor cell (OPC) maturation and to stimulate remyelination in preclinical models of multiple sclerosis31,32. The blood-brain barrier permeability of clemastine and the enhancement of remyelination in the absence of stem cell transplantation make it an attractive candidate for further clinical development (20).

Monoclonal antibodies, for example opicinumab that binds LINGO-1 (a negative regulator of development of OPC), have shown promise to be able to promote remyelination by stopping the inhibitory signals that block oligodendrocyte precursor cell maturation. Some early-phase clinical trials have reported promising benefits, but further investigation of their efficacy and safety in larger populations are needed (21).

Gene Therapy and Nanomedicine

Gene therapy and nanomedicine are emerging approaches in the treatment of MS. Gene therapy may deliver genetic material that promotes oligodendrocyte precursor cell development or suppress substances

interfering with remyelination (22). The gene therapy of multiple sclerosis has now entered into its early, but promising age with the possibility to enable direct delivery of therapeutic genes into the central nervous system without systemic administration (23). Nanomedicine, involving the use of nanoparticles for drug or gene delivery, offers great promise (24).

Nanoparticles can be engineered to cross the blood-brain barrier and deliver therapeutic drugs directly to the injured region (25). This could lead to a more effective and accurate delivery of remyelination-promoting medicines with reduced side effects associated with conventional drug delivery. However, more studies are needed to improve those technology to ensure their safety in clinical application (26).

DISCUSSION

Remyelination strategies have emerged as one of the most promising and important areas for multiple sclerosis research. This is particularly relevant to progressive multiple sclerosis where remyelination is either minimal or non-existent, thereby resulting in slow but relentless deficit of neurological function (27). Although existing therapies, in particular immune-modulating drugs, have been effective to combat inflammation in MS they exhibit little or no direct pro-remyelinating potential. It follows that the focus of therapy is moving towards new treatments which promote regeneration of the CNS, in particular remyelination (28).

The complex and heterogeneous nature of MS represents a major difficulty in studies on the disease. The damage to myelin and axon degeneration are the major causes of disability in MS (29). The disease's pathophysiology consists of a complex interplay among factors, namely immune-mediated inflammation, neuronal injury, and the lack of endogenous healing processes. Understanding these components and their interactions as the disease progress is crucial for developing meaningful treatments (30). In this article we will discuss the problems and possible remedies for remyelination therapy. We will concentrate on the reasons why remyelination fails, the shortcomings of existing treatments and how new strategies to address these problems now being explored are fascinating (31).

Inflammation as a Barrier to Remyelination

Inflammation within the central nervous system is a major barrier to successful remyelination in multiple sclerosis. In early stages of the disease, autoreactive T cells play a significant role in myelin destruction (32). The immune system responds and the CNS is infiltrated with immune cells, including T lymphocytes, macrophages, and microglia which destroy oligodendrocytes that produce myelin. Demyelination and axonal injury as well as neuronal distress follow (30).

However, inflammation plays a major role in the repair processes within the CNS. Inflammatory cytokines, reactive oxygen species (33) and other immune mediators contribute to an environment that interfere with the differentiation and maturation of OPCs, which are the main responsible cells for remyelination (34). Importantly, in most cases OPCs are able to migrate to demyelinated regions and mature into myelinating oligodendrocytes, which generate new layers of myelin. In MS, the inflammatory milieu not only prevents oligodendrocyte precursor cell survival and maturation at the time of lesion formation but may effectively deplete over time an already limited reserve for repair (35).

In addition, chronic inflammation can produce a milieu that hinders healing such as scar tissue or lesions containing active immune cells which fail to heal (36). This chronic inflammatory state is most prominent in the later stage of multiple sclerosis, i.e. progressive MS with ongoing inflammation and inadequate or no remyelination. The

ultimate goal is to identify drugs that will diminish inflammation whilst fostering a repair-promoting (re)myelinating milieu (37). This would involve lowering pro-inflammatory cytokines, modulation of the immune system and blocking toxic factors impeding OPC differentiation.

Limitations of Current MS Treatments

The main pharmacological treatments for MS are immunomodulatory therapy, including interferons (IFN-β) and glatiramer acetate as well as other emerging biologics such as monoclonal antibodies (natalizumab and ocrelizumab)(38). The aim of such therapies is to modulate the immune response, and consequently decrease the frequency of relapses. Thus, these drugs decrease the disease activity, reduce inflammation and prevent new lesions by partially suppressing the activation of immune cells against myelin (39).

Immunotherapy Limits: Inflammation Controlled, Repair Lacking

On the other hand, immunomodulatory agents are effective in controlling RRSMS but have only a mild (if any) effect on remyelination. "The goal of these treatments is to decrease the inflammation associated with the disease and decrease both how many relapses patients have, as well as how severe they are, not to repair the myelin once it has been damaged," she adds (40). With disease progression, CNS regenerative potential decreases and remyelination is less efficient. These therapies have little effect on the course of the disease or recovery in secondary progressive MS (SPMS) and primary progressive MS (PPMS), which is characterized by a lack or restriction of remyelination (Remyelination, 41).

And responses to immunomodulatory therapy can be highly variable between patients. Some patients with RRMS respond well to these medications, whereas others are poorly responsive (42). It suggests a need for more-individualised therapies. This variation emphasizes the need for therapies that are anti-inflammatory, promote healing and regeneration within the CNS (43).

The Promise of Remyelination-Based Therapies

In light of the restricted efficacy of current therapeutics, there is increasing enthusiasm for developing drugs that specifically enhance remyelination in MS (44). Several strategies have demonstrated impressive potential in preclinical models and early phase clinical studies. These approaches include stem cell therapies, growth factors and small molecules, as well as gene therapies. The aim of these treatments is to induce regenerative mechanisms in the CNS, to repair damaged myelin, and to improve neural function (45).

Stem Cell Therapies

Stem cell transplantation is one of the most promising approaches to promote remyelination (46). OPCs are important for the process of remyelination but their function is impaired in MS as a result of inflammation, injury and an unfavourable environment within the CNS. The transplantation of exogenous stem cells, which include NSCs, MSCs and iPSCs, is one such most promising approach. These stem cells are able to differentiate into oligodendrocytes and thus contribute to remyelination (47).

The success of stem cell- based intervention in inducing the differentiation of OPCs into mature oligodendrocyte, remyelination and improving functional recovery had been demonstrated in previous preclinical studies (48). Clinical studies on MS patients have shown positive results, and some patients even reported improvements in their neurological functions as well as the quality of life (49). However, major challenges are still to be tackled in light of these encouraging results. For example, the survival and integration of transplanted stem cells within the host CNS is difficult to achieve. 2,3 This work indicates

that DSBs in these implanted cells are formed as soon as we expect the stem cell to survive long enough to contribute meaningfully to tissue function. In addition, the risks associated with immunological rejection, tumorigenesis and other side effects must be addressed (50).

Another major problem remains, in that enough viable stem cells do not reach the sites of the central nervous system to which they are desired. The BBB is a barrier that blocks potentially. Stem cell transfer is also impaired by toxic chemicals (51). Scientists are attempting to develop techniques including targeted methods such as gene editing and nanoparticle-mediated delivery and ultrasonic strategies to address these challenges and increase the specific locati0n of stem cell (15, 52).

Growth Factors and Small Molecules

Another potential approach can be the application of growth factors and small molecules to enhance remyelination. Studies haveshownthatIGF-1,FGF-2andBDNFwhich are growth factors, enhance the survival and differentiation of OPCs (53). These enhance the CNSs endogenous abilities to regenerate by stimulating oligodendroglial precursor cell differentiation and oligodendrogenesis, new myelin synthesis (54).

Although growth factors have a relatively low molecular weight and size, which should theoretically facilitate their access to the CNS, an important concern regarding these molecules is entry into the brain through BBB (55). Nanoparticle-mediated delivery systems are being considered for a solution to overcome this drawback, enabling the targeting of these agents to demyelinated sites within the brain and spinal cord (56). Clemastine fumarate, an antihistamine, represents a small molecule with positive preclinical data and pilot human trials showing efficacy by enhancing oligodendrocyte precursor cell differentiation to remyelinating oligodendrocytes (57). Clemastine is of particular interest due to its ability to cross the blood-brain barrier and its oral availability contrasting with other drugs, which make it a more accessible therapeutic option (58).

Another approach being studied is to attack certain molecules that interfere with remyelination. LINGO-1 is a protein which prevents OPCs from difif erentiating into oligodendrocytes (59). Opicinumab is a LINGO-1 monoclonal antibody antagonist. Monoclonal antibodies targeting CSPGs, such as opicinumab, have shown encouraging results in preclinical and early clinical investigations by promoting immature oligodendrocyte precursor cell differentiation (and remyelination) (60).

Gene Therapy

Gene therapy, entailing the direct insertion of genetic material into the CNS to modify gene expression, holds significant promise for remyelination. Gene therapies can be designed to promote the proliferation of OPCs or to inhibit factors that impede remyelination (61).

The ability to deliver genes directly to the affected regions of the CNS may address several limitations of existing therapeutics, like the incapacity of growth factors to penetrate the BBB (62).

Although gene therapy for MS is in its preliminary stages, preclinical studies have demonstrated encouraging outcomes. Before gene therapy can be widely implemented in clinical practice, the challenges of safely and successfully delivering genes to the CNS, together with concerns over potential immune responses and off-target effects, must be addressed (33).

CONCLUSION

Remyelination-based therapies represent a promising novel strategy for the treatment of multiple sclerosis. While current immunomodulatory medications effectively manage inflammation, there is a necessity for more efficacious therapies to repair myelin loss

and restore function, especially in progressive disease forms. Stem cell therapies, growth factors, small molecules, and gene therapies possess significant potential; nonetheless, substantial challenges remain, including enhancing delivery methods, ensuring safety, and surmounting biological impediments such as the blood-brain barrier. Ongoing research and clinical trials are essential to enhance existing medicines and develop personalized treatments for patients with multiple sclerosis. This will provide patients with optimism for an improved quality of life and a reduction in long-term disability.

Authors's Contribution

Sevak Hatamian: data curation; editing and review. The author read and confirmed the final manuscript.

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Advancements in 3D Bioprinting for Functional Tissue Engineering in Regenerative Medicine

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ABSTRACT

3D bioprinting is a breakthrough fabrication technology in regenerative medicine It offers great promise for fabricating hierarchical and heterogeneous tissues and organs with similar architecture as those of the natural ones. This review discusses recent advances in 3D bioprinting and the progress made for fabricating functional tissues, which have regenerative therapy applications. We cover the development of bioprinting methodologies, bioink composition and optimization, and incorporation of cellular and molecular signals for improving tissue function. An overview of the literature on key applications in skin, cartilage, bone and cardiovascular tissues is provided, including both preclinical achievements and clinical barriers/goals. In addition, we also talk about the contribution of bioprinted tissues for drug screening, disease modelling and personalized medicine. Regulatory and ethical aspects associated with the clinical translation of bioprinted tissues are also highlighted in this review. We present an up-to-date analysis of the recent literature (including studies from Nature, The Lancet, and BMC) as well as a data-rich viewpoint on 3D bioprinting to date in regenerative medicine.

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INTRODUCTION

Regenerative medicine has seen remarkable progress due to the introduction of 3D bioprinting. Conventional tissue engineering strategies usually involve the use of static scaffolds and two-dimensional cell culturing systems, which do not reflect the complex composition and function compared with native tissues (1, 2). 3D bioprinting combats these challenges by providing the ability to deposit living cells and biomaterials on a layer-by-layer basis, thereby being able to produce tissue constructs with defined spatial orientation and cellular complexity (3).

Three-dimensional 3D bioprinting offers a paradigm shift in tissue engineering, enabling cells and biomaterials to be engineered together to create intricate tissue architectures. By finely patterning the materials during their deposition (4), it is feasible to generate tissues that parallel the architecture and function of native organs. This ability carries important implications for regenerative medicine, and may provide potential answers in organ transplantation, disease modeling and drug screening (5).

The progress of 3D bioprinting technologies has been accelerated by the development in several aspects. It is essential to develop bioinks, which are biocompatible teach that sustain the viability and functioning of the cells (6). These bioinks not only need to be able to support structure, but also encourage cell growth and differentiation. Furthermore, the development of printing techniques also improved the resolution and complexity of printed structures, as tissue with more complicated architecture could be created (7).

One of the most exciting possibilities for 3D bioprinting is for regenerative medicine. Bioprinted skin replacements, for example, have been produced to help victims of burns as a substitute for conventional skin grafts. Also, bioprinted bone and cartilage tissues are being investigated as therapeutic approaches for musculoskeletal diseases. These applications also illustrate the multiple uses of 3D bioprinting technology for producing functional tissues that may be used to repair or replace damaged organs (8).

Although some problems persist even in the face of these accomplishments. Functional vascularization is a big challenge to achieve in bioprinted tissues due to the limited diffusion of nutrients and oxygen in large constructs. Additionally, more studies need to focus on the long-term stability and integration of BIOP tissues in the human body (9).

In summary, 3D bioprinting is a huge step for the area of regenerative medicine. Despite remaining obstacles, translating into the development of robust studies and advanced technologies has helped to improve this field significantly. With these challenges overcome, the vision of 3D bioprinting leading a paradigm shift in treating a number of different conditions comes closer to reality (10).

Technological Evolution and Techniques

The technical development of 3D bio-printing has been characterized by iterative improvements in printing modalities, bioink compositions, and hardware systems, which together have allowed for the creation of progressively more intricate tissue constructs. Inkjet-based and extrusion-based systems have been widely used for early bioprinting techniques due to their disparate pros and cons (11). Inkjet bioprinting, based on the concept of conventional office inkjet printers, involves a controlled jetting process to eject picoliter droplets of cell-laden bioinks onto a surface. Thereby, deposition with high resolution within a couple of tens of micrometres (20–50 μm) can be achieved typically, which is particularly suitable to replicate fine tissue microarchitectures, like for capillary networks or neuronal layers (12). However, this method is restricted by the low viscosity range (\textless ~10 mPa·s) of bioinks that it can accommodate and may not allow incorporation of higher-cell-density suspensions or mechanically stiff hydrogels that more closely mimic the extracellular matrix (13).

In extrusion-based bioprinting, bioinks are deposited via continuous printing of filaments through a nozzle (2–300 μm), and it is capable of handling a wide range of liquid viscosities (306 × 10^7 mPa·s)(14). This makes it possible to, for example, print viscous hydrogels and composite bio-materials and even cell–laden polymer matrices that supply structural integrity to larger tissue constructs. Extrusion-based bioprinting allows the generation of larger tissue volumes and mechanically supporting scaffolds, but it generally has lower spatial resolution (100–200 μm), which could compromise microarchitecture precision (15). Furthermore, shear stress in extrusion may influence cell viability, and so nozzle size, extrusion pressure and bioink rheology must be optimized to preserve functional cellular phenotypes (16).

More recently, hybrid bioprinting systems have been developed, which combine several printing modalities within the same system. Examples include systems which combine extrusion and inkjet processes that enable simultaneous deposition of mechanically-stable scaffold structures and high resolution cell patterns leading to improvement in both architectural fidelity and biological performance (17). Nozzle-free or laser-assisted bioprinting (LAB) is another technique that uses laser-induced forward transfer to deposit cell-laden droplets with high resolution (10–50 μm), so as to avoid using nozzles and reduce mechanical stress. LAB is highly suitable for printing high-viscosity bioinks (ICHs, 40 – 60 mPa/s and ECMs, ~10 Beta mPa) and sensitive cell types with low resistance to shear stress, such as neurons or myoblasts, yet scalability remains a hurdle (18).

Further developments are multi-material printing abilities, microfluidics-assisted bioprinting for graded pattern generation and real-time monitoring systems to confirm sharp layer superimposition and cell positions (19). Taken together, these technological advances are allowing the production of more sophisticated tissue constructs (e.g., vascularized bone, layered skin equivalents and organoids) and bringing 3D bioprinting closer to clinical translation in regenerative medicine. Iterative improvements to the instrumentation will further converge high-resolution, high-throughput, and multi-material strategies because of its small field-of-view (FOV and slow tip displacement (20).

Bioinks: Composition and Optimization

Bioink preparation and optimization are a cornerstone in 3D bioprinting due to its dual role as a structural support and regulator of the local biology. An ideal bioink should meet several key requirements: high biocompatibility for the survival and proliferation of cells, proper mechanical properties to retain its shape during and after printing, adjustability in degradation rate at a similar pace as cell maturation, and bioactivity promoting vascularization that influences cell differentiation and tissue growth (21). Optimization of these parameters can be difficult as they are typically interdependent: e.g., increasing the polymer concentration could improve mechanical stability at the same time that it increases viscosity, which could compromise printability and reduce cell viability (22).

Owing to their biocompatibility and the resemblance of

their structure to native extracellular matrices (ECM), natural polymers have been extensively used. One such biomaterial is alginate, extracted from brown algae, that has been utilized for its mild gelation through ionic crosslinking with divalent cations like Ca^{2+} , which allows encapsulation of delicate cell types (23). Unfortunately, alginate does not contain cell-adhesive motifs and must therefore be modified with RGD peptides or combined with other ECM proteins. Gelatin is a denatured collagen with good cell spreading characteristics and bioresorbability, which can be modified to form gelatin methacrylate (GelMA) for UV-crosslinking purposes that provide spatial control during printing (24). Collogen per se, the most frequent ECM protein in mammals, presents intrinsic signaling cues for cell attachment, proliferation and lineage-committed differentiation; however, its mechanical stability is typically insufficient to be used alone and must be reinforced with synthetic polymers or crosslinkers. Hyaluronic acid and fibrin are also commonly used materials to mimic tissue-specific ECM environments, especially in the case of cartilage and vascular tissues, where they promote cell migration and angiogenesis (25).

Tunability of synthetic polymers such as PEG (polyethylene glycol), PLA (polylactic acid), PGA (polyglycolic acid) and PCL 106 (polycaprolactone)), in mechanical properties, degradation rates, and chemical functionalization is offered. For example, PEG-based hydrogels have been designed with tunable Young's modulus from 0.5 to 50 kPa to mimic soft tissue or cartilage microenvironment, and PCL provides superior mechanical support for load-bearing structures, e.g., bone tissue scaffolds. Combining synthetic and natural polymers allows to combination of the biological cues of natural matrices, with the strong mechanical features of synthetics: this offers new possibilities in bioink formulations for various tissue types (26).

Besides the structural composition, the introduction of bioactive molecules is also important for the interaction with cells and the maturation of tissues. Growth factors (for example, VEGF, BMP-2 and FGF-2) may be incorporated into bioinks or attached to polymer backbones for sustained localized signaling for stimulating angiogenesis, osteogenesis or fibroblast proliferation (27). Short peptides, like RGD, IKVAV and YIGSR that are analogues of specific ECM binding domains, are used to promote integrin-mediated adhesion and cytoskeletal assembly. In addition, extracellular vesicles, cytokines or small bioactive molecules can be supplemented to modulate the cellular metabolism, differentiation paths and immunomodulatory responses to further enhance the functionality of tissue (28).

Tuning rheological properties to enable fast extrusion and cell protection through shear-thinning behavior, and a rapid recovery of viscosity for printed shape preservation is often sought. Ionic, thermal, enzymatic and photo-crosslinking are the crosslink types applied depending on the requirements for the mechanical strength, degradation or biocompatibility (29). Technologically more advanced methods also make use of gradient bioinks where mechanical and biological factors change in space within a construct, to mimic tissue inhomogeneity as well as to improve the maturation of complex structures like osteochondral interfaces or vascularized tissue (30).

Cellular and Molecular Integration

For effective tissue engineering, cellular and molecular elements must be assembled into the organized systems found in native tissues. Enrichment with the right cell types is not enough: the microenvironment, with associated biochemical signals, mechanical influences and spatial organization; also strongly instructs to determine cell behaviour, differentiation and tissue maturation (31). There is a need to carefully select the cell components as per the tissue. For example, vasculature tissue requires the presence of endothelial cells to establish a perfusible network and the fibroblasts are needed for the synthesis and remodeling of the extracellular matrix (ECM). Osteoblasts, osteoclasts and mesenchymal stem cells in bone tissue must work together dynamically for the mineralization and architecture of bones to be correct (32).

Exact proportions of hepatocytes, Kupffer cells and hepatic stellate cells are also necessary in liver constructs to mimic metabolic and detoxification functions. The organization of cells in bioprinted constructs is also an important factor for tissue function (33). Native tissues have a hierarchical structure and heterogeneous cell types distribution, such as in the skin where keratinocytes build up the epidermal layer, melanocytes scattered among with for coloring cutaneous layers, while below is the dermis housing fibroblasts living in ECM equilibrium (34). It is critical to reproduce this organization in vitro to obtain a morphology and function which are physiologically relevant. Sophisticated 3D bioprinting techniques involving extrusion-based, inkjet, and laser-assisted methods facilitate accurate multi-cell deposition in predetermined patterns with spatial heterogeneity that closely resembles that of the in vivo tissue (35). The multi-nozzle printing and microfluidic-assisted systems allow for even greater control of the ability to gradient cell density, ECM composition, and growth factors, which are critical in directing tissue development.

At the molecular level, cells and their microenvironments are composed of extracellular matrix (ECM) components, soluble signaling factors, and mechanical

signals (36). ECM proteins like collagen, laminin, and fibronectin have been proven to offer not only structural support but also biochemical signals to direct cell adhesion, migration and differentiation. Soluble factors such as growth factors (e.g., VEGF, BMPs, FGFs) play a pivotal role in both lineage-specific differentiation induction and angiogenesis in the tissue constructs (37). Mechanical stimuli, e.g. substrate stiffness and shear stress, regulate the cytoskeletal organisation, mechanotransduction signalling pathways and gene expression, which dictate cell fate decisions. Advanced bioprinting permits the introduction of these molecular signals in regions defined by location, generating microenvironments that closely mimic native tissue niches (38).

Vascularization remains a significant challenge for the engineering of functional tissues, as diffusion is inadequate to maintain cell viability in constructs over 200–500 μm. While approaches to incorporate endothelial cells, pericytes and angiogenic factors within bioprinted constructs have proven effective at creating perfusable vascular networks (39). Endothelial cells and supporting stromal cells co-cultured in defined spatial geometry can self-assemble into lumenized capillary-like structures, which can be modified using VEGF gradients to promote vessel sprouting and maturity. Such strategies are essential for the long-term survival and function of tissues, especially thicker or metabolically active constructs such as heart muscle or liver organoids (40).

The incorporation of immune cells, or factors to modulate the immune response in bioprinted constructs, can further replicate a more physiologically appropriate microenvironment for enhanced tissue homeostasis and tunable integration following implantation (41). For instance, macrophages in 3D tissues can affect ECM turnover and angiogenesis, or T-cell interactions could be crucial for particular immunocompetent tissue models (42). Moreover, with the help of advanced 3D bioprinting platforms, it also becomes possible to tailor temporal and spatial stimuli dynamically, for example, through temporarily controlled deposition of growth factors or staged maturation of cell populations in a printed construct so that the resulting tissue more closely follows developmental processes leading to better functional performance (43).

Applications in Regenerative Medicine

The uses of 3D bioprinted tissues for regenerative medicine are wide-ranging/in the breadth of clinical applications, from wound healing, musculoskeletal repair, to organ construct and disease modeling/ disease models or physiologically relevant in vitro drug/platforms. In dermatology, the production of bioprinted skin substitutes is an area of particular interest because there is a clinical need for effective therapies against burns, chronic ulcers or other severe traumatic injuries to the skin (44). For such constructs, keratinocytes are generally added to make an epidermal layer, and fibroblasts are dispersed in a dermal like extracellular matrix, occasionally with additional melanocytes or endothelial cells to enhance pigmentation and vascularisation. Research studies have already shown that bioprinted skin substitutes can increase wound healing, angiogenesis and barrier function restoration more efficiently compared to conventional grafts, leading to a 30–40% rise in re-epithelialization rates – all from preclinical testing (45). In addition, skin equivalents with well-defined dermal epidermal junctions that are beneficial for (i) enhanced structural fidelity and iii) function have also been achieved using stratifying bioprinting approaches (46).

For the field of cartilage repair, 3D printing offers the potential to generate constructs that mimic the anisotropic and viscoelastic response of native cartilage. By employing hydrogels loaded with chondrocytes or mesenchymal stem cells (MSCs), the compressive moduli of bioprinted cartilage constructs could reach 0.2 to 2 MPa, which is similar to native articular cartilage (47). These constructs dictate cell and ECM component deposition across space, which thereby influence cellular differentiation, matrix production and ingrowth with the host tissue. Moreover, gradient-based bioprinting methods enable the generation of osteochondral tissue with a gradient from cartilage to sub-chondral bone, which contributes to the long-term function for joint repair purposes. Preclinical proof in rabbits and pigs revealed significantly-enhanced defect filling, less inflammation, as well as joint mechanics rescue and accordingly full clinical translation potential (48).

3D bioprinting has also proven advantageous in the field of bone tissue engineering, especially for patient-specific scaffolds corresponding to defect geometries from CT or MRI images. Osteoprogenitor cells are mixed with hydroxyapatite, tricalcium phosphate or polycaprolactone to generate scaffolds that stimulate osteogenesis and vascularity (49). The addition of anabolic molecules, such as BMP-2 or VEGF, locally improves bone mineralization and vascular growth, with up to forty to sixty percent more bone volume fraction found in vivo within the implanted scaffolds compared to non-bioactive controls. These techniques allow more predictable outcomes for craniofacial, orthopedic and dental reconstructions and decrease dependence on autologous bone grafts with the associated donor site morbidity (50).

Vascularization represents an important challenge for the clinical translation of bioprinted tissues because cell survival is limited within fabricated constructs larger than 200-500 μm due to diffusion (51). This

challenge is beginning to be overcome with advances in 3D bioprinting that have introduced perfusable vascular networks and microfluidic-supported designs. Simultaneous co-printing of endothelial cells and supportive stromal cells in the presence of angiogenic growth factors enables to construction of interconnected capillary-like structures, while sacrificial bioinks are used for forming hollow channels, which, after being endothelialized into vessels, become functional (52). In preclinical settings, the vascularized bioprinted tissues show increased oxygen and nutrient supply along with decreased necrosis and better integration with the host vasculature following implantation. For instance, for bioprinted heart patches, it has been demonstrated that pre-formed microvasculature enhances cardiomyocyte survival, raises contractile function, and increases engraftment rates, demonstrating the therapeutic potential of vascularized constructs for regenerative application to metabolically demanding tissue (53).

Preclinical and Clinical Insights

A wealth of preclinical studies have presented convincing data, validating the feasibility and therapeutic effects of 3D bioprinted tissue in various tissues. Nothing in dermatology Their Review discusses the wide utilization of bioprinted skin constructs Pioneers biofrinted skins concepts have been thoroughly examined on murine, porcine, and rabbit models (54). These reports indicate that tissue equivalents containing keratinocytes and fibroblasts, often in combination with endothelial cells, improve wound contraction but also enhance functional tissue integration. Histological analysis demonstrates organized epidermal layers and development of dermal papillae and deposition of native-like extracellular matrix, with increased vascularity in constructs containing pre-vascularized networks (55). Over quantitative scales, wound closure rates in treated animal models frequently increase by 30–50% over conventional grafts and superior tensile strength and barrier function suggest better tissue maturation. These findings highlight the translational potential of bioprinted dermal substitutes for burns, chronic ulcers, and other difficult wounds (56).

Bioprinted bone constructs have also performed successfully in preclinical models. Using osteogenic cells seeded onto composites of hydroxyapatite, tricalcium phosphate, or biodegradable polymer scaffold, such constructs have demonstrated substantial ostintegration and new bone formation in small- and large-animal models (57). Using micro-computed tomography (micro-CT) studies often describe a 40–60% rise of bone volume fraction within implanted scaffolds over 8–12 weeks, with evidence of vascular infiltration and mineralization morphologically similar to native bone architecture (58). For craniofacial and orthopedic defect applications, anatomically relevant geometries from imaging data increase scaffold fit and mechanical stability to promote functional repair and limit further surgical procedures. Similarly, preclinical studies have demonstrated that the addition of angiogenic factors including VEGF facilitates neovascularization, an important aspect of long-term tissue survival and remodeling (59).

Notwithstanding this optimism, the translation of bioprinted tissue constructs from preclinical models toward human clinics faces multiple significant challenges. The first is the technical challenge of scaling up production simultaneously with maintaining cell viability, uniformity, and structural fidelity (60). The volumes of constructs intended for human implantation are frequently many orders of magnitude higher than required for animal studies, and require tuning bioprinting speed, nozzle geometry, and bioink viscoelastic properties to ensure that the cells maintain viability during deposition (61). Second, it is important to maintain the long-term function of implanted tissues. Although short-term results including initial engraftment, vascularization, structural integrity can be obtained in preclinical models, longitudinal studies will be required for demonstrating maintenance of tissue function, integration with host tissues and lack of detrimental immune or fibrotic encapsulation. For instance, in the field of bone tissue engineering, preservation of load-bearing capacity and prevention of resorption over long time periods is still a priority (62).

Regulatory requirements further complicate clinical translation. Regulatory agencies, including the FDA and EMA, mandate rigorous preclinical testing, including biocompatibility, toxicity, tumorigenicity, and immunogenicity assessments, before permitting clinical trials (63). Inflammation is a key driver of cancer initiation, metastasis and resistance to therapy. The ability to regulate inflammation by itself, and in synergy with conventional and newer anticancer agents has significant potential to increase the sensitivity of treatment and eventually improve patient outcomes. Having developed an improved understanding of the complex interplay between inflammation and the tumour microenvironment, there is now a clear imperative to develop personalised and disease-context specific anti-inflammatory therapies. In the years to come, we need to focus on finding new ways for patient stratification, novel and safe anti-inflammatory drugs and their integration in clinical practice. PAVE'ing the way and advancing these efforts into well-designed clinical trials will be important for translating new preclinical data to rational, effective therapies that can benefit more patients with cancer (64).

Early-phase clinical trials have begun exploring bioprinted tissue applications. For example, pilot

studies of bioprinted skin grafts in patients with burn injuries have reported favorable engraftment rates and minimal adverse events, although sample sizes remain limited and follow-up durations are short. Similarly, bioprinted cartilage and bone scaffolds have been implanted in small cohorts for reconstructive surgeries, demonstrating feasibility but highlighting challenges in achieving full functional restoration and integration (65).

Regulatory and Ethical Considerations

For the translation of 3D bioprinted organs into clinical use, it will be necessary to have a full and robust regulatory process that assures safety, reproducibility and efficacy for the patient. Regulatory bodies, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (2), and other national health authorities mandate stringent preclinical and clinical evaluation of bioprinted constructs prior to their approval for human use (66). From pre-clinical data it should be clear, that the carrier is biocompatible (bio-compatibility investigation), non-toxic and nonimmunogenetic, long-standing implanted in a living system without any damage or loss of its structural stability, functional integration and/or induction of an undesired tissue response like fibrosis or tumorigenicity. For constructs integrated with multiple cell types or bioactive factors, additional characterization of cellular responses, gene signatures and biomolecular interactions is needed to guarantee the predictability of biological outcomes (67). Standardization of bioink formulation, printing conditions and post-processing procedures are necessary to guarantee reproducibility from batch to batch which is essential for regulatory approval (68).

Regulatory and ethical control is also required in the area of post-market monitoring following approval for clinical use of bioprinted tissues. Continuous surveillance for long-term results, complications and biological integration is required to maintain safety and effectiveness (69). Data obtained from these surveillance programs can be used to facilitate an iterative cycle of refinement in bioink compositions, printing modalities and clinical practice that will improve regulatory compliance and patient benefit (70).

Future Perspectives

The transformative nature of the 3D bioprinting process in regenerative medicine will revolutionize tissue engineering, due to rapid strides made in biomaterials, 3D printing techniques and cell biology. The ultimate goal is to develop 3D, in vitro vascularized and innervated tissues suitable for organ replacement or repair (71). This is currently an active area of research, as investigators are exploring a number of advanced “smart” bioinks such as stimuli-responsive hydrogels and composite formulations that include natural ECM components and synthetic polymers those can respond dynamically to host physiology and regulate stiffness and degradation, provide biochemical cues for promoting integration and long-term activity. These bioinks have been developed to mimic the tissue-specific mechanical heterogeneity, consistent with that of osteochondral or myocardial interfaces (72).

Collectively, these approaches will drive the development of personalized regenerative strategies encapsulating patient-derived cells, OOC platforms and rich disease models to impact applications in tissue replacement, drug discovery and disease modeling by closing the gap between the bench and bedside (73).

CONCLUSION

3D bioprinting is a transformative technology in regenerative medicine that enables the fabrication of functional patterned tissue with well-defined microarchitecture and biomimetic microenvironment. Preclinical models have shown the greatest potential for skin, cartilage and bone repair but improvements in vascularization, bioink development and multi-cellular integration are slowly overcoming some of it’s limitations. The ultimate clinical promise of 3D bioprinting will be actualized by continued interdisciplinary synergy between materials science, cellular biology, engineering and clinical medicine and rigorous regulatory mandate for ethical considerations. With these converging efforts, 3D bioprinting is emerging as a potential pillar of personalized regenerative medicine solutions to support tissue transplantation and organ repairs while also enabling drug testing against patient-specific disease models.

Authors’s Contribution

Farnaz Roshan Mehr and Fatemeh Gabeleh data curation; editing and review. The authors read and confirmed the final manuscript.

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Consent for publication

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Chitosan-Cefixime as Personalized Antibacterial Agent Against E. coli O157:H7

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ABSTRACT

Antibiotics are widely accessible. Nevertheless, food-borne bacteria exhibit a vast array of resistance. Utilizing natural ingredients like chitosan and chitosan-cefixime nanoparticles, which have potent antibacterial qualities, in conjunction with innovative technologies like chitosan loaded with antibiotics, the present research seeks to combat germs that are resistant to many drugs. Five strains of Escherichia coli O157:H7 were utilized to determine antibiotic resistance. The antibacterial properties of free cefixime and chitosan-cefixime nanoparticles were evaluated against strains of harmful bacteria. The findings demonstrated that E. coli O157:H7 comparatively had significant resistance to many antibiotics.

On the other hand, c chitosan-cefixime nanoparticles showed strong antibacterial activity against E. coli O157:H7, but free cefixime did not demonstrate any inhibitory zone. When compared to strains 1, 2, 3, 4, and 5 of E. coli O157:H7, the inhibition zones of chitosan-cefixime nanoparticles were 23.3 mm, 19.8 mm, 16.9 mm, 18.2 mm, and 22.4 mm, respectively. According to the results, chitosan-cefixime nanoparticles have better antibacterial action against dangerous pathogens than free cefixime. Therefore, using chitosan-cefixime nanoparticles for food preservation could be suggested.

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INTRODUCTION

The food industry strives to generate safe and high-quality food items because food safety is an important issue for many nations these days (1). Bacillus, Campylobacter, Clostridium, Escherichia, Shigella, Staphylococcus, and Yersinia are the species of bacteria that cause potential health dangers (2, 3). Staphylococcus and Listeria monocytogenes cause fatal diseases like meningoencephalitis and listeriosis, as well as serious illnesses like bacteremia and listeriosis (4). E. Coli is one of the 12 bacterial genera that the World Health Organization has identified as the most dangerous to human health. Interestingly, E. Coli's resistance to antibiotics has been steadily increasing (5).

Bacteria are becoming increasingly resistant to drugs. Using antibiotics excessively or incorrectly will worsen this resistance. The usage of some natural compounds that are generally accepted as safe (GRAS) has increased due to consumers' inclination to avoid meals that contain chemicals that may negatively impact their health (6).

Antibiotics have been utilized for many years in the medical and cosmetic industries, as well as antimicrobial agents, fungicides, and antiparasitic compounds (7). Cefixime is prescribed for the treatment of bacterial infections of the ears, throat, tonsils, and urinary system, as well as bronchitis (infection of the respiratory tubes going to the lungs) and gonorrhea (a sexually transmitted illness). Cefixime belongs to

a group of drugs known as cephalosporin antibiotics (8). When Gram-negative bacteria become resistant to aminopenicillins, cefaclor, and sulfonamides, cefixime, a third-generation cephalosporin, may be utilized as a second line of therapy (8, 9). More than 90% of E. Coli strains were shown to be sensitive to cefixime (9). In the last decade, resistance to this antibiotic has been reported in E. coli strains. One of the solutions to deal with antibiotic resistance is the use of polymer nanoparticles such as chitosan (10).

Because of its great biological properties and natural source, chitosan is a suitable biomaterial for the preservation of food (11). A naturally occurring bioactive substance, nano-chitosan inhibits harmful bacteria, including Listeria monocytogenes and Staphylococcus aureus (12). In addition to being used as carriers of antibiotics, edible coatings and films derived from chitosan offer high promise for use in food product preservation. Combining antibiotics with chitosan films improves their antimicrobial efficiency and their ability to combat food-borne bacteria and postharvest fungus in food items when compared to pure films and coatings (13).

This in vitro investigation's purpose was to assess the antibacterial efficacy of a cefixime solution containing chitosan and cefixime against E. coli O157:H7, which is resistant to many drugs.

MATERIALS AND METHODS

Pathogenic bacterial strains

The ZistYar Sanaat Microbiological Resource Center (ZYS CO., Iran) provided us with four pathogenic strains of E. coli O157:H7. For subsequent tests, the test bacteria were maintained at 4 °C after being cultivated on Mueller Hinton agar (MHA) and subsequently in tryptic soy broth (TSB) at 37 °C for 24 hours. A 100 ml flask filled with 50 ml of tryptic soy broth was contaminated with a loopful of each evaluated pathogenic bacterium (10^6 CFU/ml), as measured by the plate count experiment. The flask was then incubated for 24 hours at 37 °C and 150 rpm in a shaker incubator.

Antibiotics

Table 1 lists five popular antibiotics utilized in medical treatment that belong to various categories (Oxoid, UK). Sterilized Petri plates with MHA were streaked with one milliliter of each bacterial inoculum (10^6 CFU/ml). After placing the 20 antibiotic disks (Table 1) in the middle of the infected plates, they were incubated for 24 hours at 37 °C. The Clinical Laboratory Standard Committee (14) classified the examined bacteria's response findings to various antibiotics as sensitive, intermediate, and resistant.

Preparation of chitosan-cefixime nanoparticle

One milliliter of pure water, one milliliter of hydrogen chloride (pH=4.5), and one gram of chitosan powder (Sigma-Aldrich, USA) were combined and stirred for an hour at 800 rpm utilizing a magnetic stirrer. After that, it was centrifuged for five minutes at 1000 rpm. One milliliter of ethanol was used to dissolve 50 mg of myristic acid and 100 mg of N-hydroxysuccinimide (NHS). The resultant solution was then applied drop-wise to chitosan for 24 hours. After that, chitosan nanogels (pH=8.5) were precipitated by raising the pH of the process with diluted sodium hydroxide (0.1 M). After dissolving the chitosan nanogel with diluted hydrochloric acid, the liquid was sonicated for half an hour utilizing an ultrasonic homogenizer. Nine milliliters of PBS were mixed with one gram of cefixime powder. After adding 10 milliliters of

Table 1. E. Coli O157:H7›s susceptibility to several antibiotics.

Antibiotics	E. Coli O157:H7				
	Strain 1	Strain 2	Strain 3	Strain 4	Strain 5
Ampicillin	15.5mm/ I	17.8mm/S	17.3mm/S	9.8mm/R	6.2mm/R
Cephalexin	11.4mm/R	13.1 mm/R	12.8mm/R	15.3mm/I	11.2mm/R
Amikacin	9.8mm/R	15.7mm/I	13.9mm/I	7.9mm/R	9.2mm/R
Rifampicin	16.4 mm/I	16.2mm/I	19.3mm/S	18.9mm/W	12.1mm/R
cefixime	9.8mm/R	10.3mm/R	6.4mm/R	8.8mm/R	11.2mm/R

R: Resistant; I: Intermediate; S: Sensitive;

CLSI 2017: Clinical Laboratory Standards Institute 2017

cefixime solution to the chitosan solution, sonication was performed. Cefixime was encapsulated in chitosan by continuing the sonication for fifteen minutes.

Antibacterial activity of chitosan-cefixime nanoparticle using agar well diffusion assay

Sterile MHA was covered with one milliliter of the E. coli O157:H7 inoculum. 100 µl of chitosan-cefixime nanoparticle was added to each well after the 9-mm diameter well was cut out of the agar utilizing a sterilized cork borer. After one hour at room temperature, the plates underwent incubation for twenty-four hours at 37 °C. The positive control was a cefixime disk (30 µg) purchased commercially. Millimeters were used to measure the inhibitory zone.

STATISTICAL ANALYSIS

SPSS software version 16 was used to compute the statistical evaluation for this research, and one-way analysis of variance (ANOVA) was performed on the data. Additionally, Tukey's HSD post-statistical procedure was used to quantify the difference in target gene expression between the control and treatment samples.

RESULTS

Sensitivity of pathogenic bacterial strains to different antibiotics

As Table 1 shows, E. coli O157:H7 strain 3 exhibited more resistance than strains 1, 2, 4, and 5. The studied antibiotic cefixime caused resistance in E. Coli O157:H7 strains 1, 2, 3, 4, and 5 of 9.8mm, 10.3mm, 6.4mm, 8.8mm, and 11.2mm, respectively. Based on the findings, the five E. Coli O157:H7 strains may be categorized as multi-drug-resistant bacteria.

Morphology of the chitosan-cefixime nanoparticle

Chitosan-cefixime nanoparticles had spherical shapes with an average size of 77.31±4.2 nm. Utilizing dynamic light scattering (DLS), the average diameters of the chitosan-cefixime nanoparticles were 162.7 ± 3.13 nm (Table 2). In this investigation, the DLS-measured nanoparticle sizes were larger than the SEM-measured ones.

Antibacterial activity of chitosan-cefixime nanoparticle

Cefixime and chitosan-cefixime nanoparticles significantly reduced the development of the investigated bacterial strains, as seen in Table 3. Nevertheless, distinct inhibitory zones were noted depending on the kind of pathogenic bacteria and the solution employed at a 2% concentration. Cefixime did not exhibit antibacterial activity against the various strains of E. coli O157:H7; the inhibition zones for strains 1, 2, 3, 4, and 5 were 11.5 mm, 9.3 mm, 6.9 mm, 8.8 mm, and 10.2 mm, respectively. The inhibition zones of chitosan-cefixime nanoparticles against strains 1, 2, 3, 4, and 5 of E. coli O157:H7 were 23.3 mm, 19.8 mm, 16.9 mm, 18.2 mm, and 22.4 mm,

Table2. Chitosan-cefixime nanoparticle synthesis and characterization. Mean ± SD, n = 3, is used to represent the data.

Nanomaterials	Polydispersity index (PDI)	Surface charge (mv)	Ty-CsNG size (nm) (SEM)	Hydrodynamic diameter (nm)
Chitosan-cefixime	0.178± 0.012	3.44 ± 1.21	77.31±4.2	162.7 ± 3.13

Table 3. E. Coli O157:H7›s susceptibility to chitosan-cefixime nanoparticle.

Antibiotics	E. Coli O157:H7				
	Strain 1	Strain 2	Strain 3	Strain 4	Strain 5
chitosan-cefixime nanoparticle	23.3 mm/S	19.8 mm/S	16.9 mm/S	18.2 mm/S	22.4 mm/S
cefixime	11.5 mm/R	9.3 mm/R	6.9 mm/R	8.8 mm/R	10.2 mm/R

R: Resistant; I: Intermediate; S: Sensitive;

CLSI 2017: Clinical Laboratory Standards Institute 2017

respectively.

DISCUSSION

One of the most important problems facing public health worldwide today is bacterial multidrug resistance. According to prior research, the strains of E. coli O157:H7 may be categorized as multi-drug-resistant bacteria (15). This might be explained by the lipopolysaccharides found in E. coli O157:H7's cell wall, which serve as a potent barrier against antibiotics and make bacteria resistant to a number of them. Furthermore, by hydrolyzing the b-lactam ring in the antibiotics, members of the Enterobacteriaceae family may create b-lactamases, which can make the bacteria resistant to b-lactam antibiotics (15, 16).

Furthermore, every strain of E. coli O157:H7 exhibited multidrug resistance. These findings are consistent with those of prior research (16). Innate and acquired resistance are the two forms of resistance that E. coli O157:H7 strains exhibit, which may be the cause of their multidrug resistance. A wide range of antibiotics, including the majority of cephalosporins and other b-lactams, are naturally resistant to E. coli O157:H7 (17).

Since cefixime was unable to stop the development of the investigated bacterial strains, new and improved antibacterials are required to overcome this problem (18). On the other hand, the inhibitory zone of the chitosan-cefixime nanoparticle was larger. These findings concur with those previously published (19). The bioactive volatile components of chitosan-cefixime nanoparticles may be responsible for their antibacterial action (20). Furthermore, compared to E. coli O157:H7 Strain 3, E. coli O157:H7 Strain 1 showed greater sensitivity to chitosan-cefixime nanoparticles. Numerous factors, such as the greater resistance of certain strains of Gram-negative bacteria, may account for this.

The chitosan-cefixime nanoparticle has shown encouraging antibacterial efficacy against the pathogenic bacterium E. coli O157:H7. Compared to free cefixime, the chitosan-cefixime nanoparticle displayed a larger inhibitory zone against E. coli O157:H7. These findings are consistent with earlier reports (21). Nano-chitosan demonstrated a larger inhibition zone than chitosan at the same dosage, despite the fact that 2% chitosan demonstrated antibacterial activity against the bacterial strains that were investigated. The characteristics of nano-chitosan might explain this.

CONCLUSION

One of the most important problems facing public health worldwide today is bacterial multidrug resistance. Therefore, to overcome this obstacle, new and improved antibacterials are required. The findings obtained suggest that the antibacterial activity of chitosan-cefixime nanoparticles is superior to that of free cefixime against harmful microorganisms. Consequently, it may be advised to employ chitosan-cefixime nanoparticles for food preservation.

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Availability of data and materials

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

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Not applicable.

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Metabolic Syndrome and Inflammatory Diseases: An Elaborate Review of Mechanisms and Management

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ABSTRACT

Rheumatic inflammatory diseases, besides affecting joints and other bodily systems, are linked to heightened mortality and morbidity. Cardiovascular reasons are among the most prevalent mortality factors in individuals with these disorders, attributable to the disease's etiology and pathophysiology, chronic inflammation, and the pharmacological treatments employed. Although rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, and gout exhibit distinct pathophysiology and symptoms, persistent inflammation remains their shared pathophysiological characteristic. Metabolic syndrome has recently been linked to several of these disorders. The investigation of metabolic syndrome in inflammatory rheumatic diseases is significant for multiple reasons, including its correlation with cardiovascular disease onset, the emergence of a pre-inflammatory condition, treatment selection, and associated monitoring. This review article initially explores the significance of metabolic syndrome in rheumatic diseases, followed by a detailed analysis of each condition individually. This study concludes, through a review of previous studies, that abdominal obesity in rheumatoid arthritis and lupus patients, abdominal obesity and hypertension in psoriatic arthritis patients, and hypertriglyceridemia and hypertension in gout are significant elements of metabolic syndrome warranting increased focus.

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INTRODUCTION

Rheumatic inflammatory diseases, in addition to affecting joints and other internal organs, are associated with mortality and morbidity (1, 2). One of the most widespread causes of death in people with these disorders is cardiovascular, which occurs due to the etiology and pathophysiology of the disease and chronic inflammation, as well as the pharmacological therapy administered (3). Despite the different pathophysiology and symptoms of rheumatoid arthritis systemic lupus erythematosus, psoriatic arthritis and gout, persistent inflammation is their common pathological feature (4).

Metabolic syndrome has been just recently identified across several of these disorders. The study of metabolic syndrome in inflammatory rheumatic conditions has several important issues, such as an association with cardiovascular diseases development and pre-inflammatory disease, a choice of approach to treatment, and monitoring. This review paper first examines the meaningfulness of metabolic syndrome (5).

Cardiovascular diseases and stroke are some of the top causes of death worldwide, and the occurrence of this disease is on the increase (6). Known risk determinants in cardiovascular disease include age, sex, high blood pressure, diabetes, smoking and high levels of cholesterol; however, chronic inflammation

has of late been identified as another risk factor (7). Inflammatory rheumatic diseases correlate with an excess mortality risk as a result of cardiovascular disease and, possibly as a consequence of chronic inflammation, treatment, or a change in physical performance due to pain or the inability to move.

The reasons behind the increased prevalence of atherosclerosis risk factors and metabolic syndrome among rheumatic diseases individuals are poorly understood (8). Renal involvement, such as renal failure or drug-induced renal effects, and long-term glucocorticoid use are covered in the generality of rheumatic illnesses, and finally each condition is looked at in detail (9). This paper finds, by reviewing the literature that exists on the topic, that abdominal obesity in rheumatoid arthritis and lupus patients and in the case of psoriatic arthritis patients, abdominal obesity and hypertension are important aspects of the metabolic syndrome that require more attention. Evaluating hypertriglyceridemia and hypertension in the case of gout is also an important component of metabolic syndrome requiring more attention. Such drugs as calcineurin inhibitors and nonsteroidal anti-inflammatory agents may also lead to the development of hypertension, poor glucose tolerance, and obesity (10).

Metabolic syndrome (Met S) is a condition with proinflammatory features where a group of cardiovascular risk factors, such as hyperlipidemia, obesity, elevated fasting glucose, and hypertension occur, and its prevalence is increasing worldwide. This situation strongly predicts type 2 diabetes, stroke and cardiovascular disease (11).

Metabolic syndrome is capable of causing insulin resistance through the secretion of inflammatory cytokines such as interleukin-6 and tumor necrosis factor (TNF-alpha)(12, 13). Patients with metabolic syndrome have increased L-selectin, thrombospondin, IL-1b, IL-1 RA, CRP, leptin, and P-selectin (14). Visceral adiposity has been observed to induce IL-6, TNF-alpha and adiponectin production. Elevated increases of CRP in rheumatic inflammatory disorders associate to increased risk to vascular diseases (15). It has been shown that metabolic syndrome is associated with modest chronic inflammation (16). Metabolic syndrome prevalence has been projected to be 15.7 in men and 2.14 in women across the European continent, 34 percent across the American region, and 10-20 percent across Asia (17). Several definitions of metabolic syndrome suggested, and the two most common are those of Adult Treatment Panel III (ATP) and those of International Diabetes Federation (IDF) (18).

According to the National Cholesterol Education Program NCEP ATP III definition, a patient is considered to have metabolic syndrome when he or she possesses three or more of the following conditions: 1- waist circumference greater than 102 cm in men and 88 cm in the case of women, 2- triglyceride levels more than 150 mg/dl, 3- HDL-cholesterol levels below 40 mg/dl in men and 50 mg/dl in women (19). High blood pressure of more than 130/85 mm Hg or taking an antihypertensive drug. Fasting glucose level is more than 100 mg/dl or treatment of diabetes (20). Understanding the metabolic syndrome and its breakdown in rheumatic diseases can help prioritize patient assessments to guide rheumatologists in not only early diagnosis and treatment of rheumatic syndromes, but also secondary prevention of the cardiovascular complications that accompany such diseases by providing suitable diagnostic interventions and prescriptions and appropriate guidelines (21, 22). This paper reviews the prevalence of metabolic syndrome and its individual aspects in the four unique conditions including rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis and gout.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease, which is characterized by increased cardiovascular mortality (23). CVD constitutes more than 50 percent of deaths in rheumatoid arthritis patients. Mortality is also 1.5 and 1.6 times higher in individuals with rheumatoid arthritis as compared to that of the general population (23). Whereas the etiology of death is similar to that of the general population, cardiovascular disease occurs at an earlier age in patients with rheumatoid arthritis (24). The probability of myocardial ischemia and lethal myocardium inflection is 1.63 in rheumatoid arthritis patients in comparison to healthy individuals. Cardiovascular diseases result in the death of 40-50 percent of patients with rheumatoid arthritis (25). Several factors, including long-standing inflammation, disease-modifying drugs, and lack of physical activity of rheumatoid arthritis patients, are risk factors to cardiovascular risk. It is estimated that prevalence ofmetabolic syndrome among patients with rheumatoid arthritis is 30.65 percent, with a range of 14.32 to 37.83 percent (26).

Current research on metabolic syndrome in rheumatoid arthritis (RA) have enlightened researchers on the intricate relationships shared between the two diseases (27). In one study, there was also no significant relationship between metabolic syndrome and an elevated probability of rheumatoid arthritis (28). It also found no significant relation between activity level of RA and developing metabolic syndrome. This implies that despite the inflammatory properties of the system, RA does not increase the likelihood of metabolic syndrome, contravening some of the previous assumptions (29). However, in comparison, another

study presented interesting results in male RA patients that showed a lower incidence of hyperglycemia and dyslipidemia in comparison with a control patient group (30). This finding suggests the possible gender-specific differences in the presentation of RA and related metabolic disruptions, which should be further investigated in terms of biological and hormonal processes leading to these facts (31). Another research was conducted on women with RA concerned with their vulnerability to the metabolic syndrome. The results indicated that more than one-half of the interviewees had metabolic syndrome (32). Nevertheless, the research could not provide the definite connection that existed between the disease activity and development of metabolic syndrome. This demonstrates the possible role of other factors, e.g., age, lifestyle, genetics, or the prolonged use of medication, in the pathogenesis of metabolic syndrome in this age group. In spite of the inconsistent results, there were still some common trends (33). It was also noted that patients with active or chronic rheumatoid arthritis have a tendency of having high blood glucose levels. The presence of metabolic syndrome, also, seemed to be correlated with the activity of the disease and functional impairment. These findings have the significance of the need to monitor metabolic health of RA patients, and by addressing metabolic complications, improvements can be made in the overall outcomes (34).

Collectively, they highlight the importance of individualised treatment on metabolic comorbidities of RA. Future research is needed to determine the cause of these associations and whether there are such interventions that can exert effects on both inflammation and metabolic health (35).

A related autoimmune disease, systemic lupus erythematosus (SLE) (1), is also linked to cardiovascular morbidity (36). SLE is characterized by widespread organ involvement and a large burden of metabolic syndrome, a pro-inflammatory condition associated with exacerbation of morbidity and mortality risks (37). Cardiovascular disease is also a major cause of mortality among SLE patients with women having a 5-6fold increased risk of cardiovascular morbidity compared with the general population (38). In women within the age groups of 35-44, the risk can get up to 50 times more. Despite improved survival rates during the earlier stages of the illness, cardiovascular disease is still the cardinal kill of SLE patients (39).

Many young SLE patients have cardiovascular risk features like dyslipidemia, hypertension, and an increased level of steroid use, which increases the risk of atherosclerosis (40). There is a strong correlation between the inflammatory process that takes place in the body and predisposition to cardiovascular disease as inflammation is also a hallmark of atherosclerotic plaques (41). The oxidation of low-density lipoprotein (OxLDL) plays a key role in the development of atherosclerosis contributing to the immunological activation and inflammation of plaques (42). This has the potential to further damage endothelial integrity and repair mechanisms. The contribution of autoantibodies, activity of the disease, clinical manifestations of a patient, the use of drugs, and treatment of the disease related to the hypertension and dyslipidemia facilitate the cardiovascular involvement in SLE patients (43).

Glucocorticoid role in the pathogenesis of metabolic syndrome in systemic lupus erythematosus is complex (44). At low doses glucocorticoids have potential of improving vascular functions due to their anti-inflammatory effects (45). At higher doses, particularly with pulse corticosteroid treatment, however, they can present with metabolic issues, such as the development of metabolic syndrome. Recent research shows that hydroxychloroquine and other antimalarial medication may decrease risk of atherosclerosis development code in patients with systemic lupus erythematosus through lowering level of inflammation (46). What is more is that, hydroxychloroquine has also shown to be effective in the management of diabetes and dyslipidemia, further pointing at the potential use of this drug to prevent cardiovascular events (47).

A research by Mobini et al. (2023) studied the relationship between the rheumatoid arthritis (RA) disease activity and the metabolic syndrome, which indicated that the levels of blood glucose and active RA and chronic RA showed similar results but there was no correlation between the duration of illness and metabolic syndrome (27). There is some correlation between the administration of high-dose corticosteroids in patients with systemic lupus erythematosus and the dramatic increase in the propensity toward metabolic syndrome and cardiovascular disease (48). The elevated risk is likely to rely on the influence of corticosteroids on glucose metabolism, lipid profiles, and blood pressure which are critical aspects of metabolic syndrome (49). Enhanced use of corticosteroids could increase the severity of these effects, therefore, requiring close administration and monitoring of SLE patients undergoing corticosteroid administration (50).

Otherwise, evidence suggests that a combination of glucocorticoids and hydroxychloroquine could have beneficial effects against cardiovascular disease, in patients with systemic lupus erythematosus (1, 51). This combination therapy appears to reduce whole-body inflammation which plays a major role in injury to the vasculature and cardiovascular risk in SLE. Further, hydroxychloroquine can be used to supplement vascularization, improving endothelial performance and reducing the likelihood of thrombosis, thereby supplementing the existing therapeutic enhancements hydroxychloroquine introduces (51).

These results emphasize the importance of

individualizing treatment strategies that can balance the treatment of SLE symptoms with diminishing future risks, such as metabolic syndrome and cardiovascular disease (52). The possibility to combine their use creates a huge potential in terms of improving patient outcomes and decreasing unwanted effects with glucocorticoids and hydroxychloroquine. Further research is needed to optimize dosing regimes and explore the basic mechanisms of these drugs with the aim of maximizing efficacy (53).

These developments also show the ongoing study relating to the complex relationship between autoimmune conditions, e.g., rheumatoid arthritis, and systemic lupus erythematosus, cardiovascular risk factors, metabolic syndrome and the implications of the remedial interventions (54).

Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory disease affecting the skin and joints with an incidence rate of 0.1 to 1.23 per one hundred thousand members of the investigated population, depending on the group of people in question (55). There are a few seminal works that have exhibited an initial enrollment that psoriasis and metabolic syndrome (MetS) are associated; yet, it is revealed that there are significant inconsistencies with relationship between psoriasis and psoriatic arthritis with MetS (56). It has been observed that the prevalence MetS is significantly higher in patients with PsA in comparison to patients with only psoriasis. We note that the risk of obesity and hypertension is significantly increased in Psoriatic Arthritis (PsA) patients, whereas the frequency of Metabolic Syndrome (MetS) estimates to 23.5-58.1% of individuals in this cohort (57).

Moreover, PsA patients often exhibit substantially higher intima-media thickness (IMT) in the carotid artery than psoriasis patients and this is an indicator of atherosclerosis, suggesting an increased risk of cardiovascular disease in PsA subjects (58). A remarkable finding is the increased risk of cardiovascular disease (CVD) which is a leading cause of death in subjects with PsA and the association between metabolic syndrome (MetS) and increased CVD risk (59). Compared to psoriasis, carotid IMT is higher in PsA patients, and MetS management can both help control the disease activity and prevent cardiovascular sequelae (60).

A growing body of research has intrinsically recognized the importance of inflammation in the development of insulin resistance, endothelial dysfunction, and atherosclerosis in PsA, all of which increase risk of myocardial infarction and stroke (61). Hydroxychloroquine and glucocorticoids are less commonly used in patients with psoriatic arthritis (PsA) compared with rheumatoid arthritis (RA) and systemic lupus erythematosus (1, 62). The prevalence of hyperuricemia associated with PsA is markedly high, and it may have contributed to the differences in the risk of MetS and cardiovascular event related to PsA, RA and SLE. Furthermore, it has been identified that obesity is a great contributor to the occurrence of Metabolic Syndrome to Psoriatic Arthritis patients. MetS greatly predominates among patients with PsA compared to the community with more than one out of every three patients affected by MetS (10).

A number of clinical studies have enhanced our understanding of the correlation between PsA and MetS (63). Evidence indicates that patients with PsA have a significantly high prevalence of MetS than the general population with MetS mainly being characterized by obesity, hypertension and dyslipidemia thus increasing the risk of developing cardiovascular diseases (64). Additionally, studies show that PsA patients with MetS face a higher risk of getting type 2 diabetes and atherosclerosis, which further dictates the need to mitigate MetS among PsA patients to minimize these risks (65).

Obesity has been identified as one of the major contributory factors that lead to the manifestation of MetS in PsA patients as it worsens both the disease activity and metabolic disorder (66). Studies related to the pro-inflammatory cytokines (e.g., TNF-alpha, IL-6, IL- 17) implicated with PsA have shown that they are involved in insulin resistance and metabolic dysfunction, and that they can be targeted to diminish the impact of MetS in PsA patients (67). Anti-TNF medications have demonstrated an improvement in disease activity and metabolic disorder, such as significant loss of visceral fat and lipid profile, it may be considered a way of treating MetS in PsA (68).

Agreement has been made with the fact that persons with PsA have elevated carotid intensor media thickness (IMT), which is indicative of the relationship between inflammation and cardiovascular morbiditty. Statin drugs were shown to be able to reduce the cardiovascular risk in terms of improving lipid profile and reducing the inflammation in patients with PsA and Mets (69). Weight loss management strategies including lifestyle changes and medical approaches have led to the improvement of PsA disease activity as well as MetS (69).

Patients with PsA and MetS are at significantly higher risk of cardiovascular events compared with the general population and the need to screen and treat MetS at earlier stages is critical (69). Biologic Therapy, e.g., IL-17 blocking, has been shown to improve insulin resistance and visceral fat content at the expense of disease activity and coverage of the metabolic pathways. The combination with methotrexate and biologics and in particular TNF inhibitors have demonstrated synergy in terms of disease and metabolic control compared to

methotrexate alone (70).

Additionally, biologic therapy that targets IL-12/23 and IL-17 has shown improvement in cardiovascular risk factors and disease activity, and thus their importance in the treatment of both PsA and Mets (71). Studies have proven a larger prevalence of MetS among PsA patients with increased risk of cardiovascular events. The upstream effects of early anti-inflammatory therapies and cardiovascular risk treatment have proved effective in the alleviation of patient outcomes (72).

The evidence therefore points to an irrevocable relationship between PsA and MetS and in this the inflammatory process plays a central role in this metabolic insult. Effective treatment of these conditions particularly using biological drugs is vital in improving patient prognosis and preventing cardiovascular complications (73). A multidisciplinary approach that includes periodic cardiovascular assessment, anti-inflammatory treatment, and lifestyle changes, must be employed to improve treatment in PsA patients with MetS (74).

Gout

Gout is an inflammatory arthritis caused by deposition of monosodium urate (MSU) crystal in joints and soft tissues and resulting in bouts of acute pain and inflammation. It is tightly connected to hyperuricemia that occurs when serum uric acid levels exceed the solubility of the MSU crystals (75). The worldwide incidence of gout is estimated at 0.1-0.10 of the population with high rates in men, particularly those in the middle age and old age categories (76). In addition to the typical inflammatory manifestations, gout is commonly accompanied by metabolic disorders that encompass obesity, dyslipidemia, hyperglycemia, and hypertension and compose metabolic syndrome (MetS). Recent studies provided clear evidence of high proportion of Metabolic Syndrome (MetS) in gout patients that varied between 30 and 82 percent, and approximately 70 percent of the gout patients exhibited two or more aspects of MetS (77).

Gout is closely connected with the metabolic syndrome, whereby the cardiovascular risks associated with a metabolic syndrome are largely due to endothelial dysfunction. Higher levels of uric acid suppress arterial performance and reduce the availability of nitric oxide, therefore, increasing the risk of atherosclerosis and cardiac events (78). Cardiovascular is still a significant cause of morbidity and mortality among patients with gout. Research suggests that patients with gout and metabolic syndrome have a very high chance of cardiovascular complications including myocardial infarctions and cerebrocardiovascular accidents when compared to the normal population (79).

Recent studies have examined the effects that obesity has on the development of gout and the related metabolic issues. Abdominal obesity increases the risk of hyperuricemia and gout exacerbations significantly, as well as promotes insulin resistance and dyslipidemia (80). Studies have further established the relationship between gout and insulin resistance concluding that gout patients have a higher rate of insulin resistance and that hyperuricemia may have a dual role in gout progression and development of metabolic syndrome (81).

Recent investigations have concentrated on the effects of urate-lowering treatments on metabolic syndrome in patients with gout. Allopurinol, an antioxidant acting as a xanthine inhibitor has proved to improve serum lipid levels, lower blood pressure, and prevent insulin resistance hence putting into effect very crucial drivers of metabolic syndrome (82). The prolonged use of urate-lowering drugs has been associated with a lowering of central adiposity, and thus the ability to improve metabolic factors in people with gout (83).

A key element in the correlation between gout and metabolic syndrome is inflammatory cytokines. The elevated levels of pro-inflammatory cytokines, namely TNF-alpha and IL- 6, in gout patients with metabolic syndrome, worsen systemic inflammation, insulin resistance and endothelial functioning therefore increasing the risk of cardiovascular and metabolic insults. Targeting these inflammatory pathways provide a potential method of treatment (84).

In brief, there are shared risk factors between gout and metabolic syndrome including hyperuricemia, obesity, resistance to insulin, and dyslipidemia. People with such diseases face a higher threat of cardiovascular events (85). Urate-lowering therapy, and particularly allopurinol, has the advantageous double effects of reducing gout and restoring metabolic disturbances. Lifestyle changes including weight loss and avoiding alcohol are essential to the treatment. Future studies ought to focus on the molecular mechanisms underlying links between gout and metabolic syndrome, understand the long-term outcomes of urate-lowering treatments, and be able to address shifts in frequency and severity across different populations to develop more individualized treatment plans (86).

DISCUSSION

The relationship between metabolic syndrome (MetS) and inflammatory rheumatologic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (1), psoriatic arthritis (PsA), and gout is complicated and influenced by several major determinants (87). These include chronic inflammations, pathogenic activity, treatment regimens and the demographics of the patients. In the past decade, several studies have explored the prevalence of MetS in other disorders, finding that they carry a

higher CV disease and resultant risks when compared to the general population (88).

Metabolic syndrome (MetS) in rheumatoid arthritis (RA) is estimated at 54.5%, and the prevalence depends on the demographic data, definition, and disease duration (89). Recent reports further demonstrate that more than 40 percent of rheumatoid arthritis cases are diagnosed with metabolic syndrome with a higher incidence in women as compared to men, a demonstration of gender-specific differences in the metabolic impacts of the condition (89). Common factors of MetS in RA patients include increased abdominal obesity, high triglycerides, and blood pressure. Pro-inflammatory cytokine polymerase chain reaction (TNF-alpha and IL-6) is crucial in mediating insulin resistance and increases risk of atherosclerosis and eventual cardiovascular problems (11). Some rheumatoid arthritis medications as methotrexate and hydroxychloroquine have proved to improve the lipids status and reduce reliance on corticosteroids, which are known to aggravate metabolic syndrome (90). This sheds light on the ability of anti-inflammatory drugs to correct metabolic abnormalities and reduce the cardiovascular risks in rheumatoid arthritis thereby providing a better management of the disease as a whole (91).

The rates of MetS are more than twice the highest in SLE patients, with more than 50% developing MetS as compared to those of the general population (92). Although corticosteroids are a major treatment of SLE, their use contributes immensely to development of MetS through the development of central obesity, insulin resistance as well as dyslipidemia. The presence of increased levels of cytokines such as TNF- alpha, IL- 6 and interferon alpha is related to the pathophysiology of Metabolic Syndrome in Systemic Lupus Erythematosus. These cytokines enhance cardiovascular disease and insulin resistance. Inhibiting the immunity of IFN-alpha may dampen the exertion of MetS and promote cardiovascular outcomes in individuals with SLE (93).

Psoriatic arthritis (PsA) is highly correlated with metabolic syndrome (MetS) with a prevalence of between 38&ndashgraved confinetti trifilab in55 percent. The most common MetS factors that are present in PsA include abdominal obesity, hypertriglyceridemia, and hypertension with a significant cardiovascular risk (94). IL-17, IL-23 cytokines play a central role in endothelial dysfunction and insulin resistance and, therefore, they should contribute to the metabolic syndrome in psoriatic arthritis. Targeting these cytokines has potential therapeutic benefits to reduce inflammation and metabolic dysfunction, especially in those with large cutaneous disease burden (95).

The prevalence of components of MetS is high in gout, which is an inflammatory disease caused by the aggregation of urate crystals. Abdominal obesity, hypertriglyceridemia, and hypertension are also common among gout patients and this condition is also associated with an elevated risk of cardiovascular events, particularly among patients with such comorbidities as obesity and hypertension (96). Management of Urate-lowering therapies such as allopurinol, could reduce cardiovascular risk by improving endothelial activity; further long-duration trials are however necessary. Colchicine, a medication which is currently mostly used in the management of gout, has shown the promise of reducing cardiovascular events through the reduction of systemic inflammation, but the processes by which this works are yet to be investigated (97).

As well as disease-specific factors, socio-demographic factors such as age, sex, ethnic, and socio-economic position also have an important impact on prevalence and severity of MetS among patients with inflammatory rheumatic diseases. Patients with low socio-economic status have a high risk of Metabolic Syndrome occurrence, which can be explained by the poorly available healthcare services, the lack of physical potential, and unhealthy nutritional habits (98). Inflammatory rheumatic disease has a higher prevalence of MetS than that of the general population. Chronic inflammation, the use of corticosteroids, and disease related criteria augment the risk of metabolic issues and heart disease in such individuals (99). Actively screening Metabolic Syndrome and proper care management of inflammation with medication like methotrexate, hydroxychloroquine and urate lowing medications are necessary in risk abatement. Future research should focus on the underlying processes that link these conditions to MetS, especially the role of cytokines and biomarkers as future potential targets of treatment. Regional analysis is critical to the understanding of how socio-demographic factors influence the prevalence of MetS and assist with the development of region-specific care plans in different populations (100).

CONCLUSION

Keeping track of the conditions and the usefulness of comorbidities and taking necessary action to control it, it can be presumed that one takes a preventive approach to the complications and loss of life associated with the illness. There is an existing relationship between inflammatory rheumatic diseases and cardiovascular diseases. This accompanies the involvement of the joint inflammation. When efficacious medicines to adjust the inflammation in rheumatic diseases are available, patients can enjoy the enlarged quality of life and increased lifespan. These drugs can also be useful bearing in mind the high prevalence of the metabolic syndrome. The displayed higher incidence

of metabolic syndrome in patients with gout and psoriatic arthritis is an indication that these patients require more emphasis on factors that predispose them to cardiovascular diseases. Recognizing what metabolic syndrome subsets are involved in each individual can help to select the treatment. This review article postulated that the abdominal obesity of patients with rheumatoid arthritis and lupus, abdominal obesity and hypertension of patients with psoriatic arthritis and hypertriglyceridemia and hypertension in gout subjects are important aspects of metabolic syndrome that require heightened attention. The analysis of previous studies was used to draw the conclusions.

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New FRET-Base Approach for Detection of HPV High Risk Genotype by DNA Capturing

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ABSTRACT

Human Papillomavirus (HPV) is a highly prevalent virus responsible for several types of cancers, including cervical, throat, and anogenital cancers. Early detection and diagnosis are crucial for preventing the progression of HPV-related diseases. In this study, we introduce a new approach based on Förster Resonance Energy Transfer (FRET) method to identify viral DNA, which was designed for the conserved region of the L1 gene sequence in high-risk genotypes 16, 18, 31 and 33. In order to create suitable temperature conditions for the attachment and also to identify the fluorescent signal, real real-time PCR device was used. The results of the specificity test showed 100% specificity, and the limit of detection level of the method was reported to be 1000 copies/µl of the virus in the sample. The results of clinical sensitivity in the range of 86-96% between different genotypes and the rate of false negative results was in the range of 14-22%. Based on this, it can be said that maybe the developed method cannot be proposed as a suitable alternative, but due to the response time and lower cost, it can be proposed as a quick screening method.

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INTRODUCTION

Human papillomaviruses (HPVs) are a large and diverse group of epitheliotropic double-stranded DNA viruses (1). As one of the most common sexually transmitted infections globally, HPV poses significant public health challenges. HPV infection is widespread, with studies indicating that a significant majority of sexually active individuals will acquire HPV at some point in their lives. According to the World Health Organization (WHO), nearly 80% of sexually active people are expected to be infected with HPV at least once (2). The prevalence varies by geographical region, sexual behavior, and demographic factors. High-risk HPV types, particularly HPV 16 and 18, are responsible for the majority of cervical cancer cases, highlighting the need for targeted screening and vaccination efforts. The importance of early detection cannot be overstated, as it plays a crucial role in preventing the progression of HPV-related diseases, including cervical, anal, and oropharyngeal cancers (3). Understanding the epidemiology of HPV and the methods used for its detection is vital for effective prevention and management strategies (4). Based on WHO guidelines, Women should be screened for cervical cancer every 5–10 years starting at age 30. The global strategy encourages a minimum of two lifetime screens with a high-performance HPV test by age 35 and again by age 45 years (5). Precancers rarely cause symptoms, which is why regular cervical cancer screening is important, even if you have been vaccinated against HPV (6). Cervical

screening can detect multiple HPV types, including the highest risk types, HPV 16 and 18. HPV 16 and 18 have been linked to 70% to 80% of the cases worldwide (7).

The detection of HPV can be achieved through several methods, each with its own advantages and limitations. Pap smears have been the standard screening tool for cervical cancer (8). This method involves collecting cells from the cervix to identify any precancerous changes. However, it does not directly detect the virus. HPV DNA Testing is the more specific method for HPV detection; This method involves testing cervical samples for the presence of HPV DNA (9). This test is often recommended for women aged 30 and older as part of co-testing with Pap smears. HPV RNA Testing is the newer approach that detects the presence of HPV mRNA, which indicates active viral replication. This method can help differentiate between transient infections, which often resolve on their own, and persistent infections that may lead to cancer (10).

The basis of all methods based on DNA and RNA is the amplification of a specific part of the virus genome by PCR and then identifying the presence of the virus in the sample with electrophoresis or fluorescent probes or hybrid methods (11). In the meantime, the use of the real-time PCR method and the use of TaqMan probes is known as the gold standard. In this method, due to the diversity of the viral genome, its types can be separated. One of the disadvantages of this method is the time-consuming and high cost of testing (12). In this study, we introduce a new approach based on Förster Resonance Energy Transfer (FRET) method to identify viral DNA, which does not require a replication step and alternating temperature cycles. In this method, a special type of probe is used, which, unlike the TaqMan method, does not require hydrolysis, and the detection process can be monitored in real time using real-time PCR devices.

MATERIALS AND METHODS

Viral Variants and DNA Extraction

Pathogenic high-risk genotype of HPV viruses including 16, 18, 31 and 33 were collected from Razi Laboratory (Karaj, Iran). All the samples were taken in a period of three months from female patients who were positive for the desired genotypes by TaqMan real-time pcr test. The samples were vaginal swabs that were kept at refrigerator temperature. The viral DNA/RNA kit (FAVORGEN Biotech, Taiwan), according to the manufacturer's instructions performed DNA extraction. Extracted DNA was eluted with 50μl AE buffer and stored at -20°C until amplification.

Primer Designing for Viral Genomes

The mentioned high-risk genotype whole-genome sequences were obtained from The Papillomavirus Episteme (PaVE) was used to align the conserved domain of viral-specific genes (https://pave.niaid.nih.gov/). Using oligo7 (https://www.oligo.net/), a pairs of particular oligonucleotides for the L1 common conserved region was designed. Genescript, Inc. produced the oligonucleotide indicated in Table 1 (GeneScript, Jiangsu, China). At the 5' end of one of the oligonucleotides, the fluorescent FAM was placed as a fluorescent donor, and at the 5' end of the other oligonucleotide, the BHQ molecule was placed as a quencher. (Figure 1). If it is not attached to the template strand, the FAM dye will signal, and if both oligonucleotides are attached to the template, the fluorescent signal will be turned off due to the proximity of the quencher to the FAM dye.

Preparation of Standard Plasmid

In this research, 4 recombinant vectors were employed and were constructed as positive controls. To acquire the recombinant plasmids pcDNA3.1(+)/16, pcDNA3.1(+)/18, pcDNA3.1(+)/31, and pcDNA3.1(+)/33, particular target segments were first generated using the primers (Table 2), and then

Table 1. Primer sequence for amplification of the L1 gene region.

Genotype	Primer Sequence	Tm °C	PaVE ID
HPV 16 L1	5'- TTGCTGATGCAGGTGACTTT-3'	60	HPV16REF
	5'- CAAAAAGCATGCAACCGAAT-3'		
HPV 18 L1	5'- GCCCCTGCCTCTACACAGTA-3'	60	HPV18REF
	5'- ATAGCCCAACAAGCAACACC-3'		
HPV 31 L1	5'- GTGCCTGCGTGGAGTGAC-3'	60	HPV31REF
	5'- CCAGTGCTGCACATGTTTTT-3'		
HPV 33 L1	5'- CCACAGTGTACCTGCCTCCT-3'	60	HPV33REF
	5'- GGGTAGGGCAAGCAATACAA-3'		

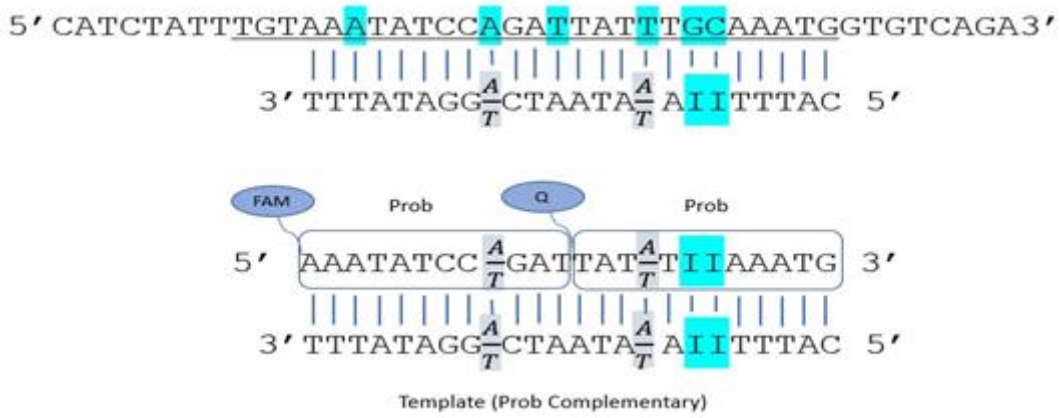

Fig1. The schematic diagram of the designed probe structure and the target sequence: as can be seen, the probe consists of two oligonucleotide fragments, one of which has a fluorescent molecule at the 5› end and the other a quencher molecule, so that when attached to the target sequence, the fluorescent signal is turned off, and the device can detect signal changes.

these sequences were introduced into the pcDNA3.1(+) plasmid (Shenzhen, China) (vector and genome map in figure 2). The vector copy number was determined by using the following equation: copy number (copies/µL) =NA (copies/mol) concentration (g/µL)/ MW (g/mol), where NA is Avogadro's number and MW is the reference times (https://www.technologynetworks.com/tn/tools/copynumbercalculator).

Set up the method

In this study, a real-time PCR device (ABI StepOnePlus, Thermo Fisher Scientific, USA) was used to establish the binding to template conditions and measure the fluorescent amount. Prepared PCR buffer (200 mM Tris-HCl (pH 8.4), 500 mM KCl) was used to create buffer conditions. The probe concentration was considered 10 mM for this study, and Temperature and time conditions were established according to Table 2.

Sensitivity and Specificity Analysis of the FRET Approach

a)Specificity analysis of the FRET: Probe blast analysis was used to assess the specificity of FRET. Also, HSV1, HSV2, and HIV were used to test the specificity of the FRET approach.

b)The FRET technique's efficiency: By using a 10-fold gradient dilution method, each one of the recombinant DNA vectors was diluted from 1 × 10^6 to 1 × 10^0 copies/µL. After that, FRET was carried out to determine the limit of detection (LOD). FRET reaction was performed for each sample with 3 replications.

c)Detection limit, analytic sensitivity, and normal range: Two inactive positive samples of 16, 18, 31, and 33 viruses at a concentration of 1 × 106 copies/µL were evaluated at the Virology Research Center to verify the technique. Each sample received 3 replications of the FRET procedure.

Comparative test with the reference method

To validate the FRET technique in this study, an IVD mark kit for high-risk HPV (Sacace, Italy, CAS No. V67-100FRT) was prepared. FRET technique and IVD mark kit were performed on 100 clinical samples. The results obtained from the FRET technique in this study were compared with the results of the IVD mark kit was repeated 3 times.

RESULTS

Construction and Identification of Recombinant Plasmids

Virulence genes of 16, 18, 31, and 33 genotypes were cloned into the eukaryotic expression vector pcDNA3.1(+), as shown in Figure 2, separately. DNA sequencing revealed that the gene sequences from the 4 recombinant plasmids were identical to the 16, 18, 31, and 33 genotypes. BamHI and EcoRV were used to digest the plasmids that had been constructed. The digestion products were separated electrophoretically, indicating that the recombinant plasmid was successfully constructed.

Table2. Time and temperature conditions.

Temperature	Time	Number of cycles
95°C	1min	10
65°C	1min	

*Data collection at 65°C and on the FAM Channel

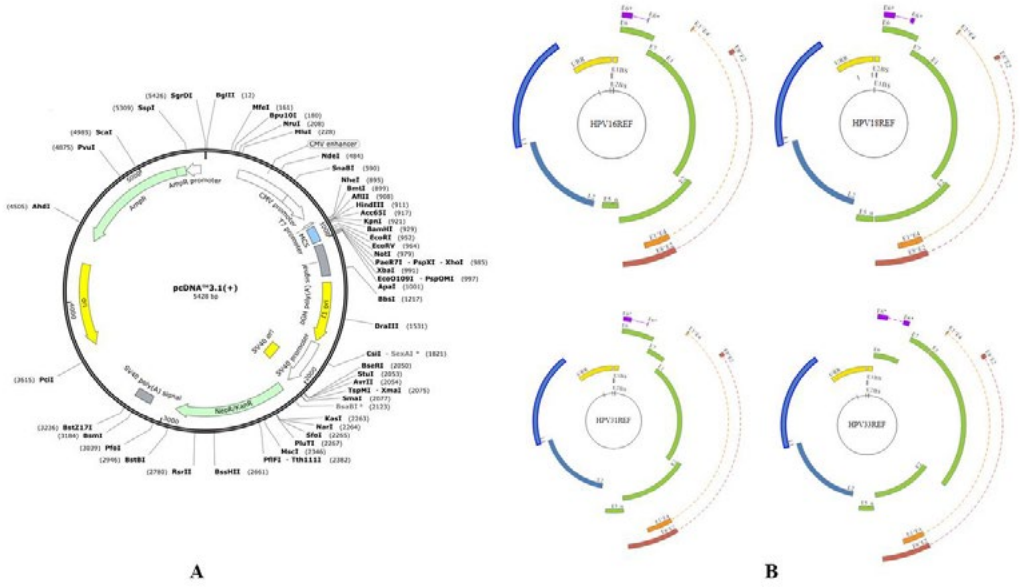

Fig2. A) Schematic structure of the plasmid used to create the positive control vector. B) Genome structure of four high-risk HPV types (16,18,31,33) in this study probe was designed for the conserved region of the L1 gene.

The FRET Approach Has a High Level of Specificity

These 4 viruses, as well as HSV 1/2 and HIV cDNA, were used to test the specificity of the FRET approach. The curve for each viral pathogen was apparent for FRET evaluation. The extracted genome of the viruses was evaluated separately with the HPV specific probe and under the same conditions, and the results showed that no signal of binding to their genome was recorded.

The FRET Technique's Efficiency and LOD measurement

The FRET approach efficiency for each viral sample was assayed by a positive control (Recombinant plasmids). According to the results of the minimum detectable amount of virus in this kit is 1000 (1 × 10^3) copies. Therefore, the performance of this kit is equal to 1000 copies of the number. In the next step, this approach was tested for verification with virus samples.

Compare with the reference kit and use Clinical Samples

FRET developed technology and IVD-marked real-time PCR kits were used to investigate a total of 120 clinical specimens. 30 samples for each high-risk genotype and 100 healthy samples as a negative control. Table 3 shows the positive rate of each virus. As can be seen in Table 3, the reference kit was able to fully identify all positive and negative samples (100% rate), compared to the FRET technique, 86.6% for genotype 16, 96.6% for genotype 18, 86.6% for genotype 31, and 83.3% for genotype 33 of positive samples have been identified and all negative samples were reported completely without signal.

DISCUSSION

Human papillomavirus (HPV) is a major cause of cervical cancer, genital warts, and other anogenital and oropharyngeal cancers. Due to the importance of early detection of HPV infection in managing and reducing the risk of cancer caused by this virus, screening programs have been put on the agenda of the health systems of all countries (13). Early and accurate detection of HPV infection is crucial for prevention, timely treatment, and improving patient outcomes. Traditional methods for HPV detection include PCR (Polymerase Chain Reaction), in situ hybridization, and serological assays, but emerging molecular techniques such as Fluorescence Resonance Energy Transfer (FRET) offer a promising approach for sensitive and specific detection (14).

Molecular and epidemiologic studies have solidified the association between high-risk strains of genital HPV and squamous cell carcinoma of the cervix. The incidence of cervical cancer and its associated mortality have declined in recent years, largely due to the widespread implementation of screening programs (15). Screening for cervical cancer remains an important public health and economic concern throughout the world. Large-scale studies to evaluate management options for women with abnormal Pap smear results have been conducted, and these studies highlighted the potential utilization of HPV DNA testing in the management of women with Undetermined Significance (ASCUS) Pap smear results (16).

Golden standard method that used detection and

Table 3. Compare with reference kit and use Clinical Samples results

Method	16 Pos	18 Pos	31 Pos	33 Pos	Neg
IVD Mark Kit	30/30 (100%)	30/30 (100%)	30/30 (100%)	30/30 (100%)	100/100 (100%)
FRET Approach	26/30 (86.6%)	29/30 (96.6%)	26/30 (86.6%)	25/30 (83.3%)	100/100 (100%)

genotyping HPV is TaqMan probe real-time PCR, Taqman probes also follow the FRET system, so that the donner molecule is at a certain distance from the quencher, which causes no signal to be emitted, but after attaching to the template sequence and during the DNA polymerization process by the polymerase enzyme, the probe is hydrolyzed and the molecule The donner is released from the quencher trap and the fluorescent signal is detected by the device (17). The requirement of this technique is the amplification of the target sequence by PCR. This makes even small amounts of virus detectable in the sample because it increases during the PCR process. But the use of TaqMan probes, in addition to the high cost, requires an amplification process, which makes the screening process time-consuming.

Several FRET-based methods have been proposed to identify different pathogens. In this study, we developed a special type of FRET probes, which do not require an amplification process to use them, and it costs less for testing, because a large number of genotypes can be identified using one probe (18-20). This probe actually consists of two labeled oligonucleotide sequences, whose binding site is on the sequence of the template, and if it is attached to the template strand, as the donor molecule is placed next to the quencher, the signal is turned off, exactly the opposite of the action of TaqMan probes (21). In a similar study conducted by Rezanejad et al., this method was used to identify the COVID-19 virus. In this specific study, the researchers designed a FRET-based probe by conjugating fluorescent molecules to DNA sequences that are complementary to the target COVID-19 viral RNA or DNA. When the probe binds to the target sequence, a change in fluorescence occurs due to the energy transfer between the fluorophores, which can be measured. This method provides a rapid and highly sensitive detection system, useful for diagnosing infections by detecting viral genetic material without the need for complex equipment or lengthy procedures (22).

In this study, the desired probe was designed for the conserved region of the L1 gene sequence in high-risk genotypes 16, 18, 31 and 33. In order to create suitable temperature conditions for the attachment and also to identify the fluorescent signal, real real-time PCR device was used. Vectors containing target sequences were used to perform sensitivity, specificity and limit of detection tests. The results showed that this method could detect the amount of viral particles up to 1000 copies/µl. Also, the results of the clinical analysis test and comparison with the reference kit showed that the sensitivity of this method is in the range of 86-96% and the rate of false negative results was in the range of 14-22%.

The false negative results were significantly higher than the reference method. Based on this, it can be said that maybe the developed method cannot be proposed as a suitable alternative, but due to the response time and lower cost, it can be proposed as a quick screening method. TaqMan probes, which rely on PCR amplification, can detect extremely low viral loads; the FRET probe's lack of amplification reduces its ability to detect minimal amounts of HPV DNA, potentially leading to false negatives in cases with low viral titers. This trade-off between speed and sensitivity highlights the need for further refinement of FRET technology to ensure that diagnostic accuracy is not compromised in favor of efficiency. Consequently, while the FRET probe holds potential as a rapid diagnostic tool for high-risk HPV strains, its lower sensitivity may limit its application in certain clinical scenarios, particularly in early or low-level infection.

CONCLUSION

In conclusion, the FRET-based HPV detection method offers significant advancements in real-time, PCR-independent diagnostics, but its reduced sensitivity compared to TaqMan probes requires careful consideration, especially in settings where detecting low viral loads is critical. Continued research is necessary to optimize these probes for broader clinical use. The development of this method using real-time fluorescent signal detection devices that have a higher detection power can be effective in increasing the sensitivity of this method.

Declarations

Consent for publication

Not applicable.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Authors's Contribution

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Consent for publication

Not Applicable

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Managing Inflammation in Cancer Therapy: Effects of Inflammation Control on Metastasis and Treatment Response

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ABSTRACT

Chronic inflammation plays a critical role in cancer development and progression. Moreover, it has long been recognized as essential for tumor development, survival, metastasis, and treatment resistance. This review intends to systematically discuss and explore complex interactions between cancer cells and inflammation, highlighting its importance in cancer development and its impact on treatment outcomes. Furthermore, we will discuss molecular mechanisms underlying inflammation-driven cancer development and explore its impact on metastasis, treatment sensitivity to therapies including chemotherapy, immunotherapy, and targeted therapies. Moreover, we will explore new emerging strategies to treat inflammation in cancer therapy, keeping in view its need for selective modulation to improve treatment efficiency and reduce adverse reactions, including immunosuppression and susceptibility to infections. Finally, concluding remarks for new research directions on improving anti-inflammatory strategies to optimize cancer treatment therapies are presented to explore new ways for innovative cancer therapies to emerge for improved patient survival rates and better patient prognosis.

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INTRODUCTION

Inflammation as a Driver of Cancer

Long-term irritation has to be one of the key instigators of cancerology (1). Although the exact molecular/cellular mechanisms whereby inflammation can give rise to tumors, become metastatic or resist therapies are not fully elucidated, a significant work has been done (2). We also discuss how inflammatory pathways can be manipulated to modulate responses to therapy and present an in-depth review on the complex interaction of tumors with inflammatory cells in tumor pathogenesis (3). This persistent infiltration of various immune system subtypes, particularly macrophages, neutrophils and myeloid derived suppressor cells (MDSCs), into the tumor microenvironment (TME) has been the hallmark of tumoral inflammation (4). The heterogenic population of these cells, along with the tumor microenvironment of macrophages, neutrophils and MDSCs, as well as the pro-inflammatory components of cytokine, chemokine and growth factor secretions they release play a major role in tumour cell growth control, survival advantages and immune evasion transport. As cancer cells manipulate components of the immune system to create a tumor-supporting microenvironment that enables them to survive and proliferate, the TME is critical in regulating inflammation of the tumors (5).

This inflammatory storm allows the malignant cells to grow at will, reject apoptotic markers and insidiously spread throughout local and remote matrices. The balance between pro-inflammatory and

anti-inflammatory signals tilts, over time during the course of disease, to favor chronic inflammation that eventually governs the progression of the disease as well as resistance toward therapy. This has been described for numerous diseases, including cancer (7). Obesity has become one of the biggest public health challenges worldwide due to alarming increases in its prevalence (8). Certainly, a multitude of genetic, environmental and lifestyle factors underlie obesity, but the accumulating data pointing to the gut microbiome as one of the major determinants of body weight and fat distribution is currently attracting most attention (1- 3). Through the gut micro-biota, obesity phenotype is influenced by various mechanisms such as regulation of energy extraction from diet, host metabolism control and interaction with systemic hormonal and immune pathways (6).

Alterations in the abundance and composition of gut bacteria could affect nutrient utilization and conversion to available energy (4). Lines evidence a higher Firmicutes to Bacteroidetes ratio is positively associated with increased ability to ferment complex polysaccharides into harvestable calories that can be absorbed and therefore, explain enhanced energy utilisation and fat deposition, i.e., the phenotype often reported in patients afflicted by an obesity disorder. It alters the host lipid metabolism and lipid storage, resulting in the adiposity and redistribution of body fat (8). It is also an influence on the ecology of the gut microbiota. Besides providing energy, the gut microbiota influences bile acid metabolism influencing lipid digestion and absorption directly. Bacteria present in the gut are capable of converting primary to secondary bile acids, which act as signaling molecules via receptors including TGR5 and FXR. These receptors impact energy utilization, lipid metabolism and glucose homeostasis. A dysregulation of control signals for bile acids may cause Clev.CIN and can impact lipid metabolism and increase fat storage to mediate obesity (3).

There are many studies centering on these newly developed biological therapies trying in fact to target the microbiome, attempting to improve our problems with obesity. FMT has been most effective (1, 2, 5). It encompasses the transfer of gut bacteria from a healthy donor and the possibility for FMT to alter the microbiota composition of the recipient toward a more symbiotic and metabolically favorable ecology seems promising. Conclusion: The definitive evidence for long-term safety and efficacy of this approach is unknown, yet some data indicate the potential to improve certain obesity-related metabolic parameters and overall body fat (101). Further, the application of FMT, open prebiotics and probiotics helping to modulate microbiome are promising. Prebiotics, and especially those from inulin and fructooligosaccharide (FOS don't increase only the growth of good bacteria but are also short chain fatty acid producers with an anti-obesity importance that helps to control appetite and enhance fullness factor as well as energy expenditure (2).

Through changing inflammation, gut barrier function and metabolic signaling pathways live beneficial microorganisms including Lactobacillus and Bifidobacterium species (composing probiotics) have reported different degree of success to body weight reduction or metabolic health improvement. These microbiome-based therapies represent, as already mentioned, the good complement or substitutive solutions regarding classical chains for obesity control diets and physical activity (6, 7). These strategies could potentially reduce the risk associated with both the SBO-complications (e.g., type 2 diabetes, cardiovascular diseases and certain cancer types) as well as enhance weight loss (4).

Historical Perspective on the Link Between Inflammation and Cancer

There is a known association between inflammation and cancer since a long time. Earlier studies have demonstrated that people suffering from chronic inflammatory diseases are at a greater risk of having cancer. Moreover, middle of the last century was also a milestone for understanding the molecular mechanism behind this interaction (8). Identification of important inflammatory cytokines e.g. TNF-alpha, IL-1β and angiogenic factors, VEGF as well key signaling pathways like NF-κB or MAPK has made remarkable progress in understanding the role of inflammation in cancer initiation, progression and metastases. Such molecular mediators can be further employed for developing new therapies designed to halt tumor growth and mediate control of inflammation through their interaction. Potential benefits of the current drugs targeting pro-inflammatory pathways (immune checkpoint inhibitors, and customized anti-inflammatory drugs) have been demonstrated across multiple cancer types (10). Clinics are where these therapies are being tested right now.

Therapeutic Implications: Targeting Inflammation to Improve Cancer Therapy

Recent advances in cancer therapy have brought the microenvironment and its inflammatory actors to center stage for the disease (11). By enabling the precise targeting of neoplastic cells, drugs and immunotherapies including immune checkpoint inhibitors have utterly transformed cancer treatment (12). Prolonged inflammation in the tumour microenvironment may abrogate the action of these

therapies via immunosuppression, acquisition of resistance to drugs and remodelling neovasculature for the tumor. Current cancer research primarily investigates remedies focused on the inflammatory nature of the TME, to address these issues. Manipulating the inflammatory pathways of tumors may lead to more efficacious treatments, better patient outcomes and fewer side effects (14).

Mechanisms of Inflammation in Cancer Progression

Key Molecular Pathways in Inflammation and Cancer

Cancer initiation due to inflammation is explained by several biological mechanisms. These pathways are involved in the cell survival, proliferation, migration, angiogenesis and immune evasion (15). The NF-κB pathway plays a key role in regulating pro-inflammatory cytokines, survival genes and genes associated with immune evasion (16). Upon activation by inflammatory cytokines (e.g., TNF-α and IL-1β) NF-κB translocates to the nucleus and initiates transcription of pro-survival and pro-inflammatory genes (17). This activation preserves a pro-inflammatory tumor microenvironment that facilitates tumor development.

The PI3K/AKT and MAPK pathways are also two other important signaling cascades which contribute to tumor formation during inflammation (18). These pathways play a critical role in determining tumor tone and metastatic likelihood and regulate cell proliferation, migration, resistance to death. Of these, perhaps most important in promoting tumor aggressiveness and therapy resistance is the activation of these sequences by inflammatory signals such as cytokines and growth factors (19). In addition, reactive oxygen species (20) as secondary signal molecules of developing inflammation caused by oxidative stress (20-21).

Tumor Microenvironment and Immune Cells

The tumor microenvironment (TME) is a dynamic network of tumour cells, immune cells, stromal cells and the extracellular matrix (ECM). Tumor microenvironment (TME) is shaped and rebalanced by recruitment and activation of different immune cells, including tumor-associated macrophage (TAM), neutrophil, myeloid-derived suppressor cell (MDSC), which are modulated by the signals from inflammation. Subsequently, these immune cells produce an array of cytokines, growth factors and proteolytic enzymes that are important in promoting survival, immune escape and metastatic dissemination of tumor cells (24).

Categorized into an M2 phenotype, the tumor-infiltrating macrophages (TAMs) switch to a state that significantly benefits tumor growth and inhibits antitumor immune responses (25). VEGF is important for tumor development because it offers the nutritional and oxygen conditions that facilitate the stimulation of their expansion; therefore, a pro-angiogen produced from M2 polarized TAMs provides growing (26). In addition, these macrophages suppress cytotoxic immune cells (CTL and NK) activity through secretion of immunosuppressive cytokines like IL-10 and TGF-β (27).

Even though their main function is in preventing infection, neutrophils also promote tumor growth by releasing cytokines, such as IL-8, that promote cancer cell motility and invasion (28). By targeting extracellular matrix (ECM) and further enhancing penetration of tumor cells in surrounding tissues, hidden matrix metalloproteinases (MMPs) under neutrophils together with other immune cells set up a feedback loop that exacerbates the inflammation and accelerates spreading of the tumors/growth (29).

Oxidative Stress and DNA Damage

The pro-inflammatory TME is characteristic for chronic inflammation and serves as a source of persistent reactive oxygen species (ROS) production (20), which possess multifaceted functions in the context of cancer formation and resistance against treatment. At moderate levels, ROS are signaling molecules that trigger pro-survival pathways resulting in tumor cell proliferation, immune evasion and adaptation to stress. However, when in excess, ROS result in oxidative damage of cellular components including lipids, proteins and especially DNA which will then lead to mutations, genomic instability and activation of pro-oncogenic genes (30). This genomic instability facilitates tumor growth and contributes to the more aggressive characteristic of cancer cells, including their ability to resist apoptosis (31).

Importantly ROS in this sense are also a factor of resistance to the conventional cancer therapies. Oxidative stress also promotes the survival of cancer stem cells (CSCs), a subtypethat is resistant to chemotherapy, radiotherapy and immunotherapy, resulting in tumor relapse and metastasis (32). Proinflammatory cytokines, such as IL-6 and TNF-α, sustain high levels of ROS, leading to a positive feedback loop that strengthens proliferative signaling immune suppression through attracting immunosuppressive cells (e.g., MDSCs and Tregs) and angiogenesis. The inflammation-induced fibrosis in the TME builds a physical barrier that prevents efficient delivery of chemotherapeutic drugs, also (33).

Collectively, these mechanisms describe how chronic inflammation and oxidative stress hamper treatment efforts by promoting cancer cell survival, creating an immunosuppressive environment, and

hindering drug penetrance (34). Inhibition of ROS production and inflammation signaling, including NF-κB and STAT3, could be a potential strategy to overcome resistance to therapy and increase sensitivity of tumor cells (35).

Inflammation and Metastasis

Inflammation as a Driver of Metastasis

Metastasis, the spread of cancer cells from the primary tumor site to distant organs, is a leading cause of death due to cancer, responsible for most cancer deaths. Inflammation plays a critical role in promoting metastasis through increasing motility, invasion and survival of tumor cells in distant organs (36). Pro-inflammatory cytokines, IL-6 and TNF-a as well as chemokines like IL-8 are able to enhance the motility of tumor cells and increase their invasiveness through activation of signaling pathways that lead to epithelial-to-mesenchymal transition (EMT) (37). Epithelial-mesenchymal transition (EMT), a critical process by which the epithelial tumor cells acquire mesenchymal properties, causes these tumor cells to dissociate from the bulk of the tumor and, thus, increase their ability to invade adjacent tissues (38).

Additionally, inflammatory cytokines induce the production of matrix metalloproteinases (MMPs), enzymes that promote ECM degradation. Breakdown of the ECM allows tumor cells to breach the physical barriers in neighboring tissues and escape into the bloodstream, where they can reach distant organs (39). Once circulating, these CTCs can give rise to metastatic outgrowth at distant organ sites that permits process of commiseration. In addition, inflammation may also initiate angiogenesis, the production of new blood vessels, which is critical to sustain the blood supply of the growing tumor and supported further metastasis (40). Pro-inflammatory cytokines, such as VEGF (vascular endothelial growth factor), play a central role in the angiogenic process which ensures the tumor is well nourished and provided with oxygen to grow and spread (41).

Molecular Mechanisms of Inflammation-Induced Metastasis

The activation of inflammatory cytokines in the tumor surrounding stroma leads to extracellular matrix remodeling, an important step in metastasis. ECM degradation by tumor and immune-cell derived MMPs contributes to the development of an environment conducive for tumor cell motility and invasion (42). In addition, inflammation promotes angiogenesis through upregulated secretion of VEGF as well as other pro-angiogenic factors. This neovasculature not only drives tumor growth, but provides a route for cancer cells to enter the blood stream and thereby metastisize (43).

In conclusion, inflammation directly promotes the metastatic process through several mechanisms including EMT activation, ECM degradation or angiogenesis. These activities enhance the invasive potential of tumor cells to migrate to distant organs and create new lesions.

Impact of Inflammation on Treatment Response

Chemotherapy Resistance Induced by Inflammation

Chemotherapy is still one of the main modalities for cancer treatment, but its efficacy can be plagued by chronic inflammation that occurs in the tumor microenvironment (44). In addition, pro-inflammatory cytokines, including TNF-α, IL-6 and IL-1β, stimulate signaling pathways such as NF-kB and STAT3 that support cancer cell survival by blocking apoptosis and protect tumor cells from chemotherapy-induced cell death (45). These cytokines can also increase DNA repair, resulting in more resistance to DNA-damaging chemotherapeutic agents (46). Moreover, tumor microenvironment (TME) can cause inflammation-mediated fibrosis, forming a physical barrier and preventing penetration of drug as well as leading to decreased chemotherapy agents delivered to the tumor cells (47). In addition, the inflammatory milieu also favored the maintenance of cancer stem cells (CSCs), a subset with high chemoresistance linked to tumor recurrence and metastasis after treatment (48). Neoadjuvant chemotherapy combined with inhibitors of inflammatory pathways (e.g., NF-κB) or cytokine-neutralizing antibodies can inhibit inflammation-induced tumor progression and sensitize cancer cells to chemotherapeutic regimens, providing a tempting approach for overcoming resistance and increasing efficacy of treatment (1).

Immunotherapy Resistance

Immunotherapy has become a game-changer in the way of treating cancer, harnessing the immune system to detect and destroy tumor cells. Chronic inflammation in the cancer can act to suppress immunity and may therefore limit the effectiveness of immune therapies (49). Inflammation may induce the expression of immunologic checkpoints like PD-L1 [77], which immune response repressive through binding to T-cell-expressing PD-1 receptors, thus impeding their action in countering against cancer. Meanwhile, inflammatory cytokines such as IL-10 and TGF-β help recruit immunosuppressive cells like myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), weakening immune responses and promoting pathways for immune escape (50).

In addition to stimulating immunological checkpoints, inflammation can mediate TIL immune exhaustion. The effector function of T cells

that are able to target tumor can be reduced by pro-inflammatory signals (51).

Paradoxically, acute inflammation may enhance anti-tumor immune response by allowing infiltration of immune cells such as CTLs and NK into the tumor (52). This implies that a systemic control of inflammation would increase the immunotherapy efficiency. Therefore, drugs targeting pro-inflammatory pathways alone in concert with promoting immune activation might improve the efficacy of immunotherapies (53).

Targeted Therapies and Inflammation

Targeted drugs aim at blocking specific signaling pathways which contribute to the cancer cell growth. The presence of inflammation in the TME may amend the response to these medications. These inflammatory cytokines, such as IL-6 and TNF-α can activate the PI3K/AKT pathway which is often associated with tumor cell survival, inhibition of apoptosis and metastasis 11. Such activation can render targeted drugs ineffective by eliminating therapeutic benefit of blockage (54). Also, the remodeling of extracellular matrix due to inflammation might modulate the efficacy of targeted treatment by altering tumor biomechanical properties. Furthermore, augmented stiffness in the extracellular matrix often due to inflammation makes it difficult for anticancer therapeutic payload to penetrate the tumor itself (55).

There may be a role for using targeted therapy in combination with anti-inflammatory treatments to maximize their effectiveness. Inhibitors of inflammatory cytokines or immune modulators applied together with targeted therapy might even pave the way for better drug delivery and overcome mechanisms of resistance(56).

Therapeutic Strategies for Targeting Inflammation in Cancer

Anti-Inflammatory Agents

Targeted drugs aim to block specific signaling pathways that drive the growth of cancer cells. The presence of inflammation within the TME may have an impact on the potential efficacy of these agents (57). Inflammatory cytokines, such as IL-6 and TNF-α can also activate the PI3K/AKT pathway which is commonly involved in tumor cell survival, resistance to apoptosis and metastasis. This activation may confer resistance to targeted drugs by negating the therapeutic effects of pathway blockade (58).

Moreover, inflammation-driven ECM remodeling may alter the physical characteristics of tumour which can in turn influence the effective of targeted therapy. Elevated stiffness in the extracellular matrix, often due to inflammation, may block targeted therapeutics from penetrating into the tumor. Combining targeted therapy with anti-inflammatory medications could help them work better. Entherapies that promote cytokine inhibition or immune modulation, combined with targeting therapy may provide a way to increase drug delivery and overcome resistance mechanisms (55).

Immunomodulatory Therapies

Immunomodulatory therapies are a promising avenue to combat inflammation in cancer. These immune-therapies aim to influence the body's defense system to create a preferable (ie, beneficial) inflammatory response which will improve anti-tumor immunity(59). One such approach is the use of immune checkpoint inhibitors that block inhibitory receptors expressed on immune cells, such as PD-1 and CTLA-4. By deactivating these receptors, checkpoint inhibitors release the "brakes" on the immune system and thus allow T cells or NK cells to attack tumor cells more efficiently (60).

Prolonged inflammation can cause immune cell loss and reduces sensitivity to immunotherapy, as a result, the research on regulation of inflammatory responses has become very important (61). Therapies that inhibit the recruitment of immunosuppressive cells including MDSCs or Tregs could potentially lead to an improved response to immune checkpoint inhibitors (62). Similarly, the use of agents regulating inflammatory cytokines within TME might increase effector immune cell infiltration and activation such as CTLs and NK cells (63).

Targeting Tumor-Associated Inflammatory Pathways

In addition to non-specific anti-inflammatory agents, treatments that specifically inhibit the inflammatory cascades involved in cancer progression would offer a more targeted strategy (64). The NF-κB signalling pathway is a major target for cancer therapy given its central role in inflammation and tumour formation. IKK inhibitors and other NF-κB signalling inhibitors have shown promise in preclinical studies, as they reduced tumor outgrowth and metastasis (65).

Other appealing targets include JAK/STAT and PI3K/AKT pathways which are often activated by inflammatory cytokines. Blocking these pathways can decrease inflammation and tumor progression (66). Developing personalized drugs that can specifically control inflammation in the tumor microenvironment is very attractive. Clinical trials are needed to demonstrate the safety and effectiveness of these treatments with conventional therapy for cancer (67).

Challenges and Future Directions

Specificity in Targeting Inflammation

Inflammatory targeting provides a strategy to improve the outcomes of cancer therapy, but with significant challenges for implementation. A major hurdle is to target the exact inflammatory routes promoting cancer development, and maintain the body's innate immune responses (68). Inflammation is essential for immunological surveillance, tissue repair, and immunoprotection. Overinhibition or non-specific inhibition of inflammation can compromise critical response to infection, autoimmunity, and inadequate repair (69).

To reduce or avoid these risks, drugs need to be specifically designed to inhibit pro-tumorigenic inflammatory mediators such as certain cytokines [e.g., (TNF-α and IL-6)] and signaling pathways that are elevated within the TME (70). At the same time, such therapies must preserve an antitumor immune response by retaining beneficial components of inflammation that contribute to immune activation such as those for tissue repair or attraction of cytotoxic immune cells (71). Achieving this balance requires a more detailed knowledge as to what specific roles the various inflammatory pathways play in differing types of cancer and the identification of novel, highly-target-selective, proinflammatory targets (72).

Clinical Trials and Biomarkers

An important challenge in anti-inflammatory cancer therapy is the lack of reliable biomarkers to identify patients who will respond. The inflammatory response is a complex dynamic process and varies significantly between individuals and types of tumors (73). While certain pro-inflammatory mediators, such as IL-6, TNF-α and IL-1β are known to support cancer growth, the specific inflammatory components associated with each patients disease may differ. This heterogeneity makes the prediction of patient responses to therapeutics targeting inflammation difficult (74).

To solve this problem, identifying and validating the accurate biomarkers that can reflect the inflammatory status of TME and predict therapeutic response are urgently needed. These biomarkers could include some cytokines/chemokines or signaling molecules which are increased in tumor microenvironment and being associated with poor prognosis (75). Liquid biopsy techniques such as circulating tumor DNA, RNA, and protein have the potential for non-invasive detection of these markers. In addition, IHC or gene expression profiling from tumor biopsies may help determine the inflammatory nature of some malignancies and guide personalized treatment plans (76).

The efficacy of anti-inflammation approaches will depend on clinical trials that fully evaluate their safety and effectiveness in combination with standard cancer treatments. Although the preclinical evidence suggests that anti-inflammatory drugs can enhance treatment efficiency of chemotherapy, immunotherapy, and target therapy, these findings are not easy to translate on real patients and so need a thorough test across a variety of demography before they are used in the clinic (77). Potential damaging consequences of the modulation of inflammatory responses must be considered by clinical trials, because insufficient tuning could entail unexpected consequences as immune depression or excessive local tissue damage (78).

Overcoming Therapy Resistance

Resistance to therapy is a major challenge in oncologic treatment and represents a critical barrier to successful patient management. Despite the remarkable achievements achieved in regards to chemotherapy, immunotherapy, and targeted therapeutic drugs, a number of the malignancies have delevoped resistance to drug treatments. This resistance frequently leads to relapse and metastasis, a challenging aspect in cancer treatment (79).

The inflammation is also the key stimulator for inducing this drug resistance, it up-regulate some survival signaling pathways and contributes to immune escape mechanisms exploited by cancer cells (80). The pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF)-α have the potential to activate multiple signaling pathways including NF-κB and STAT3. These pathways mediate the increased of tumor cells survival, magulating proliferation, inhibiting apoptosis and enhancing DNA repair. These activities together promote resistance to chemotherapy and radiotherapy (81, 82).

In order to successfully overcome the formidable obstacle of therapeutic resistance, a comprehensive treatment strategy is required that includes inflammation-modulating agents in combination with established treatments. This broad-ranged approach is expected to act on both the cancer cells and the inflammatory microenvironment, which interconnects with mechanisms of resistance (83). For instance, cytokine inhibitors or NF-κB antagonists, added to chemotherapy, could help reducing the inflammatory signals that protect cancer cells from the damaging processes activated by chemo (84). Likewise, a combination of inflammation-modifying interventions and immune-based approaches such as immune checkpoint inhibitors may potentiate the anti-tumour immune response by alleviating the immunosuppression that is frequently evident in locoregional tumour microenvironments (85).

In addition, the formidable challenge of overcoming resistance in cancer treatments requires accurate

targeting of cells, such as CSCs- a specific subset of cells characterized by its remarkable capacities for self-renewal and its extraordinary resistance to classic therapeutic approaches in contrast to other cell types (86). It has been shown that inflammation is a crucial element in supporting the survival of these cancer stem cells, and therefore targeting those inflammatory pathways which maintain the support provided to these resistant population of cells could result into development of more potent therapeutic strategies (87). A rationally designed multi-targeted therapy targeting the CSC population and its pro-survival inflammatory factors offers an attractive approach for improving treatment efficacy leading to the potential of overcoming resistance against current therapies (88).

The development of combination drugs that effectively and cooperatively influence both the malignant tumor cells and the associated inflammatory processes within the tumor is a very appealing approach to dramatically enhance overall therapeutic efficacy of cancer therapy (89). Due to an ability to target the cancer cells and also against a surrounding inflammatory response, these new agents may dramatically improve on clinical outcomes in patient who have failed current treatment regimens (90). Further active investigation is warranted to determine the optimal combinations of anti-inflammatory agents with existing treatments as well as the clinical applicability and safety of these multi-faceted therapeutic approaches (91).

CONCLUSION

Inflammation is an important factor in cancer development, metastasis and resistance to therapy. The capacity to modulate inflammation, both alone, and in combination with traditional as well as novel anticancer agents holds substantial potential to enhance treatment responsiveness and improve patient outcomes. With a better appreciation for the intricate relationship between inflammatory response and tumor microenvironment, personalized and context-specific anti-inflammatory interventions are emerging as an absolute necessity. In the future years, research should focus on identification of reliable biomarkers to allow patient stratification, discovery of new and safer anti-inflammatory drugs and how they can be integrated into clinical management. PAVE'ing the way and bringing forward these efforts into properly-designed clinical trials will be essential to bridge novel preclinical findings into effective, real-life interventions that can help more patients with cancer.

Authors's Contribution

Maryam Abbasi Saeidi and Mina Ekrami Noghabi data curation; editing and review. The author read and confirmed the final manuscript.

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Conflict of Interest

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Consent for publication

Not Applicable

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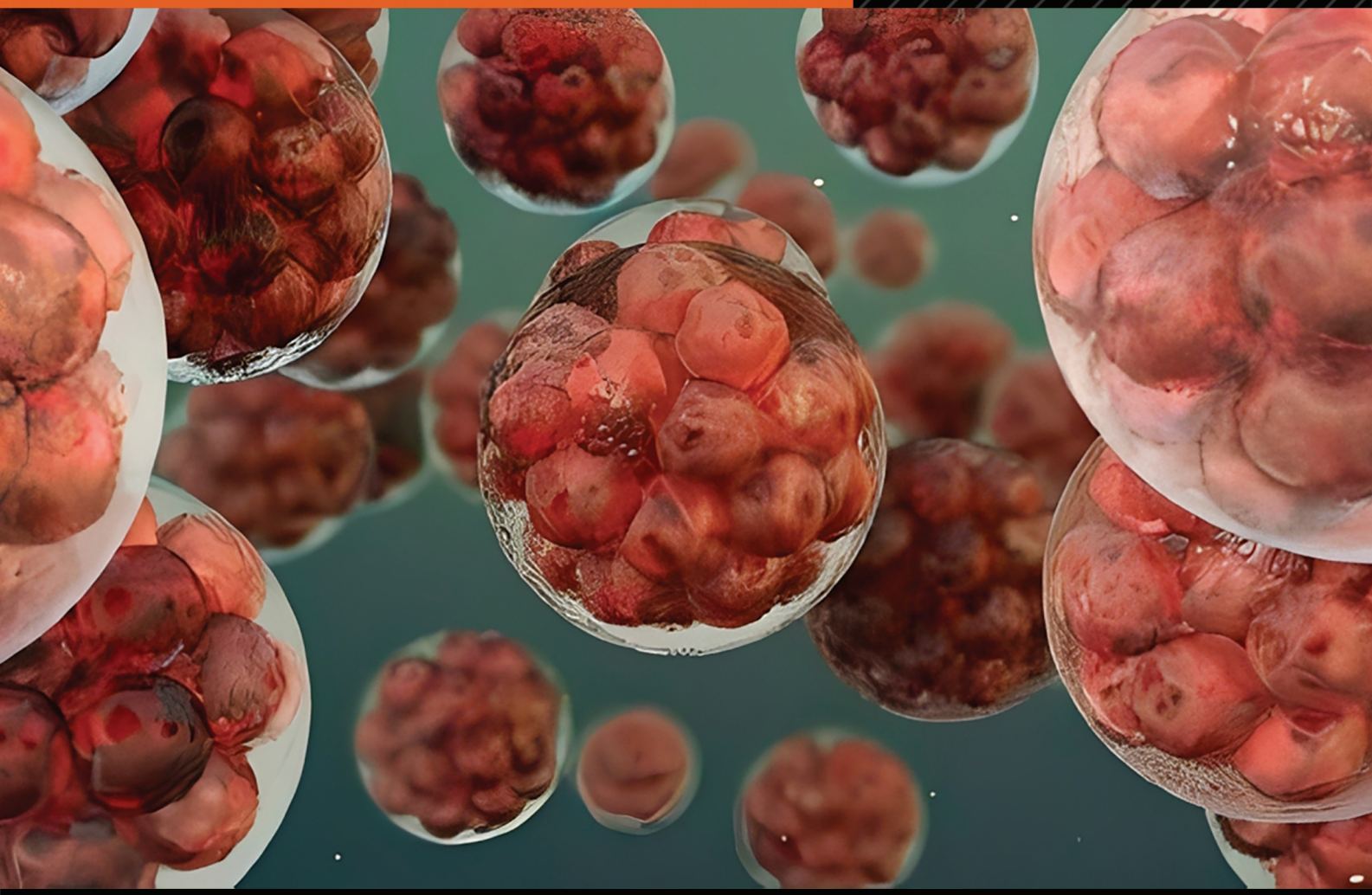

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