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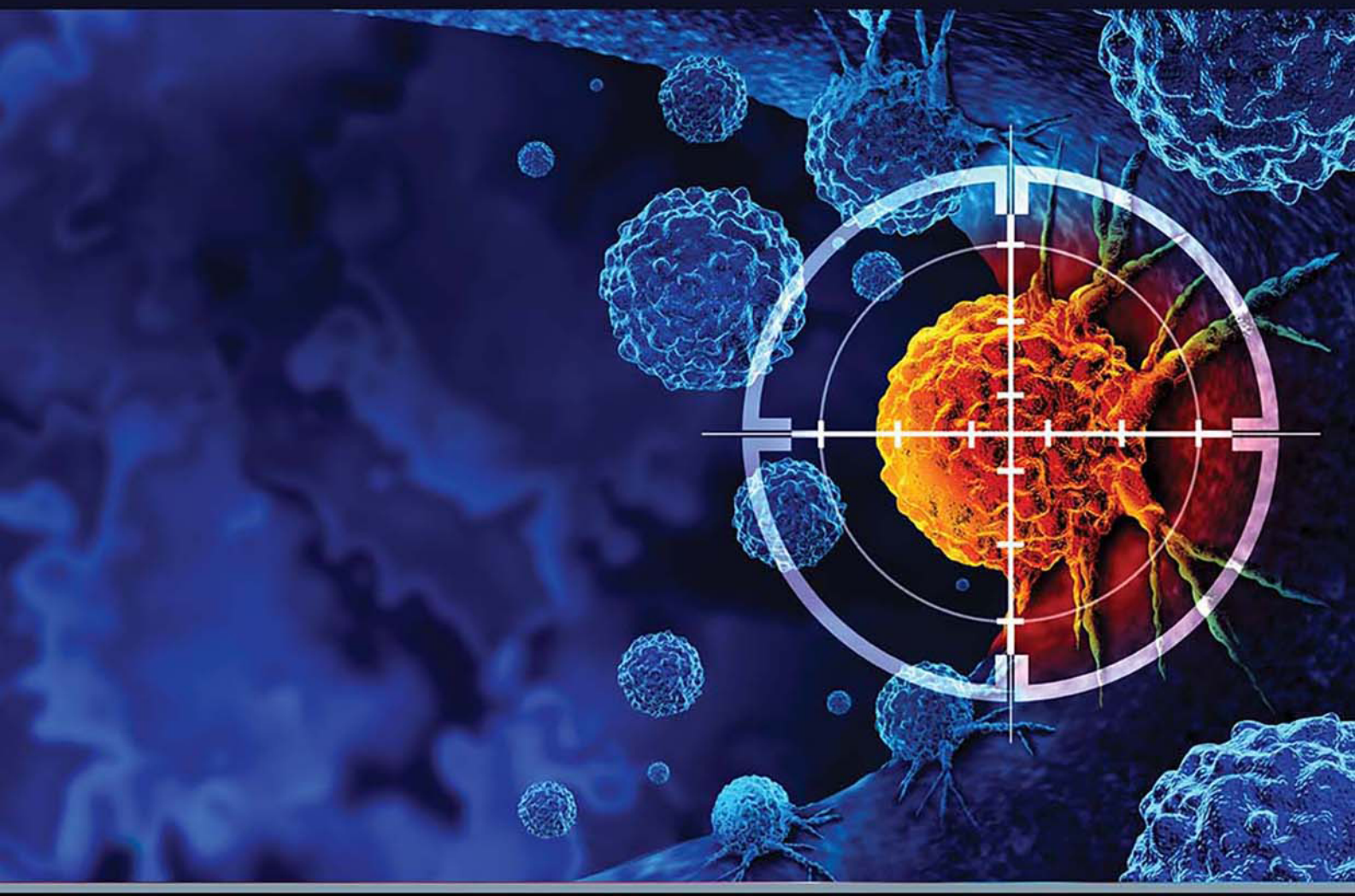

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Regulating Inflammation in Cancer: Effects on Metastasis and Treatment Outcomes

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ABSTRACT

Chronic inflammation is a pivotal element in the onset and advancement of cancer. It is crucial in tumor initiation, survival, metastasis, and therapeutic resistance. This study seeks to thoroughly examine the intricate relationship between inflammation and cancer, emphasizing the role of inflammatory processes in tumor formation and their influence on cancer therapy responses. We will investigate the molecular processes behind inflammation-induced cancer progression, analyze how inflammation affects metastasis, and assess its effects on the effectiveness of treatments like chemotherapy, immunotherapy, and targeted therapies. Furthermore, we will investigate prospective therapeutic approaches for addressing inflammation in cancer treatment, emphasizing the necessity for specific modulation to enhance treatment efficacy while mitigating adverse consequences such as immune suppression or heightened infection risk. The report finishes with a discussion on prospective research avenues focused on optimizing inflammation-targeting techniques to augment the efficacy of cancer therapies and better patient outcomes.

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INTRODUCTION

Inflammation as a Driver of Cancer

A basic driver of cancer progression is clearly chronic inflammation (1). Though much study has been done, the exact molecular and cellular processes by which inflammation drives tumor development, metastases, and therapeutic resistance remain poorly known (2). This review investigates how modulation of inflammatory pathways may improve therapeutic efficacy and offers a thorough investigation of the several roles of tumor-associated inflammation in cancer pathogenesis (3). Persistent invasion of several immune cell populations including macrophages, neutrophils, and myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment (TME) defines tumor-associated inflammation (4). Complex repertory of pro-inflammatory cytokines, chemokines, and growth factors secreted by these cells critically controls tumor cell proliferation, survival, immune evasion, and metastatic dissemination. Because neoplastic cells control immune constituents to create a supportive niche that supports tumor persistence and expansion, the TME is essential in organizing these inflammatory responses (5). This inflammatory milieu not only stimulates malignant cell proliferation but also confers resistance to apoptotic signals and helps invasion into nearby tissues and far-off metastatic sites. Over time, the dynamic equilibrium between pro-inflammatory and anti-inflammatory signals becomes disrupted, resulting in a chronic, tumor-promoting

inflammatory state that underlies cancer progression and therapeutic refractoriness (7).Obesity has become a major worldwide health concern as its frequency shockingly fast rises everywhere (8). Although a complicated interaction of genetic, environmental, and lifestyle factors clearly causes obesity, increasing evidence emphasizes the gut microbiome as the main actor in controlling body weight and distribution of fat (9). By means of the gut microbial community, several processes including modulation of energy harvest from the diet, control of host metabolism, and interaction with hormonal and immune pathways shape obesity (10). As was already noted, changes in the relative abundance and diversity of gut bacteria can affect the efficiency with which dietary nutrients are extracted and converted into useable energy (11). Higher ratios of Firmicutes to Bacteroidetes have been linked to increased capacity for fermenting complex polysaccharides into absorbable calories, so helping to explain increasing energy harvest and fat accumulation. Many times, obesity sufferers show this profile. This alters the lipid metabolism and storage of the host, so influencing adiposity and fat distribution patterns (12). This affects microbial habitat as well. Apart from producing energy, the gut flora greatly controls bile acid metabolism, so influencing the breakdown and absorption of fat directly. Gut bacteria convert primary bile acids into secondary bile acids which function as signaling molecules—by means of receptors such Takeda G-protein receptor 5 (TGR5) and farnesoid X receptor (FXR). These receptors define control of energy consumption, lipid metabolism, and glucose homeostasis. Changing the signaling routes of perturbingile acid allows dysbiosis to affect fat metabolism and increase fat storage, so fueling obesity (13). These results have spurred much research on recently developed therapeutic strategies meant to target the microbiome in order to fight obesity. Promising in changing the microbial community of the recipient towards a more balanced and metabolistically friendly profile, fecal microbiota transplantation (FMT), or transposing gut bacteria from a healthy donor to a recipient, has shown promise (11, 12). Although more clinical studies are needed to prove its long-term safety and efficacy, preliminary studies indicate that FMT may reduce adiposity (8) and improve metabolic parameters. Apart from FMT, prebiotics and probiotics are easily available and could be useful strategies to change the gut flora. Prebiotics especially help the growth of good bacteria by including inulin and fructooligosaccharides, so producing short-chain fatty acids (SCFAs), with anti-obesity effects including appetite control and higher energy expenditure (7). By altering inflammation, gut barrier function, and metabolic signaling pathways, live beneficial microorganisms such Lactobacillus and Bifidobacterium species which make up probiotics have shown different degrees of success in lowering body weight and improving metabolic health. Usually depending mostly on dietary changes and physical activity, these microbiome-based treatments show a good complement or substitute for conventional obesity control methods (8). These strategies may lower the risk of obesity-related complications, including type 2 diabetes, cardiovascular diseases, and some cancers, so improving weight loss outcomes, by tackling the fundamental bacterial causes of obesity (11).

Historical Perspective on the Link Between Inflammation and Cancer

It is well known that inflammation has been linked to cancer over the ages. Research conducted in the past has shown that those who are afflicted with chronic inflammatory disorders have a higher probability of developing cancer. Back in 1863, Rudolf Virchow proposed that cancer arises at sites of chronic inflammation. He observed leukocyte infiltration in tumor tissues, suggesting an inflammatory origin of cancer (8, 9). Furthermore, the middle of the 20th century marked a major advancement in understanding the molecular basis of this interaction (8). The identification of significant inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), as well as angiogenic factors, such as vascular endothelial growth factor (VEGF), and crucial signaling pathways, such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), has led to a more advanced understanding of the role that inflammation plays in the development, progression, and metastases of cancer. Using these molecular mediators also allows one to create fresh therapeutic approaches meant to stop tumor development and control inflammation by means of their interactions. Promising effects of the present drugs that focus on pro-inflammatory pathways—such as immune checkpoint inhibitors and tailored anti-inflammatory drugs—have been shown over several cancer types (10). Clinical environments are where these treatments are under testing right now.

Therapeutic Implications: Targeting Inflammation to Improve Cancer Therapy

New developments in cancer treatment have highlighted the importance of understanding the tumor microenvironment and its inflammatory components (11). Targeting drugs and immunotherapies—such as immune checkpoint inhibitors—by letting the exact targeting of neoplastic cells has revolutionized cancer treatment (12). Constant inflammation in the tumor microenvironment can compromise the efficacy of these treatments by means of immune suppression, generation of drug resistance, and modification of

the tumor vasculature. Modern cancer research mostly seeks solutions by concentrating on the inflammatory aspects of the tumor microenvironment (TME), so overcoming these challenges. Blocking the inflammatory cytokines TNF-α and Interleukin-6 (IL-6) may interfere with tumor-supportive signaling networks in the tumor microenvironment (11). In addition to this, ihibiting NF-κB pathway which is a central regulator of inflammatory gene expression that frequently activated in tumors, has been shown to reduce tumor progression in preclinical models and can be evaluated to be used in cancer therapy (9). Current treatments may become more efficient, patient outcomes may be improved, and side effects may be reduced by changing inflammatory paths in tumors (14).

Mechanisms of Inflammation in Cancer Progression

Key Molecular Pathways in Inflammation and Cancer

Many biological mechanisms support the explanation of the cancer development caused by inflammation. These pathways underlie important mechanisms controlling cell survival, proliferation, migration, angiogenesis, and immune evasion (15). The NF-κB signaling pathway is crucially controlling the expression of pro-inflammatory cytokines, survival genes, and genes linked with immune evasion (16). Under stimulation by inflammatory cytokines such as TNF-α and IL-1β, NF-κB moves to the nucleus, where it starts the transcription of pro-survival and pro-inflammatory genes (17). This activation keeps a pro-inflammatory tumor microenvironment that promotes tumor growth intact. The PI3K/AKT and MAPK pathways are two further crucial signaling channels that support inflammation-induced cancer development (18). Crucially influencing factors of tumor viability and metastases, these pathways regulate cellular proliferation, migration, and death resistance. Most important in raising tumor aggressiveness and therapeutic resistance is the activation of these pathways by inflammatory signals, including cytokines and growth factors (19). Moreover, reactive oxygen species (20) generated by oxidative stress brought on by inflammation act as secondary messengers in signaling pathways (21). Chronic inflammation contributes to cancer development by producing various inflammatory mediators and activating signaling pathways that facilitate tumor growth, metastasis, and the formation of new blood vessels. Prostaglandins, which are lipid molecules whose synthesis is controlled by COX, are one of these mediators that are crucial in the link between inflammation and cancer. Many cancer types frequently have overexpressed COX-2 in particular (22).

Tumor Microenvironment and Immune Cells

The tumor microenvironment (TME) is considere a dynamic network of tumor cells, immune cells, stromal cells, and extracellular matrix (ECM). Among the several immune cell types whose recruitment and activation are affected by inflammation signals are tumor-associated macrophages (TAMs), neutrophils, and myeloid-derived suppressor cells (MDSCs), thus changing the tumor microenvironment (TME). Later on these immune cells secrete a spectrum of cytokines, growth factors, and matrix-degrading enzymes supporting tumor cell survival, immune evasion, and metastatic spread (23, 24). Often polarized into an M2 phenotype, tumor-associated macrophages (TAMs) dramatically promote tumor growth and suppress anti-tumor immune responses (25). VEGF provides tumors with the necessary nutrients and oxygen for their development stimulation; thus, one of the pro-angiogens produced by M2-polarized tumor-associated macrophages supplies growth (26). Furthermore, by releasing immunosuppressive cytokines such as IL-10 and TGF-β, these macrophages reduce the activity of cytotoxic immune cells, including CTLs and NK cells (27). Cross-talk between the gut microbiome and the tumor microenvironment can also influence the functional polarization of TAMs. Recent studies suggest that microbial metabolites and signals from the gut microbiota may reprogram TAMs toward a pro-tumoral phenotype, to enhance both angiogenesis and immunosuppression (23). Although their primary goal is infection prevention, neutrophils also encourage tumor growth by secreting cytokines such as IL-8, which increase tumor cell motility and invasion (28). Targeting extracellular matrix (ECM) and increasing tumor cell penetration into surrounding tissues, matrix metalloproteinases (MMPs) buried under neutrophils and other immune cells create a feedback loop, aggravating inflammation and speeding tumor spread and growth (29).

Oxidative Stress and DNA Damage

Chronic inflammation in the tumor microenvironment (TME) leads to sustained production of reactive oxygen species (20), which play a complex role in cancer development and therapy resistance. At moderate levels, ROS act as signaling molecules that activate pro-survival pathways, promoting tumor cell proliferation, immune evasion, and adaptation to stress. Chronic infection-driven inflammation can also causes single-strand DNA breaks (SSBs) via ROS and reactive nitrogen species (RNS). This damage can escalate to double-strand breaks (DSBs), especially through NF-κB pathway activation, thereby contributing significantly to genomic instability (19, 20). However, excessive ROS cause oxidative damage to cellular components such as lipids, proteins, and particularly DNA, leading to mutations, genomic instability, and activation of oncogenes (30). This genomic instability

fuels tumor progression and enhances the aggressive phenotype of cancer cells by enabling them to evade apoptosis (31).

Importantly, ROS contribute to resistance against conventional cancer therapies. Oxidative stress supports the survival of cancer stem cells (CSCs) a subpopulation resistant to chemotherapy, radiotherapy, and immunotherapy thereby promoting tumor relapse and metastasis (32). Inflammatory cytokines like IL-6 and TNF-α maintain elevated ROS levels, creating a feedback loop that reinforces proliferative signaling, immune suppression through recruitment of immunosuppressive cells (e.g., MDSCs and Tregs), and angiogenesis. Additionally, inflammation-driven fibrosis in the TME forms a physical barrier that limits the effective delivery of chemotherapeutic drugs (33).

Together, these mechanisms illustrate how chronic inflammation and oxidative stress undermine therapeutic efficacy by enhancing tumor cell survival, fostering an immunosuppressive microenvironment, and obstructing drug delivery (34). Targeting ROS production and inflammatory pathways such as NF-κB and STAT3, alongside conventional treatments, represents a promising approach to overcoming therapy resistance and improving patient outcomes (35).

Inflammation and Metastasis

Inflammation as a Driver of Metastasis

Metastasis, the dissemination of cancer cells from the main tumor to remote organs, is a principal factor in cancer-related mortality, accounting for the majority of cancer fatalities. Inflammation is crucial in facilitating metastasis by enhancing tumor cell motility, invasion, and survival in remote organs (36). Pro-inflammatory cytokines, including IL-6 and TNF-α, along with chemokines such as IL-8, augment tumor cell motility and amplify their invasive potential by activating signaling pathways that promote epithelial-to-mesenchymal transition (EMT) (37). Epithelial-mesenchymal transition (EMT) is a pivotal process in which epithelial tumor cells attain mesenchymal characteristics, facilitating their detachment from the main tumor and enhancing their capacity to infiltrate adjacent tissues (38). Low oxygen levels (hypoxia) and prolonged inflammation combine to enhance the relationship between HIF-1 and NF-κB, which in turn stimulates the production of important transcription factors involved in EMT, such as TWIST and SNAIL. This process makes tumor cells more invasive and raises their potential to metastasise (17, 18).

Moreover, inflammatory cytokines stimulate the development of matrix metalloproteinases (MMPs), enzymes responsible for the degradation of the extracellular matrix (ECM). The deterioration of the extracellular matrix enables tumor cells to penetrate the physical barriers of adjacent tissues and enter the bloodstream, thereby accessing distant organs (39). Upon entering circulation, these circulating tumor cells (CTCs) can form metastatic lesions in remote organs, facilitating disease dissemination. Inflammation also stimulates angiogenesis, the development of new blood vessels, which is essential for maintaining the blood supply of the expanding tumor and promoting more metastatic dissemination (40). Pro-inflammatory cytokines, including VEGF (vascular endothelial growth factor), are pivotal in the angiogenic process, guaranteeing that the tumor is adequately supplied with nutrients and oxygen to sustain its growth and spread (41).

Molecular Mechanisms of Inflammation-Induced Metastasis

The stimulation of inflammatory cytokines in the tumor microenvironment results in extracellular matrix remodeling, a crucial phase in metastasis. MMPs released by tumor and immune cells degrade the ECM, promoting tumor cell mobility and invasion (42). Furthermore, inflammation facilitates angiogenesis by enhancing the release of VEGF and additional pro-angiogenic molecules. This novel vasculature not only facilitates tumor proliferation but also offers a pathway for cancer cells to infiltrate the bloodstream, thus promoting metastatic spread (43). In summary, inflammation facilitates metastasis by various pathways, including the activation of epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) breakdown, and angiogenesis. These activities augment the invasive characteristics of tumor cells, facilitating their dissemination to distant organ and the formation of new tumors.

Impact of Inflammation on Treatment Response

Chemotherapy Resistance Induced by Inflammation

Chronic inflammation also stimulates DNA repair mechanisms and activates key survival pathways like NF-κB and STAT3, while the development of inflammation-induced fibrosis acts as a barrier to drug delivery, ultimately decreasing the effectiveness of chemotherapy and contributing to tumor recurrence (25, 26). Chemotherapy remains a cornerstone of cancer treatment; however, its effectiveness is often compromised by chronic inflammation within the tumor microenvironment (44). Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β activate signaling pathways including NF-κB and STAT3, which promote cancer cell survival and inhibit apoptosis, thereby protecting tumor cells from chemotherapy-induced cell death (45). These cytokines also enhance DNA repair mechanisms, further increasing resistance to DNA-damaging chemotherapeutic agents (46). In addition, inflammation can induce fibrosis in the tumor microenvironment, creating a physical barrier

that limits drug penetration and reduces chemotherapy delivery to tumor cells (47). The inflammatory milieu also supports the maintenance of cancer stem cells, a subpopulation with high chemoresistance that contributes to tumor recurrence and metastasis after treatment (48). Combining chemotherapy with strategies that target inflammatory pathways such as NF-κB inhibitors or cytokine-neutralizing antibodies may reduce tumor-promoting inflammation and improve cancer cell sensitivity to chemotherapy, offering a promising avenue to overcome resistance and enhance therapeutic outcomes (1).

Immunotherapy Resistance

Immunotherapy has emerged as a transformative cancer treatment by utilizing the body's immune system to identify and eliminate tumor cells. Chronic inflammation within the tumor can impede the efficacy of immunotherapies by producing immune suppression (49). Inflammation can enhance the expression of immunological checkpoints such as PD-L1, which suppresses immune responses by interacting with PD-1 receptors on T cells, so obstructing their ability to target cancer cells. Inflammatory cytokines, including IL-10 and TGF-β, facilitate the recruitment of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), thereby attenuating immune responses and aiding in immune evasion (50).

Besides the activation of immunological checkpoints, inflammation may also induce immune exhaustion in tumor-infiltrating lymphocytes (TILs). Pro-inflammatory signals can deplete the effector capabilities of T lymphocytes, diminishing their efficacy in targeting tumor cells (51).

Acute inflammation might paradoxically enhance anti-tumor immunity by facilitating the infiltration of immune cells, including cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, into the tumor (52). This indicates that regulating inflammation systematically may improve the effectiveness of immunotherapy. Consequently, medicines that specifically inhibit pro-inflammatory pathways while augmenting immune activation may enhance the efficacy of immunotherapies (53).

Targeted Therapies and Inflammation

Targeted medicines seek to obstruct particular signaling pathways that promote cancer cell proliferation. The existence of inflammation in the TME can affect the effectiveness of these medicines. Inflammatory cytokines, including IL-6 and TNF-α, can activate the PI3K/AKT pathway, frequently associated with tumor cell survival, resistance to apoptosis, and metastasis (11). This activation can provide resistance to targeted medicines by circumventing the therapeutic effects of route blockage (54). Furthermore, inflammation-induced extracellular matrix remodeling can affect the efficacy of targeted therapy by modifying the tumor's physical properties. Increased extracellular matrix stiffness, frequently resulting from inflammation, can obstruct the infiltration of targeted therapeutics into the tumor (55).

Combining targeted therapy with anti-inflammatory drugs may boost their effectiveness. Utilizing inhibitors of inflammatory cytokines or immune modulators in conjunction with targeted therapy may enhance medication delivery and surmount resistance mechanisms (56).

Therapeutic Strategies for Targeting Inflammation in Cancer

Anti-Inflammatory Agents

Targeted medicines seek to obstruct particular signaling pathways that promote cancer cell proliferation. The existence of inflammation in the TME can affect the effectiveness of these medicines (57). Inflammatory cytokines, including IL-6 and TNF-α, can activate the PI3K/AKT pathway, frequently associated with tumor cell survival, resistance to apoptosis, and metastasis. This activation can provide resistance to targeted medicines by circumventing the therapeutic effects of route blockage (58).

Furthermore, inflammation-induced extracellular matrix remodeling can affect the efficacy of targeted therapy by modifying the tumor's physical properties. Increased extracellular matrix stiffness, frequently resulting from inflammation, can obstruct the infiltration of targeted therapeutics into the tumor. Combining targeted therapy with anti-inflammatory drugs may boost their effectiveness. Utilizing inhibitors of inflammatory cytokines or immune modulators in conjunction with targeted therapy may enhance medication delivery and surmount resistance mechanisms (55). Natural polyphenols—including resveratrol, kaempferol, and quercetin—have been demonstrated to inhibit the PI3K/Akt/mTOR signaling pathway and trigger apoptosis in various cancer cell lines, thereby augmenting the efficacy of targeted therapies. Additionally, inflammation-induced extracellular matrix (ECM) stiffness contributes to drug resistance by activating integrin–PI3K/Akt signaling and impeding drug infiltration (23, 40, 51).

Immunomodulatory Therapies

Immunomodulatory treatments represent a viable approach for addressing inflammation in cancer. These therapies seek to modulate the immune system to foster a more advantageous inflammatory response that bolsters anti-tumor immunity (59). One strategy involves employing immune checkpoint inhibitors that obstruct inhibitory receptors on immune cells,

including PD-1 and CTLA-4. By obstructing these receptors, checkpoint inhibitors disengage the "brakes" on the immune system, enabling T cells and NK cells to target and eradicate tumor cells more (60). Chronic inflammation can result in immunological depletion and resistance to immunotherapy, thereby rendering the control of inflammatory responses a critical research focus (61). Therapies that prevent the recruitment of immunosuppressive cells, such as MDSCs or Tregs, may augment the effectiveness of immune checkpoint inhibitors (62). Likewise, employing drugs that regulate inflammatory cytokines in the tumor microenvironment may enhance the infiltration and activation of immune cells, including cytotoxic T lymphocytes and natural killer cells (63).

Targeting Tumor-Associated Inflammatory Pathways

Alongside generic anti-inflammatory drugs, therapies that precisely target the inflammatory pathways implicated in cancer progression provide a more targeted approach (64). The NF-κB pathway is a principal target for cancer treatment because of its pivotal involvement in inflammation and tumor advancement. Inhibitors of NF-κB signaling, including IKK inhibitors, have demonstrated potential in preclinical research by diminishing tumor growth and metastasis (65). Apart from artificial NF-κB inhibitors, natural substances like polyphenols have demonstrated the capacity to inhibit NF-κB signaling, hence enhancing ferroptosis and tumor cell death. Furthermore, by increasing the effectiveness of chemotherapy and radiation therapy by suppressing NF-κB, widely used anti-inflammatory drugs such as aspirin and glucocorticoids have shown therapeutic benefits (55, 56).

Additional intriguing targets encompass JAK/STAT signaling and PI3K/AKT pathways, frequently stimulated by inflammatory cytokines. Inhibiting these pathways may diminish inflammation and tumor advancement (66). The advancement of tailored medicines that precisely regulate inflammation inside the tumor microenvironment is highly promising. Clinical trials are necessary to ascertain the safety and efficacy of these techniques in conjunction with conventional cancer therapy (67).

CHALLENGES AND FUTURE DIRECTIONS

Specificity in Targeting Inflammation

Targeting inflammation offers a potential approach to enhancing cancer therapy results; yet, substantial obstacles accompany its implementation. A principal challenge is the precise targeting of particular inflammatory pathways that promote cancer progression while preserving the body's natural immunological activities (68). Inflammation is crucial for immunological monitoring, tissue restoration, and protection against pathogens. Excessive suppression or general inhibition of inflammation may compromise essential functions, rendering the body susceptible to infections, autoimmune responses, or insufficient repair (69). To mitigate such risks, medicines must be carefully formulated to target pro-tumorigenic inflammatory mediators, including particular cytokines (e.g., TNF-α, IL-6) and signaling pathways (e.g., NF-κB, JAK/STAT), which are increased inside the tumor microenvironment (TME) (70). Simultaneously, these therapies must maintain the anti-tumor immune response by preserving advantageous elements of inflammation that facilitate immune activation, including those associated with tissue repair or the recruitment of cytotoxic immune cells (71). Attaining this equilibrium necessitates a more sophisticated comprehension of the distinct functions that diverse inflammatory pathways serve in different cancer types, alongside the discovery of innovative, highly selective inflammatory targets (72).

Clinical Trials and Biomarkers

A significant problem in inflammation-targeted cancer therapeutics is the absence of dependable biomarkers to determine which patients will benefit from these interventions. Inflammation is a complex, dynamic process that significantly differs among individuals and various tumor kinds (73). Although specific pro-inflammatory mediators such as IL-6, TNF-α, and IL-1β are associated with cancer growth, the particular inflammatory elements present in each patient's disease may vary. This variability complicates the prediction of patient responses to medicines aimed at inflammation (74). To tackle this difficulty, it is crucial to find and confirm biomarkers that can precisely indicate the inflammatory condition of the tumor microenvironment and forecast therapy effects. These biomarkers may encompass certain cytokines, chemokines, or signaling molecules that are elevated in the tumor microenvironment and correlated with unfavorable prognosis (75). Liquid biopsy methodologies, which identify circulating tumor DNA, RNA, and proteins, may be pivotal in the non-invasive detection of these biomarkers. Moreover, immunohistochemical labeling or gene expression analysis of tumor biopsies may elucidate the inflammatory characteristics of certain malignancies, hence assisting in the formulation of individualized treatment strategies (76). The success of inflammation-targeting methods will rely on clinical trials that thoroughly assess their safety and efficacy alongside conventional cancer treatments. While preclinical evidence indicates that anti-inflammatory medicines could improve the effectiveness of chemotherapy, immunotherapy, and targeted therapies, implementing these findings in

clinical settings necessitates comprehensive testing across varied patient demographics (77). Clinical trials must evaluate the possible detrimental effects of inflammatory modulation, as improper targeting may result in unforeseen outcomes, including immune suppression or severe tissue damage (78).

Overcoming Therapy Resistance

Therapeutic resistance continues to be a major impediment in oncological treatment. Notwithstanding the progress in chemotherapy, immunotherapy, and targeted medicines, numerous malignancies develop resistance to treatment, resulting in relapse and metastasis (79). Inflammation is pivotal in fostering medication resistance by activating survival signaling pathways and facilitating immune evasion mechanisms (80). Pro-inflammatory cytokines, including IL-6 and TNF-α, can activate the NF-κB and STAT3 pathways, enhancing tumor cell survival and proliferation, inhibiting apoptosis, and augmenting DNA repair mechanisms, all of which facilitate resistance to chemotherapy and radiation (81, 82).

A multimodal approach that integrates inflammation-modulating medications with conventional treatments is necessary to surmount therapy resistance. This strategy seeks to address both the cancer cells and the inflammatory milieu, which is integral to resistance mechanisms (83). For instance, the integration of anti-inflammatory medicines, such as cytokine inhibitors or NF-κB antagonists, with chemotherapy may diminish the inflammatory signals that shield cancer cells from chemotherapy-induced harm (84). Likewise, integrating inflammation-modulating treatments with immunotherapies such as immune checkpoint inhibitors may augment immune responses by mitigating immune suppression within the tumor microenvironment (85).

Moreover, surmounting resistance necessitates the targeting of cancer stem cells, a subset of cells characterized by self-renewal capabilities and notable resistance to conventional therapies (86). Inflammation has been shown to support the survival of cancer stem cells, and targeting the inflammatory pathways that sustain these cells could lead to more effective therapies (87). A combination therapy that addresses both the stem cell population and the inflammatory factors sustaining their life presents a viable strategy for enhancing treatment effects and surmounting resistance (88).

The formulation of combination medicines that simultaneously address cancer cells and tumor-associated inflammatory processes constitutes a promising approach to augmenting the efficacy of cancer treatment (89). By targeting both cancer cells and the inflammatory milieu, these medicines may enhance outcomes for patients unresponsive to existing therapy protocols (90). Ongoing research is crucial to determine the most effective combinations of anti-inflammatory medicines with current therapy and to assess the clinical viability and safety of these approaches (91).

CONCLUSION

Inflammation is a critical factor influencing cancer progression, metastasis, and resistance to therapy. Targeting inflammatory pathways, in conjunction with conventional and emerging cancer treatments, holds significant promise for enhancing therapeutic efficacy and improving patient outcomes. As our understanding of the complex interplay between inflammation and the tumor microenvironment deepens, it becomes increasingly evident that personalized and context-specific anti-inflammatory strategies will be essential. Looking forward, future research should prioritize the identification of robust biomarkers to guide patient stratification, the development of novel and safer anti-inflammatory agents, and the integration of these strategies into clinical practice. Advancing these efforts through well-designed clinical trials will be crucial for translating promising preclinical insights into effective, real-world interventions that can benefit a broader population of cancer patients.

Authors's Contribution

Irem Selmi: 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

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From Uniform to Unique: The Shift toward Personalized Dietary Plans

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ABSTRACT

Precision nutrition is now feasible thanks to recent developments in genomic and multi-omic technology, which have significantly changed our understanding of the complex interactions between nutrition, genetics, and health.Sometimes shortened to nutrigenetics, epigenetics, metagenomics, and nutrigenomics, nutritional genomics is the study of how environmental influences, gut flora, genetic variants, and gene expression affect food responses and illness risk. This new work offers significant fresh ideas for modifying mode to fit traditional food systems, cultural conventions, and personal genetic profiles. Diet evolution aims to solve the flaws in the "one-diet-fits-all" approach in view of the global increase in chronic diseases. Variations in genes and cultural standards call into doubt the health advantages of often advised diets, including the Mediterranean model, when considered in specific communities. Customized diet regimens aimed at enhancing health should take into account lifestyle, regional cuisine, microbiome variety, genetic inheritance, and other elements. Combining traditional cooking skills with modern scientific information provides a culturally sensitive, environmentally friendly, and effective method to prevent diseases and promote long-term health improvement as is becoming the case in public health strategies.

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INTRODUCTION

Combining multi-omic technologies into nutritional science to better grasp how diet interacts with human biology, genomic nutrition, also known as nutritional genomics, is a burgeoning topic leading front stage in precision medicine (1). Mostly, this discipline is defined by two associated domains: nutrigenomics and nutrigenetics (2). Nutrigenetics investigates how certain genetic variations, such as single-nucleotide polymorphisms (SNPs), affect physiological reactivity to specific foods and dietary patterns. Nutrigenomics focuses on how different parts of our diet, like vitamins and other active substances, can influence how our genes work, regardless of our inherited genetic makeup, using methods studied in transcriptomics, proteomics, and metabolomics (3).

Advances in the field have produced nutritional epigenetics and nutritional metagenomics, therefore extending the field of genomic nutrition. These subfields investigate how chromatin-level changes regulate gene activity and the role of gut bacteria, often referred to as the "second genome," in controlling host metabolic and immunological responses (4). In addition to these biological processes, physical exercise, psychological and emotional stress, and environmental toxins also influence nutritional outcomes. These elements

taken together provide a robust foundation for the development of tailored dietary programs that meet personal differences in genetics, gut flora, and lifestyle (5).

Genomic Legacy and Nutritional Transition

Dynamic by nature, both contemporary dietary changes and evolutionary events shape gene-nutrient interactions. Humans have changed dramatically over time in how they acquire and process nutrients; genes are central in regulating these needs. Historically, local surroundings and easily available food sources have affected diets (6). From pre-globalization to post-globalization diets, many countries today are switching, which harms food quality, nutrient density, and access. Along with this shift, chronic diseases have exploded, mostly from easy access to highly processed foods (7).

Human evolution has consisted of several phases of adaptation to different environmental and dietary conditions; the human genome has developed in response to nutrient availability in different ecosystems. This has led to the selection of gene variants helpful in specific environments (8). Although useful in one context, these adaptations could not be optimal as the nutritional environment changes, especially given the continuous epidemiological transition. Reduced physical activity, increased stress, and environmental pollution all affect lifestyle choices that aggravate this evolutionary mismatch and help chronic diseases to flourish (9).

Some societies still rely nutritionally on traditional diets, even while others have embraced more modern or hybridized eating patterns. These dietary changes, meanwhile, do not always translate into better health results. The global increase in obesity and related chronic diseases has impacted populations across all socioeconomic levels; urban areas see especially high rates because of the consumption of processed foods (9).

On the other hand, there is mounting evidence that maintaining or revitalizing indigenous food knowledge and upholding traditional dietary practices can significantly affect social and cultural well-being. These diets, often based on whole, natural foods, have been associated with improved general health outcomes and a decreased risk of chronic diseases (10). Before industrialization and the explosion of highly processed foods, traditional diets mirrored earlier stages of human food evolution. Thus, the emphasis of personalized nutrition plans should be on bringing back these classic, nutrient-dense foods that have historically molded human genes. These foods are not universally applicable, though; their differences will depend much on geography, ethnicity, and cultural practices (11).

Understanding the intricate link between genes, diet, and culture is vital as we negotiate the modern nutritional terrain. Personalized nutrition approaches that incorporate traditional food systems could help mitigate the health challenges posed by contemporary dietary patterns, offering a more sustainable and health-promoting model for future generations (12).

Personalized Nutrition: A Pathway to Preventing Diet-Related Chronic Diseases

Originally postulating nutrigenetics in 1977, a historic event that fundamentally changed our knowledge of the interaction between genes and diet, Dr. Richard O. Brennan predated the genomics era. At first, he used this term to explain how diet might affect genetically linked diseases, including hypoglycemia. This early realization helped one to see how important genes are for human reaction to and processing of food (13). Moreover, it underlined the need for customized diets for patients with hereditary single-gene metabolic diseases, such as phenylketonuria, who need early intervention to sufficiently control their conditions (14).

But the post-genomic era is when personalized diet as we know it now really evolved. The Human Genome Project, which showed most chronic diseases arise from complex interactions between genetic variations such as single nucleotide polymorphisms (SNPs), copy number variations, and insertion-deletion polymorphisms and environmental factors, particularly diet, especially diet, started this transforming period (15). These results unequivocally show that rather than only their genetic predispositions, a dynamic interaction between genes and environmental exposures, including dietary factors, determines diseases such as diabetes, cardiovascular disease, and obesity. Beginning simultaneously with the genomics revolution, the Human Microbiome Project aims to investigate the great variety of microorganisms living in the human body and their vital function in health (16). Since it has improved our understanding of how gut bacteria interact with human genes and affect disease outcomes, this project underlines the need for tailored dietary approaches. These findings verified that the direction of nutrition has to be from a one-size-fits-all approach and instead take into account the particular genetic and microbiotic traits (17).

Supported by multi-omic technologies (including genomics, metabolomics, and proteomics), personalized nutrition, also known as precision nutrition, has transformed healthcare by realizing that every person's biological composition is unique and, so, requires customized dietary recommendations (18). By matching nutrition therapies for individuals based on their genetic predispositions, environmental exposures, and lifestyle choices, this can help improve health outcomes (19). If significant results are to come,

though, customized nutrition must be developed in harmony with the genetic and cultural context of the target population. Although particular risk alleles are significant, equally so is the impact of dietary practices and food culture, which have molded populations for millennia (20).

For example, variations in food customs, nutritional availability, and historical practices could mean that a diet fit for one genetic population would not help another. Thus, a customized diet has to include cultural food practices that have evolved to meet the specific needs of different populations, depending on environmental and genetic elements, transcending genetic profiling (21). Realizing the interconnectedness of genetic inheritance and cultural history will help one to design major and successful nutrition interventions. Still, the development of tailored diets seems to be a reasonable and fascinating goal despite the challenges (22). Advances in genetic research, multi-omic technologies, and public health policies are driving field development while societal acceptance of customized healthcare approaches rises steadily (23). Personalized nutrition is becoming more and more valuable for governments, academic institutions, and industry players, not only for enhancing individual health but also for tackling the growing global load of diet-related chronic diseases. Moreover, the growing awareness of cultural eating habits presents an opportunity to combine traditional knowledge with modern nutritional science, thereby ensuring that customized diets are both scientifically based and culturally appropriate (24).

Even if a customized diet has great potential, its successful implementation will depend on a sophisticated strategy honoring genetic variety and cultural food practices. As this field develops, integrating genetics, nutrition, and culture will be crucial to designing diets that not only prevent disease but also enhance long-term health and well-being for people all around (25). Before the genomics age, Dr. Richard O. Brennan first proposed nutrigenetics in 1977, a landmark event that drastically altered our understanding of the link between genes and diet. Initially, he used this phrase to describe how diet might influence genetically linked diseases, including hypoglycemia. This early insight prepared one to understand how crucial genes are to the human response to and processing of nutrients (26). Furthermore, it emphasized the need for tailored diets for those with inherited single-gene metabolic disorders, such as phenylketonuria, who require early intervention to properly manage their conditions (27). But the post-genomic era is when individualized diet, as we know it now, truly developed. This important change started when the Human Genome Project was finished, showing that most long-term diseases come from complicated interactions between genetic differences, like single nucleotide polymorphisms (SNPs), copy number variations, and insertion-deletion polymorphisms, and environmental factors, especially diet. These findings clearly show that rather than only their genetic predispositions, a dynamic interaction between genes and environmental exposures, including dietary elements, defines diseases including diabetes, cardiovascular disease, and obesity (29).

Starting concurrently with the genomics revolution, the Human Microbiome Project set out to explore the enormous diversity of microorganisms inhabiting the human body and their essential role in health (30). This project underlines the need for customized dietary approaches since it has enhanced our knowledge of how gut bacteria interact with our genes and influence disease outcomes. These results confirmed that the direction of nutrition has to be away from a one-size-fits-all approach and that individualized genetic and microbiotic profiles should take the front stage (31).

Supported by multi-omic technologies (including genomics, metabolomics, and proteomics), personalized nutrition, also known as precision nutrition, has revolutionized healthcare by realizing that every person's biological composition is unique and, so, requires customized dietary recommendations (32). This could improve health outcomes by matching nutrition interventions for people based on their genetic predispositions, environmental exposures, and lifestyle choices. However, tailored nutrition needs to be developed in harmony with the genetic and cultural context of the target population (37, 38) if major results are to come (33). Although specific risk alleles are important, equally so is the influence of dietary habits and food culture, which have shaped populations for millennia. For example, variations in food customs, nutritional availability, and historical practices could mean that a diet fit for one genetic population would not help another (34). Therefore, customized nutrition must incorporate cultural food practices that have evolved to meet the specific needs of different populations based on environmental and genetic factors, extending beyond just genetic profiling. Realizing the interconnectedness of genetic inheritance and cultural history will help one create major and successful nutrition interventions (35).

Still, the development of tailored diets seems to be a reasonable and fascinating goal despite the challenges. Rising steady societal acceptance of individualized healthcare approaches is driving development in the field with advances in genetic research, multi-omic technologies, and public health policies (36). Personalized nutrition is becoming more and more important to governments, academic institutions, and industry players not only for enhancing individual health but also for helping to alleviate the growing global burden of diet-related chronic diseases. Furthermore, the growing consciousness of cultural

food practices offers a chance to combine traditional knowledge with contemporary nutritional science so that customized diets are both scientifically based and culturally relevant (37).

In essence, even if tailored nutrition has enormous potential, its successful application will depend on a sophisticated strategy that honors genetic variety and cultural food practices. As this field evolves, the integration of genetics, nutrition, and culture will be vital to developing diets that not only prevent disease but also enhance long-term health and well-being for individuals worldwide (38).

The One-Diet-fits- All Saga

Maintaining a good lifestyle at all phases of human existence depends on good nutrition. Given rising life expectancy, preventing chronic diseases is especially crucial since living free from disease greatly improves the quality of aging. In the past, mothers played a pivotal role in feeding, with their dietary habits shaping the food environment and influencing family eating patterns (39). Family recipes, often based on the local availability of food resources, passed on wisdom to younger generations by guiding their intake of vital nutrients and cooking techniques, thereby fostering a strong food culture (40).

One of the main factors determining general well-being is maintaining healthy habits all lifetime. Before industrialization, not nutrition-related chronic diseases but infectious diseases dominated death causes. Although undernutrition and overnutrition may coexist, human dietary patterns have changed with cultural changes, especially in the kinds, amounts, and locations of food eaten (41). These modifications now deviate from the biological requirements carried in our genes. Following "mom's advice" has thus become more challenging given changes in the food system, lack of tailored dietary recommendations, and global promotion of non-regionals (42).

Several convergent elements could have led to the idea of a "one-diet-fits-all" diet emerging. First, mostly because of their availability and cost, the globalization of the food supply has led to highly processed and ultra-processed products being extensively imported into underdeveloped countries, or focused marketing to underprivileged sectors (43). Many countries have embraced "globalized" foods as a result of globalization; these may vary in quality from locally grown substitutes. Second, health organizations, especially in the United States, have agreed with dietary recommendations for vital nutrients, carbohydrates, proteins, fats, vitamins, antioxidants, minerals, and fiber aimed at preventing diseases, including atherosclerosis, cancer, diabetes, and obesity (44). The rise in chronic diseases, without taking into account genetic or cultural factors, led to the unification of standard guidelines for managing chronic conditions in clinical settings, thereby promoting a dietary approach that is universally applicable.

Third, there are universal recommendations to prevent chronic diseases. Traditional diets, including the "Mediterranean diet, "Japanese diet," or "Nordic diet," fail to acknowledge the nutritional and financial advantages of local diets (45). One should realize that no one local diet is generally better or healthier than another. Trying to implement particular diets like the Mediterranean diet as a worldwide cure for chronic diseases ignores the need to appreciate food systems, food cultures, and the need for a customized nutrition approach (46).

Furthermore, many people may find these dietary recommendations unworkable when they are included in national clinical practice guidelines and might not fit their genetic makeup or regional eating patterns. Apart from complaints about the one-diet-fits-all approach, there is a growing need for customized health indicators, including cut-off values for body mass index, glucose levels, liver function tests, and fat percentages, to consider the inherent fluctuation in human body measurements (47). Therefore, depending on the particular features of every society, the movement in personalized nutrition offers a chance to provide customized, region-specific dietary recommendations aimed at preventing chronic diseases.

The Genomex Diet: Exploring the Benefits and Addressing the Challenges

The strong evidence showing how our ancestral genetics affect our food choices provides a solid foundation for creating effective and culturally appropriate public health policies. Nevertheless, the global approach to offset the negative effects of Westernized diets is paradoxical: the overwhelming support of the Mediterranean diet as the "gold standard" for prevention of chronic diseases. Occasionally this guidance ignores the particular genetic composition and cultural customs of many groups (48). Studies have shown that the Mediterranean diet, which promotes olive oil, whole grains, and limited wine intake, can reduce the risk of chronic diseases. Still, variations in food availability, cultural tastes, and genetic inclination limit its general relevance to all populations. For instance, populations in Northern Europe and Asia might not react to foods like olive oil or wheat as Mediterranean populations, whose genetic evolution has been molded by centuries of agricultural activities targeted on these foods (49).

Genomic studies suggest that some genetic variants found in particular populations affect individuals' dietary metabolism (50). With a higher frequency of this allele, individuals may benefit from more folate intake; thus, customized diets should

consider these genetic variations depending on genomic studies. Ignoring these elements when recommending diets could result in less than optimal outcomes, especially for populations with genetic predispositions distinct from those in Mediterranean countries (51). Based on the agricultural background and genetic evolution of the region, this diet stresses berries, whole grains, fatty fish, and root vegetables. Studies on Asian populations have also revealed the health benefits of traditional diets more fit for their genetic composition and food culture, which are heavy in rice, fish, and soy (52).

Moreover, diets heavy in whole grains, legumes, and vegetables common in many traditional diets worldwide may offer more health advantages to populations with higher genetic predispositions to metabolize complex carbohydrates, according to a 2022 study in Nature Genetics (53). These findings suggest that, informed by genomic insights, customized nutrition can help avoid chronic diseases and improve health outcomes across many populations. Considering these elements, the development of customized diets specific to genetic backgrounds and food cultures shows great potential (54). These programs would highlight locally grown, nutrient-dense foods that complement cultural preferences as well as genetic predispositions. By combining genomic insights with traditional eating patterns, these nutrition programs aim to provide customized food supporting global health and well-being (55).

Basically, even if the Mediterranean diet has benefits, its general relevance could not be suitable for every population. Adopting several culinary traditions and matching world public health policies with the genetic and cultural reality of different populations is a more successful approach (56). This kind of strategy not only honors cultural customs but also improves the efficiency of dietary programs in avoiding chronic diseases. The overwhelming data supporting the interaction of ancestral genetic backgrounds with dietary choices provides a strong basis for creating public health policies that are both culturally relevant and scientifically sound (57). This advice sometimes ignores the particular genetic composition and cultural customs of many groups (58).

Many clinical recommendations continue to endorse the Mediterranean diet despite this issue, often overlooking the unique genetic and cultural contexts of different populations. Studies have demonstrated that (59). Variations in food availability, cultural tastes, and genetic inclination limit the general applicability of the Mediterranean diet across all populations. For instance, populations in Northern Europe and Asia might not react to foods like olive oil or wheat as Mediterranean populations, whose genetic evolution has been molded by centuries of agricultural activities focused on these foods (60).

Genomic research has shown that some genetic variants common in particular populations affect people's nutritional metabolism. Individuals with a higher frequency of this allele may benefit from more folate intake; thus, personalized diets should consider these genetic variations according to genomic studies (61, 62).

Studies abroad also help confirm this concept. For instance, a 2023 study in The Lancet revealed that adherence to traditional dietary patterns, including the Nordic diet, was linked to better cardiovascular health in the Scandinavian population (63). This diet stresses berries, whole grains, fatty fish, and root vegetables, all of which fit the agricultural background and genetic evolution of the area. Research on Asian populations has also shown the health advantages of traditional diets more suited for their genetic makeup and food culture, which are rich in rice, fish, and soy (64).

Furthermore, a 2022 study in Nature Genetics found that diets high in whole grains, legumes, and vegetables common in many traditional diets worldwide may provide more health benefits to populations with higher genetic predispositions to metabolize complex cabohydrate. These results imply that, informed by genomic insights, tailored nutrition can help avoid chronic diseases and enhance health outcomes over many populations (65).

Given these factors, the creation of genome-based nutrition programs tailored to specific genetic backgrounds and food cultures shows enormous promise. These initiatives would stress eating locally grown, nutrient-dense foods that fit cultural tastes as well as genetic predispositions (43). These nutrition programs seek to offer individualized food that supports global health and well-being by combining genomic insights with conventional dietary patterns. In essence, even if the Mediterranean diet has advantages, its general relevance might not be suitable for every population (66). Adopting several culinary traditions and matching "global" public health policy with the genetic and cultural reality of different populations is a more successful approach. This kind of strategy not only honors cultural customs but also improves the efficiency of dietary programs in avoiding chronic diseases (67).

CONCLUSION

Combining genetic knowledge with conventional food recommendations offers a creative approach to control the world increase in chronic diseases. Although the Mediterranean diet has been much promoted for its health advantages, not every society will benefit from its all-encompassing approach. Environmental, cultural, and genetic factors affect the personal metabolism of nutrients and reactions to various dietary patterns. International studies on traditional diets appropriate

for particular genetic backgrounds, such as the Nordic diet or Asian dietary patterns, show favorable health outcomes and might be more successful in motivating long-term well-being within such groups.

Going forward, personalized dietary recommendations that honor cultural legacy and genetic predispositions will define nutrition based on genome-based data. Public health policies must change to honor and support many locally grown, culturally relevant diets that fit the genetic makeup of many civilizations. Including genetic data in dietary recommendations will enable us to create more effective, long-lasting, and customized strategies for the prevention of chronic diseases, thus strengthening the link between genes, culture, and food and enhancing world health outcomes.

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The Role of the Microbiome in Designing Personalized Therapies: Emerging Approaches in Immune and Metabolic Regulation

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ABSTRACT

The human microbiome, consisting of trillions of microorganisms living in and on the body, plays a critical role in maintaining physiological balance and health. Recent advancements in microbiome research have demonstrated its profound influence on immune function, metabolic regulation, and disease pathogenesis. Personalized therapies that integrate the microbiome into treatment strategies have emerged as a promising approach to optimize patient outcomes. This review explores the current understanding of the microbiome's role in immune and metabolic regulation and highlights emerging approaches for incorporating microbiome-based interventions into personalized therapy regimens. We discuss the potential of microbiome modulation to enhance immune responses, improve metabolic health, and provide novel therapeutic options for diseases such as cancer, diabetes, autoimmune disorders, and inflammatory bowel diseases (IBD).

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INTRODUCTION

The human microbiome, which comprises bacteria, viruses, fungi, and archaea, is a varied and always shifting community of microorganisms found at many anatomical sites on and within the human body (1). The gut, skin, oral cavity, and other mucosal surfaces have especially high microbial counts. Taken holistically, the cells of the microbiome not only outnumber human cells but also have a genomic content far more complex and varied than the human genome (2). This large reservoir of microbial genes codes for many of the numerous biochemical events necessary for host physiology, including digestion, vitamin synthesis, immune system modulation, and defense against pathogenic invaders (3, 4). Research advances motivated by high-throughput sequencing technologies and systems biology approaches over the past ten years have greatly enhanced the vital contribution of the microbiome in human health and disease (5). Now well established is the importance of the microbiome as a fundamental regulating organ influencing many different physiological processes, particularly those connected to immune surveillance and metabolic control (6).

Because of its essential role in maintaining immunological balance, enhancing nutrient absorption and metabolism, and building a necessary barrier against enteric pathogens, the gut microbiome has attracted the most scientific interest of all the microbial habitats in the human body (7). A good gut flora supports metabolic homeostasis, helps immune system development and education, and interacts intricately and usually favorably with host signaling paths (8). On the other hand, a growing number of

pathological conditions have been linked to changes in the microbiota's composition or function, known as microbial dysbiosis. Inflammatory and autoimmune diseases (e.g., rheumatoid arthritis, inflammatory bowel disease), metabolic disorders (e.g., obesity, type 2 diabetes), cardiovascular diseases, neurodevelopmental and neurodegenerative disorders, and even cancers are among them (9). The human microbiome has become a compelling target for therapeutic intervention due to its pivotal role in both health and disease. Personalized medicine, a clinical paradigm that aims to tailor medical treatment to each patient's unique characteristics, is one area in which microbiome-based strategies are being incorporated more and more (10). This method considers an individual's distinct genetic profile, lifestyle choices, environmental exposures, and—more recently—their microbial makeup. Clinicians may be able to create more precise and effective treatments with better results and fewer side effects by utilizing knowledge about a patient's microbiome (11, 12). The function of the microbiome in immune and metabolic regulation will be discussed in this review, along with new approaches to using microbiome-based therapies in individualized treatment.

The Microbiome and Immune Regulation

The human microbiome, particularly the gut flora, plays a significant role in shaping and regulating the immune system throughout life. From the time of birth, microbial colonization of the body—shaped by elements including mode of delivery, nursing, antibiotic exposure, and environmental influences—begins a complex dialogue between host and microbe needed for appropriate immune education and function (13). Early microbial exposures provide the basis of immune tolerance and defense since they help the immune system to precisely differentiate between benign environmental or dietary antigens and dangerous pathogens. The largest immune organ in the human body, gut-associated lymphoid tissue (GALT), is fundamental in this process. Especially placed at the junction of the host and the dense microbial populations of the gastrointestinal tract, GALT hosts an amazing spectrum of immune cells (15). Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on host immune cells identify microbial signals, including microbial-associated molecular patterns (MAMPs), including lipopolysaccharides and peptidoglycans, by means of pattern recognition receptors (PRRs). These interactions start signaling cascades that mold the growth and activity of the adaptive and natural branches of the immune system (16). Above all, the gut flora shapes the differentiation of immune cells, including regulatory T cells (Tregs), Th17 cells, and many dendritic cell subsets (17), so preserving mucosal immune homeostasis and preventing too strong inflammatory responses. Moreover, microbial metabolites such as short-chain fatty acids (SCFAs) like butyrate and propionate—play a significant immunomodulatory role by enhancing epithelial barrier integrity, promoting anti-inflammatory cytokine production, and supporting the expansion of regulatory immune populations (18). Often called dysbiosis, changes in the composition or operation of the microbiome can cause immune dysregulation, raising susceptibility to infections, chronic inflammation, and autoimmune diseases (19). Evidence from animal models as well as human studies has linked altered microbiota profiles to diseases including inflammatory bowel disease (IBD), allergies, rheumatoid arthritis, and multiple sclerosis (20). All things considered, the microbiome is a needed architect and immune system regulator that coordinates a well-tuned equilibrium between immune activation and tolerance. Knowing these interactions not only helps one understand immune-related diseases but also creates new directions for the microbiome.

Immune System Development and Microbial Influence

Particularly in early life, the microbiome is absolutely essential since it determines the maturation and functional calibration of the immune system. Different microbial communities during crucial developmental windows such as birth, infancy, and early childhood—allow suitable differentiation and activation of many immune cell types, including T lymphocytes, dendritic cells, macrophages, and B cells (22). These natural cues help the immune repertoire to distinguish between self and non-self as well as between benign antigens and dangerous pathogens, so guiding it (23).

Studies on germ-free animal models provide strong proof of the fundamental function of the microbiome in immune development. Germ-free mice show severe immune deficits (24), having been raised in sterile conditions and so free of any microbial colonization. Among these are underdeveloped secondary lymphoid organs, including Peyer's patches and mesenteric lymph nodes, low secretory immunoglobulin A (IgA), altered T cell populations, and inadequate responses to infections (25). These findings underline the significant part microbial-derived signals including microbial-associated molecular patterns (MAMPs) and microbial metabolites drive the structural and functional maturation of the immune system (26).

Moreover, apart from supporting immune activation and defense, the microbiome is equally vital in producing immune tolerance (27). This means encouraging the synthesis of anti-inflammatory cytokines, including IL-10 and TGF-β, as well as the spread of regulatory T cells (Tregs), which, taken together, help to control too strong or inappropriate immune responses (28). Strengthening mucosal barrier function and modifying antigen-presenting cell activity helps the microbiota

help stop the immune system from launching assaults against benign environmental agents, dietary proteins, or the body's own tissues (29).

Especially in early life, disruptions to this delicate microbial-immune balance can have long-term consequences and are mostly related to the development of autoimmune and allergic diseases, including type 1 diabetes, asthma, inflammatory bowel disease, and systemic lupus erythematosus (30). Maintaining a varied and balanced microbiome during early immune development is therefore not only fundamental for proving immune competency but also for reducing the lifetime risk of immune-mediated diseases. Especially in early life, the microbiome is absolutely essential for the maturation and functional calibration of the immune system (21). Appropriate differentiation and activation of several immune cell types, including T lymphocytes, dendritic cells, macrophages, and B cells, depend on exposure to different microbial communities during key developmental windows—such as birth, infancy, and early childhood (22). Natural stimuli like these microbial exposures help the immune system to properly distinguish between harmful pathogens and benign antigens as well as between self and non-self, so shaping the immune repertoire (23).

Studies on germ-free animal models provide convincing data on the fundamental contribution of the microbiome to immune development. Germ-free mice show severe immune deficits (24) raised in sterile surroundings and are therefore free of any microbial colonization. Among these are underdeveloped secondary lymphoid organs such as Peyer's patches and mesenteric lymph nodes, low secretory immunoglobulin A (IgA), altered T cell populations, and poor responses to infections (25). These findings underline the significant role that microbial-derived signals—including microbial-associated molecular patterns (MAMPs) and microbial metabolites—play in driving the structural and functional maturation of the immune system (26).

Moreover, outside of supporting immune activation and defense, the microbiome is equally crucial in producing immune tolerance (27). This entails encouraging the spread of regulatory T cells (Tregs) and the synthesis of anti-inflammatory cytokines like IL-10 and TGF-β, which, taken together, help control too strong or inappropriate immune responses (28). The microbiota helps stop the immune system from launching assaults against benign environmental agents, dietary proteins, or the body's own tissues by strengthening mucosal barrier function and adjusting antigen-presenting cell activity (29). Particularly in early life, disturbances to this delicate microbial-immune balance can have long-term effects and are mostly connected to the development of autoimmune and allergic diseases, including type 1 diabetes, asthma, inflammatory bowel disease, and systemic lupus erythematosus (30). Therefore, preserving a varied and balanced microbiome during early immune development is not only basic for establishing immune competency but also for lowering the lifetime risk of immune-mediated diseases. Especially in early life, the maturation and functional calibration of the immune system depend critically on the microbiome (21). Exposure to different microbial communities during important developmental windows—such as birth, infancy, and early childhood—determines appropriate differentiation and activation of many immune cell types, including T lymphocytes, dendritic cells, macrophages, and B cells (22). Natural stimuli such as these microbial exposures guide the immune repertoire by helping the system to correctly differentiate between benign antigens and harmful pathogens as well as between self and non-self (23). Research on germ-free animal models offers strong evidence about the basic role the microbiome plays in immune development. Raised in sterile surroundings and so devoid of any microbial colonization, germ-free mice show extreme immune deficits (24). Among these are low secretory immunoglobulin A (IgA), underdeveloped secondary lymphoid organs (such as Peyer's patches and mesenteric lymph nodes), changed T cell populations, and poor responses to infections (25). These findings draw attention to the crucial part microbial-derived signals—including microbial-associated molecular patterns (MAMPs) and microbial metabolites—drive in structural and functional maturation of the immune system (26). Moreover, outside of immune activation and defense, the microbiome is equally crucial in generating immune tolerance (27). This means promoting the synthesis of anti-inflammatory cytokines like IL-10 and TGF-β as well as the spread of regulatory T cells (Tregs), which, taken together, help to control too strong or inappropriate immune responses (28). Strengthening mucosal barrier function and altering antigen-presenting cell activity, the microbiota helps prevent the immune system from launching assaults against benign environmental agents, dietary proteins, or the body's own tissues (29). Especially in early life, disruptions to this delicate microbial-immune balance can have long-term consequences and are mostly related to the development of autoimmune and allergic diseases, including type 1 diabetes, asthma, inflammatory bowel disease, and systemic lupus erythematosus (30).

Regulation of Inflammatory Responses

Chronic inflammation has been linked to microbial dysbiosis, which can be defined as an imbalance in the microbiome (31). This imbalance is suspected to be the root cause of the pathogenicity of many diseases. The overproduction of pro-inflammatory cytokines

and the activation of immune cells that are brought on by dysbiosis can lead to various disorders, some of which include inflammatory bowel disease (IBD), rheumatoid arthritis, and asthma (32). On the other hand, a perfectly balanced microbiome will increase the production of anti-inflammatory cytokines, which will in turn promote immunological tolerance. This tolerance is essential for maintaining immune homeostasis (33).

Microbiome and Immune Therapy

The microbiome's central role in regulating immune responses drives growing research on its therapeutic use to raise immunotherapy's efficacy and precision (34). An increasing number of data points inside the framework of cancer treatment point to the composition and diversity of the gut microbiota as having a major influence on patient responses to immune checkpoint inhibitors (ICIs), including anti-PD-1 and anti-CTLA-4 treatments (35). These inhibitors rely on a strong and responsive immune system—one that is, in part, shaped by microbial signals—that reactives T-cells suppressed by tumor-associated mechanisms (36). Studies on particular commensal bacterial species including Akkermansia muciniphila, Bifidobacterium longum, and Faecalibacterium prausnitzii have linked improved clinical outcomes in patients undergoing ICI treatment to these organisms (37) and enhanced anti-tumor immunity. These helpful bacteria seem to help T-cell priming and proliferation, change dendritic cell function, and boost the generation of inflammatory cytokines that support tumor surveillance and destruction (38). From dietary changes and customized probiotic supplements to next-generation microbial consortia, personalized microbiome-targeted treatments from which immunotherapy outcomes in cancer patients could be improved are thus under active research as adjunct strategies (39). Reversing the gut flora to favor immunostimulatory profiles could increase therapeutic efficacy, reduce immune-related adverse events, and so extend the benefits of immunotherapy to a greater population of patients (40). Beyond cancer, the immunomodulating powers of the microbiome have opened fresh paths for the treatment of inflammatory and autoimmune diseases (41). Many autoimmune diseases, including Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), and multiple sclerosis (30), have dysbiosis that is, imbalance in the gut flora. In these disorders, inappropriate immune activation against self-antigens is often linked with altered microbial composition and compromised gut barrier function. Treatments based on the microbiome aim to reach microbial balance and immune tolerance (43). Re-establishing microbial diversity and reducing disease symptoms in some patients has shown promise with methods including fecal microbiota transplantation (FMT), in which stool from a healthy donor is transferred to a patient (44). Likewise, targeted probiotic treatments and modified microbial strains are being developed to especially change immune pathways, reduce inflammation, and increase regulatory T cell responses (45). These findings taken together show the therapeutic possibilities of microbiome modification as a novel approach for cancer prevention and management of autoimmune disease. Validation of the efficacy, safety, and personalization of these interventions will depend mostly on continuous research and clinical trials, so opening the path for microbiome-informed precision medicine (46).

The Microbiome and Metabolic Regulation

Apart from its important contribution to the immune system, the gut microbiome is a major control of host metabolism, so preserving metabolic equilibrium (47). From nutrient absorption to energy harvest to glucose use to lipid metabolism and storage, the trillions of microorganisms living in the gastrointestinal tract impact a wide spectrum of metabolic activities (48). A sophisticated network of microbial enzymes and metabolites closely interacting with host signaling paths mediates these activities (49). By fermenting indigestible dietary fibers into short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate (50), the microbiome mostly helps to regulate metabolism. For colonocytes, these SCFAs are both vital energy sources and signaling molecules; they also have systemic effects (51). SCFAs, for example, affect insulin sensitivity, lower inflammation, control appetite by gut-brain axis signaling, and alter the release of gut-derived hormones, including peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), both of which are absolutely vital for glucose homeostasis and satiety (52). Apart from SCFAs, the microbiome controls bile acid metabolism, which is necessary for the breakdown of fats and the control of cholesterol. Primary bile acids produced by the liver are transformed by gut bacteria into secondary bile acids, which function as signaling molecules binding to nuclear receptors, including G-protein-coupled bile acid receptor 1 (TGR5) (53). Controlling lipid and glucose metabolism, inflammation, and energy expenditure depends on these receptors. Therefore, changes in the microbiome can cause a great metabolic effect by dysregulation of these pathways (54, 55). Furthermore, by influencing the effectiveness of calorie extraction from food, the gut flora can control host energy balance. Research on obesity has revealed that those who have it often have different microbial populations marked by higher diet energy extraction capacity (56). All important traits of metabolic

syndrome (57): these changed microbiomes also correlate with low-grade systemic inflammation, enhanced intestinal permeability, and insulin resistance. Importantly, microbial dysbiosis has been linked to the pathogenesis of several metabolic disorders, including obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (58). Interventions aimed at modulating the gut microbiome—such as prebiotics, probiotics, synbiotics, dietary changes, and fecal microbiota transplantation—are being actively investigated for their potential to restore metabolic balance and improve clinical outcomes in these conditions (59). Importantly, microbial dysbiosis has been linked to the pathogenesis of several metabolic disorders, including obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (60). Interventions aimed at modulating the gut microbiome—such as prebiotics, probiotics, synbiotics, dietary changes, and fecal microbiota transplantation—are being actively investigated for their potential to restore metabolic balance and improve clinical outcomes in these conditions (61).

Gut Microbiota and Energy Homeostasis

Increasingly acknowledged as major determinants of host energy balance and weight control are the composition and functional capacity of the gut flora (62). Many studies have shown that individuals with obesity and those of normal weight have different gut microbiomes, implying a direct relationship between microbial ecology and metabolic phenotype (63). One of the most consistent results is a changed bacterial phyla: Firmicutes to Bacteroidetes ratio. While Bacteroidetes are decreased, the relative abundance of Firmicutes is usually higher in obese people, a change thought to improve the capacity of the microbiota to extract energy from otherwise indigestible polysaccharides (64). Microbial fermentation systems that break down complex carbohydrates into absorbable short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate (65), generate this increased energy harvest. Not only do these SCFAs offer a direct source of energy up to 10% of daily caloric intake but they also act as strong signaling molecules that change host metabolism in several respects (66). On intestinal and immune cells, for instance, SCFAs interact with G-protein-coupled receptors (e.g., GPR41 and GPR43) to affect appetite control, fat storage, and insulin output. While propionate is important in gluconeogenesis and lipid metabolism in the liver, butyrate in particular provides the main energy source for colonocytes and shows anti-inflammatory and insulin-sensitizing effects (67). Furthermore, under control by microbial metabolites are important gut hormones linked to hunger and satiety, including ghrelin, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1). By their action on the central nervous system, these hormones control food intake and impact peripheral glucose metabolism and fat storage (68). An imbalance in the gut microbial community, or dysbiosis, can reduce the synthesis of these important metabolites, so aggravating hyperphagia, insulin resistance, and lipid accumulation features of metabolic syndrome and obesity (69). Beyond SCFAs, other microbial products such as lipopolysaccharides (LPS), branched-chain amino acids (BCAAs), and secondary bile acids can also influence energy homeostasis and metabolic inflammation (70). For instance, increased translocation of LPS into the bloodstream—a consequence of increased gut permeability in dysbiosis—has been associated with low-grade chronic inflammation, or "metabolic endotoxemia," which contributes to insulin resistance and adiposity (71). Given this intricate interplay between the gut microbiome and host energy regulation, therapeutic modulation of the microbiota has emerged as a promising strategy to combat obesity and related metabolic disorders (72). Interventions such as prebiotic and probiotic supplementation, dietary fiber enrichment, fecal microbiota transplantation (FMT), and next-generation microbial therapies aim to restore a favorable microbiome composition and enhance SCFA production (73). These strategies hold potential for promoting energy balance, improving glucose metabolism, and supporting weight loss in individuals with metabolic dysfunction (74).

Microbiome and Insulin Resistance

Basic components of metabolic diseases, including type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome (75), in which case body cells fail to react properly to insulin, are insulin resistance. Rising data in recent years reveals that the gut microbiome is a main actor in the pathogenesis and possible therapy of insulin resistance since it influences glucose metabolism and insulin sensitivity (76). By synthesis of microbial metabolites, especially short-chain fatty acids (SCFAs) such as as acetate, propionate, and butyrate (77), the microbiome clearly affects insulin sensitivity. Made by fermenting dietary fibers, these SCFAs act as signaling molecules engaging specific receptors (e.g., GPR41 and GPR43) on enteroendocrine and immune cells, so activating pathways that improve insulin action (78). SCFAs not only reduce appetite and satiety but also raise pancreatic β-cell activity and insulin sensitivity in peripheral tissues by inducing the release of gut hormones,, including glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). Linked increasingly to the pathogenesis of insulin resistance is dysbiosis, defined by an imbalance in the composition and activity of the gut microbial

population (80). One finds negative metabolic and immunological effects of perturbation of the delicate equilibrium between beneficial and perhaps harmful microorganisms (81). Mostly causing both local and systemic inflammation, dysbiosis also significantly influences insulin signaling. Usually resulting from enhanced intestinal permeability, this inflammatory disease lets bacterial components,, including lipopolysaccharides (LPS), translocate into the bloodstream (82). These endotoxins in circulation start natural immune reactions that produce chronic low-grade inflammation in key metabolic tissues, including skeletal muscle, liver, and adipose tissue, so modulating the insulin receptor signaling cascade. This interference reduces the cellular insulin response, so causing metabolic dysfunction and hyperglycemia (83). Moreover, dysbiosis is associated with a reduction in beneficial microbial metabolites such as short-chain fatty acids (SCFAs), which play protective roles in maintaining insulin sensitivity by modulating gut hormone secretion, enhancing anti-inflammatory pathways, and preserving gut barrier integrity (84). The loss of these key roles aggravates metabolic abnormalities, so promoting a vicious cycle that increases insulin resistance and type 2 diabetes (85). Given the central role the microbiome performs in regulating many processes, restoring a healthy and balanced microbial ecosystem presents a possible therapeutic route (86). Dietary interventions that aim to increase the consumption of whole grains, fermented products, and foods high in fiber particularly help beneficial bacteria that are capable of producing SCFAs and other bioactive compounds to grow (87). Prebiotics which provide substrates that support the growth of such microorganisms and probiotics which add live beneficial microorganisms have shown promise in clinical and preclinical studies to improve insulin sensitivity by reducing inflammation and strengthening metabolic signaling pathways (88). Aiming not only to control blood glucose levels but also to solve underlying pathophysiological mechanisms contributing to metabolic diseases, these microbiome-targeted strategies offer a complementary approach to conventional treatments (89). Personalized medicine approaches for the prevention and treatment of insulin resistance and type 2 diabetes (90) will be advanced by ongoing research to maximize these interventions, ascertain appropriate strains and dosages, and customize therapies to individual microbiome profiles.

Microbiome and Obesity

Since its frequency shockingly fast increases everywhere, obesity has become a major global health issue (91). Although a complicated interaction of genetic, environmental, and lifestyle elements clearly causes obesity, growing evidence emphasizes the gut microbiome as the main actor in controlling body weight and distribution of fat (92). Obesity is shaped by several processes, including modulation of energy harvest from the diet, control of host metabolism, and interaction with hormonal and immune pathways (93). The gut microbial community shapes obesity by means of these mechanisms. As was already noted, differences in the relative abundance and diversity of gut bacteria can affect the efficiency with which dietary nutrients are extracted and converted into useable energy (94). Higher ratios of Firmicutes to Bacteroidetes have been linked to enhanced capacity for fermenting complex polysaccharides into absorbable calories, so helping to explain increasing energy harvest and fat accumulation. Many times, obese people show this profile. This profile changes the lipid metabolism and storage of the host, hence influencing the fat distribution patterns and adiposity (96). This profile affects microbial surroundings as well. In addition to producing energy, the gut microbiome significantly regulates bile acid metabolism, thereby directly influencing the breakdown and absorption of fat. Gut bacteria convert primary bile acids into secondary bile acids which function as signaling molecules by means of receptors like Takeda G-protein receptor 5 (TGR5) and farnesoid X receptor (FXR). These receptors specify control of energy consumption, lipid metabolism, and glucose homeostasis. Changing the signaling routes of perturbingile acid helps dysbiosis affect fat metabolism and increase fat storage, so driving obesity (98). These results have spurred much research on recently developed therapeutic strategies meant to target the microbiome to combat obesity. Promising in changing the microbial community of the recipient towards a more balanced and metabolically friendly profile, fecal microbiota transplantation (FMT), or transposing gut bacteria from a healthy donor to a recipient, has shown promise (99, 100). While more clinical research is needed to confirm its long-term safety and efficacy, preliminary studies indicate that FMT might reduce adiposity (101) and enhance metabolic parameters. Apart from FMT, prebiotics and probiotics are easily accessible and could be helpful techniques to change the gut flora. Including inulin and fructooligosaccharides, prebiotics specifically encourage the growth of beneficial bacteria, generating short-chain fatty acids (SCFAs), with anti-obesity effects including appetite control and higher energy expenditure (102). Probiotics which comprise live beneficial microorganisms such as Lactobacillus and Bifidobacterium species have shown varied degrees of success in reducing body weight and improving metabolic health by changing inflammation, gut barrier function, and metabolic signaling pathways. These microbiome-based treatments often rely primarily on diet modification and physical exercise, showing promise as a complement or alternative to traditional

obesity control strategies (104). By addressing the basic microbial causes of obesity and thereby improving weight loss outcomes, these approaches may reduce the risk of complications related to obesity, including type 2 diabetes, cardiovascular diseases, and certain cancers (105).

Personalized Approaches in Microbiome-Based Therapies

Personalized medicine represents a transformative shift in healthcare, moving away from the traditional one-size-fits-all approach toward treatments tailored to an individual's unique genetic, environmental, and lifestyle factors (106). Within this evolving paradigm, the human microbiome has emerged as a vital component due to its profound influence on health and disease. Each person harbors a distinctive microbiome profile shaped by factors such as genetics, diet, geography, age, medication use, and exposure to environmental microbes. This individuality means that microbiome-based therapies must be precisely tailored to the specific microbial landscape of each patient to achieve optimal therapeutic outcomes (107). Advances in high-throughput sequencing technologies and bioinformatics have enabled comprehensive characterization of the microbiome at the species and strain levels, as well as its functional potential (108). These technologies allow clinicians and researchers to identify microbial signatures associated with particular diseases or treatment responses, facilitating the development of precision interventions. For example, in cancer immunotherapy, the presence or absence of certain gut microbial species has been linked to patients' responses to immune checkpoint inhibitors, indicating that microbiome profiling can guide treatment decisions and improve efficacy (109).

Personalized microbiome therapies may include customized probiotic formulations designed to replenish specific beneficial bacteria that are deficient or absent in an individual's gut. Similarly, prebiotic compounds can be selected to promote the growth of target microbes that produce metabolites with therapeutic effects, such as anti-inflammatory SCFAs (110). Additionally, fecal microbiota transplantation (FMT) protocols can be refined by matching donors and recipients based on microbial compatibility to maximize safety and effectiveness (111).

Dietary interventions represent another key avenue for personalization. Since diet profoundly influences the microbiome composition and function, personalized nutrition plans that consider an individual's microbiota can optimize microbial balance and metabolic health (112). Machine learning algorithms and predictive models are increasingly being used to recommend diets that support beneficial microbes, reduce dysbiosis, and improve clinical outcomes (113).

Moreover, personalized microbiome-based therapies have the potential to reduce adverse drug reactions and enhance drug metabolism by accounting for the microbiome's role in modifying pharmacokinetics. This integration of microbiome data into pharmacogenomics promises to further refine personalized treatment regimens (114).

Despite these promising advances, challenges remain in translating personalized microbiome therapies into routine clinical practice. Variability in microbiome sampling, standardization of microbial interventions, regulatory considerations, and the need for large-scale clinical trials must be addressed. Nevertheless, ongoing research and technological innovation are rapidly overcoming these hurdles (115).

Microbiome Profiling for Personalized Medicine

The advent of advanced sequencing technologies has revolutionized our ability to characterize the human microbiome with unprecedented resolution and accuracy. Techniques such as 16S ribosomal RNA (rRNA) gene sequencing and shotgun metagenomic sequencing are at the forefront of this progress, enabling researchers and clinicians to obtain detailed insights into the composition, diversity, and functional potential of microbial communities residing in different body sites (116). 16S rRNA sequencing focuses on sequencing a specific region of the ribosomal RNA gene found in bacteria and archaea. This method allows for the identification and classification of microbes at the genus or sometimes species level, providing a snapshot of the microbial diversity and relative abundance within a sample. Its cost-effectiveness and relatively simple data analysis have made it a widely used tool in microbiome research and clinical studies (117).

Shotgun metagenomics, on the other hand, involves sequencing all genetic material present in a sample, offering a more comprehensive and detailed view. This approach not only identifies microbial species and strains with high resolution but also reveals the functional genes and metabolic pathways present in the microbial community. This functional insight is critical for understanding how microbes influence host physiology, metabolize nutrients, or modulate immune responses (118).

As sequencing costs continue to decrease and computational methods improve, microbiome profiling is becoming more accessible and feasible for routine clinical use (119). Integration with other 'omics' data, such as genomics, metabolomics, and proteomics, is further enhancing our ability to develop comprehensive, personalized health strategies that consider the complex interactions between the microbiome and host (120).

By analyzing an individual's microbiome composition, researchers can identify specific microbial species or strains that may be associated with

health or disease (121). This information can be used to design personalized interventions, such as targeted probiotic treatments, dietary modifications, or the use of prebiotics, to restore microbial balance and optimize health outcomes (122).

By leveraging these technologies, researchers can map an individual's unique microbiome profile, uncovering specific microbial species or strains that are either beneficial or potentially pathogenic (123). For example, an overabundance of certain inflammatory bacterial species might be linked to autoimmune disorders, while the presence of SCFA-producing bacteria may correlate with better metabolic health (124).

This granular understanding enables the design of personalized microbiome interventions. Targeted probiotic treatments can be formulated to introduce or augment specific beneficial strains that are deficient in an individual's microbiome (125). Similarly, prebiotics non-digestible fibers and compounds that selectively feed beneficial microbes can be tailored to support the growth of these key species. Dietary modifications can also be personalized based on microbiome data to promote a balanced microbial ecosystem that supports overall health (126).

Moreover, microbiome profiling can assist in disease risk assessment and early diagnosis, identifying microbial signatures that precede or predict disease onset. This predictive capability allows for timely, targeted interventions to prevent disease progression (127). In oncology, for instance, microbiome profiles have been used to predict responses to immunotherapy, guiding personalized treatment plans that maximize efficacy while minimizing side effects.

Gut Microbiome and Diet for Personalized Therapies

Diet is one of the most influential and modifiable factors shaping the gut microbiome throughout life. The types and amounts of food consumed directly affect the diversity, composition, and function of the microbial communities within the gastrointestinal tract (128). Given this close relationship, dietary interventions have become a cornerstone strategy for modulating the microbiome to promote health and prevent or manage disease (129).

Personalized nutrition dietary plans tailored to an individual's unique microbiome composition and metabolic profile holds significant promise in enhancing the efficacy of dietary recommendations and interventions (130). By understanding the specific microbial species and functional capacities present in a person's gut, nutritionists and clinicians can design targeted diets that foster the growth of beneficial microbes while suppressing potentially harmful ones (131). For example, individuals whose microbiomes show an overrepresentation of pathogenic or pro-inflammatory bacteria may benefit from diets rich in dietary fibers and fermented foods. Dietary fibers serve as substrates for beneficial bacteria, especially those that produce short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate (132). These SCFAs play vital roles in maintaining gut barrier integrity, regulating immune responses, and supporting metabolic health (18). Fermented foods, including yogurt, kefir, sauerkraut, and kimchi, introduce live beneficial microbes and bioactive compounds that further promote microbial diversity and balance (133).

Conversely, personalized dietary approaches may also involve reducing intake of foods that feed harmful bacteria or exacerbate dysbiosis. For example, limiting refined sugars and processed foods that can promote the growth of inflammatory microbes may be particularly important for individuals with metabolic syndrome or inflammatory bowel disease (134).

Moreover, personalized diet plans can be synergistically combined with microbiome-based therapies such as probiotics and prebiotics to enhance therapeutic outcomes. Probiotics live microorganisms that confer health benefits may colonize more effectively and exert greater beneficial effects when supported by a diet that favors their growth and activity (135). Prebiotics, which are nondigestible food components that selectively stimulate beneficial microbes, can be chosen and dosed based on the individual's microbiome to optimize microbial community shifts (136).

This tailored approach is especially critical because the efficacy of probiotics and prebiotics varies widely depending on the host's baseline microbiome composition and diet (137). For instance, a probiotic strain effective in one individual may fail to colonize or provide benefits in another with a different microbial ecosystem. Therefore, integrating microbiome profiling with personalized nutrition enables more precise and effective modulation of the gut microbiome (138).

In addition to disease prevention and management, personalized dietary modulation of the microbiome has implications for a broad range of conditions, including obesity, diabetes, autoimmune diseases, and even mental health disorders through the gut-brain axis (139). By leveraging individual microbiome data, personalized diets can be designed to restore microbial balance, reduce inflammation, and improve metabolic and immune functions (140).

In conclusion, the interplay between diet and the gut microbiome offers a powerful avenue for personalized therapies. Tailoring dietary recommendations based on individual microbiome profiles not only enhances the success of dietary interventions but also maximizes the benefits of complementary microbiome-targeted therapies, paving the way for more effective, personalized healthcare solutions.

CONCLUSION

The microbiome plays a crucial role in regulating both immune and metabolic functions, influencing the development and progression of numerous diseases. Personalized therapies that integrate microbiome modulation offer a promising approach to improving patient outcomes by restoring microbial balance and enhancing the body's natural defense mechanisms. As research advances, new technologies and therapies will emerge to harness the power of the microbiome in treating a wide range of diseases, from autoimmune disorders to metabolic diseases like obesity and diabetes. Moving forward, the combination of personalized medicine and microbiome-based interventions could transform the landscape of healthcare, offering more precise, effective, and individualized treatment strategies for patients.

Author's Contribution

Hafza Zubair was involved in the conceptualization, design and writing of the manuscript draft. The author read and confirmed the final manuscript.

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Autoimmune Diseases and Their Relationship with Environmental Pollution

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ABSTRACT

Autoimmune diseases (AIDs) are characterized by the immune system's maladaptive response against self-antigens, culminating in chronic inflammation and progressive tissue damage. Although genetic predisposition establishes baseline susceptibility, environmental pollutants—such as heavy metals, pesticides, fine particulate matter (PM2.5), and industrial chemicals—are increasingly recognized as pivotal triggers of immune dysregulation. These xenobiotics induce oxidative stress, disrupt immune tolerance by impairing regulatory T-cell function, and modulate critical signaling pathways including NF-κB, MAPK, and JAK-STAT. Epidemiological studies corroborate associations between pollutant exposure and heightened incidence or severity of conditions such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes. This review synthesizes molecular, cellular, and population-based evidence to elucidate the mechanisms by which environmental pollution contributes to the onset and progression of AIDs.

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INTRODUCTION

Autoimmune diseases (AIDs) encompass a diverse group of disorders in which the immune system mistakenly attacks the body's own cells and tissues, leading to chronic inflammation, functional impairment, and often irreversible damage (1, 2). The clinical manifestations vary widely from organ-specific conditions like Hashimoto's thyroiditis to systemic diseases such as systemic lupus erythematosus (3), rheumatoid arthritis (RA), multiple sclerosis (4), and type 1 diabetes (T1D) (5). Collectively, these diseases affect millions of individuals worldwide, and their prevalence is rising across both developed and developing nations (6).

Although genetic predisposition particularly involving human leukocyte antigen (HLA) genes and other immune-regulatory loci plays a foundational role in determining individual susceptibility, it does not fully account for disease onset. Increasingly, environmental exposures are recognized as necessary cofactors that trigger autoimmunity in genetically susceptible hosts (7).

Among these environmental factors, pollution has emerged as a major contributor. Industrial expansion, urbanization, and modern agricultural practices have led to elevated levels of airborne and waterborne toxins, including heavy metals (e.g., lead, mercury, cadmium), fine particulate matter ($PM_{2.5}$), gaseous pollutants (NO_2, O_3, SO_2), and synthetic pesticides (8). These pollutants are capable of disrupting immune homeostasis by inducing oxidative stress, damaging cellular components, impairing regulatory T-cell (Treg)

function, and modulating key signaling pathways involved in inflammation and immune surveillance—such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathways (9).

This dysregulation compromises immune tolerance, leading to aberrant immune responses and loss of self-recognition. The ensuing proinflammatory state not only increases the likelihood of developing autoimmune diseases but also exacerbates allergic responses and susceptibility to infections (10).

As the interplay between genetic and environmental risk factors becomes more evident, it emphasizes the need for integrated prevention strategies. This includes both personalized medicine approaches—taking into account individual genetic profiles—and public health policies aimed at reducing environmental toxin exposure. Raising public awareness, enhancing early detection, and implementing regulatory interventions are essential steps toward reducing the global burden of autoimmune diseases (11).

Environmental Pollutants and Their Impact on Immune System Function

Environmental pollutants exert profound effects on immune system function through multiple interconnected mechanisms. Various toxicants including heavy metals (e.g., lead, mercury, cadmium, arsenic), pesticides, industrial chemicals, and airborne particulate matter can modulate both innate and adaptive immune responses (12). These contaminants influence the activity and behavior of immune cells such as dendritic cells, macrophages, T lymphocytes, and B lymphocytes, all of which are essential for maintaining immune homeostasis and orchestrating effective responses to pathogens (13).

One of the primary ways pollutants impact immune regulation is through the alteration of cytokine production. Cytokines are pivotal signaling molecules that mediate immune cell communication and coordinate inflammation, immune activation, and resolution processes. Exposure to environmental toxins can lead to aberrant cytokine profiles, characterized by either exaggerated proinflammatory responses or impaired anti-inflammatory signaling, thereby contributing to immune dysregulation (14).

Moreover, many pollutants induce oxidative stress by generating excessive reactive oxygen species (ROS), which overwhelm the body's endogenous antioxidant defense systems. This redox imbalance compromises the integrity of immune cells and tissues, leading to chronic inflammation, DNA damage, and impaired immunoregulation (15). Persistent oxidative stress not only weakens host defenses against infections but also promotes the development of autoimmunity through mechanisms such as antigen modification, loss of tolerance, and sustained immune activation (16).

At the molecular level, several key signaling pathways are implicated in pollutant-induced immune dysfunction. These include

- **Nuclear factor kappa B (NF-κB)**: A central regulator of inflammation and immune responses, frequently activated by environmental stressors.
- **Mitogen-activated protein kinases (MAPKs)**: Involved in cellular responses to oxidative stress, cytokine production, and apoptosis.
- **Janus kinase/signal transducer and activator of transcription (JAK-STAT)**: Modulates cytokine signaling and immune cell differentiation.
- **Nuclear factor erythroid 2–related factor 2 (Nrf2)**: A master regulator of antioxidant defense mechanisms.

Among these, Nrf2 plays a particularly vital role in cellular defense by regulating the expression of genes involved in antioxidant production and detoxification. Activation of the Nrf2 pathway has emerged as a promising therapeutic strategy to counteract pollutant-induced oxidative damage. Enhancing Nrf2 signaling may bolster immune resilience by attenuating oxidative stress and reducing chronic inflammation (17).

Understanding the interaction between environmental pollutants and these signaling pathways is critical for the development of targeted therapeutic interventions. By modulating these pathways, researchers aim to create innovative strategies that mitigate the immunotoxic effects of environmental exposures and restore immune balance (18). For instance, pharmacologic Nrf2 activators, anti-inflammatory agents, and immune-modulating compounds are being investigated for their potential to enhance immune defense mechanisms in polluted environments (1).

Pollutants also exert epigenetic effects by altering gene expression through DNA methylation, histone modification, and microRNA regulation. These changes may dysregulate immune function and contribute to the development of autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis (19). Identifying pollutant-induced epigenetic markers and immune biomarkers may facilitate early diagnosis and personalized treatment strategies tailored to individuals with environmental exposure histories (20).

Immune Activation and the Role of Inflammation in Autoimmune Diseases

Chronic inflammation is a central hallmark of autoimmune diseases, stemming from the immune system's inability to distinguish self-antigens from foreign pathogens. This loss of immunological tolerance leads to sustained activation of both innate and adaptive immune responses, resulting in localized or

systemic tissue damage (21). Environmental pollutants such as airborne particulates, heavy metals, and agricultural chemicals—have been shown to intensify these immune processes by stimulating the production of key pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-17 (IL-17). These cytokines are critical mediators of inflammatory cascades and play pivotal roles in the pathogenesis of various autoimmune disorders (22).

Pollutant-induced immune activation occurs through several mechanisms. Environmental toxins stimulate antigen-presenting cells, such as dendritic cells and macrophages, which in turn promote the differentiation of pro-inflammatory T helper (Th) cell subsets particularly Th1, Th17, and T follicular helper (Tfh) cells. These cells secrete cytokines that perpetuate the inflammatory milieu, recruit additional effector immune cells to target tissues, and exacerbate tissue injury (22). For example, IL-17 produced by Th17 cells enhances neutrophil recruitment, disrupts epithelial and endothelial barriers, and increases tissue permeability, contributing to the pathophysiology of diseases such as multiple sclerosis (4). Similarly, Th1 cells, through the release of interferon-gamma (IFN-γ) and TNF-α, are implicated in the destruction of pancreatic β-cells in type 1 diabetes (T1D) (23).

This aberrant immune activity often establishes a self-perpetuating inflammatory cycle: tissue damage leads to the release of self-antigens, which further activate immune responses and sustain chronic inflammation. This cycle not only drives disease progression but also contributes to increased severity, comorbidities, and treatment resistance in autoimmune conditions (23).

Given the central role of inflammatory cytokines in disease pathogenesis, they have become prime targets for therapeutic intervention. Biologic agents that block TNF-α, IL-6, IL-17, or their receptors have shown significant clinical efficacy in managing autoimmune diseases such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, and MS (24). These targeted therapies help modulate the immune response, reduce inflammation, and minimize tissue destruction, thereby improving patient outcomes and quality of life (25).

Nonetheless, pharmacologic therapy alone may not suffice for optimal disease control. An integrative approach that combines immunomodulatory treatments with lifestyle modifications such as adopting anti-inflammatory diets, reducing environmental toxin exposure, managing stress, and engaging in regular physical activity can significantly improve therapeutic outcomes. Psychological support and patient education are also critical, as psychosocial stressors are known to influence immune regulation and disease activity (26).

Emerging advances in precision medicine hold promise for individualized therapeutic strategies. By profiling patients' cytokine signatures, genetic susceptibilities, environmental exposures, and immune cell phenotypes, clinicians can tailor interventions that specifically target dysregulated pathways. Such personalized approaches may not only enhance efficacy but also reduce the risk of adverse effects and improve long-term disease management (27).

Pollution and Immune Tolerance: Disrupting the Balance

Maintaining immune tolerance that is, avoiding the immune system from attacking its cells and tissues is a fundamental component of immune system operation. Environmental pollution can disturb this delicate balance by triggering immune system malfunction. Immune tolerance is preserved by Tregs; thus, their absence or malfunction has been linked to the beginning of autoimmune diseases (28). A Treg imbalance causes an improper immune response that might see the body's tissues as foreign invaders. Knowing the causes of Treg loss will help one to develop new approaches for the management of autoimmune diseases. Knowing the mechanisms behind Treg loss will help to find new therapeutic approaches for autoimmune diseases (29). By looking at the environmental elements causing Treg issues, researchers will be able to design tailored treatments meant to restore the balance of the immune system and increase the body's ability to distinguish it from foreign invaders. Reducing the consequences of autoimmune diseases depends on this immune balance restoration, which also may generate creative treatments enhancing the body's natural regulating systems (30).

Ultimately, a more profound understanding of Treg dynamics could offer the tools for personalized therapeutic approaches that meet the specific needs of individual patients. This knowledge helps one control autoimmune diseases. Good control of autoimmune diseases helps medical systems to lower their load and significantly raise patients' quality of life (31). By means of targeted treatments and Treg cells, researchers hope to generate more exact interventions, so mitigating symptoms and addressing the fundamental causes of these difficult disorders. These developments provide improved therapy results and long-term remission for those suffering from autoimmune diseases (32). Including these novel concepts into clinical practice as research develops could transform patient treatment in this demanding sector. By matching treatments to individual patient profiles, customized medicine approaches arising from this revolution may improve safety and efficacy. Giving Treg cell modulation top attention will help doctors to identify fresh approaches to restore immune balance and enhance the quality of life for patients with these terrible diseases (33).

By including lifestyle, environmental, and genetic

elements into treatment plans, doctors can maximize therapeutic results and improve patients quality of life. Treg function is interfered interfered with by environmental toxins, including heavy metals and pesticides, so compromising immune control and raising sensitivity to autoimmune reactions (34). Furthermore, compromising immune tolerance is epigenetic modifications induced by environmental toxins. Environmental toxins change how DNA is marked, how proteins around DNA are modified, and how certain small RNA molecules are expressed, which affects how immune cells work and how genes are expressed, making people more likely to develop autoimmune diseases (35). This complex interaction of environmental elements with genetic inclination emphasizes the need to understand how toxins affect immune system control. By addressing environmental triggers, treatment and prevention of autoimmune diseases may find new pathways and so support better health outcomes. Better health outcomes can be achieved through a multifaceted approach that includes reducing exposure to harmful substances, promoting a healthy lifestyle, and tailoring interventions based on an individual's genetic predisposition (36). This holistic perspective enhances our understanding of autoimmune diseases and paves the way for innovative therapeutic strategies. These strategies not only aim to mitigate the effects of toxins but also empower individuals to take charge of their health through education and awareness. By fostering a collaborative approach among healthcare providers, researchers, and patients, we can drive advancements in the management and treatment of autoimmune conditions (37).

Environmental Factors in Autoimmune Disease Susceptibility: A Genetic Perspective

While environmental pollution is mostly responsible for the start of autoimmune diseases, genetic inclination is rather crucial. Some people may have hereditary variations that increase their sensitivity to environmental toxins. Environmental toxins can alter genes that influence the immune system's performance, including those related to cytokine generation, immune receptor signaling, and responses to oxidative stress, thereby increasing an individual's risk of developing autoimmune diseases (38). Therefore, awareness of how genes and the surroundings interact determines better strategies to avoid and treat autoimmune diseases. In autoimmune diseases, effective preventive and therapeutic interventions are quite essential. Furthermore, by means of tailored medicine and focused treatments derived from the analysis of the particular genetic markers linked to these diseases, patient outcomes can be improved and the effects of these diseases on individuals and healthcare systems can be minimized (39). Researchers can identify new therapeutic targets and improve present treatment plans by using developments in biotechnology and genetics, thus improving patient quality of life. Furthermore, including environmental strategies and lifestyle modifications in therapy plans helps reduce the effects of autoimmune diseases and enhances general health (40). This data guides public health campaigns meant to lower exposure to hazardous pollutants and helps to identify vulnerable populations. By means of an analysis of the interactions between genes and environmental elements, scientists can better plan treatments and direct society toward reduced risks related to environmental pollutants (41). This proactive approach helps people to control their health and advance general society. Individuals who combine more environmental pollution exposure with a genetic inclination are likely to have autoimmune issues since the interaction between genetic elements and environmental exposure is complex (42).

Environmental Pollutants and Their Immunotoxicity

Heavy Metals and Autoimmune Disease Development

Over time, highly toxic heavy metals, including lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As), can accumulate in the body and fundamentally alter immune systems. Since these metals interfere with the normal immune system and might raise susceptibility to diseases and infections, this accumulation can cause several health problems. Long-term exposure thus clearly jeopardizes general health and well-being (43). These metals reduce immune tolerance, cause inflammation, and alter immune cell behavior, thus raising a person's susceptibility to autoimmune diseases. Lead: Pb; lead exposures compromise immune system performance via many routes. Pb disrupts the operation of T cells, B cells, and natural killer (NK) cells all of which are important components of immune surveillance and response (44). Studies reveal that Pb exposure can upset the equilibrium between Th1 and Th2 immune responses, thus aggravating Th2-related inflammation. Pb also causes reactive oxygen species (ROS) generation and oxidative stress, which damages tissue and activates the immune system. At the molecular level, Pb stimulates important controllers of inflammation, NF-κB and MAPK signaling pathways (45). Linked to autoimmune diseases including lupus and rheumatoid arthritis, these pathways downregulate pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. Pb also stimulates T follicular helper (Tfh) cells, which support B cell differentiation, so fostering autoantibody production a feature of many autoimmune diseases (46). A strong neurotoxin influencing the immune system as well is mercury (Hg). Mercury increases macrophage activity that generates pro-inflammatory cytokines and chemokines. Mercury exposure is well known to activate the NF-κB

pathway, thus boosting tissue damage and aggravating the inflammatory response (47). Mercury also stimulates Th17 cells, a type of T helper cell crucial for autoimmune inflammation, especially in diseases like rheumatoid arthritis and systemic lupus erythematosus (3). Oxidative stress brought on by mercury sets off the Nrf2 antioxidant pathway, producing ROS. This therefore, fuels immune dysregulation and damages cellular structures (48). Cadmium (Cd) exposure results in the accumulation of this metal in the kidneys, liver, and lungs, where it induces notable immune dysregulation. Cd stimulates inflammation by triggering the synthesis of nitric oxide (NO) and ROS, so compromising immune cell performance (49). Cd exposure causes Th1 responses that generate IFN-γ and TNF-α, so throwing off the ratio of pro- to anti-inflammatory cytokines. Cadmium exposure has been shown at the cellular level to influence dendritic cell maturation, so distorting the immune response towards inflammation (50). Furthermore, by influencing T regulatory cells (Tregs), Cd compromises immune tolerance systems and fuels the development of autoimmune diseases. Arsenic (As) exposure has been linked to rheumatoid arthritis and systemic lupus erythematosus, among several autoimmune diseases (51). Arsenic promotes Th1/Th17 polarization, which is linked to autoimmune inflammation and modulates T cell differentiation. The arrangement of arsenic also helps generate autoantibodies, which target self-antigens and set off autoimmune reactions. Arsenic interacts at the molecular level with the JAK-STAT pathway, which is essential for immune cell signaling and activates inflammatory genes. Additionally causing ROS and oxidative stress, it further disturbs the immune system and accelerates the course of autoimmune diseases (52).

Air Pollution and Autoimmune Disease

Air pollution is one often occurring environmental hazards that seriously compromises immune system performance, among other aspects of human health. Autoimmune diseases have been most connected among all the components of air pollution to ozone (O_3), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$) (53). Important elements in the beginning and aggravation of autoimmune diseases, these toxins can enter the bloodstream via the respiratory system and cause oxidative stress, systematic inflammation, and immune dysregulation. Autoimmune diseases, including type 1 diabetes (T1D), multiple sclerosis (4), rheumatoid arthritis (RA), and systemic lupus erythematosus (3), have been linked to air pollution (54). Comprising many immune cell types, signaling pathways, and molecular mechanisms, the immune system's sophisticated response to air pollutants is environmental toxins can induce tissue damage, autoimmunity, and chronic inflammation by means of specific immune system activation (55). Starting a vicious cycle that might lead to the development of chronic diseases, tissue damage can aggravate the inflammatory response even more. Public health campaigns and targeted treatments meant to reduce the effects of pollution on immune system performance depend on an awareness of these processes.Air pollution is one often occurring environmental hazard that seriously compromises human health including immune system performance (56). Among all the components of air pollution, autoimmune diseases have been most linked to ozone (O_3), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$). Important components in the beginning and aggravation of autoimmune diseases, these toxins can enter the bloodstream via the respiratory system and induce oxidative stress, systemic inflammation, and immune dysregulation (3). Autoimmune diseases, including type 1 diabetes (T1D), multiple sclerosis (4), rheumatoid arthritis (RA), and systemic lupus erythematosus (3), have been linked to air pollution. Comprising many immune cell types, signaling pathways, and molecular mechanisms, the immune system's sophisticated response to air pollutants is by means of specific immune system activation, environmental toxins can cause tissue damage, autoimmunity, and chronic inflammation (3). Tissue damage can further aggravate the inflammatory response, potentially initiating a vicious cycle that may lead to the development of chronic diseases. Public health campaigns and targeted treatments meant to reduce the effects of pollution on immune system performance depend on being aware of these processes (57).

Molecular Mechanisms of Air Pollution-Induced Autoimmune Diseases

The immune system is equipped with pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These receptors are crucial in detecting external and internal threats and initiating an immune response. Airborne pollutants, such as PM2.5, NO2, and O3, are capable of activating these PRRs, leading to a cascade of immune responses that contribute to inflammation and immune dysfunction (58).

1.Activation of Pattern Recognition Receptors (PRRs)

Pollutants in the air are recognized by Toll-like receptors (TLRs), which are a key subset of PRRs. TLRs are present on macrophages, dendritic cells, and epithelial cells, all of which are involved in initiating immune responses. Upon binding to air pollution components, TLRs activate downstream signaling

pathways that promote an inflammatory response. The most commonly involved TLRs in air pollution-induced inflammation are TLR4 and TLR2, which recognize particulate matter, and TLR9, which can be activated by the DNA fragments found in pollutants (59).

The activation of these receptors triggers several intracellular signaling pathways, most notably the NF-κB (nuclear factor kappa B) and MAPK (mitogen-activated protein kinase) pathways. These pathways are critical for regulating immune cell function, inflammatory cytokine production, and the survival of immune cells (60).

2.NF-κB Pathway and Cytokine Production

Once TLRs are activated, NF-κB quickly produces TNF-α, IL-1β, IL-6, and IL-12. These cytokines are mostly responsible for the inflammatory reaction and also significantly help autoimmune diseases to develop. Involved in inflammation, TNF-α is crucial for the development of T helper 17 (Th17) cells, which abound in autoimmune diseases including rheumatoid arthritis (RA) and multiple sclerosis (4, 61). Higher TNF-α levels also promote the synthesis of autoantibodies and B cell development, which may produce immune complexes possibly damaging tissues. More inflammatory reactions triggered by these immune complexes can aggravate tissue damage and support the progression of autoimmune diseases (62). Consequently, concentrating on TNF-α and associated cytokines has become a primary objective in the development of treatments for several diseases. Although TNF-α targeting helps some autoimmune diseases under control, some studies indicate that blocking this cytokine might cause other issues, including more susceptibility to infections (63). Moreover, there are other therapeutic modalities that concentrate on changing the immune response without particularly aiming at TNF-α, so providing a more balanced course of treatment. Another necessary cytokine causing immune cell activation and inflammation continuation is IL-1β (64). Understanding how IL-1β generates inflammation has helped to design targeted treatments meant to stop its activity. These treatments provide a better way to treat autoimmune diseases since they could lower the risk of infections related to TNF-α inhibitors and so decrease inflammation. Rising IL-1β levels in the joints and other tissues help to explain the advancement in RA and other autoimmune diseases. Essential in the transition from acute to chronic inflammation, IL-6 is a multifarious cytokine (65). This shift is significant because of changes in the body's immune response: acute inflammation, meant to react to immediate threats, can become chronic and contribute to driving continuous tissue damage and disease progression. Targeting cytokines such as IL-1β and IL-6 could help therapies break this cycle and provide better control of autoimmune diseases (66). Targeting T follicular helper (Tfh) cells and T helper 17 (Th17) cells will help encourage their differentiation since both of these cells are essential for the onset of autoimmune diseases (67). IL-6 also produces autoantibodies, so it helps B cells to proliferate and activate. In diseases including rheumatoid arthritis, lupus, and multiple sclerosis, the sustained presence of these cytokines aggravates the autoimmune process by causing tissue damage, synovial inflammation, and neuronal damage (68). Once TLRs are activated, NF-κB quickly reacts to create several substances that promote inflammation, such as TNF-α (tumor necrosis factor-alpha), IL-1β (interleukin-1 beta), IL-6, and IL-12. The inflammatory response is mostly dependent on these cytokines, which also greatly contribute to the development of autoimmune diseases (69). Involved in inflammation, TNF-α is essential for the development of T helper 17 (Th17) cells, which are present in autoimmune diseases including rheumatoid arthritis (RA) and multiple sclerosis (4). Higher TNF-α levels also stimulate B cell development and the synthesis of autoantibodies, which could lead to immune complexes maybe harm tissues (70). More inflammatory reactions triggered by these immune complexes can aggravate tissue damage and support the progression progression of autoimmune diseases. Thus, focusing on TNF-α and related cytokines has become a main goal in developing treatments for several diseases. While some autoimmune diseases may be controlled with TNF-α targeting, some studies show that blocking this cytokine may lead to other problems, including more susceptibility to infections (71). Moreover, there are other therapeutic approaches that focus on altering the immune response without especially aiming at TNF-α, so offering a more balanced course of therapy. IL-1β is another indispensable cytokine driving immune cell activation and inflammation continuation (72). Understanding how IL-1β generates inflammation has helped to design targeted treatments meant to stop its activity. These therapies offer a better approach to treating autoimmune diseases since they could reduce inflammation and lower the risk of infections connected with TNF-α inhibitors (73). Rising IL-1β levels in the joints and other tissues help to explain the advancement in RA and other autoimmune diseases. Essential in the transition from acute to chronic inflammation, IL-6 is a multifarious cytokine. 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3.MAPK Pathway and Immune Cell Activation

The MAPK pathway is another important signaling cascade activated by TLR engagement. This pathway influences various cellular processes, including cell proliferation, differentiation, survival, and immune cell activation. In the context of air pollution, the MAPK pathway plays a role in macrophage activation and the production of reactive oxygen species (ROS), which contribute to oxidative stress and further inflammation (76).

•p38 MAPK is particularly important in the activation of pro-inflammatory cytokines and immune cell differentiation. Activation of this pathway in response to pollutants has been shown to promote the expression of IL-6, TNF-α, and IL-1β in immune cells, further perpetuating inflammatory cycles (77).

4.Oxidative Stress and Immune Dysregulation

One of the key consequences of air pollution exposure is oxidative stress, which occurs due to the excessive production of reactive oxygen species (ROS), such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals. These ROS can directly damage cellular components, including DNA, lipids, and proteins, leading to cell death and the activation of immune responses (78).

The accumulation of ROS in immune cells such as macrophages, dendritic cells, and T cells can enhance the production of pro-inflammatory cytokines and trigger cellular signaling pathways like NF-κB, further promoting immune system activation. Moreover, oxidative stress can disrupt Treg (regulatory T cell) function, impairing immune tolerance and facilitating the development of autoimmune responses (79).

Oxidative stress can also lead to epigenetic modifications, such as changes in DNA methylation and histone modification, which can result in long-lasting changes in immune cell function and gene expression, further enhancing susceptibility to autoimmune diseases (80).

Molecular Mechanisms Linking Pollution to Autoimmune Diseases

Environmental pollutants, through a variety of molecular mechanisms, significantly contribute to the pathogenesis of autoimmune diseases. These mechanisms involve the activation of key inflammatory pathways, induction of oxidative stress, and disruption of immune tolerance (81). The interaction between pollutants and the immune system can lead to immune activation, an imabalance in immune cell populations, and the generation of autoreactive antibodies. In this section, we will explore the molecular pathways through which pollutants, such as heavy metals, air pollution, and other environmental toxins, contribute to the development of autoimmune diseases (82).

Inflammatory Pathways

Inflammation is a hallmark of autoimmune diseases, and many environmental pollutants contribute to immune system dysregulation through the activation of inflammatory signaling pathways. These pathways not only promote local inflammation but also perpetuate systemic immune activation, setting the stage for autoimmune responses (83).

1.NF-κB Pathway: A Key Regulator of Immune Inflammation

The NF-κB (nuclear factor kappa B) signaling pathway is one of the most critical regulators of the immune response. This pathway is activated by a variety of environmental pollutants, including heavy metals (like lead and mercury), airborne particulate matter, and pesticides (84). Under normal conditions, NF-κB is kept inactive in the cytoplasm by binding to IκB (inhibitory κB) proteins. Upon exposure to pollutants, IκB proteins are phosphorylated and degraded, releasing NF-κB dimers (usually p65/p50) to translocate to the nucleus, where they initiate the transcription of genes involved in inflammation, immune response, and cell survival (85).

Pollutants trigger NF-κB activation through various receptors, including pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). The activation of NF-κB leads to the expression of key pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-8, which are crucial in the development and progression of autoimmune diseases (86). These cytokines promote the recruitment and activation of immune cells like macrophages, T cells, and B cells, further amplifying the inflammatory response. Additionally, NF-κB also promotes angiogenesis and tissue remodeling, which can contribute to autoimmune-mediated tissue damage (87).

Recent Findings: Studies have shown that exposure to air pollution increases NF-κB activation in the lungs and synovial joints, contributing to diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (3). Chronic activation of NF-κB by environmental toxins can lead to sustained inflammation, which plays a critical role in autoimmune pathogenesis (88).

2.MAPK (Mitogen-Activated Protein Kinase) Pathway

The MAPK (Mitogen-Activated Protein Kinase) signaling pathway includes several key members, such as JNK (c-Jun N-terminal kinase), ERK (extracellular signal-regulated kinase), and p38 MAPK. These pathways regulate a wide range of cellular processes, including cell proliferation, apoptosis, immune cell activation, and inflammation (89). Many environmental pollutants, such as heavy metals, pesticides, and airborne particulate matter (PM2.5), activate MAPK pathways by engaging PRRs, cytokine receptors, and cellular stress responses (90).

MAPK pathways play an important role in immune cell differentiation and the activation of transcription factors like AP-1 (activator protein 1), which are involved in the production of inflammatory cytokines. For example, JNK activation promotes the expression of pro-inflammatory cytokines such as TNF-α and IL-6, which drive inflammation and autoimmune responses (91). Similarly, p38 MAPK is implicated in the regulation of T cell differentiation, particularly in the promotion of Th17 cells, which are associated with autoimmune diseases like multiple sclerosis (4) and rheumatoid arthritis (RA) (92).

Furthermore, ERK signaling is involved in regulating T cell activation and B cell differentiation, both of which are critical for the development of autoimmune diseases. The activation of the MAPK pathway by pollutants not only drives the inflammatory response but also enhances the ability of the immune system to mount inappropriate attacks against self-tissues (93).

Recent Findings: Studies indicate that exposure to particulate matter (PM2.5) from air pollution can activate MAPK signaling in dendritic cells and macrophages, enhancing the production of inflammatory cytokines and promoting the differentiation of autoreactive T helper cells. This activation contributes to the exacerbation of diseases such as asthma, rheumatoid arthritis, and systemic lupus erythematosus (94).

3.JAK-STAT Pathway: Key Modulator of Immune Responses

The JAK-STAT (Janus kinase-signal transducer and activator of transcription) signaling pathway is a crucial regulator of immune cell function and inflammation. It is activated by cytokines and growth factors, and it plays an essential role in the differentiation and activation of **T** cells, B cells, and myeloid cells (95). Pollutants, including arsenic, mercury, and airborne particulate matter, can activate the JAK-STAT pathway, leading to the production of pro-inflammatory cytokines, especially those involved in the Th1 and Th17 immune responses, which are implicated in autoimmune diseases (96).

When pollutants bind to their respective cytokine receptors, they activate JAKs, which then phosphorylate STAT proteins. Phosphorylated STATs translocate to the nucleus, where they induce the transcription of genes involved in immune activation, inflammation, and autoimmunity (97). For example, STAT1 is a key mediator of the Th1 response, which is involved in autoimmune diseases like multiple sclerosis (4) and type 1 diabetes (T1D). STAT3, on the other hand, is critical for the development of Th17 cells, which are involved in autoimmune diseases like rheumatoid arthritis and psoriasis (98).

Pollutants like arsenic and mercury have been shown to specifically activate JAK-STAT signaling, leading to an overproduction of Th1 and Th17 cytokines such as IFN-γ and IL-17, which contribute to the chronic inflammation and tissue damage seen in autoimmune diseases (99).

Recent Findings: Research has demonstrated that arsenic exposure can increase the expression of IL-6 and IL-17 through the activation of the JAK-STAT pathway in T cells and macrophages, leading to increased susceptibility to diseases such as rheumatoid arthritis and systemic lupus erythematosus. Furthermore, mercury exposure has been associated with the induction of a Th17 response through STAT3 activation, further implicating the JAK-STAT pathway in pollutant-induced autoimmunity (100).

Other Cellular and Molecular Mechanisms

While the activation of inflammatory pathways like NF-κB, MAPK, and JAK-STAT plays a pivotal role in pollutant-induced autoimmune diseases, additional mechanisms contribute to immune dysregulation. These include

- **Oxidative Stress and ROS Production**: Pollution-induced oxidative stress is a key mechanism through which pollutants contribute to autoimmune disease development. ROS activate NF-κB and MAPK pathways, leading to inflammation and tissue damage (101).
- **Disruption of Immune Tolerance**: Environmental pollutants may interfere with the development and function of regulatory T cells (Tregs), which are essential for maintaining immune tolerance and preventing autoimmunity. Pollutants such as heavy metals and air pollution have been shown to impair Treg function, promoting autoimmunity (102).
- **Epigenetic Modifications**: Exposure to environmental pollutants can lead to epigenetic changes, including DNA methylation, histone modifications, and the expression of non-coding RNAs, all of which can influence immune cell function and predispose individuals to autoimmune diseases (103).

3. Pathways Activated by Oxidative Stress

Oxidative stress activates several cellular

signaling pathways that exacerbate inflammation and autoimmunity. These pathways play a crucial role in immune cell activation, differentiation, and tissue damage (104).

•**NF-κB Pathway**: As mentioned earlier, oxidative stress can activate the NF-κB signaling pathway, leading to the upregulation of pro-inflammatory cytokines and chemokines that drive the inflammatory response. In T cells, macrophages, and other immune cells, NF-κB activation promotes the expression of cytokines like TNF-α, IL-6, and IL-1β, which contribute to chronic inflammation seen in autoimmune diseases (105).

•MAPK Pathway: Oxidative stress activates various MAPK signaling pathways, including JNK, ERK, and p38 MAPK. These pathways play a key role in regulating inflammation and immune cell activation. For example, JNK activation can enhance the production of IL-17 and IFN-γ in Th17 and Th1 cells, respectively, both of which are critical drivers of autoimmunity (4). Additionally, p38 MAPK activation promotes the secretion of pro-inflammatory cytokines and enhances the survival of activated immune cells (106).

•Nrf2 Pathway: The Nrf2 (nuclear factor erythroid 2-related factor 2) pathway is a key cellular defense mechanism against oxidative stress. Nrf2 regulates the expression of antioxidant genes, such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD), which protect cells from ROS-induced damage (107). However, prolonged oxidative stress can lead to the failure of the Nrf2 pathway, resulting in reduced cellular protection and increased susceptibility to immune dysregulation and autoimmune diseases (108).

•Aryl Hydrocarbon Receptor: The AhR is a ligand-activated transcription factor that responds to environmental pollutants, such as dioxins and polyaromatic hydrocarbons. AhR activation by pollutants increases ROS production and induces inflammation (109). Additionally, AhR signaling can disrupt the function of Tregs, impairing immune tolerance and promoting autoimmunity. AhR has been implicated in diseases such as rheumatoid arthritis and multiple sclerosis, where oxidative stress and dysregulated AhR signaling contribute to disease progression (110).

Genetic Mechanisms and Epigenetic Modifications

Oxidative stress, which is triggered by environmental pollutants such as heavy metals and air pollution, not only induces cellular damage but also plays a critical role in shaping genetic and epigenetic responses that influence the development of autoimmune diseases. These pollutants can lead to DNA damage, causing mutations and alterations in gene expression, which, in turn, can activate pathological immune responses and increase susceptibility to autoimmune diseases (111). Furthermore, epigenetic modifications including changes in DNA methylation, histone modifications, and non-coding RNA regulation have emerged as key mechanisms through which oxidative stress modulates the immune system and contributes to the pathogenesis of autoimmune disorders (112).

RECENT FINDINGS AND FUTURE DIRECTIONS

Recent studies have highlighted the growing concern over the role of epigenetics in autoimmune diseases triggered by environmental factors. Research on epigenetic biomarkers for autoimmune diseases, such as DNA methylation profiles and histone modifications, is expanding, with a focus on identifying early biomarkers of autoimmune disease onset (113). In addition, the interactions between epigenetic changes and immune cell plasticity are being increasingly recognized as critical mechanisms in the development of autoimmune diseases (114).

As research continues, future studies should focus on the long-term effects of pollutants on epigenetic modifications, particularly in genetically predisposed individuals. Investigating the reversibility of these epigenetic changes through interventions such as dietary modifications, antioxidant therapies, or epigenetic drugs could provide new strategies for preventing or treating autoimmune diseases associated with environmental pollution (115).

CONCLUSION

Environmental pollution plays a significant role in the development and exacerbation of autoimmune diseases. Pollutants such as heavy metals, air pollution, pesticides, and industrial chemicals can activate inflammatory pathways, induce oxidative stress, and impair immune tolerance, all of which contribute to immune dysfunction and autoimmune disease progression. The molecular mechanisms underlying these effects involve complex interactions between immune cells, signaling pathways, and genetic predisposition. Further research is needed to fully understand the genetic, molecular, and cellular mechanisms through which environmental pollutants influence autoimmune diseases. Additionally, public health initiatives aimed at reducing environmental exposure to harmful pollutants are essential to mitigate their impact on immune health.

Authors' Contribution

Farnaz Eghbalpour: data curation; editing and review. Mahnaz Saremi: investigation and writing. The authors read and confirmed the final manuscript.

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Consent for publication

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Personalized Medicine Approaches in the Management of Chronic Pain: From Genomics to Targeted Therapy

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ABSTRACT

A common and incapacitating condition, chronic pain offers a difficult field of work because of its variability and response to conventional treatments. Genomic and proteomic-based personalized medicine including epigenetic and biomarker information could help to lower treatment variability, so improving diagnosis, phenotypic classification, and individualized approaches to treatment. Recent developments in genetics and pharmacogenetics of pain, pain phenotyping techniques, and the development of focused therapies including epigenetic modulators, peptides, biologics and nanomedicine are underlined in this review. Personalized medicine seeks to match every patient's individual genetic makeup to their course of treatment. It is increasingly accepted that pain chronology involves epigenetic processes, including DNA methylation and histone modifications. Furthermore discussed are the value of biomarkers in evaluating therapy response and prognosis as well as ethical, financial, and data availability-related issues. Finally, future directions involve the use of artificial intelligence mixed with multi-omics data for tailored optimal pain management. Adopting these changes can help patients to have less chronic pain and improve the therapeutic outcomes.

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INTRODUCTION

Background information commonly defined as pain lasting more than three months, chronic pain affects 20–30% of the worldwide population and ranks as a major healthcare issue in both developed and underdeveloped areas of the world (1, 2). It is accompanied by major psychological suffering, handicap, lower productivity, and healthcare use. A reflection of this complexity and variability is neuropathic pain, inflammatory disease (e.g., rheumatoid arthritis), and musculoskeletal syndrome (e.g., fibromyalgia, chronic low back pain) (3). Generic approaches to pain management include widely used drugs, opiates, NSAIDs, antidepressants, and physiotherapy for pain. However, a variety of side effects, such as tolerance, stomach pain, and cognitive problems, are associated with these treatments, and their effectiveness varies widely among individuals. For many patients, the "one-size-fits-all" approach has been inadequate; hence, the urgent search for more individualized treatments is still necessary (4).

Personalized medicine is one of the new paradigms suggested to enhance the diagnosis, classification, and treatment of chronic pain in the past years. Personalized, or precision, medicine is the application of information about a patient's genes, proteins, epigenomes, environments, lifestyle, and preferences to prevent, diagnose, and treat diseases (5). Regarding chronic pain, it would seek to identify the biological

processes behind pain in every patient, identify predictive biomarkers of response to treatment, and select the most appropriate treatment to maximize benefit and minimize harm (6).

Genomic data has helped to clarify, for instance, genetic polymorphisms affecting drug metabolism (e.g., CYP2D6 variants impacting opioid efficacy and safety), pain perception (e.g., SCN9A mutations), and risk for chronic pain problems (7). It is increasingly accepted that pain chronology involves epigenetic processes, including DNA methylation and histone modifications. These systems could serve as both diagnostic markers and therapeutic targets. Thanks to the identification of biomarkers associated with inflammatory and neuropathic pain states by proteome and metabolomics studies, more thorough phenotyping of pain syndromes is now feasible (8). Furthermore, sophisticated tools such as functional imaging, machine learning algorithms, and multi-omics integration are beginning to enable real-time, patient-specific decision-making. These developments allow patients to be stratified into clinically significant subgroups based on molecular signatures instead of symptom clusters by themselves (9).

Personalized medicine's promise notwithstanding, it is not without difficulties in terms of chronic pain management. These include high costs, the need for standardized protocols for biomarker validation, limited access to genomic technologies in regular clinical practice, ethical questions regarding genetic testing, and the need for multidisciplinary cooperation among clinicians, researchers, and data scientists (10).

This review aims to provide a comprehensive overview of the current state of individualized medicine for chronic pain. We investigate its uses across several pain types neuropathic, inflammatory, and musculoskeletal highlight recent discoveries in genomics and molecular profiling, assess the clinical value of these approaches, and address continuing implementation challenges. With an eye toward precision therapeutics, digital health integration, and patient-centered care models, we last discuss the future paths of this developing discipline.

Genetic and Pharmacogenetics Basis of Pain

Pain is a sensory experience; environmental, psychological, and genetic elements all profoundly influence it (3). Genetic variation significantly influences personal responses to pain sensation and analgesic treatments. The main objective of personalized medicine is pain management transformation; knowledge of the genetic bases of pain helps enable focused, patient-specific treatments (11). Personalized medicine seeks to match every patient's individual genetic makeup to their course of treatment. Combining genetic knowledge about pain management strategies helps doctors make analgesics more effective and enhance patient outcomes, thus facilitating a more compassionate and effective way of treating pain (12).

Genetic Modulators of Pain Perception

Candidate gene studies and genome-wide association studies (GWAS) have found several genetic polymorphisms notably affecting pain sensitivity and susceptibility to chronic pain disorders (13). Among the genes under the most research are

COMT (Catechol-O-methyltransferase)

This enzyme breaks down important modulators of pain and stress reactions, catechol amines, including dopamine, epinephrine, and norepinephrine. Changing enzymatic activity, the COMT Val158Met polymorphism has been linked to variations in pain sensitivity. Reduced COMT activity and higher catecholamine levels cause those with the Met/Met genotype to often exhibit more pain sensitivity (14).

OPRM1 (Mu-Opioid Receptor Gene)

The A118G polymorphism (rs17999) causes changes in receptor binding and expression, thus influencing both side effect risk and opioid efficacy. Target of endogenous opioids and morphine, the OPRM1 gene codes the mu-opioid receptor. For efficient analgesia, carriers of the G allele might need more opioids, and their treatment results could be more variable (15).

SCN9A (Sodium Voltage-Gated Channel Alpha Subunit 9)

Found in peripheral neurons, this gene codes the Nav1.7 sodium channel and is fundamental for nociceptive signal propagation. From congenital insensitivity to pain to inherited erythromelalgia a disorder of extreme burning pain mutations in SCN9A have been linked to a spectrum of pain phenotypes (16). Common differences in SCN9A could also play a part in the predisposition for persistent pain. These findings underline the complex and polygenic nature of pain and suggest that the interaction of several genetic loci forms an individual's pain experience (17).

Pharmacogenetics of Pain Management

Given chronic pain, where inter-individual variability in treatment efficacy and side effect profiles is a major clinical challenge, pharmacogenetics the study of how genetic variations affect drug response is especially pertinent (18).

Opioid Analgesics

Apart from OPRM1 polymorphisms, genetic differences in drug-metabolizing enzymes, such as CYP2D6, are also quite crucial. Among the many opioids CYP2D6 breaks down are codeine, tramadol,

and oxycodone. While ultra-rapid metabolizers may be at risk of opioid toxicity, those with poor metabolizer phenotypes e.g., those resulting from loss-of-function alleles may have inadequate analgesia. Genotype-guided prescribing can thus enhance both efficacy and safety (19).

NSAIDs and COX Inhibitors

Variations in CYP2C9 and UGT enzymes affect NSAID metabolism, including those of ibuprofen and celecoxib. Some polymorphisms may increase the risk of gastrointestinal toxicity or cardiovascular events, which calls for customised dosage or drug choice (20).

Antidepressants and Anticonvulsants

Often prescribed for the treatment of neuropathic pain, drugs including amitriptyline, duloxetine, and gabapentin also affect genes. Variations in CYP2D6 and CYP1A2, for instance, could change plasma concentrations of tricyclic antidepressants, so affecting the therapeutic value of these drugs as well as the risk of sedation or cardiac side effects (19). Medications routinely prescribed for the treatment of neuropathic pain, including amitriptyline, duloxetine, and gabapentin, can also be affected by genetic factors. Variations in CYP2D6 and CYP1A2 can affect the plasma concentrations of tricyclic antidepressants, for example, influencing the therapeutic benefit as well as the risk of sedation or cardiac side effects during treatment (21).

Clinical Applications and Future Directions

Pain pharmacogenomics is still in its early years of clinical use, despite some fascinating studies. Some hospitals and pain clinics have started regularly including pharmacogenetics testing into daily operations for especially challenging or treatment-resistant pain conditions (22). Commercial pharmacogenomics panels today provide useful data for customizing analgesic regimens, even if access, cost, and provider familiarity remain challenges. Combining genetic testing into electronic health records (EHRs) with decision-support tools will enable future genotype-based, real-time prescription writing (23). Like the All of Us program run by the NIH, large-scale biobanks and precision medicine projects are expected to concurrently speed the identification of new pain-related genetic markers and improve phenotype-genotype correlations. Reducing trial-and-error prescription writing, minimizing adverse events, and improving patient outcomes depend, especially, on the integration of genetic and pharmacogenetics data in pain management (24).

Pain Phenotyping for Treatment Stratification

The treatment of chronic pain is usually based on symptom-based classifications and subjective pain ratings. Still, these conventional methods occasionally fail to adequately depict the biological variation of chronic pain syndromes. Many of them thus receive either inadequate or non-responsive treatment (25). Recent attempts in pain phenotyping seek to classify patients based on objective biological, psychological, and neurophysiological criteria to overcome this restriction. Fundamental concepts of personalised medicine: this stratification enables doctors to customize treatments to the fundamental processes generating a patient's suffering (26).

Multidimensional Pain Assessment Tools

Chronic pain is a complex and multifaceted experience that affects emotional, cognitive, functional, and physical aspects, as well as physical sensation. Given this complexity, researchers have developed multidimensional pain assessment tools that offer a thorough evaluation across basic intensity ranges (27). These devices enable doctors to customise treatments and help them to understand the whole spectrum of a patient's pain experience by capturing many elements of pain, including sensory characteristics, emotional impact, interference with daily activities, and psychological factors (28). Using descriptive words falling into sensory, affective, and evaluative categories, the McGill Pain Questionnaire (MPQ) ranks the qualitative aspects of pain among the most often used instruments. This questionnaire detects several types of pain (e.g., sharp, burning, throbbing) and catches emotional reactions connected with pain, such as fear or anger (29). The depth of the MPQ guarantees a perceptive study of the basic causes of pain and guides mechanism-based treatments. The Brief Pain Inventory (BPI) is another helpful tool for determining pain degree and the degree of influence it has on many spheres of life, including mood, job, sleep, and social events (30). The BPI can find patients who might require multidisciplinary approaches combining pharmacologic and rehabilitative treatments by means of pain estimation. Particularly evaluating functional disability resulting from pain is made possible by tools such as the Pain Disability Index (PDI), which gauges how pain limits participation in daily activities, including employment, family responsibilities, and leisure activities (31). This assessment helps one to grasp the more general consequences of chronic pain on quality of life and guides occupational therapy and rehabilitation. Apart from the physical and functional spheres, psychological and cognitive aspects are rather important for pain experience and chronicity (32). Often accompanied by multidimensional pain assessments are patient-reported outcome measurements (PROMs) assessing anxiety, depression, pain catastrophising, and coping strategies, including the Pain Catastrophising

Scale (PCS) and Beck Depression Inventory (BDI). Among other psychological or behavioral therapies, these tools help to identify individuals who might benefit from mindfulness-based interventions or cognitive behavioural therapy (CBT) (33). Modern clinical practice emphasizes more and more the need to include these multidimensional tools in regular evaluations so that the patient's pain can be totally understood. Using more accurate phenotyping of pain types and contributing factors, this all-encompassing approach helps doctor's design tailored treatment plans that not only control the physical sensation but also address the emotional and functional effects of pain (34). Furthermore, multidimensional tests help to monitor treatment efficacy constantly by guiding suitable modifications in therapeutic strategies and identifying differences among several pain areas. These tools provide consistent, validated approaches in research to evaluate outcomes and evaluate the effectiveness of new treatments among several patient groups (35). Good long-term pain management usually depends on multidimensional pain assessment tools. By accepting the complexity of pain and including sensory, emotional, cognitive, and functional evaluations, these instruments help doctors to deliver patient-centered, mechanism-based treatment that maximizes clinical outcomes and improves quality of life (27). Chronic pain is a complex, multifarious experience that influences emotional, cognitive, functional, and physical aspects as well as physical sensation. Understanding this complexity, multidimensional pain assessment instruments have been created to offer an all-encompassing assessment going beyond basic intensity ranges (36). These tools help doctors to understand the whole spectrum of a patient's pain experience by allowing them to customise treatments by capturing many aspects of pain, including sensory characteristics, emotional impact, interference with daily activities, and psychological factors (28, 37).

The McGill Pain Questionnaire (MPQ) is among the most often used instruments since it evaluates the qualitative features of pain using descriptive words falling into sensory, affective, and evaluative categories. This questionnaire distinguishes pain types (e.g., sharp, burning, throbbing) and catches emotional reactions like fear or anger linked with pain. The depth of the MPQ guarantees perceptive study of the basic causes of pain and guides mechanism-based treatments (38).

Another useful instrument for assessing pain level and the degree to which it affects many spheres of life, including mood, employment, sleep, and social events, is the Brief Pain Inventory (BPI). By means of pain estimation, the BPI can identify patients who might need multidisciplinary approaches combining pharmacologic and rehabilitative therapies (39).

Tools such as the Pain Disability Index (PDI), which measures how pain limits participation in daily roles including employment, family responsibilities, and leisure activities, enable the specific evaluation of functional disability resulting from pain. This evaluation guides occupational treatments and rehabilitation and helps one to understand the more general effects of chronic pain on quality of life (40).

In addition to physical and functional aspects, psychological and cognitive factors play a significant role in the experience of pain and its chronicity. Often accompanied by multidimensional pain assessments are patient-reported outcome measures (PROMs) assessing anxiety, depression, pain catastrophising, and coping strategies, including the Pain Catastrophising Scale (PCS) and Beck Depression Inventory (BDI) (41). These instruments enable the identification of patients who might benefit from mindfulness-based interventions or cognitive behavioural therapy (CBT), among other psychological or behavioural treatments (42).

Modern clinical practice is increasingly emphasizing the importance of incorporating these multidimensional tools into regular assessments to fully understand the patient's pain (43). This all-encompassing approach, which uses more accurate phenotyping of pain types and contributing elements, helps doctors develop customised treatment plans that manage not only the physical sensation but also the emotional and functional consequences of pain (44). Moreover, multidimensional tests help to support continuous monitoring of treatment efficacy by guiding appropriate changes in therapeutic approaches by catching changes across many pain areas. These instruments offer consistent, validated methods in research to assess results and compare the efficacy of new treatments among several patient groups (45). Effective long-term pain treatment depends on general multidimensional pain assessment instruments. These tools enable doctors to offer patient-centered, mechanism-based treatment that optimizes clinical outcomes and enhances quality of life by accepting the complexity of pain and including sensory, emotional, cognitive, and functional evaluations (46).

Functional Neuroimaging

A new tool showing central nervous system pain processing in a useful perspective is functional brain imaging. Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG), among other methods, reveal brain regions engaged in pain experience and modulation (47).

Studies have revealed different patterns of brain activity produced by different pain disorders. Often including changed activity in the thalamus

and somatosensory cortex, neuropathic pain is Hyperactivity in pain-related regions, including the anterior cingulate cortex and insula has been linked to fibromyalgia (48).

In the salience networks and default mode, chronic low back pain can result from maladaptive connectivity. These results support the hypothesis of central sensitization a condition of increased neural responsiveness in chronic pain and help distinguish between several kinds of pain. Apart from diagnosis, functional neuroimaging can help to predict response to treatments including pharmacotherapy, neuromodulation, or cognitive behavioural therapy (CBT) (49).

Biomarkers of Inflammation and Pain Mechanisms

Essential tools in comprehending the complicated biological processes underlying chronic pain and in differentiating several pain mechanisms are now molecular biomarkers. These biomarkers help doctors to identify particular pathways causing pain, so allowing them to more precisely target treatments and forecast treatment responses (47). Among the mostwell-investigated are inflammatory cytokines, neurotrophic factors, and metabolic products, which offer a window into the dynamic interactions between the peripheral nervous system, immune response, and central nervous system modulation of pain (50).

Rheumatoid arthritis, osteoarthritis, and complex regional pain syndrome (CRPS) are among the inflammatory and autoimmune diseases linked with chronic pain that routinely show elevated levels of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6) (51). At both peripheral and central levels, these molecules help to sensitize nociceptors and amplify pain signalling. These markers are helpful not only for diagnosis but also for monitoring therapeutic efficacy since elevated levels of them usually correspond with disease activity and pain intensity (52).

A key mediator of central sensitization, a phenomena whereby the central nervous system shows increased responsiveness to pain stimuli, brain-derived neurotrophic factor (BDNF) has attracted interest. In pain pathways, BDNF affects synaptic plasticity and neuronal excitability; higher BDNF expression has been associated with the onset and maintenance of chronic pain states (53). Thus, BDNF could be a useful biomarker for determining patients who run the danger of pain chronology and for evaluating the effects of therapies meant to reduce central sensitivity (54).

The body's stress response is mostly dependent on the hypothalamic-pituitary-adrenal (HPA) axis; thus, dysregulation of this axis has been linked to the pathophysiology of several pain conditions. Together with other HPA-axis markers, cortisol, the main glucocorticoid hormone produced by the adrenal glands in response to stress, reflects the complicated bidirectional link between psychological stress and pain (55). Conditions including fibromyalgia and post-traumatic stress disorder (PTSD), where chronic stress aggravates pain perception and symptom severity, have seen elevated or blunted cortisol responses (56).

Advances in high-throughput technologies have recently enabled the investigation of omics-based biomarkers, including transcriptomics, proteomics, and metabolomics to reflect the multidimensional character of pain biology (57)University of Porto, 4200-319 Porto, Portugal.Transforming Clinical Research: The Power of High-Throughput Omics Integration. While metabolomics studies reveal changes in biochemical pathways in pain states, transcriptomic profiling lets one identify gene expression patterns linked with particular pain phenotypes. These methods have great potential to create more complex pain stratification systems and allow tailored therapeutic interventions addressing the molecular heterogeneity of chronic pain (58). Together, the identification and validation of inflammation- and pain-related biomarkers present a transforming chance to improve diagnostic accuracy, track disease progression, and direct individualized treatment plans, so improving outcomes for patients with chronic pain (59).

Psychosocial Phenotyping

The experience of chronic pain is much influenced by psychological and social factors, so it affects not only the general therapy response but also long-term consequences and pain perception (60). The biopsychosocial model of pain acknowledges that, rather than only a biological phenomenon, it is a complex interaction between biological, psychological, and social elements. Therefore, a thorough understanding of the pain experience of the patient and the design of particular, effective treatment plans depend on careful pain assessment, including the evaluation of psychological aspects (61). By evaluating catastrophic thinking about pain, the Pain Catastrophising Scale (PCS) enables doctors to identify those who might be prone to chronic disabling pain or unsatisfactory treatment results. Likewise, the Beck Depression Inventory (BDI) is widely used to assess the degree of depressed symptoms, which usually accompany chronic pain and demand coordinated treatment plans (62). Knowing psychological aspects helps one to apply focused treatments different from pharmacological ones. For those who show significant degrees of catastrophising or depressed symptoms, cognitive behavioural therapy (CBT) helps them to change maladaptive thought patterns and increase coping mechanisms. Furthermore, shown to improve

psychological well-being and pain perception are integrative therapies, including acceptance and commitment therapy, biofeedback, and mindfulness-based stress reduction (63).

Targeted Therapies in Personalized Pain Medicine

Individualized pain management techniques are a range of focused treatments meant to specifically target the biological pathways causing a person to suffer. Using histone deacetylase (HDAC) inhibitors and other epigenetic treatments shows promise in changing the patterns of gene expression linked with neuropathic pain, so offering new paths for pain reduction in circumstances when traditional painkillers are not working (64). By their specific targeting of ion channels and receptors regulating neuronal excitability, treatments based on peptides, which may have fewer side effects, are able to precisely modulate pain signals. Monoclonal antibodies against key pro-inflammatory cytokines, including TNF-α and interleukins, have changed the course of treatment for inflammatory pain syndromes (65). This is so since biologics directly neutralize the molecular causes of pain and inflammation. Furthermore, developments in nanomedicine allow one to design customised drug delivery systems aiming at therapeutic agents, especially in damaged or inflammatory tissues (66). This reduces system exposure and toxicity at the same time as raising efficiency. Taken as a whole, these creative ideas show the ways in which tailored, mechanical pain management can be applied to precisely enhance the results of treatment for patients (67). Personalised treatment plans aiming at multiple objectives consist of the following elements:

Epigenetic therapies: HDAC inhibitors for neuropathic pain

Development and continuation of chronic pain depend on epigenetic control, which is reached by altering gene expression without altering the underlying DNA sequence. Especially histone deacetylases (HDACs), damage-induced modifications in chromatin remodelling enzymes can suppress genes required for neuropathic pain, anti-inflammatory signalling, neural repair, and inhibition of neurotransmission (68). Emerging as a possible class of therapy able to reverse maladaptive epigenetic changes in glial cells and sensory neurons are HDAC inhibitors HDAC, is combining trichostatin A and suberoylanilide hydroxamic acid (SAHA), has been shown in preclinical studies in animal models of neuropathic pain to lower mechanical allodynia and thermal hyperalgesia. Utilizing better isoform-selective HDAC inhibitors, constant research seeks to maximize therapeutic efficacy and reduce systemic side effects (69).

Peptide-based therapies: Targeting specific ion channels

Whether synthetic or natural, the selectiveness of peptides determines the evolution of treatments aimed at molecules involved in nociceptive signalling. One important use is aiming at voltage-gated ion channels

also known as calcium, sodium, or potassium channels which regulate the excitability of the nervous system and the beginning of pain (70). For intrathecal injection in the treatment of severe chronic pain, for example, the Food and Drug Administration (FDA) has licensed the peptide ziconotide, derived from cone snail venom. It also reduces in dorsal horn neurons the activity of N-type voltage-gated calcium channels (Cav2.2) (71). Further peptides linked to inflammatory pain and thermosensation are under development now. Either target themselves or target the inhibition of the change of transient receptor potential (TRP). Their relative specificity to their target allows these peptides to generate analgesia free from the broad receptor activation linked with conventional medications (72). Even though we still need to improve their stability, distribution, and penetration across biological barriers, peptide treatments hold great potential for individualized pain management (73).

Biologics: Monoclonal antibodies against key cytokines

Sometimes dysregulated immune responses marked by elevated levels of pro-inflammatory cytokines define chronic pain syndromes. This is particularly true in disorders including an inflammatory or autoimmune component. Monoclonal antibodies (mAbs) are a specifically targeted therapy since they can neutralize these cytokines or their receptors (74). Targeting tumour necrosis factor-alpha (TNF-α), agents including infliximab, adalimumab, interleukin-1 beta (IL-1β), or interleukin-6 (IL-6) have shown their efficacy in reducing pain and inflammation in a range of diseases, including psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis (75). These biologics have the potential to change the processes causing central and peripheral pain by sensitizing nociceptive neurons driven by cytokines. Younger monoclonal antibodies are under investigation for their possible use in the treatment of non-autoimmune chronic pain syndromes, including fibromyalgia and chronic migraine, both of which are thought to be typified by strong neuroimmune interactions (76). The application of biologics is most reasonable in well-defined patient subgroups created using exact diagnosis techniques. This is so because parenteral treatment is much sought after, and biologics are sometimes costly (77).

Future Perspectives

Combining advanced artificial intelligence and deep learning techniques with multi-omics data, including genomics, proteomics, and metabolomics,

will define personalized pain medicine's future. From this mix, one can create comprehensive, unique pain profiles reflecting the complex genetic, molecular, environmental, and psychological factors influencing pain (78). Better biomarker discovery, patient stratification, and treatment response prediction made feasible by artificial intelligence-driven models will produce more customised treatments from which to draw (79). Wearable sensors and digital health apps will also enable dynamic treatment changes and real-time monitoring, thus improving customised treatment. While validating these strategies by means of large-scale clinical studies still poses difficulties, they guarantee cost-effectiveness, address ethical and privacy issues, and foster cooperation among several professionals (80). Supported regulatory and reimbursement systems should enable the regular clinical practice to bring customised pain management (81).

CONCLUSION

Chronic pain is a complex condition with great challenges for appropriate treatment since it reacts differently to conventional drugs. Customized medicine offers each patient's unique biology and clinical profile a personalized pain management solution. Reaching this is made possible by developments in genes, proteomics, biomarkers, and targeted medications. Integration of multi-omics data with artificial intelligence and machine learning has the potential to bring about a positive change, even if there are still main challenges to overcome, such as high costs, limited access to comprehensive molecular data, and ethical questions about genetic information. Apart from customized treatment plans that maximize efficacy while simultaneously reducing side effects, these technologies could enable exact pain phenotyping. Future research stressing large-scale clinical trials and real-world studies assessing the safety, efficacy, and cost-effectiveness of tailored treatments will enable us to fully meet this promise. At last, tailored pain management can improve quality of life, alter the course of treatment for millions of people worldwide, and increase patient outcomes.

Author's Contribution

Hosein Fazli and Mehdi Rezaee were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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Genetic Basis of Thyroid Cancer: The Role of MMP2 and MMP9 Polymorphisms

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ABSTRACT

Background: Matrix metalloproteinases (MMPs) play a critical role in tumor invasion and metastasis in papillary thyroid carcinoma (PTC). This study investigates the association of MMP2 (rs7201) and MMP9 (rs17576) polymorphisms with PTC risk and clinical characteristics, aiming to inform personalized medicine approaches. Methods: A case-control study was conducted with 210 PTC patients and 210 controls. Genotype frequencies were analyzed using Chi-Square tests, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Associations with clinical characteristics (T Status, N Status, Stage) were assessed in PTC patients.
Results: The MMP2 rs7201 CC genotype was significantly associated with increased PTC risk (OR = 3.524, 95% CI = 1.809–6.867, p = 0.001) and advanced T Status (T3: 48.6%, p = 0.029), but not with N Status (p = 0.509) or Stage (p = 0.461). The C allele was more frequent in cases (44%) than controls (32%) (OR = 1.590, p = 0.001). Conversely, MMP9 rs17576 showed no association with PTC risk (GG: OR = 0.727, p = 0.277) or clinical characteristics (p > 0.05). Both polymorphisms were in Hardy-Weinberg equilibrium in controls.
Conclusion: The MMP2 rs7201 CC genotype and C allele are associated with increased PTC risk and tumor progression, highlighting their potential as biomarkers for personalized risk stratification. These findings support genotype-based screening to identify high-risk PTC patients, enabling tailored surveillance

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INTRODUCTION

Thyroid cancer (TC), particularly papillary thyroid carcinoma (PTC), is a significant health concern due to its increasing incidence and potential for metastasis and recurrence (1). TC is a genetically simple disease, characterized by a relatively low somatic mutation burden in each tumor. Driver mutations, which confer a selective growth advantage and promote cancer development, have been identified in over 90% of TC cases (2). In the last 30 years, the availability of the genome sequence has greatly contributed to the understanding of the molecular mechanisms underlying TC (2).

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that play a pivotal role in extracellular matrix (ECM) remodeling (3). This family includes over 20 enzymes, each with distinct substrate specificities and tissue distributions. MMPs are involved in normal physiological processes such as wound healing, angiogenesis, and tissue repair.

However, their dysregulation is strongly implicated in pathological conditions, including cancer (3, 4).

In cancer, MMPs contribute to tumor progression by degrading ECM components, facilitating tumor invasion, metastasis, and angiogenesis. Among the MMP family, MMP-2 and MMP-9 are particularly significant due to their ability to degrade type IV collagen, a major component of the basement membrane. This activity is critical for cancer cells to invade surrounding tissues and establish metastases (5). Additionally, MMP-2 and MMP-9 are involved in modulating the tumor microenvironment, influencing cell-cell and cell-ECM interactions, and promoting angiogenesis (6, 7). Serum levels of MMP-2 and MMP-9 play critical roles in the progression and prognosis of thyroid cancer, particularly papillary thyroid carcinoma (PTC). Elevated preoperative serum MMP-2 levels have been identified as a potential biomarker for diagnosing PTC, distinguishing it from benign thyroid nodules (BTNs) with high sensitivity and specificity (8). MMP-2 levels are significantly correlated with tumor burden, lymph node metastasis (LNM), and structurally persistent or recurrent disease (SPRD) (8, 9). Similarly, serum MMP-9 levels are elevated in thyroid cancer patients and are linked to tumor aggressiveness, invasion, and metastasis (10).

The rs7201 polymorphism in MMP-2 and the rs17576 polymorphism in MMP-9 are associated with altered gene expression and serum levels (11, 12). This paper aims to unravel the genetic basis of thyroid cancer by exploring the roles of MMP-2 and MMP-9 polymorphisms, thereby contributing to the identification of potential biomarkers for diagnosis and prognosis. The exploration of genetic variations in thyroid cancer is crucial, as it may lead to personalized treatment strategies and improved patient outcomes. Understanding the interplay between these polymorphisms and thyroid cancer progression could pave the way for novel therapeutic interventions.

MATERIALS AND METHODS

The study population consisted of 420 subjects, including both men and women (210 patients with papillary thyroid carcinoma and 210 controls as the reference group), matched for age (± 5 years) and sex. The study was conducted using a case-control design. Patient samples were collected from Namazi Hospital in Shiraz, and control subjects were selected from the general population after confirmation of their health status by a specialist physician. Ethical approvals for recruitment were obtained from the local Ethics Committee of Arsanjan University (IR.IAU.KAU.REC.1403.049) and informed consent was obtained from all individuals.

Following the collection of peripheral blood samples from all study participants, DNA extraction was performed using the salting-out method, as previously described (13). Genotyping for MMP2 (rs7201) and MMP9 (rs17576) polymorphisms was conducted using the Tetra-primer Amplification Refractory Mutation System Polymerase Chain Reaction (Tetra-ARMS PCR). Genomic sequences of the MMP2 and MMP9 genes, including the flanking regions of the target polymorphisms, were retrieved from the NCBI database. Primers were designed using Primer1 software (14), which facilitates the creation of two outer (forward outer, FO; reverse outer, RO) and two inner (forward inner, FI; reverse inner, RI) primers specific to each allele (Table 1). The FI and RI primers amplify the C and A alleles for rs7201, and the G and

Table 1. Sequences and annealing temperatures of primers used for Tetra-ARMS PCR genotyping of MMP2 (rs7201) and MMP9 (rs17576) polymorphisms

Polymorphism	Primers	Sequence(5'to3')	Annealing Temperatures
MMP-9	FI(G allele):	CGCCCCAGGACTCTACACACG	
rs17567	RI(A allele):	GTTTCCCATCAGCATTGCCGTACT	**66° C**
	FO	CTTCTGCCCCAGCGAGAGTGAG	
	RO	TGGGAGGGAAGAGCCGCGTTTTG	
MMP-2	FI(C allele):	CAGAGCCACCCCTAAAGAGGTC	
rs7201	RI(A allele):	GGCTGCGTTGAAAATATCAAGGT	**62° C**
	FO	GCCTATTACCTGAAGCTGGAGAAC	
	RO	TAAGGCAGCCAGCAGTGAAAAG	

FI: forward inner primer; RI: reverse inner primer; FO: forward outer primer; RO: reverse outer primer. The FI and RI primers are allele-specific, amplifying the C/A alleles for rs7201 and G/A alleles for rs17576.

A alleles for rs17576, respectively, producing distinct band sizes for each genotype (Figure 1). A schematic of the Tetra-ARMS PCR mechanism is provided in Figure 1 to illustrate allele-specific amplification.

The Tetra-ARMS PCR reaction was performed in a 12.5 µL volume, containing 10 pmol of FI and RI primers and 3 pmol of FO and RO primers. PCR products were electrophoresed on a 2% agarose gel, stained with DNA Safe Stain, and visualized to determine genotypes based on band patterns (Figure 2).

The association between various risk factors and susceptibility to thyroid cancer was investigated using statistical analysis, logistic regression, and the calculation of odds ratios (OR) with 95% confidence intervals. Additionally, mean comparisons were performed using a T-test via SPSS 20 software.

RESULTS

Study Population Characteristics

This case-control study included 420 participants (210 cases with confirmed papillary thyroid carcinoma and 210 healthy controls) recruited from Namazi Hospital, Shiraz, Iran, between October 2015 and January 2017. The case and control groups were matched for age (±5 years) and sex. The overall study population comprised 354 females (84.3%) and 66 males (15.7%). The mean age of the control group was 40.54 ± 12.88 years, and that of the case group was 40.31 ± 13.94 years, with no statistically significant difference between the groups (p = 0.864).

The clinical features of the 210 patients with papillary thyroid carcinoma are summarized in Table 2. Tumor size was classified as T1 in 81 patients (41%), T2 in 63 patients (31.8%), T3 in 52 patients (26.3%), and T4 in 2 patients (1%). Regarding lymph node involvement, 23 patients (12.2%) were classified as N0 (no regional lymph node metastasis), 112 (59.6%) as Nx (lymph nodes not assessable), 27 (14.4%) as N1 (regional lymph node metastasis), 16 (8.5%) as N1a, and 10 (5.3%) as N1b. Distant metastasis status was Mx (not assessable) in 196 patients (99.5%) and M1 (distant metastasis) in 1 patient (0.5%). Disease staging revealed that 107 patients (75.9%) were in Stage I, 11 (7.8%) in Stage II, 20 (14.2%) in Stage III, and 3 (2.1%)

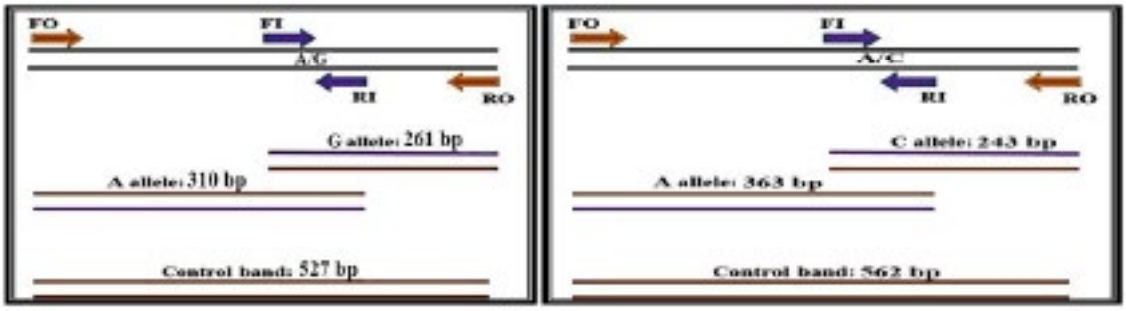

Fig.1 Mechanism of Tetra-ARMS PCR primers for detecting MMP9 (rs17576) (A) and MMP2 (rs7201) (B) polymorphisms. The schematic illustrates the binding of forward outer (FO), reverse outer (RO), forward inner (FI), and reverse inner (RI) primers to the target genomic DNA, producing allele-specific amplicons for each polymorphism.

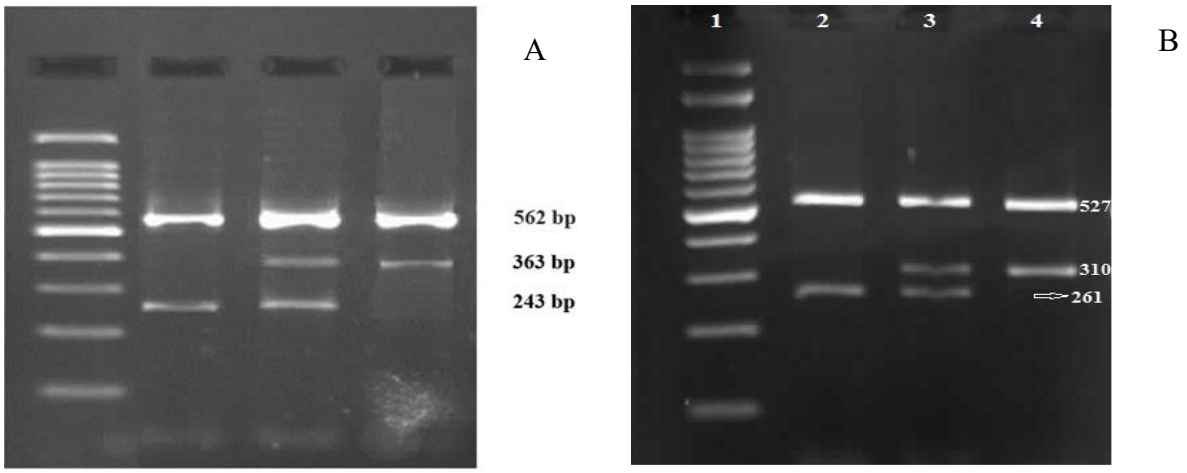

Fig.2 Representative agarose gel electrophoresis showing banding patterns for MMP2-A (rs7201) and MMP9- B (rs17576) genotypes. Distinct band sizes indicate AA, AC, and CC genotypes for rs7201, and AA, AG, and GG genotypes for rs17576, confirming successful amplification and genotyping.

Table 2. Clinical characteristics of patients with papillary thyroid carcinoma (PTC)

Characteristic	Case (n=210)
Mean age at diagnosis, years (Mean ± SD)	43.69 ± 7.622
T Status, n (%)	
T1	81 (41%)
T2	63 (31.8%)
T3	52 (26.3%)
T4	2 (1%)
N Status, n (%)	
N0	23 (12.2%)
Nx	112 (59.6%)
N1	27 (14.4%)
N1a	16 (8.5%)
N1b	10 (5.3%)
M Status, n (%)	
Mx	196 (99.5%)
M1	1 (0.5%)
Stage, n (%)	
I	107 (75.9%)
II	11 (7.8%)
III	20 (14.2%)
IV	3 (2.1%)

in Stage IV. The mean age at diagnosis was 43.69 ± 7.622 years.

Association of MMP2 rs7201 Genotypes with Thyroid Cancer Risk

The distribution of MMP2 rs7201 genotypes and their association with papillary thyroid carcinoma are presented in Table 3. The control group was in Hardy-Weinberg equilibrium for the rs7201 polymorphism (χ^2 = 2.915, df = 1, p = 0.088). A significant difference in distribution of AA, AC, and CC genotypes was observed between the case and control groups. The AC genotype was associated with an increased risk of thyroid cancer (OR = 1.600, 95% CI = 1.052–2.435, p = 0.028). Similarly, the CC genotype showed a stronger association with disease risk (OR = 3.524, 95% CI = 1.809–6.867, p = 0.001). Allelic analysis revealed that the C allele was significantly more frequent in the case group compared to the control group (OR = 1.590, 95% CI = 1.198–2.110, p = 0.001), indicating that individuals carrying the C allele had an approximately 1.6-fold higher risk of developing thyroid cancer compared to those with the A allele.

Association of MMP9 rs17576 Genotypes with Thyroid Cancer Risk

The distribution of MMP9 rs17576 genotypes and their association with papillary thyroid carcinoma are detailed in Table 4. The control group conformed to Hardy-Weinberg equilibrium for the rs17576 polymorphism (χ^2 = 2.410, df = 1, p = 0.120). No statistically significant differences in genotype frequencies were observed between the case and control groups. Allelic analysis indicated that the G allele frequency was similar in cases (38%) and controls (40%) (OR = 0.905, 95% CI = 0.685–1.194, p = 0.479), suggesting no link between the G allele and thyroid cancer susceptibility.

Association of MMP2 and MMP9 Genotypes with Clinical Characteristics

Table 3. Association of MMP2 rs7201 Genotypes and Alleles with Thyroid Cancer

MMP2 Polymorphism	Control, n (%)	Case, n (%)	OR (95% CI)	P-value
Genotype				
AA	92 (43.8%)	62 (29.5%)	1 (Reference)	-
AC	102 (48.6%)	110 (52.4%)	1.600 (1.052–2.435)	0.028
CC	16 (7.6%)	38 (18.1%)	3.524 (1.809–6.867)	0.001
Allele				
A	268 (64%)	234 (56%)	1 (Reference)	-
C	134 (32%)	186 (44%)	1.590 (1.198–2.110)	0.001

Table 4. Association of MMP9 rs17576 Genotypes and Alleles with Thyroid Cancer

MMP9 Polymorphism	Control, n (%)	Case, n (%)	OR (95% CI)	P-value
Genotype				
AA	81 (38.6%)	80 (38.1%)	1 (Reference)	-
AG	90 (42.9%)	102 (48.6%)	1.148 (0.755–1.745)	0.520
GG	39 (18.6%)	28 (13.3%)	0.727 (0.409–1.292)	0.277
Allele				
A	252 (60%)	262 (62%)	1 (Reference)	-
G	168 (40%)	158 (38%)	0.905 (0.685–1.194)	0.479

Table 5. Distribution and Association of MMP2 (rs7201) and MMP9 (rs17576) Genotypes with Clinical Characteristics in Papillary Thyroid Carcinoma

Genotype	T Status, n (%)	N Status, n (%)	Stage, n (%)
MMP2 rs7201	T1 (n=81) / T2 (n=63) / T3 (n=54)	N0/Nx (n=135) / N1 (n=53)	Stage I (n=107) / Stage II-IV (n=34)
AA	27 (45.8%) / 18 (30.5%) / 14 (23.7%)	42 (77.8%) / 12 (22.2%)	30 (71.4%) / 12 (28.6%)
AC	46 (44.2%) / 35 (33.7%) / 23 (22.1%)	69 (69.7%) / 30 (30.3%)	55 (75.3%) / 18 (24.7%)
CC	8 (22.9%) / 10 (28.6%) / 17 (48.6%)	24 (68.6%) / 11 (31.4%)	22 (84.6%) / 4 (15.4%)
p-value	**0.029**	0.509	0.461
MMP9 rs17576			
AA	32 (43.2%) / 24 (32.4%) / 18 (24.3%)	48 (69.6%) / 21 (30.4%)	45 (78.9%) / 12 (21.1%)
AG	38 (39.6%) / 28 (29.2%) / 30 (31.3%)	67 (72.8%) / 25 (27.2%)	43 (69.4%) / 19 (30.6%)
GG	11 (39.3%) / 11 (39.3%) / 6 (21.4%)	20 (74.1%) / 7 (25.9%)	19 (86.4%) / 3 (13.6%)
p-value	0.733	0.866	0.217

The distribution and association of MMP2 (rs7201) and MMP9 (rs17576) genotypes with clinical characteristics in patients with papillary thyroid carcinoma are presented in Table 3-6. For MMP2 rs7201, a significant association was observed with T Status ($\chi^2 = 10.774$, df = 4, p = 0.029). Notably, the CC genotype was more prevalent in T3 (48.6%) compared to T1 (22.9%), suggesting a potential role

in tumor progression. In contrast, no significant associations were found for rs7201 with N Status (χ^2 = 1.350, df = 2, p = 0.509) or Stage (χ^2 = 1.551, df = 2, p = 0.461). For MMP9 rs17576, no significant associations were observed with T Status (χ^2 = 2.013, df = 4, p = 0.733), N Status (χ^2 = 0.287, df = 2, p = 0.866), or Stage (χ^2 = 3.057, df = 2, p = 0.217), indicating that rs17576 genotypes are unlikely to influence these clinical characteristics in this cohort.

DISCUSSION

In this study, we investigated the association of MMP2 rs7201 and MMP9 rs17576 polymorphisms with the susceptibility and clinical characteristics of papillary thyroid carcinoma (PTC). Our findings revealed a significant association between the MMP2 rs7201 polymorphism and thyroid cancer risk, particularly among individuals carrying the AC and CC genotypes. The C allele was significantly more frequent among cases, suggesting it may play a role in increasing susceptibility to thyroid malignancy. Conversely, the MMP9 rs17576 polymorphism did not show any statistically significant association with thyroid cancer risk or clinical staging.

The association between MMP2 polymorphisms and cancer risk has been previously documented in various malignancies. MMP2 encodes for a type IV collagenase that plays a critical role in extracellular matrix degradation, thereby facilitating tumor invasion and metastasis. The rs7201 polymorphism is located in the 3′ untranslated region (3′UTR) of the gene and may influence mRNA stability and gene expression levels (11). Our results are consistent with studies reporting increased cancer susceptibility linked to the C allele of rs7201 in other cancers, such as Head and Neck Squamous Cell Carcinoma (15) and lung carcinoma (16).

The significant association of the CC genotype with advanced tumor stage (T3) observed in our study supports the hypothesis that MMP2 rs7201 variants may contribute not only to the initiation but also to the progression of PTC. Although the association between rs7201 and lymph node metastasis or clinical stage was not statistically significant, a trend toward higher frequency of the CC genotype in more aggressive tumor types was observed. This may warrant further investigation in larger patient cohorts.

On the other hand, our findings do not support a role for the MMP9 rs17576 polymorphism in thyroid cancer susceptibility. This is in agreement with some previous studies that failed to find associations between rs17576 and cancer risk (17, 18), although others have reported significant correlations in esophageal squamous cell carcinoma (19), gastric (20), or prostate cancers (21). It is possible that the functional effect of rs17576 is tissue-specific or modulated by other genetic or environmental factors not assessed in our study.

It is noteworthy that the Hardy-Weinberg equilibrium was maintained in both control groups for the two polymorphisms, indicating the reliability of our genotyping data. The allelic analysis further confirmed the association of the MMP2 rs7201 C allele with PTC risk, while no allelic differences were found in MMP9 rs17576.

The significant association observed between the MMP2 rs7201 C allele and increased risk of papillary thyroid carcinoma highlights the potential utility of this genetic marker in the context of personalized medicine. In light of the current shift toward precision oncology, such genetic variations may serve as valuable tools for individualized risk assessment, early detection strategies, and potentially for tailoring follow-up and therapeutic interventions based on a patient's molecular profile. As noted by Ashley (2015), the integration of genomic data into clinical decision-making represents a transformative step in modern medicine, enabling more effective and targeted management of complex diseases like cancer (22).

Our study has several strengths, including a well-characterized patient population and analysis of clinical-pathological parameters. However, it also has limitations. First, the sample size, particularly for certain clinical subgroups such as N1 (n=53) and Stage II-IV (n=34), was relatively small, which may have limited the statistical power to detect associations with N Status and Stage. Second, the control group was selected from the general population without screening for potential confounders such as family history of thyroid disease, exposure to environmental risk factors (e.g., radiation), or other genetic predispositions, which could influence the observed associations. Third, the study focused on two polymorphisms, and other genetic variants in MMP2, MMP9, or related pathways (e.g., BRAF, TERT) may interact to influence PTC risk and progression. Fourth, the retrospective nature of the study may introduce selection bias, and prospective studies are needed to validate our findings. Finally, functional studies are required to elucidate the mechanistic effects of the rs7201 and rs17576 polymorphisms on MMP2 and MMP9 expression and activity in PTC.

In conclusion, our findings suggest that the MMP2 rs7201 C allele, particularly in the homozygous CC genotype, may be a genetic risk factor for papillary thyroid cancer. This polymorphism could serve as a potential biomarker for early detection or disease progression, pending validation in larger, multi-center studies. In contrast, MMP9 rs17576 does not appear to play a significant role in PTC susceptibility in our population.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Author contributions

Leila Kohan Supervision, Methodology, Reviewing and Editing, Yasam Taabodi and Elahe Kohan Sample collection, Investigations, Statistical analysis, Original draft preparation and Data collection

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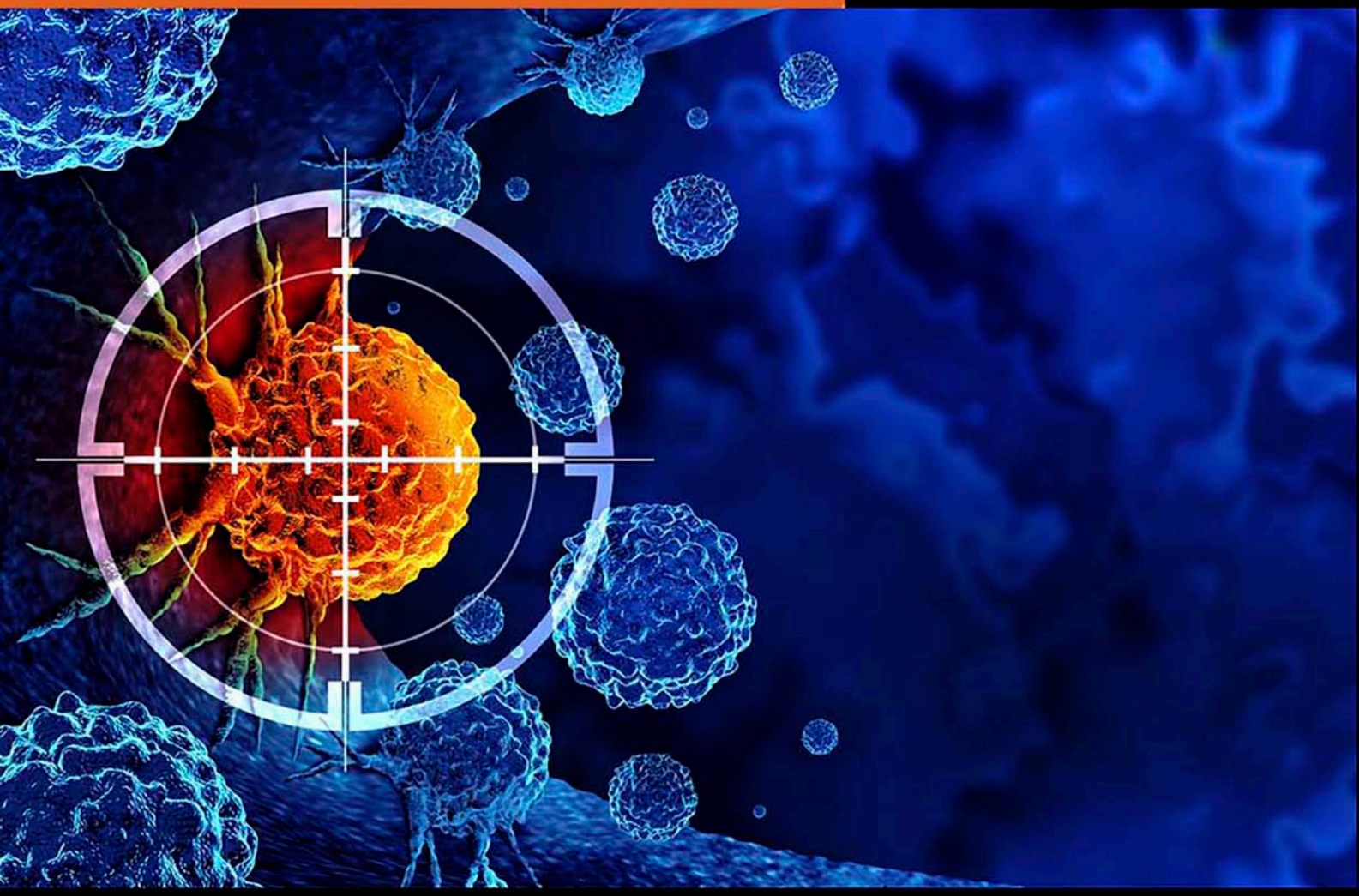

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