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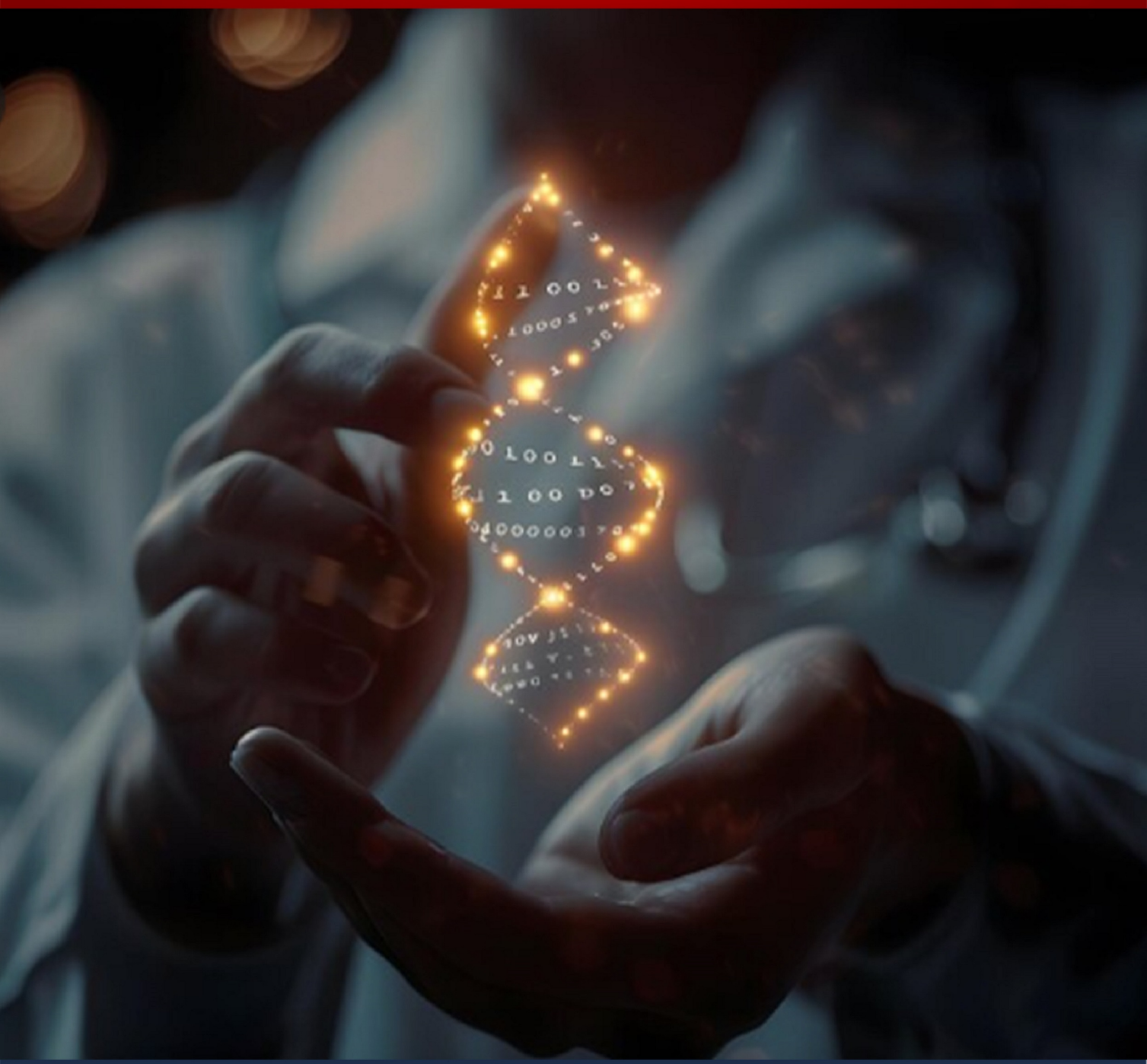

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Targeted Therapy for Colorectal Cancer Using Probiotics as an Advanced Therapy

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Abstract

Colorectal cancer (CRC) is among the most prevalent cancers globally and continues to represent a significant contributor to cancer-related morbidity and mortality. Despite significant advancements in surgical techniques, chemotherapy, targeted treatments, and immunotherapeutic approaches, and variable treatment responses continue to limit clinical outcomes. Accumulating evidence suggests that the intestinal microbiota is closely involved in the development of colorectal cancer and may modulate tumor growth, host immune responses, and the efficacy of anticancer therapies. Probiotics have therefore emerged as promising microbiota-modulating agents with potential applications in CRC prevention and therapy. This review summarizes current evidence regarding the therapeutic potential of probiotics in CRC, focusing on their anticancer mechanisms, probiotic-derived metabolites, advanced targeted delivery systems.

Probiotics may contribute to cancer prevention and control through several interconnected mechanisms, including the re-establishment of gut microbial homeostasis, strengthening of the intestinal barrier, regulation of inflammatory and immune pathways, suppression of cancer-cell growth, promotion of programmed cell death, and generation of biologically active compounds, notably short-chain fatty acids. Recent progress in synthetic biology and advanced encapsulation techniques has facilitated the design of engineered probiotic systems that can serve as vehicles for targeted delivery of therapeutic agents. Although preclinical findings are encouraging, clinical evidence remains heterogeneous and insufficient to establish probiotics as standalone anticancer treatments. Strain specificity, dosage, formulation, safety, and interactions with conventional therapies remain important challenges. Future research should emphasize precision probiotic selection, engineered microbial therapeutics, targeted delivery platforms, and integration with chemotherapy and immunotherapy. Overall, probiotics represent a promising foundation for developing advanced, targeted, and personalized microbiome-based therapeutic strategies for CRC.

Keywords: Colorectal cancer, Probiotics; Gut microbiome, Targeted therapy, Microbial metabolites.

Introduction

Colorectal Cancer: Current Challenges and Therapeutic Limitations

Colorectal cancer (CRC) ranks among the most frequently diagnosed and deadly cancers globally and constitutes a substantial burden on public health. Although substantial advances in early detection, surgical management, chemotherapy, molecularly

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targeted therapy, and immunotherapy have improved clinical outcomes, the treatment of CRC remains challenging, particularly in patients with locally advanced or metastatic disease. The molecular heterogeneity of CRC, including alterations in pathways involving KRAS, NRAS, BRAF, EGFR, HER2, and the mismatch repair (MMR)/ microsatellite instability (MSI) system, contributes to considerable interpatient and intratumoral variability in therapeutic response. Consequently, treatment selection increasingly depends on molecular profiling and predictive biomarkers; however, the clinical benefit of targeted approaches remains restricted to specific molecular subgroups (1-2).

Despite these therapeutic advances, primary and acquired drug resistance remains one of the major limitations in CRC management. Resistance can arise through secondary genetic alterations, activation of alternative signaling pathways, clonal selection, tumor-cell plasticity, and interactions with the tumor microenvironment. Moreover, chemotherapy-associated toxicity and the limited efficacy of immunotherapy in many patients, particularly those with mismatch repair-proficient/microsatellite-stable tumors, further emphasize the need for novel therapeutic strategies.The complexity of these resistance mechanisms highlights the importance of developing approaches that can selectively target tumor-associated pathways while minimizing systemic toxicity. In this context, modulation of the gut microbiota and the use of probiotics have emerged as promising complementary strategies, potentially providing a biological basis for more targeted and advanced therapeutic approaches in CRC (1-3).

The Gut Microbiome and Colorectal Cancer

Growing evidence has established the gut microbiota as a key component of the tumor microenvironment in colorectal cancer (CRC), with complex interactions between intestinal microorganisms, epithelial cells, immune responses, and microbial metabolites contributing to colorectal carcinogenesis. Disruption of the normal intestinal microbial ecosystem, commonly referred to as gut dysbiosis, is frequently observed in individuals with colorectal cancer. This condition involves substantial shifts in the abundance, diversity, and relative distribution of bacterial populations, resulting in an imbalance between potentially harmful microorganisms and health-promoting commensal species. Several bacterial taxa have been implicated in colorectal tumorigenesis, with *Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis*, and genotoxic strains of *Escherichia coli* receiving particular attention. These microorganisms may contribute to colorectal carcinogenesis by promoting a persistent inflammatory state and altering the local intestinal environment in ways that favor tumor initiation and progression (2-4).

The contribution of the intestinal microbiota to colorectal cancer extends beyond changes in the composition of bacterial communities. A major part of its biological activity is mediated through metabolites generated during microbial metabolism. Compounds such as short-chain fatty acids (SCFAs), modified bile acids, indole-derived molecules, polyamines, and other signaling metabolites can interact with intestinal epithelial cells and immune populations, thereby affecting multiple processes involved in intestinal homeostasis and tumor biology. Through these interactions, microbial metabolites may regulate epithelial barrier function, inflammatory responses, immune activity, cellular proliferation, and programmed cell death. Depending on the microbial environment and metabolic profile, these effects may either promote malignant transformation or contribute to the maintenance of antitumor conditions (4-5).

The microbiota can also modify how patients respond to anticancer therapies by influencing both treatment effectiveness and therapy-associated adverse effects. These interactions are particularly relevant to chemotherapy and immune-based treatments, in which the intestinal microbial environment may affect drug activity, host immune responses, and treatment tolerance. Therefore, strategies aimed at reshaping or controlling the gut microbiota have emerged as a potential component of CRC management. In this context, probiotics and other microbiome-directed approaches (4-5).

Probiotics and Their Therapeutic Potential in CRC

Probiotics have gained considerable attention as potential microbiome-based interventions in colorectal cancer because of their capacity to influence the intestinal ecosystem and host–microbe interactions. Their biological activity is not limited to a single pathway; rather, different probiotic strains may exert beneficial effects through multiple mechanisms. These include reshaping an imbalanced microbial community, strengthening epithelial barrier function, and regulating local inflammatory processes and host immune activity. Probiotic microorganisms can also generate metabolites with biological activity, particularly short-chain fatty acids, which may contribute to maintaining intestinal homeostasis. Furthermore, by competing with harmful bacteria and reducing the abundance or activity of microorganisms associated with carcinogenesis, probiotics may create a less favorable environment for tumor development. Experimental findings have additionally indicated that some probiotic strains can directly affect malignant cells by reducing their proliferative capacity, promoting programmed cell

death, and altering molecular pathways involved in colorectal tumor growth. Taken together, these diverse interactions with the intestinal microbiota, epithelial tissue, immune system, and tumor cells provide a biological basis for considering probiotics as potential agents for both CRC prevention and therapeutic management (4- 6).

Beyond their direct antitumor effects, probiotics may have potential as adjunctive therapeutic agents alongside conventional CRC treatments. Evidence from clinical and preclinical studies indicates that probiotic supplementation may help alleviate treatment-associated gastrointestinal complications, improve intestinal microbiota composition, and potentially enhance the therapeutic efficacy of chemotherapy and other anticancer interventions. However, the effects of probiotics are highly dependent on bacterial strain, dose, formulation, treatment duration, and host-specific factors. Therefore, despite promising findings, further well-designed clinical studies are required to establish strain-specific efficacy, optimal dosing regimens, safety profiles, and potential interactions with anticancer therapies. These considerations are particularly relevant to the development of probiotics as advanced and targeted therapeutic strategies for CRC (6- 7).

Targeted Anticancer Mechanisms of Probiotics

Probiotics exert anticancer effects against colorectal cancer (CRC) through multiple, interconnected molecular and cellular mechanisms. At the cellular level, probiotics may exert anticancer activity by directly altering molecular processes that control the survival and growth of colorectal tumor cells. Certain probiotic strains and the metabolites they produce have been reported to interfere with mechanisms responsible for uncontrolled cell division and to activate pathways associated with apoptosis. This activity may involve enhancement of apoptotic mediators, including BAX and caspase proteins, together with a reduction in the expression or activity of anti-apoptotic factors such as BCL-2. Probiotic-associated effects have also been linked to changes in major intracellular signaling networks, including the PI3K/AKT, MAPK, and NF-κB pathways, which play important roles in tumor-cell proliferation, survival, and inflammatory responses. Among microbiota-derived compounds, short-chain fatty acids (SCFAs) have attracted particular interest because of their ability to interact with colorectal epithelial and tumor cells. Butyrate, one of the principal SCFAs generated by intestinal bacteria, may alter cellular metabolism and gene regulation and thereby contribute to the suppression of malignant-cell growth and induction of apoptotic responses (6- 7).

Beyond direct effects on tumor cells, probiotics can modify the tumor-associated inflammatory and immune microenvironment, providing an additional mechanism for targeted anticancer activity. Probiotic strains and their metabolites may suppress pro-inflammatory signaling, including the TLR4/MyD88/NF-κB and NLRP3 pathways, while promoting intestinal barrier integrity and regulating cytokine production. Furthermore, modulation of host immunity can enhance antitumor responses through increased activity of cytotoxic immune cells and improved immune surveillance. These combined effects, direct inhibition of tumor growth, induction of apoptosis, attenuation of chronic inflammation, and enhancement of antitumor immunity, support the potential of probiotics and probiotic-derived molecules as microbiota-based therapeutic tools for CRC (8- 9).

Probiotic-Derived Metabolites as Therapeutic Targets

Probiotic-derived metabolites have emerged as important mediators of the anticancer effects associated with beneficial microorganisms and represent promising therapeutic targets in colorectal cancer (CRC). Among these metabolites, short-chain fatty acids (SCFAs), particularly butyrate, acetate, and propionate, have received considerable attention because of their ability to regulate intestinal epithelial homeostasis, inflammatory responses, and tumor-cell behavior. Butyrate can function as an energy substrate for normal colonocytes while exerting antitumor effects suppression of proliferative signaling, and induction of apoptosis in colorectal cancer cells. Importantly, supplementation with SCFA-producing probiotics may increase the local availability of these metabolites and consequently contribute to restoration of a metabolically favorable intestinal environment.

Beyond SCFAs, probiotic-associated metabolites and bioactive compounds, including bacteriocins, exopolysaccharides, lactate, indole derivatives, and other microbial products, may influence CRC through modulation of inflammation, intestinal barrier integrity, immune responses, and tumor-associated signaling pathways. In contrast, dysbiosis can increase the production of potentially tumor-promoting metabolites, highlighting the importance of restoring a favorable microbial metabolic profile rather than simply increasing bacterial abundance. Therefore, targeting probiotic-derived metabolites represents a potentially more precise therapeutic strategy, in which specific microbial metabolic pathways could be manipulated through probiotics, prebiotics, dietary substrates, postbiotics, or engineered microbial systems to enhance beneficial metabolites and suppress pro-tumorigenic metabolic

signals (10- 11).

Advanced and Targeted Probiotic-Based Therapies

Recent advances in synthetic biology, nanotechnology, and drug-delivery systems have expanded the therapeutic potential of probiotics beyond their conventional role in microbiota modulation. Engineered probiotics can be genetically modified to express therapeutic proteins, peptides, enzymes, or immunomodulatory molecules and may be designed to preferentially localize within the tumor microenvironment. For example, engineered Escherichia coli Nissle 1917 has been investigated as a tumor-targeting probiotic platform capable of delivering anticancer molecules directly to colorectal tumors. Such approaches can potentially increase local therapeutic concentrations while reducing systemic exposure and off-target toxicity. In addition, inducible genetic circuits may allow therapeutic payloads to be expressed in response to specific characteristics of the tumor microenvironment, providing an additional level of spatial and functional control.

Another emerging strategy involves targeted delivery and encapsulation of probiotics to improve their survival during gastrointestinal transit and enhance their accumulation at the colorectal tumor site. Advanced micro- and nano-encapsulation systems can protect probiotic cells from gastric acidity, bile salts, and other adverse gastrointestinal conditions while improving mucosal adhesion, colon-specific release, and bacterial viability.[2] Single-cell encapsulation and responsive nanocoatings represent particularly promising approaches because they can provide controlled release in response to specific physicochemical or biological characteristics of the intestinal and tumor microenvironment.[2] Collectively, these technologies may transform probiotics from conventional microbiome-modulating agents into precision therapeutic platforms capable of targeted delivery, controlled release, and localized anticancer activity in CRC. However, their clinical translation still requires rigorous evaluation of safety, stability, targeting specificity, dosing, and long-term effects (12- 13).

Preclinical and Clinical Evidence Supporting the Therapeutic Potential

Preclinical evidence provides substantial support for the potential anticancer activity of probiotics in colorectal cancer (CRC). Findings obtained from in vitro experiments and preclinical animal models suggest that probiotic microorganisms, especially species belonging to the *Lactobacillus* and *Bifidobacterium* groups, may interfere with the development of colorectal tumors. Their proposed anticancer activity appears to involve several interconnected processes, such as limiting the growth of malignant cells, activating apoptotic mechanisms, reducing intestinal and systemic inflammatory activity, and improving epithelial barrier integrity. In addition, these microorganisms may influence host immune regulation and modify microbial metabolic processes, which can collectively contribute to creating an intestinal environment less favorable to colorectal carcinogenesis.

A systematic assessment of preclinical animal research indicated that most of the studies analyzed reported beneficial effects associated with probiotic interventions in colorectal lesions or tumor development following probiotic administration, although considerable heterogeneity in probiotic strains, doses, experimental models, and study quality limits direct comparison between studies.

Clinical evidence is encouraging but remains less conclusive than the preclinical literature. Randomized controlled trials in patients with CRC have suggested that probiotic supplementation can improve gut microbial composition, reduce postoperative complications and treatment-associated gastrointestinal toxicity, and modulate inflammatory responses. However, clinical outcomes are highly dependent on the probiotic strain, formulation, dose, treatment duration, disease stage, and concomitant anticancer therapy. Importantly, current evidence does not yet establish probiotics as a stand-alone anticancer treatment, and larger, well-designed, strain-specific clinical trials are required to determine their therapeutic efficacy and optimal integration with chemotherapy, immunotherapy, and other targeted treatments (14- 15).

Challenges and Safety Considerations

Despite the promising therapeutic potential of probiotics in colorectal cancer (CRC), several challenges limit their translation into standardized clinical applications. One of the major concerns is the strain-specific nature of probiotic effects, as different strains within the same species may exhibit substantially different biological activities, mechanisms of action, and safety profiles. In addition, variability in dosage, formulation, viability, treatment duration, and host-specific factors can contribute to inconsistent outcomes among clinical studies. Safety assessment is particularly important when probiotics are considered as adjunctive therapies in cancer patients, who may have altered intestinal barriers or compromised immune function. Potential risks include opportunistic infections, gastrointestinal adverse effects, metabolic disturbances.

The development of probiotics as advanced therapeutic platforms also requires rigorous evaluation of genetic stability, virulence-associated

factors, antibiotic-resistance determinants, and product quality. These considerations become even more critical for engineered or next-generation probiotics designed to deliver therapeutic molecules directly to the tumor microenvironment. Current evidence emphasizes the importance of strain-level identification, whole-genome sequencing, standardized manufacturing, and systematic monitoring of adverse events before clinical translation. Furthermore, the heterogeneity of CRC and the complex interactions between probiotics, the resident microbiome, host immunity, and anticancer drugs make it difficult to predict therapeutic responses on an individual basis (16- 17).

Future Perspectives

The future development of probiotic-based therapies for colorectal cancer (CRC) is likely to move from conventional, non-specific supplementation toward precision microbiome medicine. Advances in genomics, metabolomics, and microbiome profiling may enable the selection of specific probiotic strains according to the individual patient's microbial composition, tumor characteristics, and therapeutic response. In parallel, engineered probiotics and next-generation live biotherapeutics could be designed to sense tumor-associated signals and selectively deliver therapeutic molecules within the colorectal tumor microenvironment. Such programmable systems may provide greater targeting specificity and allow controlled production of anticancer proteins, immune-modulating factors, or therapeutic metabolites directly at the site of disease.

Another promising direction is the integration of probiotics with nanotechnology, targeted delivery systems, chemotherapy, and immunotherapy. Advanced encapsulation strategies may improve probiotic survival during gastrointestinal transit, enhance colon-specific delivery, and facilitate controlled release at the tumor site. Furthermore, combining microbiome modulation with immune checkpoint inhibitors or other targeted therapies could potentially overcome treatment resistance by reshaping the tumor-associated microbial and immune environment. Future research should therefore focus on strain-specific mechanisms, patient stratification using multi-omics approaches, standardized clinical protocols, and long-term safety evaluation. Ultimately, the development of personalized and engineered probiotic platforms may transform probiotics from conventional dietary supplements into precision living therapeutics for CRC (18- 19).

Conclusion

Colorectal cancer (CRC) arises from a complex interplay of genetic, environmental, microbial, and host-related factors, with the intestinal microbiota increasingly recognized as an important regulator of disease development and progression. Changes in the gut microbial ecosystem may affect tumorigenesis, immune-system activity, and the response of patients to anticancer interventions. Within this context, probiotics have attracted attention as potential microbiome-directed agents. Their proposed protective and therapeutic activities include rebalancing intestinal microbial communities, strengthening the epithelial barrier, regulating immune and inflammatory processes, generating biologically active metabolites, and restricting the proliferation and survival of colorectal cancer cells. Nevertheless, current evidence supports probiotics primarily as a complementary or adjunctive therapeutic strategy, rather than an established standalone treatment for CRC. The heterogeneity of probiotic strains, treatment protocols, patient populations, and clinical endpoints remains a major obstacle to translating promising experimental findings into standardized clinical applications.

Future development of probiotic-based CRC therapy should therefore focus on precision and targeted approaches, including strain-specific selection, engineered probiotics, targeted delivery systems, and integration with chemotherapy and immunotherapy. Recent advances in encapsulation technologies and live bacterial therapeutics provide opportunities to improve probiotic survival, colon-specific delivery, and localized release of therapeutic molecules within the tumor microenvironment. Large-scale, well-controlled clinical trials combined with multi-omics and microbiome profiling will be essential for identifying responsive patient populations and establishing optimal dosage, safety, and therapeutic combinations. Ultimately, the transition from conventional probiotic supplementation toward precision microbiome-based and engineered probiotic therapeutics may provide a promising avenue for improving the prevention and treatment of CRC (20- 21).

Overall, the available evidence supports a biologically plausible role for probiotics in CRC, particularly through modulation of the gut microbiome, intestinal barrier, inflammation, and microbial metabolites. However, the clinical evidence remains heterogeneous. Notably, the phase III trial by Mego et al. did not demonstrate a significant reduction in severe irinotecan-induced diarrhea in the overall population, highlighting the importance of strain specificity, patient selection, and personalized probiotic interventions (22- 25).

Taken together, the available evidence suggests that probiotics may serve as a valuable adjunct in the management of colorectal cancer by acting at multiple levels of the gut–tumor axis. Their

Table 1. Selected preclinical and clinical studies investigating probiotic-based approaches in colorectal cancer.

Study	Study type / Model	Probiotic intervention	Main objective	Key findings
Peluzio et al., 2020 (1)	Systematic review of preclinical and clinical studies	Probiotics and synbiotics	To evaluate the potential of probiotics/synbiotics in CRC prevention and identify their underlying mechanisms	Probiotics and synbiotics were associated with reduced inflammation, inhibition of tumor growth, induction of apoptosis, modulation of immune responses, improvement of intestinal barrier function, and production of potentially anticarcinogenic metabolites.
Wierzbicka et al., 2021 (2)	Systematic review of 6 clinical trials; 457 patients with CRC	Probiotics/synbiotics	To determine whether probiotic administration could modulate the gut microbiota in patients with CRC	Probiotic/synbiotic supplementation increased beneficial bacteria, including Lactobacillus and Bifidobacterium, while reducing potentially harmful bacteria. Improvements in intestinal permeability, tight-junction function, and inflammatory parameters were also reported.
Dikeocha et al., 2021 (3)	Systematic review of 23 randomized controlled trials To evaluate the clinical effects of probiotics in patients with CRC	Various Lactobacillus and Bifidobacterium-based preparations	To evaluate the clinical effects of probiotics in patients with CRC	Probiotic supplementation was associated with improved gut microbiota diversity, reduced postoperative infectious complications, decreased chemotherapy-related adverse effects, improved quality of life, and shorter hospital stays.
Mego et al., 2023 (4)	Phase III randomized, double-blind, placebo-controlled trial; 242 metastatic CRC patients	Bifidobacterium animalis BB-12 + Lacticaseibacillus rhamnosus GG To determine whether probiotics could prevent irinotecan-induced diarrhea	To determine whether probiotics could prevent irinotecan-induced diarrhea	The primary endpoint was not met: grade 3/4 diarrhea was 7.9% with probiotics vs 11.8% with placebo (P=0.38). However, a subgroup of patients with colostomy showed a potential benefit, including better diarrhea-free survival and reduced loperamide use. No probiotic-related infections were observed.
Yang et al., 2024 (5)	Preclinical study; AOM/DSS-induced CRC mouse model	Limosilactobacillus fermentum GR-3	To investigate whether a probiotic strain could prevent or attenuate colorectal tumorigenesis through microbiome modulation	GR-3 reduced tumor incidence by 51.2%, attenuated intestinal barrier disruption and inflammation, increased beneficial SCFA-associated bacteria and metabolites, and reduced potentially harmful secondary bile acids.

potential benefits include reshaping the intestinal microbial community, reinforcing epithelial barrier function, influencing host inflammatory and immune pathways, generating metabolites with potentially protective properties, and limiting the growth and viability of malignant cells. Nevertheless, substantial variation among probiotic strains, study designs, treatment protocols, and patient populations makes the existing clinical findings difficult to generalize. Therefore, although probiotics represent a promising complementary approach, current evidence does not support their use as an independent replacement for established anticancer therapies. Further well-designed clinical trials are required to determine

the most effective strains, doses, formulations, and treatment combinations for CRC (25- 27). Differences in probiotic strains, dosage, formulation, treatment duration, patient characteristics, and concomitant anticancer therapies represent major barriers to clinical translation. Future research should therefore move toward precision probiotic therapy, with strain-specific selection based on patient microbiome profiles and tumor characteristics. Advances in next-generation probiotics, engineered microorganisms, targeted encapsulation, and controlled delivery systems may enable localized delivery of therapeutic molecules to colorectal tumors and improve treatment efficacy while minimizing systemic effects. Large-scale randomized clinical trials combined with multi-omics approaches will be essential to establish optimal strains, doses, treatment combinations, and safety profiles, potentially transforming probiotics from conventional supplements into precision microbiome-based therapeutics for CRC.

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Data Availability

The data underlying the findings of this study can be obtained from the corresponding author upon reasonable request.

Declarations

Competing Interests

The authors confirm that they have no financial or non-financial conflicts of interest, nor any personal relationships that could be perceived as having influenced the research or its findings.

Ethics Approval and Consent to Participate

Not applicable.

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Not applicable.

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Predictive Genetic Biomarkers of Chemotherapy Response in Common Cancers: Current Evidence and Perspectives for Targeted Therapies

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Abstract

Predictive genetic Biomarkers have assumed a central role to the evolution of precision oncology by enabling individualized cancer treatment and improving therapeutic outcomes. This review comprehensively summarizes the current landscape of genetic biomarkers used to predict chemotherapy response across major various solid tumors, such as those affecting the breast and colorectum, lung, and other common cancers. We discuss the molecular basis of chemotherapy sensitivity and resistance, highlighting key mechanisms such as DNA repair alterations, gene mutations, epigenetic modifications, and tumor heterogeneity. Furthermore, we present a structured classification of predictive biomarkers, ranging from germline and somatic variants to gene-expression signatures and multi-omics-based profiles. The clinical utility of biomarker-guided targeted therapies is also evaluated, emphasizing their role in optimizing treatment selection, minimizing toxicity, and enhancing survival outcomes. Despite significant advances in genomic technologies, challenges remain in biomarker validation, standardization, and clinical translation, especially in relation to of tumor heterogeneity and real-world implementation. Emerging approaches such as liquid biopsy and AI-based technologies, and integrated multi-omics analysis are expected to further refine predictive accuracy and support dynamic treatment monitoring. Additionally, ongoing research in diverse solid tumors highlights the expanding applicability of biomarkers in immunotherapy and targeted therapy selection. Overall, This review emphasizes the profound impact of impact of predictive genetic biomarkers in modern oncology and their critical role in advancing personalized cancer therapy.

Keywords: Predictive genetic biomarkers; Chemotherapy response; Precision oncology; Targeted therapy; Molecular profiling.

Introduction

Despite considerable progress in diagnostic and therapeutic approaches, cancer continues to represent a major global burden of morbidity and mortality. Traditional chemotherapy has long served as a cornerstone of cancer management; however, significant interpatient variability in therapeutic response and treatment-related toxicity continues to limit its effectiveness. Recent developments in precision oncology have highlighted the importance of predictive genetic biomarkers in selecting patients who are most likely to benefit from

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targeted therapeutic regimens. Genetic alterations, including somatic mutations, germline variants, and gene-expression signatures, have demonstrated considerable potential for predicting chemotherapy sensitivity and resistance, thereby enabling more personalized treatment strategies and improved clinical outcomes (1, 41).

The rapid evolution of genomic technologies, particularly NGS-based sequencing and molecular characterization platforms, has accelerated the discovery and clinical application of predictive biomarkers across multiple cancer types. These biomarkers not only facilitate treatment selection but also contribute to reducing unnecessary toxicity and healthcare costs associated with ineffective therapies. Furthermore, emerging methods such as liquid biopsy, pharmacogenomics, and multi-omics integration are expanding the scope of biomarker-guided precision medicine. Despite these advances, challenges related to biomarker validation, tumor diversity and clinical implementation remain substantial barriers to widespread adoption. Consequently, comprehensive evaluation of predictive genetic biomarkers is essential for advancing individualized cancer therapy and optimizing chemotherapy response prediction (1, 42).

Genetic Biomarkers as Predictors of Chemotherapy Response

Genetic biomarkers have emerged as critical tools in modern oncology for predicting individual responses to chemotherapeutic agents and facilitating personalized treatment strategies. Variations in both germline and somatic genes can influence drug absorption, metabolism, transport, and cellular sensitivity, thereby affecting treatment efficacy and toxicity. Advances in pharmacogenomics have advanced the detection of genetic alterations linked to with resistance or sensitivity to commonly used anticancer drugs. Biomarkers such as gene genetic variants, including SNPs, copy-number variations, and epigenetic alterations provide valuable insights into tumor behavior and therapeutic outcomes. Bringing these findings molecular indicators into clinical practice has improved patient stratification and optimized drug selection. Furthermore, biomarker-guided chemotherapy can reduce unnecessary exposure to ineffective treatments and minimize adverse effects. As precision oncology advances, genetic biomarkers are becoming increasingly important for tailoring treatment decisions to the molecular characteristics of individual patients and tumors. (1, 2)

Several Studies have revealed that the predictive value of genetic biomarkers across several major cancer types, including breast cancer, colorectal, lung, and ovarian malignancies. Alterations in DNA repair genes, drug-metabolizing enzymes, mismatch repair pathways, and regulatory microRNAs have have been linked to variable responses to platinum-containing agents, taxanes, fluoropyrimidines, and other cytotoxic agents. New findings additionally highlight the role of epigenetic biomarkers and gene-expression signatures in recognizing individuals most likely to benefit from certain chemotherapy regimens. Despite the progress achieved, several limitations remain. regarding biomarker validation, standardization and clinical integration implementation. Large-scale prospective scientific studies and multidimensional omics approaches are expected to improve the reliability and applicability of predictive biomarkers in routine oncology practice. Ultimately, the integration of genomic information with targeted these treatment approaches may contribute to greater therapeutic efficacy and improved clinical outcomes (3, 4).

Classification of Predictive Genetic Biomarkers

Predictive genetic biomarkers may be grouped into different categories according to their biological origin, molecular characteristics, and clinical applications. The most widely recognized groups include germline genetic variants, somatic mutations, gene-expression signatures, epigenetic alterations, and pharmacogenomic markers. Germline biomarkers are inherited genetic variations that influence drug metabolism, toxicity, and treatment outcomes, whereas somatic biomarkers arise within tumor cells and directly affect therapeutic sensitivity or resistance. In addition, gene-expression profiles provide valuable information regarding tumor behavior and response to specific chemotherapeutic agents. Epigenetic biomarkers, including DNA methylation patterns and histone modifications, further contribute to treatment stratification by regulating gene activity without altering DNA sequences. The classification of these biomarkers is essential for determining patients with the highest potential to benefit from individualized treatment strategies and for advancing precision oncology. Advances in next-generation, high-throughput sequencing approaches have significantly expanded the spectrum of clinically relevant predictive biomarkers available for cancer management (5, 6).

Another important classification approach categorizes predictive biomarkers according to their functional roles in therapeutic decision-making. Pharmacodynamic biomarkers reflect the biological effects of treatment on tumor cells, while pharmacokinetic biomarkers influence drug absorption, distribution, metabolism, and elimination. Molecular predictive biomarkers may also be classified as single-gene markers, multigene panels, or integrated multi-omics signatures that combine genomic, transcriptomic, and epigenomic

data. Clinically validated examples include RAS mutations in colorectal cancer, BRCA1/2 alterations in breast and ovarian cancers, and microsatellite instability status in multiple solid tumors. These biomarkers not only predict chemotherapy response but also facilitate the choice of individualized targeted therapies and immunotherapeutic approaches. As biomarker research progresses, comprehensive molecular characterization is likely to enhance treatment personalization and improve clinical outcomes across diverse cancer types (7, 8).

Molecular Basis of Chemotherapy Resistance and Sensitivity

The cellular response to chemotherapeutic agents is governed by a complex network of molecular mechanisms that determine either drug sensitivity or resistance. Chemotherapy sensitivity is often associated with efficient drug uptake, activation of apoptotic pathways, intact DNA damage responses, and susceptibility to oxidative stress. In contrast, resistance develops through genetic and epigenetic alterations that enable tumor cells to survive cytotoxic insults. Key mechanisms include enhanced ABC transporter–driven drug efflux and increased DNA repair capacity capacity, dysregulation of apoptosis-related proteins, and alterations in cell-cycle checkpoints. Mutations affecting tumor suppressor genes and oncogenic signaling pathways further contribute to therapeutic failure. Tumor heterogeneity and clonal evolution also play significant roles in generating resistant cellular subpopulations during treatment. Understanding these molecular determinants is vital for determining predictive biomarkers and developing strategies to improve chemotherapy clinical efficacy and patient-related outcomes (9, 10).

Recent evidence has reinforced the significance of cellular plasticity, metabolic reprogramming, tumor stem cells and their complex interactions within the tumor microenvironment as critical drivers of chemotherapy resistance. Alterations in major intracellular signaling networks such as PI3K/AKT/mTOR, MAPK, Wnt/β-catenin, and NF-κB can promote survival and reduce drug-induced apoptosis. In addition, epigenetic modifications, non-coding RNAs, and transcriptional reprogramming contribute to adaptive resistance mechanisms that emerge during treatment. Conversely, tumors exhibiting defective DNA repair systems or impaired stress-response pathways often demonstrate increased sensitivity to DNA-damaging agents and other cytotoxic drugs. Advances in multi-omics technologies have improved the characterization of these molecular processes and facilitated the discovery of potential new therapeutic targets. Further investigation understanding of resistance and sensitivity mechanisms is expected to support the the formulation of individualized therapeutic regimens approaches and enhance the effectiveness of precision oncology (11, 12).

Biomarkers in Breast Cancer

Breast cancer is a biologically diverse disease defined by diverse molecular subtypes, each showing different biological profiles and therapeutic responses. The identification of predictive biomarkers has have established themselves as an integral part of precision oncology, supporting the optimization of therapeutic approaches selection and improve patient outcomes. Established biomarkers estrogen receptor (ER), progesterone receptor (PR), and HER2 are commonly evaluated to guide systemic therapy and predict responsiveness to both chemotherapy and targeted treatments. In addition, genomic assays and gene-expression signatures have enhanced risk stratification and treatment decision-making in early-stage disease. Recent advances in molecular profiling have also revealed the significance of tumor-infiltrating lymphocytes, ctDNA and other promising biomarkers in predicting therapeutic efficacy. These biomarkers contribute to individualized treatment approaches by determining which patients are most likely to benefit from targeted interventions while avoiding unnecessary toxicity. Consequently, biomarker-guided management has have evolved into an integral part of modern breast cancer care and precision medicine (13, 14).

Beyond traditional molecular markers, extensive research has focused on identifying novel genetic and epigenetic predictors of chemotherapy response in breast cancer. Alterations in BRCA1 and BRCA2 genes, DNA repair pathways, immune-related signatures, and molecular subtyping profiles have demonstrated predictive value for sensitivity to platinum-based agents and other cytotoxic therapies. Furthermore, advances in advanced genomic sequencing and liquid biopsy-based methods technologies have facilitated the detection of dynamic biomarkers that reflect tumor evolution during treatment. Predictive biomarkers are especially important for triple-negative and HER2-positive breast cancer subtypes, where treatment responses can vary substantially among patients. Despite significant progress, challenges related to tumor heterogeneity, biomarker validation, and clinical implementation remain unresolved. Ongoing translational research and extensive prospective studies are expected to improve the combination of predictive adoption of biomarkers in routine clinical practice and further advance tailored treatment approaches in breast cancer (15, 16).

Biomarkers in Colorectal Cancer

CRC is one of the most frequently occurring cancer

types worldwide and exhibits considerable molecular heterogeneity that influences disease progression and therapeutic response. The identification of predictive biomarkers has become increasingly important to refine therapeutic strategies and achieve better clinical outcomes in patients with CRC. Molecular biomarkers such as mutations in RAS and BRAF, together with MSI, dMMR, and HER2 status amplification have have shown strong potential for predicting responses to chemotherapy, targeted therapies, and immunotherapy. In addition to tissue-based markers, ctDNA and other cell-free DNA components nucleic acids, and microRNA profiles have emerged as promising biomarkers for non-invasive assessment of disease monitoring and therapeutic selection. Advances in genomic and transcriptomic technologies have facilitated the discovery of novel molecular signatures associated with therapeutic sensitivity and resistance. These innovations have contributed to substantially to the implementation of precision medicine approaches in colorectal cancer management. Consequently, biomarker-driven therapeutic decision-making is increasingly recognized as a cornerstone of personalized CRC treatment (17, 18).

Recent research has expanded the spectrum of clinically relevant biomarkers beyond conventional genetic alterations to include epigenetic modifications, tumor mutational burden, immune-related signatures, and molecular subtypes. Predictive biomarkers represent a valuable tool a critical role in identifying patients who may derive greater benefit from anti-EGFR therapies, immune checkpoint inhibitors, and combination treatment regimens. For example, RAS mutational status remains a key determinant of clinical response to anti-EGFR-targeted antibodies, while MSI-high tumors exhibit enhanced responsiveness to immunotherapy. Furthermore, comprehensive molecular profiling has improved the understanding of resistance mechanisms and enabled the development of individualized treatment strategies. Despite these advances, challenges related to biomarker validation, standardization, and accessibility continue to limit widespread clinical implementation. Future studies integrating integrative omics approaches coupled with AI technologies -based analyses are may further improve predictive biomarker discovery and improve therapeutic outcomes in colorectal cancer patients (19, 20).

Biomarkers in Lung Cancer

Globally, lung cancer remains a major contributor to cancer-related mortality, with significant molecular heterogeneity influencing disease progression and therapeutic response. The characterization of predictive biomarkers has transformed the management of lung cancer by enabling patient-specific therapeutic approaches and improving clinical outcomes. In non-small cell lung cancer (NSCLC), genomic alterations including mutations affecting EGFR, KRAS, and BRAF and rearrangements involving ALK, ROS1, RET, and NTRK, have been recognized as critical determinants of treatment selection and response prediction. In addition to genetic alterations, biomarkers including PD-L1 levels, tumor mutational burden, and circulating tumor DNA have demonstrated substantial clinical value in guiding targeted therapies and immunotherapeutic interventions. Technological advances in next-generation sequencing have facilitated comprehensive molecular profiling, allowing clinicians to identify actionable alterations and optimize therapeutic decision-making. As a result, biomarker-driven treatment has become a fundamental component of precision oncology in lung cancer management (21, 22).

Recent investigations have expanded the spectrum of predictive biomarkers beyond established genomic drivers to include epigenetic signatures, liquid biopsy markers, radiomic features, and multi-omics profiles. Emerging evidence suggests that circulating tumor cells (CTCs) and extracellular vesicles (EVs), and gene-expression signatures may provide valuable a better understanding of treatment response, disease monitoring, and resistance-related mechanisms. Furthermore, the application of AI and machine learning approaches approaches has accelerated biomarker discovery and improved the interpretation of complex molecular datasets. These innovations have enhanced the ability to predict chemotherapy sensitivity, identify resistance pathways, and monitor tumor evolution throughout treatment. Despite substantial progress, challenges related to biomarker standardization, clinical validation, and accessibility continue to limit widespread implementation. Future research focusing on integrated molecular profiling and real-time biomarker assessment is expected to further improve personalized therapeutic strategies and patient outcomes in lung cancer (23, 24).

Biomarkers in Other Common Solid Tumors

Beyond breast, colorectal, and lung cancers, a wide spectrum of other solid tumors including pancreatic, prostate, gastric, and ovarian cancers also exhibit complex molecular landscapes that can be exploited for predictive biomarker development. These tumors are characterized by substantial genetic heterogeneity, which significantly influences treatment response and clinical outcomes. Clinically used biomarkers such as CA-125 in ovarian cancer and PSA in prostate cancer, and CA19-9 in pancreatic cancer have long been used in clinical practice, although their predictive accuracy for chemotherapy response remains

limited. Recent advances in molecular oncology have shifted the focus toward genomic and transcriptomic biomarkers, such as BRCA1/2 mutations together with impaired homologous recombination repair, and mismatch repair deficiency, which provide more robust predictive value for targeted therapies and platinum-based chemotherapy. In addition, TMB and MSI are increasingly regarded as biomarkers relevant to a wide range of cancer types. with therapeutic implications across multiple solid tumor types. The integration of these molecular markers into clinical workflows has enhanced patient stratification and facilitated more individualized treatment approaches. However, variability in tumor biology and biomarker expression continues to pose challenges for standardization and clinical implementation (25, 26).

In addition to genomic alterations, Emerging research underscores the significance of of circulating and microenvironment-derived biomarkers in other solid tumors. Liquid biopsy components including circulating tumor DNA (ctDNA), as well as circulating tumor cells (CTCs), and non-coding RNAs have demonstrated promising utility in early detection, treatment monitoring, and prediction of therapeutic resistance. Furthermore, immune-related biomarkers, including PD-L1 levels and tumor-infiltrating lymphocytes (TILs), are increasingly recognized for their role in guiding immunotherapy across diverse tumor types. Advances in multi-omics technologies and AI-driven analytical platforms have further improved the identification of novel predictive signatures in heterogeneous tumor populations. These innovations are particularly relevant for cancers with limited therapeutic options, where traditional biomarkers fail to capture the full spectrum of tumor behavior. Despite significant progress, challenges such as assay standardization, inter-tumoral variability, and limited prospective validation studies remain major barriers. Future research focusing on integrative biomarker panels is expected to enhance predictive accuracy and support precision oncology in these malignancies (27, 28).

Clinical Utility of Biomarker-Guided Targeted Therapies

The clinical utility of biomarker-guided targeted therapies has transformed modern oncology by enabling precise patient stratification and individualized therapeutic selection. Predictive biomarkers play a central contribution to identifying patients who are most likely to respond favorably to specific targeted agents, thereby increasing treatment efficacy and limiting unnecessary toxicity. In various solid tumors, genomic alterations such as EGFR alterations and ALK rearrangements, and HER2 amplification have become established indicators for the use of corresponding agents targeting tyrosine kinases and monoclonal antibodies. Similarly, biomarkers such as PD-L1 levels and tumor mutational burden guide immunotherapy decisions across multiple cancer types. The integration of biomarker testing into standard clinical practice has led to considerable improvements in response rates and progression-free survival in selected patient populations. Moreover, companion diagnostic platforms and next-generation sequencing technologies have facilitated rapid and comprehensive molecular profiling. These advances collectively highlight the critical importance of biomarker-driven approaches in modern precision oncology practice (29, 30).

Despite substantial progress, multiple barriers limit the widespread clinical implementation of biomarker-guided targeted therapies. Variations in tumor heterogeneity across and within tumors frequently contribute to differences in biomarker expression. and inconsistent treatment responses. Additionally, resistance mechanisms frequently emerge through secondary mutations, pathway reactivation, or bypass signaling, reducing long-term treatment efficacy. Approaches based on liquid biopsy, such as circulating tumor DNA and circulating tumor cells, have gained recognition as promising tools for real-time monitoring of therapeutic response and resistance evolution. Furthermore, the use of integrated multi-omics data and artificial intelligence is enhancing the predictive accuracy of biomarker-based models. However, issues related to assay standardization, cost-effectiveness, and accessibility remain significant barriers to widespread clinical adoption. Continuing clinical trials and translational research efforts are expected to refine biomarker-guided strategies and expand their utility across diverse cancer types (31, 32).

Challenges in Clinical Implementation and Translational Research

Despite remarkable advances in identifying predictive genetic biomarkers and developing targeted therapies, their successful translation for widespread adoption in clinical practice remains limited by multiple interrelated challenges. One of the major barriers is the insufficient standardization in biomarker detection methods, including variability in assay platforms, sample processing, and interpretation of molecular data. In addition, tumor heterogeneity both spatial and temporal significantly complicates the reproducibility and reliability of biomarker-based predictions across patient populations. Many promising biomarkers fail to progress beyond early-phase studies due to insufficient validation in large, prospective, multi-center clinical trials. Furthermore, the gap between preclinical discoveries and clinical application remains wide, partly due to complex regulatory requirements

and limited integration between laboratory research and clinical oncology workflows. The absence of harmonized guidelines for biomarker qualification further delays clinical adoption and contributes to inconsistent implementation across healthcare systems. These limitations collectively restrict the full realization of precision oncology in everyday clinical practice (33, 34).

Another critical issue in translational research is the difficulty in demonstrating clear clinical utility and cost-effectiveness of biomarker-guided strategies in real-world settings. Although liquid biopsy, multi-omics profiling, and artificial intelligence-based models have shown great promise, their integration into routine care is still in early stages due to limited prospective validation and infrastructure constraints. Variability in healthcare resources, particularly between developed and developing regions, further exacerbates disparities in access to advanced molecular diagnostics. In addition, resistance mechanisms and tumor evolution over time reduce the long-term predictive accuracy of many currently available biomarkers. Ethical considerations, data sharing limitations, and regulatory uncertainties also pose significant obstacles to large-scale implementation. To overcome these challenges, future translational research must focus on robust clinical trial designs, standardized analytical pipelines, and interdisciplinary collaboration between researchers, clinicians, and regulatory agencies. Ultimately, translating scientific discoveries into clinical practice is essential for maximizing the impact of predictive biomarkers in precision oncology (35, 36).

Future Directions in Precision Oncology

Breast cancer is a highly heterogeneous malignancy with various molecular subtypes that significantly influence clinical prognosis and response to therapy. The identification of predictive biomarkers has have established themselves as a key pillar of precision oncology, supporting individualized treatment strategies and improved clinical outcomes. Established molecular biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and HER2 remain fundamental in guiding systemic therapy selection. In addition, genomic molecular assays such as Oncotype DX and MammaPrint have enhanced risk stratification in early-stage disease and reduced overtreatment. The rapid evolution of next-generation sequencing technologies has further enabled the discovery of novel genetic alterations associated with chemotherapy sensitivity and resistance. Circulating tumor DNA and liquid biopsy techniques approaches have also emerged as promising non-invasive tools for real-time disease monitoring. These developments collectively highlight the increasing importance of molecular profiling in modern breast cancer management (37, 38).

Beyond traditional biomarkers, emerging evidence has emphasized the importance of immune-related signatures, tumor microenvironment characteristics, and epigenetic modifications in forecasting treatment response. Biomarkers such as BRCA1/2-associated alterations and impaired homologous recombination repair are particularly important in identifying patients potentially benefiting from platinum-based chemotherapy and PARP inhibitors. Furthermore, gene-expression profiling has improved the understanding of intrinsic tumor subtypes and their therapeutic vulnerabilities. Despite these advances, challenges remain in clinical validation, assay harmonization and integration into routine practice. Inter-patient and intra-tumoral heterogeneity further complicate biomarker interpretation and clinical decision-making. Ongoing translational research is focusing on multi-omics integration and artificial intelligence-based predictive models to improve accuracy and clinical utility. These innovations are expected to significantly advance personalized treatment strategies in breast cancer (39, 40).

Conclusions

The growing body of research supports the central role of predictive genetic biomarkers in transforming cancer management from a standardized approach to a more tailored and individualized therapeutic strategy. Across major cancer types such as breast, colorectal, lung, and other solid tumors, biomarker-guided decision-making has demonstrated clear clinical value in predicting chemotherapy response, optimizing targeted therapy selection, and improving patient outcomes. Advances in genomic technologies, including next-generation sequencing and liquid biopsy platforms, have significantly expanded the range of detectable biomarkers and enabled continuous monitoring of tumor evolution. Despite these advancements, variability in biomarker performance, tumor heterogeneity, and lack of inadequate standardization continues to impede universal clinical implementation. Moreover, the combination of multi-omics information with AI-driven approaches has shown promise but still requires robust validation in large-scale prospective studies. Collectively, current evidence highlights that predictive genetic biomarkers are indispensable tools in modern precision oncology, yet their full clinical potential remains partially unrealized.

Looking forward, the future of biomarker-guided advancing cancer therapy relies on the integration of comprehensive molecular profiling with adaptive clinical trial designs and translational research frameworks. Harmonization of laboratory methods, improved bioinformatics pipelines, and stronger collaboration between researchers, clinicians, and

Table 1. Selected preclinical and clinical studies investigating probiotic-based approaches in colorectal cancer.

No.	Study (Author & Year)	Biomarker Type	Clinical Relevance	Key Findings	Ref
1	Derouane et al., 2022	Gene expression (BRCA-related)	Chemotherapy response	Improved prediction of neoadjuvant response	37
2	Tarighati et al., 2023	ER/PR/HER2	Treatment selection	Strong predictive value for targeted therapy	38
3	Wang et al., 2023	Immune signatures	Immunotherapy response	Correlates with checkpoint inhibitor efficacy	39
4	van den Ende et al., 2023	Genomic profiling	TNBC therapy response	Identifies platinum-sensitive patients	40
5	Telli et al., 2021	HRD score	PARP inhibitor response	Predicts sensitivity in BRCA-like tumors	41
6	Schmid et al., 2020	Tumor infiltrating lymphocytes	Prognosis	Higher TILs associated with better survival	42
7	Turner et al., 2019	ctDNA	Disease monitoring	Early detection of relapse	43
8	Cortazar et al., 2019	Pathologic complete response markers	Neoadjuvant therapy	Predictor of long-term survival	44

regulatory agencies will be essential to overcome existing translational barriers. In addition, expanding equitable access to advanced diagnostic technologies across healthcare systems will be critical to reduce disparities in cancer care. The development of standardized biomarker panels and clinically validated predictive models is expected to enhance treatment accuracy and cost-effectiveness. Ultimately, continued progress in understanding tumor biology and therapeutic resistance mechanisms will further strengthen the role of predictive biomarkers in guiding targeted therapies. This evolution will pave the way toward truly personalized oncology, where treatment decisions are driven by precise molecular characterization rather than empirical approaches, leading to enhanced survival and overall quality of life in patients with cancer.

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The authors declare no competing interests

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Niosome-Based Nanotechnology in Breast Cancer Therapy: Advances in Targeted Drug Delivery

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Abstract

Breast cancer remains a leading health concern among women worldwide, owing to its high incidence and substantial impact on morbidity and healthcare systems. Despite significant advances in diagnostic and therapeutic approaches, tumor molecular heterogeneity, drug resistance, disease recurrence, and treatment-associated systemic adverse effects remain major obstacles to achieving effective and safe therapy. In recent years, nanotechnology has provided promising opportunities for improving cancer treatment. Among various nanocarriers, niosomes have attracted considerable attention because of their favorable stability, surface modification potential, and controlled drug-release properties. This review examines the structure and composition of niosomes, their preparation and optimization methods, and their applications in the delivery of anticancer drugs. Furthermore, the role of modified and targeted niosomes in enhancing drug accumulation and penetration into tumor tissue while reducing systemic toxicity is discussed. In addition to conventional chemotherapeutic agents, the potential of niosomes for delivering novel anticancer therapeutics, including DNA, siRNA, miRNA, and other biological agents, is also addressed. Available evidence suggests that targeted niosomes can improve therapeutic efficacy by enhancing cellular uptake and controlling drug release while reducing drug exposure in healthy tissues. However, challenges including formulation instability, precise control of physicochemical properties, potential toxicity, manufacturing scalability, and limited clinical evidence remain. The development of smart, multifunctional, and personalized niosomal systems may shape the future of this technology in precision breast cancer therapy.

Keywords: Nanobiotechnology, Niosomes, Nanodrug Delivery, Targeted Delivery, Cancer Therapy.

Introduction

Breast malignancies continue to impose a substantial global health burden, with breast cancer accounting for a significant proportion of cancer cases and deaths among women. Although chemotherapy remains an important component of treatment, its clinical utility can be compromised by nonspecific distribution of therapeutic compounds, damage to healthy tissues, inadequate drug accumulation at the tumor site, and the emergence of resistance. In recent years, nanomedicine has attracted increasing attention as a means of overcoming some of these limitations. Among the available nanocarrier systems, niosomes have emerged as versatile vesicular platforms

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for the delivery of anticancer drugs. Their structural properties can facilitate the protection of encapsulated agents, improve drug solubility and stability, provide sustained or controlled drug release, and enhance interaction with cancer cells. By potentially increasing drug deposition within tumor tissue while reducing exposure to normal organs, niosome-mediated delivery may improve therapeutic performance and reduce treatment-associated toxicity, highlighting its potential as a strategy for developing more efficient breast cancer therapies (1, 2).

Breast Cancer: Epidemiology, Molecular Subtypes, and Therapeutic Challenges

Breast cancer represents a substantial global health burden and is currently the leading cancer diagnosis among women. Global epidemiological estimates indicate that nearly 2.4 million women were newly diagnosed with the disease in 2024, while approximately 694,000 deaths were attributed to breast cancer during the same period. However, the burden of disease is not uniformly distributed worldwide, as both incidence and survival differ considerably between populations and geographic regions. These disparities are influenced by a combination of biological, lifestyle, reproductive, and socioeconomic determinants. Established risk factors include increasing age, genetic and familial predisposition, reproductive and hormonal characteristics, excess body weight, alcohol intake, and differences in the availability of early detection and effective cancer treatment. From a biological perspective, breast cancer encompasses a diverse group of tumors rather than representing a single disease entity. Molecular and immunohistochemical characteristics, particularly the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), together with indicators of cellular proliferation, provide the basis for clinically relevant tumor classification. Major molecular categories include Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC). Identification of these distinct subtypes is essential because they differ in their patterns of tumor growth, prognosis, and sensitivity to treatment. Accordingly, therapeutic decisions are increasingly guided by tumor biology; endocrine-based approaches are commonly used for hormone receptor-positive disease, whereas tumors exhibiting HER2 overexpression or amplification may be candidates for HER2-directed therapies (1,2).

Despite significant advances in early detection, surgery, radiotherapy, chemotherapy, hormonal therapy, and targeted treatments, the management of breast cancer continues to face considerable challenges. Intratumoral and intertumoral heterogeneity, the development of drug resistance, disease recurrence, and metastasis are among the major factors limiting therapeutic success. Therefore, accurate characterization of the molecular features of tumors and the development of personalized medicine and targeted therapeutic approaches represent important future directions for the effective management of breast cancer ((1, 2).

Nanotechnology in Breast Cancer Treatment: Principles, Advantages, and Future Perspectives

In recent years, advances in nanomedicine have opened new possibilities for improving the therapeutic management of breast cancer. The fundamental principle of this technology is the use of nanoscale structures and nanocarriers capable of delivering anticancer drugs while improving their pharmacokinetic properties, bioavailability, and tissue distribution. Nanocarriers can protect drugs from premature degradation, thereby increasing the effective drug concentration at the tumor site. Moreover, surface modification of nanoparticles with ligands, antibodies, or other targeting molecules can facilitate more specific recognition of cancer cells. This approach is particularly important in heterogeneous malignancies such as breast cancer and in where selective targeting may enhance antitumor efficacy while reducing drug exposure to healthy tissues and consequently minimizing systemic adverse effects (3, 4).

Despite promising results, the translation of nanotechnology-based systems from laboratory studies to clinical applications remains challenging because of factors such as manufacturing complexity, precise control of particle size and surface properties, stability, safety, accumulation in non-target organs, and differences between animal models and clinical conditions. In addition to drug delivery, combining nanobiotechnology with gene therapy, RNA-based therapy, immunotherapy, and diagnostic approaches may facilitate the development of theranostic platforms and personalized treatment strategies (3, 4).

Niosomes: Structure, Composition, Properties, and Mechanisms of Action

Niosomes are vesicular nanocarriers formed through the spontaneous organization of nonionic amphiphilic surfactants in an aqueous medium. Their membranes are commonly stabilized with cholesterol or related membrane-modifying substances, while certain formulations may also incorporate agents that alter the surface charge. The resulting architecture is characterized by one or multiple surfactant layers, with the nonpolar segments concentrated within the membrane and the polar groups exposed toward the aqueous phase. This structural organization provides niosomes with the ability to accommodate therapeutic molecules with different physicochemical

properties: water-soluble agents can be entrapped in the internal aqueous compartment, whereas lipophilic compounds can be incorporated into the hydrophobic membrane domain. Depending primarily on vesicle diameter and lamellar organization, these carriers are generally categorized into small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Such structural differences can influence important formulation characteristics, including drug-loading capacity, stability, release behavior, and interactions with biological tissues. The type and ratio of surfactant, cholesterol content, physicochemical properties of the payload, and hydration conditions are important factors determining the size, morphology, stability, encapsulation efficiency, and drug-release behavior of niosomes (5, 6).

The mechanism of action of niosomes as drug delivery systems is based on the encapsulation, protection, transport, and controlled release of active compounds. Following administration, niosomes can modify pharmacokinetic and biodistribution profiles, potentially prolonging its residence time in the biological environment. Interactions between niosomes and cell membranes, as well as cellular uptake through mechanisms such as endocytosis, can facilitate intracellular delivery of the encapsulated payload. Moreover, surface modification of niosomes can enhance active targeting of specific tissues. Their tunable size and composition, relatively favorable biocompatibility, ability to encapsulate diverse compounds, and surface-engineering potential make niosomes promising carriers for anticancer drugs as well as biological molecules. However, phenomena such as vesicle aggregation, physical instability, and drug leakage or degradation may compromise their performance and therefore need to be carefully considered during formulation and optimization (5, 6).

Methods of Niosome Preparation and Optimization for Drug Delivery Applications

The fabrication of niosomal carriers can be achieved through a range of formulation strategies, with the choice of technique being influenced by factors such as drug characteristics, desired vesicle dimensions, lamellar structure, loading capacity, and the intended therapeutic application. Several approaches have been described, including thin-film hydration, reverse-phase evaporation, solvent or ether injection, sonication, microfluidization, the bubble technique, and proniosome conversion methods. Among these approaches, thin-film hydration is one of the most widely employed procedures. In this technique, the selected nonionic surfactant and cholesterol are first solubilized in a suitable organic solvent. Removal of the solvent under controlled conditions produces a dry surfactant-containing film, which is subsequently exposed to an aqueous hydration medium. Hydration causes the components to reorganize spontaneously and form closed vesicular structures capable of entrapping the desired therapeutic compound. Other techniques, particularly microfluidization and mechanical size-reduction methods such as ball milling, can provide greater control over vesicle dimensions and particle-size uniformity. These approaches may therefore be advantageous when reproducibility, formulation consistency, and potential scale-up for pharmaceutical manufacturing are important considerations (7, 8).

Optimization of niosomal formulations aims to achieve an appropriate particle size, narrow size distribution, high encapsulation efficiency, adequate physical and chemical stability, and a desirable drug-release profile. The surfactant-to-cholesterol ratio, type and concentration of surfactant, drug concentration, hydrophilicity of the active compound, hydration temperature, sonication time and intensity, and other processing conditions are among the major factors influencing the final properties of niosomes. Particle size, polydispersity index (PDI), and zeta potential are commonly evaluated to assess the uniformity and stability of the formulation. Appropriate adjustment of these parameters can improve drug encapsulation, regulate drug release, and enhance overall drug-delivery performance. Therefore, the use of systematic approaches such as Design of Experiments (DoE) and quality-by-design strategies can be valuable for developing reproducible niosomal formulations with improved performance and potential scalability (7, 8).

Niosomal Systems for Anticancer Drug Encapsulation and Targeted Delivery

Niosomes, as nanoscale vesicular systems, have considerable role for loading of anticancer agents with different physicochemical properties. Accordingly, drugs such as doxorubicin, paclitaxel, docetaxel, methotrexate, as well as various natural anticancer compounds, can be incorporated into niosomal formulations. Drug encapsulation within niosomes can protect the therapeutic agent from premature degradation, improve its solubility and stability, and alter its biodistribution, thereby facilitating more effective delivery to tumor tissue. Moreover, the use of niosomes containing more than one therapeutic agent can enable the co-delivery of drugs or the combination of drugs with bioactive compounds and genetic materials, potentially producing synergistic therapeutic effects (9, 10).

Drug delivery by niosomes can occur through enhanced interaction of the carrier with cells, cellular uptake via endocytosis, and subsequent release of the encapsulated cargo within or around the target cells. Physicochemical characteristics including bilayer composition play important roles in the

biological fate of niosomes. Furthermore, surface modification of niosomes with targeting ligands or specific recognition molecules can facilitate more selective delivery of therapeutic agents to cancer cells. Recent reviews have demonstrated that, in addition to conventional chemotherapeutic drugs, niosomes have the potential to co-deliver drugs and nucleic acid molecules such as siRNA, miRNA, shRNA, and DNA, which may contribute to overcoming drug resistance and developing combination therapies for cancer. However, achieving optimal therapeutic performance requires careful optimization of vesicle size and uniformity, formulation stability, encapsulation efficiency, and drug-release profiles (9, 10).

Targeted Niosomal Nanocarriers for Selective Delivery to Breast Cancer Cells

Specific targeting of breast cancer cells is an important strategy in the development of advanced drug delivery systems, as it can increase drug accumulation in tumor tissue while reducing exposure of healthy tissues and, consequently, systemic toxicity. Nanostructured niosomes can be surface-modified to incorporate ligands and recognition molecules that specifically interact with receptors overexpressed on breast cancer cells. Important molecular targets in this approach include HER2, folate receptors, CD44, and EGFR. In active targeting, the ligand present on the niosomal surface interacts with a specific receptor expressed on tumor cells, thereby enhancing cellular binding and endocytosis and facilitating the intracellular delivery of the encapsulated drug. Studies have shown that modification of niosomes with folic acid or hyaluronic acid can enhance cellular uptake and selective cytotoxicity in breast cancer models (11, 12).

One promising approach involves the use of specific antibodies, such as trastuzumab, for targeting HER2-positive breast cancer cells. In one study, pH-sensitive niosomes containing palbociclib and conjugated with trastuzumab demonstrated enhanced cellular uptake and increased induction of apoptosis in HER2-overexpressing cells, while drug release was also achieved in a pH-dependent manner (2). In another study, cetuximab-conjugated niosomes were developed for EGFR targeting and the simultaneous delivery of doxorubicin and vitexin, resulting in increased cellular uptake and enhanced antitumor activity compared with non-targeted formulations. However, further evaluation of targeting specificity, safety, pharmacokinetics, and therapeutic efficacy in animal models and clinical studies remains necessary (11, 12).

Modified and Targeted Niosomes for Enhanced Drug Penetration into Tumors

Modified and targeted niosomes can improve drug delivery to tumor tissues by combining nanoscale properties with active targeting and responsiveness to the tumor microenvironment. Surface Engineering Strategies for Niosomal Nanocarriers with molecules including, hyaluronic acid, folic acid, or other specific ligands enables recognition of overexpressed receptors on tumor cells and enhances cellular uptake. The development of stimuli-responsive niosomes, such as pH-sensitive systems, can promote preferential drug release within the acidic tumor microenvironment or intracellular compartments. Furthermore, studies suggest that combining active targeting with optimized physicochemical properties of niosomes can improve the accumulation, and penetration of therapeutic cargo into tumor tissues (14).

Niosome-Based Strategies for Enhancing Therapeutic Outcomes and Minimizing Treatment-Related Toxicity in Breast Cancer

Niosomes, can improve the bioavailability, and biodistribution of anticancer drugs, thereby enhancing the therapeutic efficacy of breast cancer treatment. Drug encapsulation within niosomal structures also enables controlled release and, in some designs, stimulus-responsive release mechanisms, such as pH-sensitive drug release, which may increase the effective drug concentration at the tumor site. This feature is particularly relevant for drugs such as doxorubicin, whose systemic administration is associated with significant adverse effects. Studies have demonstrated that drug-loaded niosomes can provide improved cellular uptake and antitumor activity compared with free drugs, while targeted niosomal systems may further enhance the delivery of therapeutic agents to tumor cells (15, 16).

Application of Niosomes in the Delivery of Novel Anticancer Compounds: Gene Therapy, RNA, and Biological Agents

Niosomes, owing to their vesicular structure, surface-modification capability, and ability to encapsulate compounds with diverse physicochemical properties, have attracted considerable attention as non-viral carriers for the delivery of genetic materials and biological agents in cancer therapy. In gene therapy, niosomes can be employed to deliver DNA, plasmids, and oligonucleotides to target cells while protecting their cargo from enzymatic degradation and facilitating cellular uptake. Moreover, cationic niosomes can promote the encapsulation and delivery of nucleic acids through electrostatic interactions between the positively charged vesicle surface and negatively charged nucleic acid molecules. In the field of RNA-based therapy, molecules such as siRNA, miRNA, shRNA, and lncRNA have emerged as potential niosomal cargos. These RNA molecules can regulate genes involved in cancer cell

proliferation, survival, invasion, and drug resistance, thereby enabling the targeting of molecular pathways associated with tumor progression (17, 18).

One of the advanced applications of niosomes is the co-delivery of genetic materials with chemotherapeutic drugs or other biological agents, which may provide synergistic therapeutic effects and help overcome drug resistance. For example, cationic and PEGylated niosomes have been investigated for the delivery of miRNA-33a to MCF-7 breast cancer cells, demonstrating the potential of these systems for improving intracellular RNA delivery (2). In addition to RNA, niosomes have the potential to transport proteins and other therapeutic macromolecules, while surface modification can further enhance selective tumor targeting and intracellular delivery. Nevertheless, several challenges remain, including the instability of RNA under physiological conditions, endosomal escape, control of surface charge, potential cytotoxicity, and precise intracellular release of the therapeutic cargo. Therefore, the development of smart, targeted, and multifunctional niosomal systems may provide an important platform for integrating gene therapy, RNA therapy, and conventional chemotherapy, contributing to the development of more precise and personalized approaches to cancer treatment (17, 18).

Challenges, Limitations, and Future Perspectives of Niosomes in Breast Cancer Therapy

Despite the considerable potential of niosomes to improve the efficacy of anticancer drug delivery, their application is associated with several challenges. Physical instability, vesicle aggregation and fusion, leakage of encapsulated drugs, reduced encapsulation efficiency, and limited shelf life are among the major limitations of niosomal formulations. In addition, the type and concentration of surfactants may affect cellular toxicity and biocompatibility, while some conventional preparation methods involve organic solvents, high production costs, long processing times, and difficulties in controlling product characteristics, which may limit their scalability for industrial production. Furthermore, specific tumor targeting under in vivo conditions is more complex than in cellular models because serum proteins, immune responses, biological barriers, and variations in receptor expression can influence the biodistribution and cellular uptake of niosomes. Therefore, standardization of critical parameters, including particle size, surface charge, encapsulation efficiency, and drug-release profile, together with comprehensive evaluation of toxicity and stability, is essential for the successful translation of niosomal systems into clinical applications (19, 20).

The future of niosomes in breast cancer therapy is moving toward the development of smart, targeted, stimuli-responsive, and multifunctional delivery systems. Surface modification of niosomes with specific ligands and antibodies, the design of pH- or enzyme-responsive systems, and the co-delivery of chemotherapeutic drugs with RNA, siRNA, miRNA, or other biological agents may enable more precise treatment and help overcome therapeutic resistance. In addition, advanced manufacturing approaches such as microfluidics and the development of dry or lyophilized formulations may improve particle uniformity, stability, and scalability. However, realizing the full clinical potential of niosomes requires long-term studies addressing safety and pharmacokinetics, standardization of manufacturing processes, determination of the relationship between nanocarrier characteristics and therapeutic outcomes, and well-designed clinical trials. Ultimately, integrating niosomal drug delivery with personalized medicine and multimodal therapeutic strategies may represent an important future direction for targeted breast cancer treatment (21-25).

Conclusion and Future Perspectives

Overall, the available evidence indicates that niosomes, as non-ionic nanocarriers, have considerable potential for improving breast cancer therapy. They can overcome some limitations of conventional treatments by enhancing drug stability and bioavailability, enabling controlled drug release, facilitating targeted delivery to tumor cells, and allowing the co-delivery of chemotherapeutic agents and biological compounds. Preclinical evidence also suggests that niosomal formulations may enhance antitumor efficacy while reducing drug exposure to healthy tissues. However, several challenges—including the instability of some formulations, drug leakage, difficulties in standardization and large-scale production, potential surfactant-related toxicity, and the limited number of extensive clinical studies—remain major barriers to their clinical translation (25-28).

In the future, the development of smart, targeted, and tumor microenvironment-responsive niosomes, together with the incorporation of specific ligands, co-delivery of drugs with siRNA/miRNA and other biological agents, and integration of diagnostic and therapeutic functions, may facilitate the development of more precise and personalized approaches to breast cancer treatment (28-30). Nevertheless, realizing this potential will require well-standardized in vivo studies, comprehensive evaluation of the relationship between nanocarrier characteristics and therapeutic responses, long-term safety assessments, standardization of manufacturing processes, and well-designed clinical trials.

Table 1. Selected preclinical and clinical studies investigating probiotic-based approaches in colorectal cancer.

Study	Study Objective	Main Findings	Significance for Challenges and Future Perspectives
Sahrayi et al., 2021 (21)	Design of letrozole- and cyclophosphamide-loaded niosomes for co-delivery of the drugs and surface modification with folic acid for targeted delivery to breast cancer cells.	Folic acid-decorated niosomes exhibited pH-dependent drug release, enhanced cellular uptake, and greater cytotoxicity compared with non-targeted formulations. Increased expression of apoptosis-related genes and decreased expression of some genes associated with proliferation and invasion were also observed.	Demonstrates the potential of niosomes for combination therapy and active targeting. However, the findings are predominantly preclinical, highlighting the need for further evaluation of safety and efficacy in animal models and clinical studies.
Akbarzadeh et al., 2021 (22)	Preparation and optimization of curcumin-loaded niosomes coated with calcium alginate to improve curcumin delivery for breast cancer treatment.	The optimized formulation improved the drug-delivery properties of curcumin and enhanced its anticancer activity in in vitro studies.	Indicates that formulation optimization and polymeric coatings may help overcome stability and delivery limitations of poorly soluble compounds. However, translation of these findings to in vivo conditions remains challenging.
Saharkhiz et al., 2023 (23)	Development of a pH-sensitive niosomal formulation for separate, co-administered, and co-loaded delivery of doxorubicin and curcumin.	Particles of approximately 200 nm were produced, with encapsulation efficiencies of approximately 77% for doxorubicin and 79% for curcumin. Co-loading of the drugs increased cell death to approximately 79%, and pH-dependent drug release was observed.	Supports the potential of multi-drug co-delivery and smart drug release within the tumor microenvironment. Nevertheless, particle size, formulation stability, and actual in vivo efficacy require further investigation.
Malathi et al., 2023 (24)	Development of cetuximab-targeted niosomes for simultaneous delivery of doxorubicin and vitexin and targeting of EGFR.	Antibody-conjugated niosomes demonstrated greater anticancer activity than non-antibody formulations, with cytotoxicity reaching approximately 63% versus 53%. Effective cellular uptake and antitumor activity were also reported in a murine breast cancer model.	Demonstrates the potential of active targeting and reduction of nonspecific drug distribution. However, the complexity of antibody conjugation and formulation quality control represents a major challenge for industrial and clinical development.
Faddah et al., 2024 (25)	Preparation and optimization of doxorubicin-loaded niosomes coated with hyaluronic acid for targeted delivery to breast cancer cells.	Niosome size increased from approximately 120 to 183 nm following hyaluronic acid coating. Doxorubicin encapsulation efficiency was approximately 94.1%, with sustained and prolonged drug release for up to 48 h. The targeted formulation showed greater activity against MCF-7 cells than against CD44-negative cells.	Demonstrates that targeted coating, improved stability, and controlled drug release can enhance niosomal performance. However, long-term stability, manufacturing scalability, and confirmation of safety in in vivo and clinical studies remain essential.

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Not applicable.

Declarations

Competing Interest

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The Role of Genetics and Gut Microbiome in Determining Response to Biologics in Inflammatory Bowel Diseases (IBD)

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Abstract

The advent of biologic therapies has significantly transformed the management of inflammatory bowel disease (IBD), yet achieving sustained clinical remission remains a challenge due to high rates of primary non-response and secondary loss of response. This review explores the complex interplay between host genetics and the gut microbiome as primary determinants of therapeutic outcomes. We argue that the clinical efficacy of biologics is not merely a consequence of drug-target interactions but is deeply rooted in a multi-factorial biological landscape. Genetic polymorphisms, particularly those involved in immune regulation and drug metabolism, play a critical role in shaping the pharmacokinetics and immunogenicity of biological agents. Simultaneously, the gut microbiome acts as a dynamic modulator of systemic inflammation, where specific microbial signatures and metabolites, such as short-chain fatty acids, influence how patients respond to treatment. The integration of these two domains through multi-omics approaches is paving the way for precision medicine in IBD, allowing for the identification of predictive biomarkers that can guide personalized drug selection. Despite the promise of these markers, successful clinical implementation requires the standardization of bioinformatics pipelines and the inclusion of more diverse, global patient cohorts. Ultimately, understanding the synergy between the host genome and the microbial ecosystem is essential for optimizing biologic therapy, reducing healthcare burdens, and improving the long-term quality of life for individuals living with IBD.

Keywords: Inflammatory Bowel Disease (IBD), Gut Microbiome, Genetics, Biologics, Precision Medicine.

Introduction

The Landscape of Biologic Therapy in IBD

Biologic therapies have fundamentally transformed the management of inflammatory bowel diseases (IBD) by targeting specific inflammatory cytokines and leukocyte trafficking pathways. Agents such as anti-TNF antibodies, anti-integrins, and anti-IL-12/23 have demonstrated significant efficacy in inducing and maintaining clinical and endoscopic remission in both Crohn's disease and ulcerative colitis (1).

Despite these advancements, a considerable

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proportion of patients fail to achieve primary clinical response or experience secondary loss of response over time, which remains a major therapeutic challenge. This clinical heterogeneity complicates the treatment algorithm, leading to frequent trial-and-error approaches that delay optimal disease control and expose patients to unnecessary drug toxicity (2).

The current landscape is shifting toward the identification of early predictors that can distinguish responders from non-responders before the initiation of costly and potentially ineffective biologic agents. Clinical, biochemical, and histological markers have been explored, but they often lack the sensitivity and specificity required to guide personalized treatment decisions in routine clinical practice (3).

Therefore, there is an urgent need to incorporate molecular profiling, including genomic and microbial signatures, to refine the selection of biological therapies. By integrating these complex datasets, clinicians aim to transition from a "one-size-fits-all" model to a more precise therapeutic strategy that maximizes efficacy while minimizing the morbidity associated with active, untreated disease (4).

Genetic Architecture of IBD: Key Susceptibility Loci

The genetic architecture of IBD is highly complex, involving hundreds of susceptibility loci identified through large-scale genome-wide association studies (GWAS) over the past few years. These risk variants primarily cluster in pathways related to innate immunity, autophagy, intestinal barrier integrity, and adaptive immune responses that define individual disease risk profiles (5).

Key genes such as NOD2, IL23R, and ATG16L1 serve as cornerstones for our understanding of host susceptibility, highlighting the fundamental role of disrupted host-microbe homeostasis in disease pathogenesis. These variants contribute significantly to the disease phenotype, influencing factors such as disease location, severity, and the natural history of the inflammation (6).

Beyond the identification of disease risk, these genetic loci provide critical insights into the biological heterogeneity of IBD patients, which likely influences the effectiveness of specific therapeutic interventions. The variability in these genes suggests that the molecular drivers of inflammation differ widely among individuals, necessitating an approach that acknowledges genetic diversity (7).

Recent studies are now moving beyond simple association to functional genomics, aiming to understand how specific risk alleles alter cellular function and immune signaling. This deeper mechanistic understanding is essential for deciphering why certain patient subgroups respond differently to biologic therapies compared to others, bridging the gap between genetic risk and therapeutic outcome (8).

Pharmacogenetics: Genetic Predictors of Response to Biologics

Pharmacogenetics in the context of IBD focuses on identifying host genetic variations that influence the pharmacokinetics and pharmacodynamics of biologic agents. A well-known example is the association between HLA-DQA1*05 allele variants and the formation of anti-drug antibodies (ADAs), particularly in patients treated with anti-TNF agents like infliximab (9).

These genetic markers are pivotal because they predict which patients are likely to develop immunogenicity, a leading cause of secondary loss of response to biological therapy. By screening for these specific variants, clinicians can potentially implement proactive therapeutic drug monitoring or choose alternative biological classes with lower immunogenic potential for high-risk individuals (10).

Beyond immunogenicity, genetic variations in cytokine receptors and signaling molecules may dictate the primary sensitivity of the inflamed tissue to the therapeutic drug. For instance, SNPs in the IL23R gene may impact the efficacy of anti-IL-23 therapies, indicating that the baseline genetic profile of the host is a significant determinant of drug success (11).

As we move forward, the challenge lies in validating these pharmacogenetic markers across diverse patient cohorts to ensure their generalizability. Incorporating such genetic data into clinical decision-making tools represents a concrete step toward predictive medicine, moving us closer to optimizing treatment efficacy and reducing the clinical burden of non-response in IBD (12).

The Gut Microbiome Composition in IBD Patients

The gut microbiome in IBD patients is characterized by a significant state of dysbiosis, marked by decreased microbial diversity and an altered abundance of specific bacterial taxa. This shift is frequently associated with a reduction in commensal bacteria, such as Faecalibacterium prausnitzii, and an expansion of pro-inflammatory pathobionts like Enterobacteriaceae (13).

This dysbiotic environment is not merely a consequence of intestinal inflammation but also an active driver of the disease, perpetuating the immune cascade and undermining barrier function. The instability of the microbiome in IBD creates a unique ecological niche that deviates significantly from the healthy state, creating systemic effects on host physiology (14).

Recent metagenomic studies have highlighted the inter-individual variability in microbial composition, which correlates with disease severity and the specific

location of intestinal inflammation. Understanding this variability is crucial, as the baseline microbial ecosystem sets the stage for how the host immune system interacts with therapeutic biologics introduced during treatment (15).

Consequently, characterizing the unique microbial signature of each patient is emerging as a critical diagnostic and prognostic step in IBD management. By documenting these alterations, researchers aim to identify the specific microbial pathways that are compromised, potentially paving the way for targeted microbiome-based therapies that work in synergy with biological drugs (16).

Microbial Signatures as Biomarkers for Treatment Outcome

Microbial signatures are increasingly recognized as powerful, non-invasive biomarkers capable of predicting clinical responses to biological therapy in IBD patients. Specific baseline microbial profiles have been identified that distinguish responders from non-responders to agents like anti-integrin (vedolizumab) and anti-TNF therapies (17).

For instance, high microbial diversity and specific bacterial metabolic activities at baseline have been associated with better clinical outcomes following vedolizumab treatment. These predictive signatures provide a functional roadmap, suggesting that the existing microbial community might influence the drug's mechanism of action directly within the gut mucosa (18).

The utility of these signatures lies in their potential to spare patients from the cycle of ineffective treatments and associated side effects. By analyzing fecal samples through high-throughput sequencing, clinicians can categorize patients into "likely responders" or "likely non-responders," enabling a more calculated and informed choice of initial biological therapy (19).

However, the field must address the challenge of validating these signatures across different populations and geographical settings, where diet and environment also influence microbial composition. Establishing a standardized "microbial predictive index" will be essential for integrating these findings into clinical practice and realizing the promise of personalized medicine in IBD (20).

Microbial Metabolomics: Functional Drivers of Drug Efficacy

Beyond simple bacterial composition, the functional output of the microbiome, known as the metabolome, plays a decisive role in modulating host immune responses and drug efficacy. Microbial metabolites, such as short-chain fatty acids (SCFAs) and bile acids, act as critical signaling molecules that influence inflammation and intestinal permeability (21).

In IBD patients, the deficiency of protective metabolites like butyrate often correlates with a refractory disease state, hindering the success of biological therapies. Conversely, the presence of specific metabolic pathways in the gut environment can promote the stability of the intestinal barrier, thereby enhancing the local effect of administered biologic drugs (22).

Research into microbial metabolomics is revealing how these compounds influence the host's immune cells, potentially altering the sensitivity to biologics by shifting the inflammatory balance. This suggests that the metabolic profile of the gut environment could serve as a functional biomarker, offering a dynamic view of how the gut ecosystem interacts with therapy (23).

Future therapeutic strategies may involve manipulating these metabolic pathways, perhaps through diet or postbiotic interventions, to restore a favorable environment for biologic efficacy. Decoding the "metabolic language" between the microbiome and the host provides a unique opportunity to optimize treatment protocols and improve remission rates in challenging IBD cases (24).

Host-Microbiome Interplay: A Multi-Omics Perspective

The interaction between host genetics and the gut microbiome constitutes a complex, bidirectional regulatory system that dictates the pathobiology of IBD. Genetic variations in the host, particularly those related to immune regulation, profoundly shape the structure of the microbial community, which in turn influences the host's inflammatory state (25).

To fully understand this interplay, a multi-omics approach integrating genomics, transcriptomics, and metagenomics is required to capture the full scope of biological data. This comprehensive strategy allows researchers to observe how host susceptibility loci and microbial dysbiosis act in concert to define the disease phenotype and clinical outcomes (26).

Such integrated analyses are shedding light on how certain host genotypes create a "permissive" environment for specific pathobionts to thrive, exacerbating the inflammatory process. By viewing the host and its microbiome as a single holobiont, we gain a more nuanced perspective on why therapy efficacy varies so dramatically among individuals (27).

Ultimately, the goal of this multi-omics research is to create predictive models that account for both the host's genetic background and their resident microbial ecosystem. This integrative perspective is essential for developing precise, personalized treatment plans that account for the unique

biological landscape of each IBD patient (28).

Impact of Biologics on Restoring the Microbial Ecosystem

Biologic therapies, primarily targeting pro-inflammatory cytokines, have shown a potential role in reshaping the dysbiotic gut environment of IBD patients toward a more balanced state. Successful treatment with anti-TNF or anti-integrin agents is often associated with an increase in microbial diversity and the restoration of key commensal taxa. This shift suggests that reducing mucosal inflammation can indirectly foster a more hospitable niche for beneficial bacteria to thrive (29).

The restoration of the microbial ecosystem is often characterized by the recovery of butyrate-producing species, such as *Faecalibacterium prausnitzii*, which are typically depleted during active disease. Studies indicate that clinical responders to biologics exhibit a more significant microbial "restitution" compared to non-responders, whose microbiome remains in a state of persistent dysbiosis. This recovery is a critical component of achieving long-term mucosal healing and therapeutic stability (30).

Despite these positive shifts, it remains unclear whether biologics can completely revert the IBD microbiome to a truly healthy state or if a "scar" of dysbiosis persists. Some evidence suggests that while certain bacterial groups recover, the overall ecological network may still lack the resilience found in healthy individuals. The timing of biological intervention and the baseline severity of inflammation appear to be major determinants of the extent of microbial recovery (31).

Future research is increasingly focused on using microbial restoration as a functional readout for the success of biological therapies in clinical practice. Integrating microbiome monitoring into the therapeutic framework could provide a dynamic view of how the gut ecosystem responds to various biological agents over time. Understanding these interactions is essential for developing adjuvant therapies that actively promote microbial recovery alongside systemic immune modulation (32). (Table 1).

Precision Medicine in IBD: Integrating Genetics and Metagenomics

The shift toward precision medicine in IBD aims to replace the traditional "one-size-fits-all" strategy with a more personalized approach. By integrating genomic data with longitudinal metagenomic profiling, clinicians can better predict individual disease trajectories and therapeutic responses. This multi-layered data integration allows for the identification of specific biological drivers that are unique to each patient's inflammatory profile (41).

Genetic risk scores, when combined with microbial diversity indices, provide a more robust framework for risk stratification in Crohn's disease and ulcerative colitis. These predictive models utilize machine learning to analyze the complex interactions between host susceptibility loci and microbial dysbiosis. Such integration is crucial for identifying patients who are likely to experience early disease progression or complications (42).

Metagenomic sequencing offers functional insights into the microbial community, complementing the structural data provided by host genetics. Understanding how specific genetic mutations influence the metabolic output of the gut microbiota is key to tailoring dietary and pharmacological interventions. This synergy between host and microbe data is the cornerstone of developing next-generation diagnostic tools in clinical gastroenterology (43).

Despite the promise of precision medicine, integrating these vast datasets into routine clinical practice remains a significant challenge. Standardizing bioinformatics pipelines and ensuring the reproducibility of multi-omics findings are essential steps for clinical validation. As technology advances, the goal is to provide real-time, actionable insights that guide the selection of the most effective biologic therapy (44).

Future Directions: Moving Towards Clinical Implementation

The integration of genetics and the gut microbiome has fundamentally altered our understanding of therapeutic responses in IBD. While significant progress has been made in identifying biomarkers for biologic efficacy, translating these findings into the clinic requires large-scale validation. Current evidence strongly supports the role of multi-omics in refining treatment algorithms and improving long-term patient outcomes (45).

Future clinical implementation will likely depend on the development of point-of-care diagnostic kits that assess both host and microbial signatures. These tools must be cost-effective and provide rapid results to assist clinicians in making timely therapeutic decisions during routine visits. Transitioning from discovery-based research to practical, bedside application is the next frontier in the management of chronic inflammation (46).

Addressing the heterogeneity of IBD through personalized medicine will require a global effort to include diverse patient populations in omics research. Most current data are derived from Western cohorts, which may not fully reflect the genetic and microbial diversity seen globally. Expanding research to include varied ethnicities and environments will ensure that precision medicine benefits all patients regardless of their background (47).

the path toward clinical implementation of precision

Table 1. Selected preclinical and clinical studies investigating probiotic-based approaches in colorectal cancer.

No.	Author (Year)	Biologic Agent	Key Findings	Ref #
1	Aden et al. (2019)	Infliximab	Significant increase in Firmicutes and decrease in Proteobacteria in responders.	(33)
2	Doherty et al. (2020)	Vedolizumab	Observed a rise in microbial richness and restoration of anaerobic species.	(34)
3	Thomas et al. (2021)	Adalimumab	Restoration of SCFAs-producing bacteria correlated with clinical remission.	(35)
4	Zhuang et al. (2022)	Ustekinumab	Significant shifts in fungal (mycobiome) and bacterial diversity toward health.	(36)
5	Smith et al. (2023)	Risankizumab	Improvement in microbial network stability and reduction in pathobionts.	(37)
6	Gomez et al. (2024)	Infliximab	Responders showed a 40% increase in Faecalibacterium abundance after 14 weeks.	(38)
7	Miller et al. (2024)	Vedolizumab	Early microbial shifts (week 6) predicted long-term endoscopic healing.	(39)
8	Chen et al. (2025)	Anti-TNF + Diet	Combined therapy led to superior restoration of microbial diversity vs monotherapy.	(40)

medicine in IBD is paved with both opportunities and technical hurdles. Collaborative efforts between researchers, clinicians, and regulatory bodies are essential to establish standardized protocols for omics-based testing. As we move closer to 2030, the vision of a truly personalized therapeutic landscape for IBD is becoming an achievable reality (48).

Conclusion

In conclusion, the therapeutic landscape of Inflammatory Bowel Disease (IBD) is undergoing a paradigm shift from empirical prescribing to a more tailored, precision-based approach. As detailed in this review, the clinical response to biologic agents is not merely a product of drug-target interaction but is significantly modulated by the complex interplay between host genetics and the gut microbial ecosystem. Genetic polymorphisms related to immune regulation and drug metabolism, alongside microbial signatures and functional metabolites like short-chain fatty acids, have emerged as pivotal determinants of treatment efficacy and the risk of immunogenicity.

Evidence suggests that while biologics can induce clinical remission, their success is often mirrored by a partial restoration of the microbial ecosystem, highlighting the microbiome's role as both a driver and a marker of therapeutic success. However, despite the identification of numerous predictive biomarkers, the transition from bench to bedside remains incomplete. The current reliance on Western-centric cohorts and the lack of standardized multi-omics pipelines present significant hurdles to the universal application of these findings in routine clinical practice.

Moving forward, the integration of metagenomic and genomic data into robust, machine-learning-based predictive models holds the potential to revolutionize IBD management. By identifying "non-responders" before the initiation of therapy, clinicians can optimize drug selection, reduce healthcare costs, and minimize the risk of adverse events. Future research must prioritize large-scale, longitudinal studies across diverse global populations to validate these biomarkers and ensure that the benefits of precision medicine are accessible to all patients.

Ultimately, achieving long-term mucosal healing and improving the quality of life for IBD patients will depend on our ability to harness the synergy between the host and its microbiome. As we refine our understanding of these interactions, the goal of a truly personalized therapeutic strategy where the right drug is delivered to the right patient at the optimal time is becoming an increasingly attainable reality in the field of gastroenterology.

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The Oral-Gut Microbiome Axis: Mechanisms Influencing Periodontal Therapeutic Response and Strategies for Microbiome Restoration

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Abstract

The oral-gut axis represents a bidirectional relationship between oral and intestinal microbial communities and plays an important role in the development and progression of periodontal diseases. Periodontitis, traditionally regarded as a localized inflammatory disorder, is increasingly recognized as a condition with systemic implications. This review summarizes current evidence on the biological mechanisms linking oral and gut microbiota, with particular emphasis on the translocation of periodontal pathogens, including *Porphyromonas gingivalis* and *Tannerella forsythia,* into the gastrointestinal tract. These pathogens may promote gut dysbiosis, impair intestinal barrier integrity, and contribute to systemic inflammation. Conversely, gut dysbiosis may aggravate periodontal inflammation through circulating pro-inflammatory mediators and bacterial endotoxins, creating a vicious cycle that can impair tissue healing and reduce treatment effectiveness.Individual differences in baseline microbiome composition and host immune responses may partly explain the variable outcomes observed following conventional periodontal therapies such as scaling and root planing. Therefore, microbiome assessment may support the development of personalized periodontal treatment strategies. Microbiome-modulating interventions, including probiotics, prebiotics, dietary modifications, engineered probiotics, and fecal microbiota transplantation, have emerged as potential adjunctive approaches to restore microbial homeostasis and improve clinical outcomes. Furthermore, multi-omics technologies may facilitate microbial profiling and prediction of treatment responses within a precision-medicine framework.Overall, targeting both oral and gut microbial health may represent a promising paradigm shift toward integrated and personalized periodontal care. However, large-scale randomized controlled trials are required to establish the clinical efficacy and standardized application of microbiome-focused therapies.

Keywords: Oral-Gut Axis, Periodontal Disease, Microbiome Dysbiosis, Probiotics; Antimicrobial Stewardship.

Introduction

Growing evidence indicates that communication between the oral and intestinal microbiota plays an important role in shaping the development of periodontal diseases and influencing their clinical response to treatment. Accumulating evidence indicates that disturbances in the oral microbial ecosystem can extend beyond localized inflammation.

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Such microbial imbalance may promote the dissemination of periodontal pathogens into the gastrointestinal tract, where they can modify the composition of the gut microbiota and compromise intestinal barrier function. This oral-gut axis influences systemic immune homeostasis, potentially modulating the severity of periodontitis and its response to conventional therapies such as scaling and root planing. Understanding this bidirectional communication is crucial for elucidating why patients exhibit heterogeneous responses to standard periodontal interventions, highlighting the need to consider the broader microbial ecosystem beyond the periodontal pocket (1, 2, 25, 28).

Furthermore, the restoration of microbial balance through targeted interventions offers promising avenues for improving therapeutic efficacy in periodontal diseases. Strategies aimed at correcting dysbiosis, including probiotics, prebiotics, and microbiome-transplant therapies, are being investigated for their ability to synergize with traditional treatments and enhance clinical outcomes. By modulating the oral and gut microbiota, these adjunctive therapies may reduce systemic inflammation and promote tissue regeneration, addressing the limitations of mechanical debridement alone. Integrating microbiome-based approaches into clinical practice represents a paradigm shift towards personalized periodontal care, potentially leading to more sustainable and effective management of periodontal diseases (3, 4, 24, 29, 30).

The Oral-Gut Microbiome Axis: Conceptual Framework and Historical Context

Periodontal disease is now understood from a broader systemic perspective rather than solely as an infection restricted to the periodontal pocket. This evolving view highlights the two-way interactions that occur between the oral and intestinal microbiota and their potential contribution to disease development.This “oral-gut axis” suggests that dysbiosis in one site can precipitate microbial shifts in the other, influencing systemic health and disease progression. Current models of the oral-gut connection suggest that certain oral pathogens, including *Porphyromonas gingivalis*, may withstand gastric conditions and subsequently establish themselves within the intestinal environment. Their presence in the gut may interfere with the integrity of the intestinal barrier and modulate host immune responses.This paradigm shift necessitates a reevaluation of periodontal therapy, moving beyond local mechanical debridement to consider the broader microbial ecosystem (12, 22).

Furthermore, the historical context of this relationship highlights a growing recognition of the interconnectedness of mucosal surfaces in the body. Evidence from experimental and clinical studies indicates that microorganisms originating in the oral cavity may contribute to the intestinal microbial pool. Conversely, inflammatory processes within the gut can intensify periodontal tissue damage by promoting the systemic release of pro-inflammatory cytokines (25, 26).

Understanding the evolutionary and ecological principles governing these microbial communities is essential for developing effective therapeutic strategies. By acknowledging the oral-gut axis, clinicians can better predict patient responses to treatment and identify individuals at higher risk for systemic complications associated with chronic periodontitis (7, 25).

Mechanisms of Oral Pathogen Translocation to the Gut

The translocation of oral bacteria to the gastrointestinal tract occurs through several mechanisms, including swallowing, hematogenous spread, and lymphatic dissemination. Periodontal pathogens, particularly anaerobic gram-negative bacteria, are highly adapted to survive in hypoxic environments and can evade host immune responses in the gut. Following their arrival in the intestinal tract, these microorganisms may impair the protective mucosal barrier and consequently increase intestinal permeability, a phenomenon often described as “leaky gut.” As a result, microbial products such as lipopolysaccharides (LPS) may gain access to the bloodstream and promote persistent, low-grade systemic inflammation. This inflammatory response may, in turn, contribute to the aggravation of periodontal disease as well as other systemic disorders (25, 26, 28).

Beyond this,the metabolic activity of translocated oral bacteria can alter the gut microbial metabolome, influencing the synthesis of short-chain fatty acids (SCFAs) and other signaling molecules. (SCFAs), particularly butyrate, are essential for preserving intestinal homeostasis and modulating host immune activity.A reduction in SCFA-producing bacteria due to oral pathogen invasion can compromise gut barrier function and promote inflammation. Understanding these underlying mechanisms helps explain the relationship between the severity of periodontal disease and alterations in the gut microbiota. These findings also suggest that therapeutic strategies aimed at modulating the microbiome may offer a promising approach for restoring microbial equilibrium (28).

Impact of Gut Dysbiosis on Periodontal Inflammation and Healing

An imbalance in the gut microbiota, marked by a reduction in beneficial microorganisms and an expansion of potentially pathogenic species, may

intensify periodontal inflammation by activating systemic immune pathways. The intestinal microbiota is an important regulator of immune system development and function. Disruption of this microbial environment may alter the balance between Th17 and Treg cells, potentially enhancing pro-inflammatory immune activity in distant tissues, including the periodontal tissues.Systemic circulation of gut-derived inflammatory mediators, including LPS and pro-inflammatory cytokines, can sensitize periodontal tissues to bacterial challenges, accelerating tissue destruction and impairing healing after periodontal therapy (28).

Moreover, The composition and activity of the gut microbiota may affect periodontal treatment outcomes by shaping the host immune response following mechanical debridement.Patients with significant gut dysbiosis may exhibit a blunted healing response to scaling and root planing due to persistent systemic inflammation. Conversely, restoration of gut microbial balance can enhance the anti-inflammatory environment, facilitating tissue regeneration and stability. These observations highlight the need to consider intestinal health as part of periodontal disease management. Integrating strategies aimed at maintaining or improving gut health may therefore contribute to better overall therapeutic outcomes (23, 28).

Heterogeneity in Therapeutic Response: The Role of Microbial Variability

One of the greatest challenges in periodontal therapy is the heterogeneity in patient responses to standard treatments such as scaling and root planing (SRP). This variability is increasingly attributed to differences in the baseline composition of the oral and gut microbiomes. Individuals with a more stable and diverse gut microbiota, marked by a greater representation of beneficial microbial taxa, may exhibit a more favorable response to scaling and root planing (SRP) compared with patients experiencing pronounced microbial dysbiosis. Microbial profiling can therefore serve as a predictive tool for identifying patients who are likely to be non-responders and may require adjunctive therapies (22, 23).

Furthermore, the presence of specific pathogenic consortia in the oral cavity, often supported by gut-derived inflammatory signals, can render periodontal pockets resistant to conventional cleaning. These resilient biofilms are protected by an extracellular matrix that shields bacteria from antimicrobial agents and host immune cells. Understanding the microbial ecology of these resistant communities is crucial for developing targeted strategies to disrupt biofilm integrity and restore health. Personalized treatment plans based on microbiome analysis offer a promising avenue for improving therapeutic success rates (7, 21).

Probiotics and Prebiotics as Adjunctive Therapies

Probiotics and prebiotics are increasingly being considered as valuable adjuncts to conventional periodontal treatment, with the potential to improve therapeutic effectiveness (24, 29, 30).

Probiotics are beneficial live microorganisms that may limit the establishment of pathogenic bacteria by competing with them for available nutrients and attachment sites. Through this competitive interaction, they may help reduce the colonization of harmful microorganisms in both the oral cavity and the gastrointestinal tract.Specific strains, including *Lactobacillus* and *Bifidobacterium*, may provide additional benefits when combined with scaling and root planing (SRP). Studies have reported their potential to alleviate periodontal inflammation and promote improvements in clinical attachment levels. Beyond their potential periodontal benefits, probiotics may contribute to the reestablishment of a balanced gut microbial community. By supporting microbial homeostasis, they may help attenuate systemic inflammation and promote overall physiological health (24, 29).

Prebiotics are non-digestible dietary components that selectively promote the proliferation of beneficial microorganisms. By supporting the growth of these bacteria, they may contribute to the regulation and maintenance of a balanced microbiome. By providing substrates for SCFA-producing bacteria, prebiotics can enhance gut barrier function and reduce systemic inflammation. Synbiotics, which combine probiotics with prebiotics, may exert complementary effects by supplying beneficial microorganisms while simultaneously providing substrates that support their growth. However, further clinical investigation is still required to determine the long-term safety and therapeutic effectiveness of these approaches in the management of periodontal disease (30).

Microbiome-Based Approaches: FMT and Microbial Engineering

Fecal microbiota transplantation (FMT) is a microbiome-based intervention in which stool obtained from a healthy donor is administered to a recipient with the aim of reestablishing microbial diversity and restoring normal microbial functions. While primarily used for gastrointestinal disorders, FMT has shown potential in treating systemic conditions influenced by gut dysbiosis, including periodontal disease. Restoration of a balanced intestinal microbiota through FMT may help attenuate systemic inflammation and enhance the host immune response against periodontal pathogens.Although direct application of FMT to periodontal disease is still in its early stages, the concept of microbiome

engineering offers exciting possibilities for targeted therapeutic interventions (30).

Microbiome engineering techniques, such as the use of engineered probiotics or bacteriophages, allow for precise manipulation of microbial communities. These approaches can target specific pathogenic species while sparing beneficial bacteria, minimizing the risk of unintended ecological disruptions. For example, bacteriophages can be designed to lyse Porphyromonas gingivalis in the oral cavity, while engineered Lactobacillus strains can produce anti-inflammatory molecules in the gut. These innovative strategies represent the future of personalized periodontal therapy, offering highly targeted and effective treatments (26, 30).

Dietary Interventions and Microbiome Modulation

Dietary patterns are important determinants of the composition and functional activity of both oral and intestinal microbial communities. Frequent consumption of refined carbohydrates and foods rich in saturated fats may favor the proliferation of potentially pathogenic microorganisms while diminishing microbial diversity. These alterations can contribute to the progression of periodontal inflammation and further disrupt the balance of the gut microbiota. In contrast, a diet abundant in dietary fiber, fruits, and vegetables may promote the proliferation of beneficial microorganisms and increase SCFA production. These metabolites can contribute to maintaining microbial homeostasis and exerting anti-inflammatory effects within the host.Nutritional interventions, therefore, offer a non-invasive and accessible means of modulating the microbiome to improve periodontal health (25, 26).

Certain dietary constituents, including polyphenolic compounds and omega-3 fatty acids, may positively influence the composition and activity of the microbiome while contributing to the reduction of inflammatory processes. Polyphenol-rich foods, including tea, coffee, and berries, may influence the microbiome by limiting the proliferation of periodontal pathogens while supporting beneficial intestinal bacteria. In addition, omega-3 fatty acids obtained from sources such as fish and flaxseeds possess anti-inflammatory properties that may contribute to the resolution of periodontal inflammatory processes.Incorporating these dietary elements into daily habits can support microbial balance and enhance the outcomes of periodontal therapy (25).

Precision Medicine Approaches in Periodontal Therapy

Precision medicine in periodontal therapy involves tailoring treatment strategies to the individual patient's microbial profile, genetic background, and lifestyle factors. The integration of metagenomic, metabolomic, and transcriptomic information can provide clinicians with a more comprehensive view of an individual's microbial environment and immune profile, potentially supporting a more precise assessment of host–microbiome interactions. This information can be used to predict disease progression, identify risk factors, and select the most effective therapeutic interventions. Precision medicine aims to move away from a one-size-fits-all approach towards personalized care that maximizes efficacy and minimizes side effects (22, 27).

The implementation of precision medicine in periodontics requires the development of robust diagnostic tools and decision-support systems. Rapid microbial testing platforms can provide real-time information on pathogen load and resistance patterns, guiding antibiotic selection and treatment planning. Artificial intelligence algorithms can analyze complex microbial data to generate personalized treatment recommendations. With the increasing availability and accessibility of these advanced technologies, precision medicine has the potential to transform periodontal disease management. Such an approach could enable more effective patient care, improve clinical outcomes, and potentially reduce the overall burden of healthcare costs (27).

Clinical Trials and Evidence-Based Guidelines

The evidence base for microbiome-targeted interventions in periodontal disease is growing, with numerous clinical trials investigating the efficacy of probiotics, prebiotics, and dietary modifications. These studies have demonstrated varying degrees of success, highlighting the need for standardized protocols and larger sample sizes to draw definitive conclusions. Systematic reviews and meta-analyses are essential for synthesizing current evidence and identifying gaps in knowledge. Based on this evidence, professional organizations are developing evidence-based guidelines to recommend microbiome-targeted therapies as adjuncts to conventional periodontal treatment. Despite the promising results, challenges remain in translating research findings into clinical practice. Issues such as strain specificity, dosage, and duration of treatment need to be addressed to ensure optimal outcomes. Additionally, patient adherence to probiotic and dietary regimens can be a barrier to success. Further studies should incorporate extended follow-up periods to determine whether microbiome alterations can be maintained over time and to clarify their long-term effects on periodontal health. Collaboration between researchers, clinicians, and industry partners is crucial for advancing the field

and implementing evidence-based guidelines (24, 29, 30).

Future Perspectives and Limitations of Microbiome-Based Therapies

The future of microbiome-based therapies in periodontal disease holds great promise, but also faces significant challenges. Advances in sequencing technologies and computational bioinformatics are expected to facilitate a more comprehensive analysis of microbial communities, allowing researchers to better elucidate their composition, diversity, and functional activities.However, standardization of methods and data interpretation remains a critical issue. Additionally, the complexity of host-microbe interactions requires a multidisciplinary approach involving microbiologists, immunologists, and clinicians. Regulatory frameworks for probiotics and microbiome therapies need to be established to ensure safety and efficacy (25, 26, 27).

Furthermore, public education and awareness are essential for the successful implementation of microbiome-targeted interventions. Patients need to understand the role of the microbiome in health and disease and the importance of lifestyle modifications. Ethical considerations, such as privacy and consent in microbiome data collection, must also be addressed. As the field matures, it is expected that microbiome-based therapies will become an integral part of routine periodontal care, offering new hope for patients with chronic periodontitis (26, 27).

Conclusion

The integration of the oral-gut microbiome axis

Table 1. Overview of Key Studies Investigating the Oral–Gut Microbiome Axis and Its Implications for Periodontal Disease and Therapeutic Outcomes.

Ref	Author and Publication Year	Study Characteristics & Participants	Primary Intervention / Research Focus	Major Findings
(25)	Wang et al. (2019)	Cross-Sectional Study (Chronic Periodontitis Patients)	Oral-Gut Microbiome Comparison	Identified significant dysbiosis in both oral and gut microbiomes in periodontitis patients. Porphyromonas gingivalis was detected in the gut, correlating with increased intestinal permeability markers.
(28)	Zhang et al. (2019)	Longitudinal Cohort Study	Impact of SRP on Gut Microbiota	Scaling and root planing (SRP) significantly altered gut microbial composition, increasing diversity and reducing pathogenic taxa. This shift was associated with reduced systemic inflammation (CRP levels).
(29, 18)	Zhao et al. (2018)	Randomized Controlled Trial (Periodontitis)	Adjunctive Probiotics (L. reuteri)	Adjunctive administration of *Lactobacillus reuteri* alongside SRP resulted in a significant reduction in probing depth and bleeding on probing compared with SRP alone.Gut microbiome analysis showed improved microbial balance.
(26)	Zaura et al. (2019)	Review & Mechanistic Study	Oral-Gut Axis Mechanisms	Detailed mechanisms of oral pathogen translocation to the gut. Highlighted that oral anaerobes can survive gastric acid and colonize the intestine, triggering local and systemic immune responses.
(6)	Chen et al. (2019)	Case-Control Study	Microbial Biomarkers in Saliva and Stool	Identified specific microbial signatures in saliva and stool that could distinguish periodontitis patients from healthy controls. Proposed a combined oral-gut diagnostic model for early detection.
(24)	Wagener et al. (2018)	Systematic Review	Probiotics in Periodontal Therapy	Meta-analysis confirmed that probiotics reduce periodontal inflammation and improve clinical attachment levels. Suggested that strain-specific effects are crucial for therapeutic success.
(30)	Zhu et al. (2019)	Experimental Animal Study	FMT-Based Microbiome Therapy	Administration of FMT derived from healthy donors to mice with experimentally induced periodontitis resulted in reduced alveolar bone loss and attenuation of gingival inflammation. Demonstrated that gut microbiota modulation can directly impact periodontal health.
(20)	Ramseier et al. (2018)	Systematic Review	Periodontitis and Systemic Health	Reviewed the bidirectional relationship between periodontitis and diabetes. Highlighted that improving periodontal health can improve glycemic control, partly mediated by gut microbiome changes.
(7)	Darveau (2018)	Hypothesis Paper	Dysbiosis and Homeostasis	Proposed that periodontitis is a state of dysbiosis where the host fails to maintain homeostasis with the microbiome. Suggested that restoring microbial balance is key to treatment success.
(22)	Tonetti et al. (2018)	Consensus Statement	Periodontitis as a Multifactorial Disease	Emphasized the role of environmental and microbial factors in periodontitis. Advocated for personalized treatment approaches based on individual microbial profiles and host response.

into periodontal science represents a transformative shift in our understanding of periodontal disease pathogenesis and management. The evidence reviewed underscores that periodontitis is not an isolated oral condition but a systemic inflammatory disorder influenced by the complex interplay between oral and gut microbial ecosystems. Dysbiosis in either compartment can precipitate or exacerbate disease in the other, creating a feedback loop that drives chronic inflammation and tissue destruction. This bidirectional relationship explains the heterogeneity in patient responses to conventional mechanical therapies and highlights the limitations of treating the mouth in isolation from the gut (25, 28).

A comprehensive microbiome-targeted approach may provide substantial benefits for improving clinical outcomes and enhancing patients' quality of life. The incorporation of probiotics, prebiotics, and dietary interventions as adjuncts to conventional periodontal therapy may support microbial homeostasis, alleviate systemic inflammation, and increase the therapeutic effectiveness of established treatments such as scaling and root planing.Emerging technologies, including precision medicine approaches and microbiome engineering, hold promise for delivering highly personalized and effective interventions. Nevertheless, further evidence from large-scale, long-term randomized controlled trials is necessary before these microbiome-based approaches can be reliably incorporated into routine clinical practice (24, 29, 30).

Despite the promising prospects, challenges remain in standardizing diagnostic tools, defining optimal therapeutic protocols, and ensuring cost-effectiveness. Future research must focus on elucidating the specific mechanisms of host-microbe interactions and developing robust biomarkers for predicting treatment response. Additionally, public health initiatives are needed to educate both healthcare providers and patients about the importance of microbiome health in periodontal and overall systemic well-being. By adopting a multidisciplinary approach that bridges periodontology, gastroenterology, and microbiology, the medical community can develop comprehensive strategies to combat periodontal disease, ultimately improving global health outcomes and reducing the burden of chronic inflammatory conditions (24,27,30).

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No datasets were generated or analyzed during this study. All information was obtained from previously published sources.

Competing Interests

The author declares no competing interests.

Ethics Approval and Consent to Participate

Ethics approval and consent to participate were not applicable because this study is a literature review and involved no human or animal participants.

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Not applicable.

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Therapeutic Potential of Neural Stem Cells for Regenerating Damaged Neural Pathways: Current Evidence and Future Directions

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Abstract

Neural stem cells (NSCs) represent a promising therapeutic strategy for repairing damaged neural circuits in the central nervous system (CNS). The therapeutic promise of NSCs stems from their dual capacity for sustained self-renewal and differentiation into neurons, astrocytes, and oligodendrocytes, which collectively support the regeneration of injured neural tissue and the recovery of neurological function. Beyond direct cell replacement, NSCs exert powerful paracrine effects through the secretion of neurotrophic factors, cytokines, and extracellular vesicles that modulate inflammation, enhance neuronal survival, and promote axonal regeneration. Increasing evidence indicates that NSC-mediated immunomodulation plays a central role in shifting the post-injury microenvironment from a neurotoxic to a regenerative state, primarily through regulation of microglial polarization and suppression of pro-inflammatory signaling pathways.

In addition, NSCs contribute to neural repair by enhancing synaptic plasticity, supporting remyelination, stabilizing the blood–brain barrier, and facilitating angiogenesis. Accumulating preclinical evidence suggests that both NSC transplantation and the therapeutic application of NSC-derived secretomes lead to significant functional improvement in animal models of spinal cord injury, stroke, and traumatic brain injury. However, clinical translation remains limited by challenges such as poor cell survival, immune rejection, tumorigenic risk, and lack of standardized delivery protocols. Emerging strategies, including gene-edited NSCs, biomaterial scaffolds, and exosome-based cell-free therapies, are being developed to overcome these limitations. Overall, NSCs provide a multifaceted regenerative platform with strong potential for future clinical applications in neurological disorders, although further large-scale clinical studies are essential to validate the long-term safety and efficacy of these therapies.

Keywords: Neural stem cells, CNS regeneration, Neuroplasticity, Immunomodulation; Axonal regeneration.

Introduction

Damage to neural pathways resulting from spinal cord injury, traumatic brain injury, stroke, and neurodegenerative disorders remains one of the greatest challenges in modern neuroscience. Unlike the peripheral nervous system, the adult central

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nervous system (CNS) exhibits limited regenerative capacity due to inhibitory microenvironments, glial scar formation, chronic inflammation, and reduced intrinsic neuronal growth potential (1, 2). Consequently, the restoration of functional neural circuits following injury is often incomplete, leading to persistent neurological deficits and disability. Recent advances in regenerative medicine have highlighted neural stem cells (NSCs) as promising therapeutic candidates because of their ability to self-renew, differentiate into neurons and glial cells, modulate immune responses, and secrete neurotrophic factors that support tissue repair (3, 4). Experimental studies have demonstrated that endogenous and transplanted NSCs can promote axonal regeneration, remyelination, synaptic plasticity, and reconstruction of disrupted neural networks after CNS injury (5, 6). Furthermore, emerging biomaterial-based approaches, including hydrogel-supported NSC transplantation, have shown enhanced cell survival and integration within injured tissues, thereby improving functional outcomes in preclinical models (7). These findings have generated significant interest in NSC-based therapies as a potential strategy for restoring damaged neural pathways and improving neurological recovery.

In recent years, substantial progress has been made in understanding the mechanisms through which NSCs contribute to neural regeneration and circuit reconstruction. Beyond direct cell replacement, NSCs exert paracrine effects by releasing extracellular vesicles, cytokines, and growth factors that attenuate neuroinflammation and stimulate endogenous repair processes (8). Advances in stem cell engineering, gene editing technologies, and the manipulation of endogenous neural stem/progenitor cell populations have further expanded the therapeutic potential of NSCs in spinal cord injury and other CNS disorders (5, 9). Preliminary clinical evidence supports the safety and feasibility of neural stem cell transplantation in chronic spinal cord injury and stroke (10, 11). Nevertheless, several challenges remain, including limited cell survival, insufficient functional integration, tumorigenic risk, immune rejection, and ethical considerations associated with stem cell sources (3, 7). Therefore, a comprehensive evaluation of current evidence is essential to determine the translational potential of NSC-based therapies. This review aims to summarize recent advances in neural stem cell biology, explore their role in regenerating damaged neural pathways, and discuss future directions for clinical application.

Biology and Characteristics of Neural Stem Cells

NSCs are characterized by their self-renewal capacity and multilineage differentiation potential, allowing them to generate the principal neural cell types that support central nervous system development and regeneration (13, 14).The adult mammalian brain contains two principal neurogenic niches that harbor NSCs: the SVZ and the SGZ of the hippocampal dentate gyrus (15, 16). These specialized microenvironments consist of endothelial cells, astrocytes, microglia, and extracellular matrix components that tightly regulate NSC fate decisions (15). Recent single-cell transcriptomic analyses have demonstrated that NSCs are highly heterogeneous, comprising multiple subpopulations with distinct transcriptional signatures and regenerative capacities (16). This heterogeneity enables adaptive neurogenic responses under both physiological and pathological conditions. NSCs maintain a dynamic equilibrium between quiescence and activation, which is essential for preserving long-term regenerative potential (17). Disruption of this balance contributes to impaired neurogenesis and reduced neural repair capacity.

NSC function is tightly regulated by a network of conserved signaling pathways, including Notch, Wnt/β-catenin, Sonic Hedgehog (Shh), and BMP signaling, which collectively coordinate stem cell maintenance and differentiation (13, 17). Notch signaling is primarily responsible for maintaining NSC quiescence, whereas Wnt signaling promotes activation and neuronal differentiation (17, 18). Beyond classical signaling pathways, epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs serve as critical regulators of gene expression that influence NSC fate decisions (18). In addition, metabolic regulation and mitochondrial dynamics significantly influence NSC proliferation and differentiation capacity (19). Age-associated alterations in these molecular pathways result in a progressive decline in neurogenic potential (17). Therefore, targeting these regulatory networks represents a promising strategy for enhancing endogenous neural repair mechanisms.

Beyond intrinsic properties, NSCs actively interact with their microenvironment through paracrine signaling and cell-cell communication (14, 16). They secrete cytokines, neurotrophic factors, and extracellular vesicles that regulate inflammation, support enhance synaptic plasticity and neuronal survival (16). NSCs also respond to neurotransmitters such as GABA and glutamate, which influence their proliferation and differentiation dynamics (13). Bidirectional communication between NSCs, neurons, and immune cells forms a complex regulatory network within neurogenic niches (15). This network is essential for maintaining CNS homeostasis and facilitating repair processes following injury. Collectively, these features highlight NSCs as key

regulators of neural plasticity and regeneration.

Sources and Classification of Neural Stem Cells

The adult CNS contains two principal neurogenic niches that serve as the primary reservoirs of NSCs: the SVZ along the lateral ventricles and the SGZ located in the dentate gyrus of the hippocampus (15, 20). Neurogenesis in the SVZ involves the formation of intermediate progenitor cells from NSCs, followed by the differentiation of these progenitors into neuroblasts that migrate through the rostral migratory stream to the olfactory bulb (20). Conversely, NSCs in the SGZ generate granule neurons that integrate into hippocampal neural circuits, thereby supporting cognitive functions, particularly learning and memory (16). These region-specific neurogenic processes reflect functional specialization within the CNS. Developmentally, adult NSCs originate from embryonic radial glial cells that persist as quiescent stem cells after birth (21). This lineage relationship underlies the lifelong, albeit limited, regenerative capacity of the brain.

In addition to classical neurogenic niches, emerging evidence suggests the presence of NSC-like populations in non-canonical regions such as the hypothalamus, striatum, and spinal cord (20). These cells exhibit restricted neurogenic activity under specific physiological or injury conditions. Moreover, cellular reprogramming studies have demonstrated that astrocytes and pericytes can be converted into induced neural stem cells (iNSCs) using defined transcription factors (19). This finding expands the concept of NSC origin beyond traditional developmental pathways. Furthermore, induced pluripotent stem cell (iPSC)-derived neural progenitors provide an exogenous and scalable source for regenerative applications (18). However, challenges such as incomplete maturation and functional heterogeneity remain.

NSCs can also be classified based on their functional states, including quiescent NSCs (qNSCs) and activated NSCs (aNSCs) (17, 21). Quiescent NSCs serve as a long-term reservoir, preserving stem cell pools and preventing depletion (21). Activated NSCs, in contrast, enter the cell cycle in response to injury or physiological demands and contribute to tissue regeneration (17). Recent single-cell sequencing studies suggest that NSC states exist along a dynamic continuum rather than discrete categories (16). This plasticity is regulated by both intrinsic genetic programs and extrinsic niche-derived signals. Understanding these functional states is critical for optimizing therapeutic strategies aimed at enhancing neurodegeneration.

Mechanisms of Neural Pathway Damage in the Central Nervous System

Neural pathway damage in the CNS occurs due to traumatic, ischemic, inflammatory, and neurodegenerative processes, including traumatic brain injury, spinal cord injury, stroke, and diseases such as multiple sclerosis (22, 23). These conditions lead to axonal disruption, neuronal apoptosis, demyelination, and synaptic loss, ultimately impairing neural circuit connectivity. A major barrier to regeneration is forming of a glial scar composed of reactive astrocytes and extracellular matrix molecules (22). This scar physically and chemically inhibits axonal regrowth. Additionally, inhibitory molecules such as Nogo-A, MAG, and chondroitin sulfate proteoglycans further restrict neural regeneration (23). Together, these factors create a non-permissive environment for repair.

Neuroinflammation is recognized as a major driver of secondary injury progression after CNS damage. Following CNS injury, inflammatory cytokines released by activated microglia and infiltrating immune cells, including TNF-α, IL-1β, and IL-6, contribute to neuronal degeneration. This process is further intensified by oxidative stress and mitochondrial dysfunction, which impair cellular energy production and increase tissue damage (22). Glutamate-induced excitotoxicity promotes excessive intracellular calcium accumulation, thereby triggering neuronal degeneration and cell death (23). Chronic inflammation also suppresses endogenous NSC activation and migration, limiting intrinsic repair capacity. Therefore, modulation of inflammatory pathways is a critical therapeutic target in CNS injury.

At the network level, disruption of long-range axonal connections leads to severe functional deficits, including motor impairment, cognitive dysfunction, and sensory loss (22). Although compensatory plasticity mechanisms exist, they are often insufficient for full functional recovery (23). Aging further worsens outcomes by reducing NSC activity and regenerative responsiveness (21). The severity of functional impairment is influenced not only by primary injury but also by failure of endogenous repair signaling (20). Enhancing intrinsic regenerative capacity, particularly through NSC-based strategies, represents a promising therapeutic approach for restoring damaged neural pathways.

Molecular Mechanisms of Neural Stem Cell–Mediated Neural Regeneration

Neural stem cells (NSCs) promote regeneration of damaged neural pathways through highly coordinated molecular signaling networks that regulate proliferation, differentiation, and neuronal integration (24, 25, 26). Among these, the Wnt/β-catenin pathway plays a central role in promoting neuronal lineage commitment and enhancing neurogenic activity following CNS injury (24). The

Notch signaling pathway, in contrast, maintains NSC quiescence under physiological conditions but becomes dynamically regulated after injury to balance self-renewal and differentiation (25). Sonic Hedgehog (Shh) signaling also contributes significantly by enhancing NSC proliferation and guiding neural patterning during regeneration (26). These pathways interact in a tightly regulated manner, ensuring controlled neurogenesis without depletion of the stem cell pool. Dysregulation of these mechanisms leads to impaired regenerative responses and incomplete neural repair (Table 1).

Epigenetic regulation is another fundamental mechanism underlying NSC-mediated neural repair. Histone modification, DNA methylation, and chromatin remodeling collectively regulate transcriptional programs involved in NSC activation and lineage specification (27, 28). MicroRNAs (miRNAs) and long non-coding RNAs further refine gene expression by post-transcriptional regulation of key regenerative genes (27). These epigenetic mechanisms enable NSCs to respond dynamically to injury-induced environmental cues such as inflammation and hypoxia. Additionally, metabolic reprogramming from glycolysis toward oxidative phosphorylation is essential for NSC differentiation and maturation (29). Mitochondrial dynamics also influence NSC fate decisions and regenerative capacity (28). Together, these processes establish the molecular basis of NSC plasticity in CNS repair.

Neural regeneration mediated by NSCs extends beyond cell replacement, as these cells actively modulate the injured microenvironment through paracrine signaling. This effect is largely attributed to the secretion of neurotrophic factors, including BDNF, GDNF, and VEGF (30). These molecules enhance neuronal survival, promote angiogenesis, and reduce apoptotic signaling in injured tissue (30, 31). NSC-derived extracellular vesicles (EVs) carry proteins, lipids, and regulatory RNAs that modulate gene expression in recipient cells (31). These EVs also suppress neuroinflammation and enhance endogenous repair mechanisms (32). Furthermore, NSCs interact with immune cells, particularly microglia, to regulate inflammatory responses and promote a regenerative microenvironment (33). This dual role of NSCs as both cellular replacements and secretory regulators highlights their therapeutic potential.

Neural Stem Cells and Axonal Regrowth After Neural Injury

Axonal regeneration in the central nervous system (CNS) is severely limited due to both intrinsic neuronal constraints and inhibitory extracellular environments (34, 35). Neural stem cells (NSCs) contribute to axonal regrowth by creating a permissive environment that supports axonal elongation, synaptic reconnection, and circuit remodeling (34). Experimental models of spinal cord injury and stroke have demonstrated that NSC transplantation significantly enhances axonal sprouting and functional recovery (35). This regenerative effect is mediated in part by secretion of neurotrophic factors such as BDNF, NGF, and NT-3 (30). These factors promote neuronal survival and stimulate axonal extension in damaged neural networks. Additionally, NSCs differentiate into oligodendrocyte lineage cells, contributing to remyelination and improved signal conduction (6, 35).

A major barrier to axonal regeneration is the presence of inhibitory molecules in the injured CNS environment, including Nogo-A, MAG, OMgp, and chondroitin sulfate proteoglycans (CSPGs) (34, 36). NSCs counteract these inhibitory signals by modulating extracellular matrix composition and

Table 1. Major Molecular Mechanisms and Regenerative Functions of Neural Stem Cells in CNS Repair

Molecular Mechanism/Pathway	Biological Function in NSCs	Regenerative Outcome in CNS Injury	References
Wnt/β-catenin signaling	Promotes neuronals differentiation and NSC activation	Enhanced neurogenesis and neural repair	(24,25)
Notch signaling	Maintains NSC quiescence and self-renewal	Preservation of stem cell pool balance	(25)
Sonic Hedgehog (Shh) pathway	Stimulates NSC proliferation and neural patterning	Improved of stem cell pool balance	(26)
Epigenetic regulation (DNA methylation, histone modification, miRNAs)	Controls gene expression and lineage specification	Adaptive response to injury microenviroment	(27,28)
Neurotrophic factor secretion (BDNF, GDNF, VEGF)	Supports neuronal survival and angiogenesis	Axonal regeneration and reduced apoptosis	(30,31)
Extracellular vehicles (EVs)/exosomes	Transfer regulatory RNAs and proteins	Suppression of neuroinflammation and promotion of endogenous repair	(31,32)
Immunomodulation of microglia	Shifts microglia from M1 to M2 phenotype	Reduced inflammatory damage and improved tissue repair	(33,41)
Remyelination support	Differentiation into oligodendrocyte lineage cells	Restoration of neural signal conduction	(6,35)

reducing glial scar formation (36). They suppress reactive astrocyte activation and decrease deposition of inhibitory CSPGs, thereby improving axonal growth conditions (36). NSCs also promote synaptic plasticity, facilitating the formation of new functional connections between surviving neurons (35). Moreover, NSC-derived exosomes have been shown to enhance axonal regeneration by transferring regenerative microRNAs to host neurons (31). These combined mechanisms significantly enhance structural and functional recovery after CNS injury.

Recent advances in biomaterials and tissue engineering have further improved NSC-based axonal regeneration strategies. Hydrogels, nanofiber scaffolds, and 3D-printed matrices provide structural support for NSC survival and axonal guidance (7, 37). These biomaterials enhance cell retention, improve spatial organization, and facilitate directed axonal growth across lesion sites (37). Genetically modified NSCs expressing enhanced growth-promoting or anti-inhibitory molecules have shown superior regenerative outcomes in preclinical models (38). In addition, combining NSC therapy with electrical stimulation and rehabilitative training further enhances axonal plasticity and functional recovery (35). These multimodal approaches represent a promising direction for improving outcomes in CNS injury repair.

Immunomodulatory and Neuroprotective Effects of Neural Stem Cells

Following injury to the central nervous system (CNS), neural stem cells (NSCs) serve as key regulators of the immune response. After CNS damage, microglial activation, together with the recruitment of immune cells from the periphery, contributes to excessive production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which amplify secondary neuronal damage (39, 40). NSCs counteract this inflammatory cascade by secreting anti-inflammatory cytokines including IL-10 and TGF-β, thereby promoting a shift from M1 to M2 microglial polarization (41). This shift creates a regenerative microenvironment that supports tissue repair and limits neurodegeneration. In addition, NSCs interact directly with resident immune cells, regulating both innate and adaptive immune responses in the CNS (42). NSC-derived extracellular vesicles further enhance immunomodulation by transferring microRNAs that suppress inflammatory signaling pathways (43).

Beyond immune regulation, NSCs provide strong neuroprotective effects in injured neural tissue. They secrete neurotrophic factors such as GDNF, BDNF, NGF, and VEGF, which promote neuronal survival and synaptic stabilization (44). These factors reduce apoptosis, enhance axonal integrity, and improve resistance to oxidative stress (45). NSCs also contribute to blood–brain barrier (BBB) stabilization, thereby reducing infiltration of toxic molecules and immune cells into neural tissue (46). Furthermore, NSCs regulate glutamate excitotoxicity and calcium imbalance, which are key drivers of neuronal death after injury (47). These combined effects significantly improve structural preservation and functional recovery in CNS disorders.

Importantly, the therapeutic impact of NSCs is largely mediated through paracrine signaling rather than direct neuronal replacement. Their secretome includes cytokines, growth factors, and extracellular vesicles that modulate multiple signaling pathways in host cells (43, 48). NSC-derived exosomes can reproduce many of the regenerative effects observed in cell transplantation models (43). This has shifted current therapeutic strategies toward cell-free regenerative medicine. Overall, NSCs function as both immune regulators and neuroprotective mediators in CNS repair.

Clinical Applications of Neural Stem Cells in Neurological Disorders

Therapeutic approaches utilizing neural stem cells (NSCs) have gained considerable attention as potential treatments for various neurological conditions, such as spinal cord injury (SCI), stroke, traumatic brain injury (TBI), and neurodegenerative diseases (49, 50). Preclinical studies consistently demonstrate that NSC transplantation enhances neurogenesis, axonal regeneration, and remyelination, leading to improved functional outcomes (51). In SCI models, NSCs integrate into host neural circuits and contribute to reconstruction of disrupted pathways (52). In ischemic stroke models, they promote angiogenesis and neuronal survival, improving both motor and cognitive recovery (53). These findings strongly support the translational potential of NSC-based therapies (Table 2).

Early-phase clinical trials have evaluated the safety and feasibility of NSC transplantation in CNS injury patients. Overall, these studies report acceptable safety profiles with no significant tumor formation or severe immune rejection (54, 55). Some patients show modest improvements in motor and sensory functions, although outcomes remain variable (55). Differences in cell source, delivery route, timing of intervention, and injury heterogeneity contribute to inconsistent results (54). Common delivery methods include intrathecal, intracerebral, and intravenous administration (56). However, lack of standardized clinical protocols remains a major limitation in translating NSC therapies.

In addition to cell transplantation, NSC-derived extracellular vesicles and secretome-based therapies have gained increasing attention (43, 57). These

Table 1. Major Molecular Mechanisms and Regenerative Functions of Neural Stem Cells in CNS Repair

Neurological Disorder	Therapeutic Effects of NSCs	Major Benefits	Current Limitations	Key References
Spinal cord injury (SCI)	Axonal regeneration, remyelination, neural circuit reconstruction	Improved motor recovery and neural connectivity	Poor cell survival, inhibitory microenvironment	(50,52)
Ischemic stroke	Promotion angiogenesis and neuronal survival	Recovery of motor and cognitive function	Variable clinical outcomes	(49,53)
Traumatic brain injury (TBI)	Neuroprotection and anti-inflammatory effects	Reduced neuronal apoptosis and enhanced repair	Limited long-term integration	(40,45)
Multiple sclerosis (MS)	Immunomodulation and remyelination	Reduction of inflammatory damag	Immune rejection risk	(39,41)
Neurodegeneratve disorders	Neurotrophic support and synaptic stabilization	Potential slowing of neurodegeneration	Tumorigenic risk and delivery challenges	(44,55)
Exosome-based therapies	Cell-free regenerative signaling	Lower tumorigenic and immunogenic risk	Standardization regulatory concerns	(43,57)
Gene-edited NSCs	Enhanced regenerative capacity	Improved therapeutic precision	Ethical and regulatory concerns	(59,65)

approaches reduce risks associated with live cell transplantation while maintaining regenerative effects (57). Biomaterial-assisted delivery systems such as hydrogels and nanoscaffolds improve NSC survival, localization, and integration (58). Gene-edited NSCs with enhanced regenerative properties are also under investigation (59). Despite these advances, long-term safety, optimal dosing, and functional integration remain unresolved challenges (54). Large-scale randomized clinical trials are essential for clinical validation.

Challenges, Limitations, and Future Perspectives

Despite promising progress, several biological and technical challenges limit the clinical translation of NSC-based therapies. One major limitation is poor survival of transplanted NSCs in the hostile post-injury microenvironment categorized by inflammation, oxidative stress, and inhibitory extracellular matrix molecules (60, 61). These factors significantly reduce cell viability and functional integration. Another concern is the risk of uncontrolled proliferation and tumorigenesis, particularly with pluripotent stem cell-derived NSCs (62). Immune rejection in allogeneic transplantation also remains a critical barrier (63). These limitations collectively reduce therapeutic consistency.

Technical challenges include the absence of standardized protocols for NSC derivation, expansion, and transplantation (64). Variability in manufacturing methods leads to inconsistent biological and functional outcomes. Additionally, precise control of NSC differentiation and incorporation into existing neural circuits remains difficult (60). The complexity of CNS architecture further complicates reconstruction of functional connectivity. Ethical concerns regarding embryonic stem cell sources also influence clinical translation pathways (62). Therefore, regulatory standardization is essential for clinical advancement.

Future directions focus on overcoming these limitations through advanced biomedical strategies. Gene-editing technologies such as CRISPR/Cas9 allocate precise enhancement of NSC safety and regenerative capacity (59, 65). Biomaterial scaffolds, nanotechnology, and 3D bioprinting provide structural guidance for axonal growth and neural network reconstruction (58, 66). Exosomes derived from neural stem cells (NSC-derived exosomes) have emerged as a promising cell-free therapeutic approach, offering the potential for enhanced safety compared with cell-based therapies (43, 57). Combination therapies integrating NSCs with pharmacological agents, rehabilitation, and electrical stimulation further enhance functional recovery (67). Ultimately, multidisciplinary approaches will be essential for successful clinical translation.

Controversies and Limitations (Critical View of NSC-Based Therapies)

Despite substantial progress in neural stem cell (NSC)-based therapies, several important controversies and limitations remain that restrict their full clinical translation. One of the most significant challenges is the limited survival and poor functional integration of transplanted NSCs within the injured central nervous system (CNS). Following injury, the local microenvironment becomes strongly detrimental to tissue repair, largely as a result of sustained inflammation, oxidative damage, excitotoxic processes, and inhibitory extracellular matrix molecules, including chondroitin sulfate proteoglycans (68, 69). These factors severely impair NSC survival, differentiation, and synaptic integration, leading to inconsistent and often transient functional recovery in experimental models (69).

Another concern associated with NSC-based therapy is the potential for tumor formation and aberrant cell proliferation, especially when neural stem cells are generated from embryonic stem cells

(ESCs) or induced pluripotent stem cells (iPSCs) (70). Even small populations of undifferentiated cells can form teratomas or aberrant tissue structures, raising serious safety concerns for clinical application. In addition, immune rejection remains a critical barrier, especially in allogeneic transplantation, where host immune responses can eliminate grafted cells or reduce their therapeutic efficacy (71). Although immunosuppressive strategies may mitigate rejection, they introduce risks such as systemic immunosuppression and increased susceptibility to infection (71).

A further controversy concerns the mechanism of action of NSCs. While early studies emphasized direct cell replacement, more recent evidence indicates that the majority of therapeutic benefits are mediated across paracrine signaling and extracellular vesicle (EV)-based mechanisms rather than long-term neuronal integration (43, 72). This shift has raised important questions regarding whether NSCs should be used primarily as regenerative grafts or as biological sources for secretome- and exosome-based therapies. However, the optimal balance between these mechanisms remains unclear and likely depends on injury type and disease context.

Finally, the lack of standardized protocols for NSC derivation, expansion, differentiation, and transplantation remains a major translational barrier (73). Variability in cell preparation methods, delivery routes, timing of transplantation, and injury models leads to inconsistent outcomes across studies. Ethical concerns related to the use of embryonic stem cells further complicate regulatory approval and clinical implementation (70). Together, these issues highlight the need for improved standardization, safety optimization, and mechanistic clarity in future NSC research.

Conclusion

Neural stem cells (NSCs) have emerged as a versatile therapeutic approach with considerable potential for promoting repair and recovery following injuries to the central nervous system (CNS). Their regenerative potential extends beyond simple cell replacement, encompassing neuroprotection, immunomodulation, and the secretion of bioactive molecules that reshape the injured neural microenvironment. Through the regulation of inflammatory responses, enhancement of neuronal survival, promotion of axonal regeneration, and support of remyelination, NSCs contribute to both structural and functional recovery in diverse neurological conditions.

Findings from preclinical studies provide substantial evidence for the therapeutic effectiveness of NSC-based strategies in experimental models of stroke, spinal cord injury, and traumatic brain injury. However, clinical translation remains limited due to challenges such as poor cell survival, variability in transplantation outcomes, immune rejection, and safety concerns including tumorigenicity. Despite these challenges, recent progress in biomaterials, gene-editing technologies, and cell-free strategies, particularly exosome-based therapies, is opening new avenues for enhancing the therapeutic potential of NSC-based approaches. Collectively, NSCs hold substantial promise as a next-generation regenerative therapy for CNS disorders, although further optimization and validation are essential for routine clinical application.

Future Directions

Future research should address improving the survival, integration, and functional maturation of transplanted NSCs within the hostile post-injury CNS environment. Advanced biomaterial scaffolds, 3D bioprinting technologies, and hydrogel-based delivery systems are expected to enhance cell retention and guide axonal growth. In parallel, gene-editing approaches such as CRISPR/Cas9 may be used to engineer NSCs with enhanced regenerative capacity, reduced immunogenicity, and improved safety profiles. Another major direction is the development of standardized, clinically scalable NSC production protocols to ensure reproducibility across studies and clinical trials.

In addition, increasing attention is being directed toward NSC-derived extracellular vesicles and secretome-based therapies as safer, cell-free alternatives. Such strategies could help mitigate several of the potential risks inherent to the transplantation of living cells while retaining therapeutic efficacy. Combination therapies integrating NSCs with pharmacological agents, electrical stimulation, and rehabilitation strategies may further enhance functional recovery. Ultimately, interdisciplinary approaches combining stem cell biology, bioengineering, and clinical neuroscience will be essential to accelerate translation from bench to bedside.

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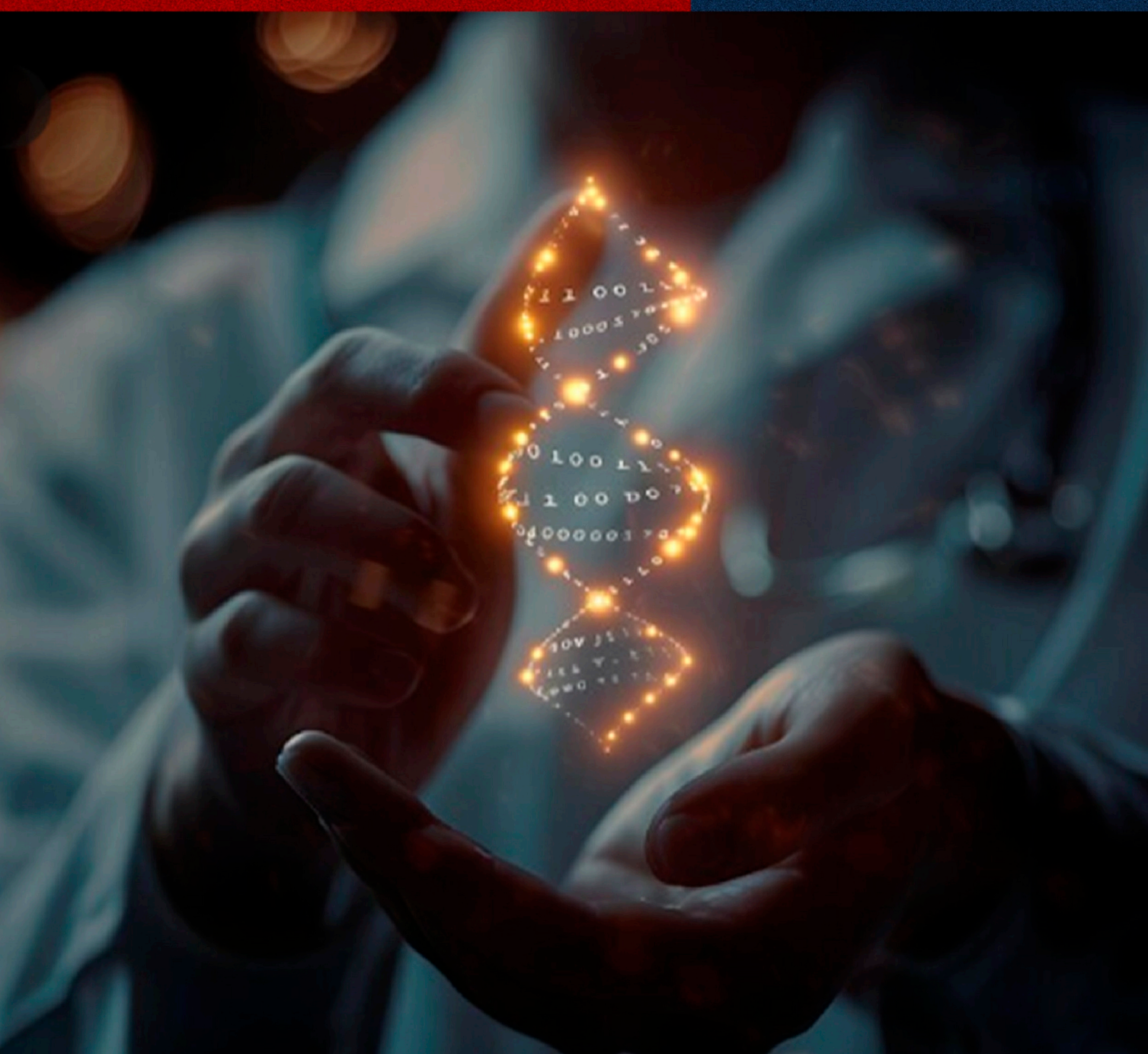

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