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A Review from the Standpoint of Multi - Omics and Microbial - Host Interaction on the Mechanisms, Diagnosis, and Novel Therapeutic Strategies for Inflammatory Bowel Disease

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Abstract. Inflammatory Bowel Disease (IBD) is a chronic intestinal inflammation that results from the interplay of gut microbiota dysbiosis, host genetic susceptibility, and environmental factors, and it encompasses the major clinical entities Crohn's disease and ulcerative colitis, both of which have been increasing in global prevalence and thus impose growing health burdens. Importantly, gut microbiota dysbiosis is now recognized as a fundamental driving force in IBD pathogenesis.Because the paper discusses IBD in the context of fungi, viruses, and multi-omics technologies, it provides a very logical and thorough review of the pathogenesis, diagnostic value, and therapeutic strategies of IBD. Importantly, the authors clearly outline that patients with IBD have reduced microbial diversity, loss of beneficial bacteria, enrichment of pathogenic microorganisms, lower levels of beneficial metabolites, and accumulation of toxic substances, all of which damage the intestinal barrier and perturb immune and metabolic homeostasis.Since neurological symptoms are mediated via the gut - brain axis, it is logical and promising to use multi - omics data together with serum anti - glycan antibodies, fecal biomarkers, and machine learning models for early prediction, subtyping, disease activity assessment, and treatment response prediction. Therapeutically, microbiota - targeted approaches such as fecal microbiota transplantation and synthetic microbiota supplementation offer important possibilities.Engineered probiotics, precise pathogen elimination, and dietary interventions all modulate metabolic pathways involving short-chain fatty acids, GABA, and 5-HT, thus repairing the intestinal barrier, inhibiting inflammation, and alleviating pain. Therefore, the microbe-host-glycan interaction network is a very natural and important entry point for investigating IBD pathogenesis. As such, future work should focus on multi-center large-sample studies to optimize diagnostic models, improve the colonization stability and targeting precision of engineered strains, and develop individualized therapeutic systems that integrate diet, microbiota, neural, and immune factors, thereby establishing clear new theoretical foundations and clinical translation pathways for IBD.

Keywords: inflammatory bowel disease, gut microbiota, multi-omics, microbial-host interaction, and therapeutic strategies

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1. Background

1.1. Introduction to Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a group of chronic, non-specific inflammatory intestinal diseases that arise from the interplay of several factors: gut microbiota dysbiosis, host genetic susceptibility, and environmental factors, and therefore has well-defined pathological features: ongoing intestinal mucosal inflammation, defective intestinal barrier function, and dysregulated immune response.the disease is associated with aberrant T cell immune responses, and clinically it is most clearly characterized by recurrent episodes of intestinal inflammation, with typical manifestations of diarrhea, abdominal pain, and mucopurulent bloody stools. Severe cases can lead to intestinal strictures, perforation, and fistula formation, while prolonged disease course significantly increases the risk of intestinal fibrosis, strictures, and even carcinogenesis.The Delphi survey carried out by the Human Microbiome Action Consortium showed that 92.93% of the respondents unequivocally accepted a causal relationship between the gut microbiome and IBD. Therefore, dysbiosis is widely regarded as one of the major initiating factors of intestinal inflammation, whereas genetic, environmental, dietary, immune, and neuronal factors are all intricately linked via the gut microbiome.the intestinal immune system has been extensively studied in the literature, and IBD is most appropriately regarded as consisting of two well-defined subtypes: Crohn's disease (CD) and Ulcerative Colitis (UC). Specifically, UC is characterized by colonic inflammation that is superficial and continuous, predominantly affecting the mucosa and submucosa, whereas CD involves inflammation anywhere in the gastrointestinal tract from the mouth to the anus, with the terminal ileum and adjacent colon being the sites most commonly affected.the disease presents as transmural, focal inflammation, and its global prevalence is increasing, especially in newly industrialized countries. In Western countries, the prevalence of IBD has already reached 0.5% of the population. North America now has over three million IBD patients, and the annual economic burden of IBD in the US alone exceeds $6 billion. Importantly, incidence is essentially equal between males and females.Female patients have a lower quality of life and higher opioid use rates, and abdominal pain is undoubtedly the most debilitating core symptom of IBD, occurring in approximately 70% of patients during active inflammation and in 20%-60% of patients in clinical and endoscopic remission. Importantly, many such patients also have overlapping irritable bowel syndrome (IBS)-like symptoms.The incidence of chronic abdominal pain is approximately 2-3 times that of the healthy population, and it forms a clear vicious cycle with anxiety, depression, sleep disturbances, and fatigue, thus severely impairing patients' quality of life. Current clinical treatment for IBD is predominantly anti-inflammatory and immunosuppressive, but it is well established that many patients do not respond adequately or suffer from serious side effects, and irreversible intestinal tissue damage is frequently present by the time of diagnosis [1]. Therefore, there is a growing and logical shift in research toward the preclinical phase before disease onset, with the ultimate goal of developing preventive intervention strategies to address the global IBD epidemic.

1.2. Introduction to the gut microbiota

The gut microbiota is a highly diverse microbial community inhabiting the human gastrointestinal tract, comprising approximately 10^{13}–10^{14} microorganisms, namely bacteria, archaea, fungi, protozoa, and viruses (mainly bacteriophages) [2,3]. Bacteria make up over 99% of this community and encode a total number of genes that is more than 100 times greater than the human genome. Of

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particular note, the phyla Firmicutes and Bacteroidetes together account. since about 90% of the total gut microbial mass is composed of the dominant flora [4,5], healthy individuals generally have a relatively stable core microbiota structure, and it is well established that its diversity, functional stability, and the abundance and metabolic activity of core functional microbes are all essential foundations for host health. More importantly, this community has evolved in close association with the host over long periods, hence the tight symbiosis.Because the composition is determined by diet, stress, inflammation, and environmental factors, it exhibits considerable inter-individual and intra-individual variability. More importantly, the gut microbiota plays a critical role in regulating host physiological homeostasis, and its core functions are well exemplified metabolically: it ferments dietary fibers and host mucosal components [6]. Glycans are discussed here along with the fact that the genome encodes roughly 10,000 glycan - degrading enzymes, which is vastly greater than the ~17 found in the human genome [7]. More importantly, different microbial phyla have distinct preferences for glycan metabolism and therefore produce characteristic metabolites: short - chain fatty acids (SCFAs), UDP - N - acetylglucosamine, bile acid metabolites, and neurotransmitters such as γ - aminobutyric acid (GABA) and serotonin (5 - HT) [8]. SCFAs provide energy for colonic epithelial cells, regulate intestinal mucosal barrier integrity and immune cell function, and inhibit intestinal inflammation [9]. Dietary glycans such as human milk oligosaccharides can selectively and powerfully shape the gut microbiota structure during early life [10]. Importantly, they also have immunological functions in regulating the development, activation, and balance of host innate and adaptive immune cells.the microbiota shapes the intestinal mucosal immune barrier, thereby resisting pathogen invasion and colonization, and it also exerts systemic effects via the gut-brain axis, influencing intestinal nerve function and pain perception. Importantly, the viral community, which is dominated by bacteriophages, directly regulates microbiota structure by infecting bacteria, while alterations in eukaryotic viruses and gut fungal composition are clearly linked to IBD pathological processes [11-13].

1.3. Association between IBD and the gut microbiota

Dysbiosis is properly defined as abnormal changes in the composition, abundance, diversity, and function of the gut microbial community, and it has a direct causal relationship with the pathogenesis of IBD, therefore being one of the core driving factors of IBD. More importantly, the pathogenesis of IBD is highly complex, with a central feature being an aberrant immune response to intestinal commensal bacteria.chronic mucosal inflammation and tissue damage are well established as features of the condition, but more importantly, both inflammation itself and psychological factors such as stress (acting through the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system) can directly disrupt gut microbiota balance, thus creating a vicious cycle of "inflammation - dysbiosis". At the genetic level, variations in IBD-associated risk genes play a critical role.The genes CARD9,IL23R, ATG16L1 all influence host recognition of microbes and the subsequent immune response to them, thereby directly exacerbating the imbalance in microbe - host interactions. Moreover, serological studies have consistently shown elevated levels of microbe - associated antibodies, such as anti - Saccharomyces cerevisiae mannan antibodies (ASCAs), in CD patients even before the onset of clinical symptoms [14,15]. The observation that gut microbiota composition is similar in first - degree relatives and changes predictably during inflammation resolution provides strong support for this association.

Gut dysbiosis in IBD patients is well established to manifest as decreased abundance of beneficial bacteria, increased proportion of pathogenic bacteria, and reduced microbial diversity, all of which perturb the host-microbiome symbiosis. At the bacterial level, α-diversity is markedly

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reduced, with clear reductions in the relative abundance of Bacteroidetes and Firmicutes.The intestinal microbiota of CD patients shows substantial decreases in beneficial bacteria such as Faecalibacterium prausnitzii and Blautia spp., accompanied by an increase in Gammaproteobacteria [16-18]. More importantly, Adherent - invasive Escherichia coli (AIEC) is conspicuously enriched in the intestines of CD patients, and the abundance of other pathogens including Clostridioides difficile, pathogenic E. coli, and Salmonella also rises. At the fungal level, the gut fungal community shows decreased biodiversity with an increased ratio of Basidiomycota to Ascomycota, which can be directly attributed to the increased prevalence and abundance of Candida albicans and the concomitant decrease in Saccharomyces cerevisiae. In contrast, changes in the virome remain a matter of controversy: some studies report reduced diversity and major compositional shifts, whereas others find only minor changes with little pathological significance [19].

Dysbiosis exerts its main effects on the onset and progression of IBD via three well-defined pathways, and the most direct and important of these is the impairment of intestinal barrier function in the pathogenesis of inflammatory bowel disease, which manifests as damage to tight junctions between intestinal epithelial cells, increased intestinal permeability, and thereby enhanced translocation of incompletely digested food antigens and pathogens into the submucosa.Since flagellin produced by Enterobacteriaceae triggers immune responses by activating host Toll-like receptor signaling pathways and initiating downstream inflammatory cascades [20], it is logical to consider that harmful metabolites such as hydrogen sulfide directly damage intestinal epithelial tight junctions. At the same time, altered microbiota composition modulates host immune responses by promoting the activation of intestinal.Mucosal immune cells including T cells and macrophages produce excessive amounts of inflammatory cytokines such as TNF, IFN - γ ,and IL - 17,thereby aggravating local inflammation [21]. More importantly, the abnormal microbiota can activate innate immune cells such as macrophages and dendritic cells through pattern recognition receptors like NOD2,and at the same time suppress regulatory T cell function.the text describes how glycan structures can contribute to the overactivation of Th1 and Th17 cell subsets, and then goes on very naturally to discuss glycan mimicry by pathogenic bacteria, wherein bacteria expressing glycan structures similar to host mucosal glycans can trigger autoimmune responses. A classic and well-documented example is the lipo-oligosaccharide of Campylobacter jejuni, which mimics host gangliosides and induces inflammation resembling that of IBD.Dysbiosis is clearly evident in IBD patients, with major alterations in gut microbiota pathways concerned with amino acid biosynthesis, carbohydrate metabolism, oxidative stress, and bile salt metabolism. Most importantly, dysregulation of sulfur metabolism pathways represents a central and well-supported mechanism underlying intestinal inflammation [22]. Specifically, dysfunctional microbial metabolism leads to the production of harmful sulfur metabolites and hydrogen sulfide that damage intestinal epithelial cells, while the protective metabolites short-chain fatty acids and gamma-aminobutyric acid decrease, thus creating a damaging vicious cycle of dysbiosis, barrier dysfunction, and inflammation.

Since SCFAs are well established as major metabolites of the gut microbiota with anti-inflammatory and intestinal epithelial barrier - repairing properties due to their ability to inhibit histone deacetylase (HDAC) activity, activate G protein - coupled receptors (GPR41/43), and modulate other pathways, their reduced production therefore weakens both nutritional support for intestinal epithelial cells and their anti - inflammatory actions.Bile acid metabolism dysregulation (i. e., reduced secondary bile acid production) decreases the inhibitory effect of bile acids on pathogens such as C. difficile, thus directly worsening microbial ecological imbalance. More importantly, intestinal microbial metabolic function is already profoundly altered in IBD patients, and many of

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the resulting metabolites modulate IBD progression and pain perception by affecting intestinal mucosal barrier function. The text provides a clear and well-organized discussion of the relationship between immune responses, neural signaling, and IBD-induced intestinal mucosal barrier damage, namely that IBD causes the gut microbiota and its metabolites to become more accessible to intestinal nerve endings and immune cells, thereby worsening inflammation and pain. More importantly, microbial patterns (e. g., multi-bacterial biomarker panels) have already been established as reliable non-invasive diagnostic tools for IBD, with their compositional changes capable of predicting disease progression, relapse risk, and treatment response [23,24].

1.4. Purpose of this review

This review intends to systematically examine the current state of knowledge about the trans - kingdom gut microbiome in IBD, with a focus on bacterial and fungal components and their metabolites, then move on to discuss microbiome - mediated intestinal homeostasis and IBD pathogenesis, neuroimmune inflammatory regulatory mechanisms, and the relationship between the microbiome and IBD treatment, thereby clarifying disease mechanisms, identifying new research directions and therapeutic opportunities, and ultimately providing a solid theoretical basis for IBD diagnosis, treatment, and dietary interventions [25].

2. Microbial features mediating IBD

The gut microbiota of IBD patients shows well-defined, multidimensional, and multilevel alterations in composition, diversity, metabolic function, and host interaction, with the most striking features being first that microbial diversity is greatly reduced, namely α-diversity (species richness, evenness) is diminished and β-diversity is clearly distinct from that of healthy controls, reaching its fullest extent during active disease. Importantly, the microbiota has a clear " pro - inflammatory enrichment, beneficial depletion " profile.

In IBD patients, the abundance of Firmicutes, namely Faecalibacterium prausnitzii, Roseburia spp., and Blautia spp., as well as Bacteroidetes, is reduced, whereas Proteobacteria, especially Enterobacteriaceae containing adherent-invasive Escherichia coli, and Gammaproteobacteria are markedly increased [26-29]. More importantly, there are specific and reproducible shifts in the functional microbiota related to short-chain fatty acid production.the bacteria Bifidobacterium, Phocaeicola vulgatus, and Christensenellaceae show greatly reduced abundance, hence their production of acetate, propionate, and butyrate is impaired, which in turn weakens the energy supply, barrier function, and anti-inflammatory regulation of the intestinal epithelium [30]. This situation is accompanied by an increase in pathogenic or opportunistic pathogens such as adherent - invasive E.coli, Clostridioides difficile, Campylobacter jejuni, Clostridium spp. such as C. hathewayi and C. bolteae, and Akkermansia muciniphila are all abnormally enriched [31-34], and they directly disrupt the intestinal barrier, induce persistent inflammation, by adhering to and invading epithelial cells, secreting toxins, degrading the mucus layer, and activating the NF - κB inflammatory pathway [35].Fungal communities are clearly and profoundly disrupted, with α - diversity reduced and increased abundance of Candida albicans, Malassezia restricta, and Debaryomyces hansenii, all of which disrupt epithelial integrity either by producing candidalysin, activating the CARD9 pathway, or secreting CCL5 to recruit pro - inflammatory immune cells [36]. In contrast, the abundance of Saccharomyces cerevisiae.the fact that e decreases is well established, and virome changes in Crohn's disease are both debatable and highly characteristic: there is increased abundance of Caudovirales phages in Crohn's disease patients, and imbalanced phage lysis

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can cause reduction of beneficial bacteria, expansion of pathogens, and activation of the TLR4 and NF-κB pathways either by carrying virulence genes or by releasing endotoxins [11-13]. Some eukaryotic viruses, such as murine norovirus and Enterovirus B, are also implicated.The agent can disrupt Paneth cell function or directly infect epithelial cells, thereby aggravating inflammation. More importantly, metabolic functions are globally perturbed, with aberrant sulfur metabolism causing the accumulation of toxic hydrogen sulfide, which in turn inhibits mitochondrial function. Short-chain fatty acid synthesis pathway genes ackA and butA are downregulated, and bile acid metabolism is dysregulated, leading to reduced secondary bile acids [26]. Branched-chain amino acids and their derivatives accumulate, while insufficient UDP-GlcNAc production impairs host N-glycosylation modifications, exposing mannose-enriched glycans that trigger abnormal immune activation.

Glycan metabolism-related mechanisms are elegantly and consistently illustrated in the text: beneficial bacteria (e. g., Blautia spp., bifidobacteria) degrade dietary and mucosal glycans to generate SCFAs and thereby promote IL-22 secretion [37], whereas pathogens (e. g., AIEC, C. jejuni) use glycan-binding proteins or glycan mimicry to enhance colonization and induce autoimmunity [38]. Consequently, the mucosal microbiota is more pathologic.compared with fecal microbiota, the intestinal mucosal microbiota has a higher proportion of pathogenic colonizers and closer physical contact with the epithelium, hence it holds greater potential for use in IBD diagnosis and treatment efficacy assessment. More importantly, the microbial features of IBD have evolved from the classical "compositional imbalance" paradigm to a multi-kingdom (bacteria, fungi, viruses), multi-omics integrated perspective centered on functional dysregulation, with strain specificity, metabolite dynamics, and host-microbiota-glycan interactions all now recognized as central to disease pathogenesis.

3. The role of the microbiota in IBD

3.1. Classification models for prediction and auxiliary diagnosis

Since the potential of the gut microbiota as an IBD biomarker is well established by the characteristic compositional and functional changes observed in IBD patients, and because these changes can be reliably detected by multi-omics technologies, it is logical to consider them for disease prediction and diagnosis.

Experts have reached a clear and well-supported consensus: multi-omics approaches such as metagenomics, metatranscriptomics, metaproteomics, and metabolomics should be integrated to examine the taxonomic composition, gene expression, protein profiles, and metabolite features of the gut microbiota, which in turn will allow the construction of more specific, sensitive diagnostic classification models. Specifically, metagenomics is ideal for identifying IBD-associated microbial abundance changes (e. g., increased Enterobacteriaceae, decreased Bifidobacterium), whereas metabolomics is particularly suited for detecting characteristic metabolite changes such as sulfur metabolites and SCFAs. Thus, combining multi-dimensional data yields markedly better model performance.

A complete " discovery - validation - clinical translation " pipeline should be established, and along the way, the critical importance of standardized validation in multicenter, large-sample cohorts must be clearly emphasized. Moreover, it is essential to focus on microbial functional output (metabolites, enzyme activity) rather than merely using compositional data to maximize clinical utility. Thus, biomarkers derived from abnormal microbial sulfur metabolism function are likely to be more accurate reflections of disease state than those based solely on microbial abundance.

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Although the construction and application of gut microbiota-based prediction and auxiliary diagnosis classification models for IBD have not yet been fully worked out, there is already clear and solid evidence that IBD patients' gut microbiota have distinct compositional and functional features that can serve as reliable biomarkers: reduced F. prausnitzii abundance, AIEC enrichment, decreased SCFAs, and so on. since imbalances in GABA-producing microbiota are clearly associated with IBD disease states (active/remission) and pain severity, future large cohort studies investigating differences between healthy individuals and IBD patients at different disease stages and subtypes are ideally suited for constructing classification models based on microbiota composition, metabolites, and related pathway molecules, thereby offering new technical approaches for early prediction, auxiliary diagnosis, disease subtyping, and progression monitoring of IBD.

Alterations in gut microbiota-glycan interactions can be reliably detected via serum biomarkers and multi-omics data, thus offering strong evidence for IBD prediction and diagnosis. With regard to serum anti-glycan antibody biomarkers, Anti-Saccharomyces cerevisiae Antibodies (ASCA) are a textbook example of a specific biomarker for CD. They recognize mannan glycans on the cell walls of S. cerevisiae and C. albicans, and also cross-react with mannose-enriched glycans present on host mucosa. ASCA seropositivity is observed in 50%–70% of CD patients, which is markedly higher than in UC patients (10%–15%) and healthy controls (0%–6%). More importantly, its agalactosylated subtype (agal-ASCA) can be detected up to 6 years before diagnosis and predicts CD risk and progression by activating NF-κB and CARD9 signaling, thereby inducing inflammasome activation [39].

Other anti - glycan antibodies, namely anti - mannobioside (AMCA) ,anti - laminaribioside (ALCA) ,and anti - chitobioside (ACCA) antibodies, recognize glycan structures on pathogens and are prominently present in the serum of CD patients with complications such as strictures and fistulas [40]. More importantly, their production is directly and mechanistically linked to dysbiosis: pathogen overgrowth exposes the intestinal mucosa to higher levels of microbial glycan antigens, which then drive B cell activation and subsequent antibody production.

The PREDICTS cohort study has done an extremely careful and well-structured analysis of multi-omics data-based classification models using thousands of longitudinal pre-diagnosis samples from the US Department of Defense serum repository, and thus clearly identified abnormal activation of protein glycosylation and microbiota metabolic pathways as early predictors of CD. Specifically, reduced N-glycan branching mediated by MGAT5 and elevated serum agalactosylated IgG levels were associated with reduced Blautia spp. and increased AIEC in the gut microbiota, and their combination allowed prediction of CD risk up to 5 years before diagnosis with high accuracy [41].

Because a fecal mucus glycan marker model can analyze O - and N - glycan profiles from adherent fecal mucus, it is possible to construct a reliable non - invasive diagnostic model for distinguishing healthy subjects from IBD patients, and more importantly, the model also provides information on intestinal barrier function and dysbiosis degree.

In multi-omics-driven diagnostic models, shotgun metagenomic sequencing has clearly shown that IBD patients have reduced abundance of the beneficial genera Prevotella and Roseburia, and increased abundance of the pathogens AIEC and A. muciniphila [26]. Thus, combining the relative abundances of these genera allows the construction of robust diagnostic models for distinguishing IBD from health (AUC>0. 85). Functionally, the expression levels of SCFA synthesis genes (e. g.,but, acss) and bile acid metabolism genes (e. g.,baiCD) provide excellent supplementary diagnostic markers.

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From the available metabolomic data it is clear that IBD patients have markedly reduced fecal butyrate, propionate, elevated primary bile acids (cholic acid, chenodeoxycholic acid), and altered tryptophan metabolites (e. g., indolepyruvic acid, indoleacetic acid) [42]. A combined " SCFA+bile acid " model therefore achieves 89% specificity for UC diagnosis.

Since elevated serum ASCA levels in CD patients correlate with disease activity and can be detected up to 5 years before flare-up [14], it is logical and useful to note that the combination of anti-E. coli outer membrane protein C (anti - OmpC) and anti - flagellin (anti - CBir1) antibodies achieves a CD diagnostic sensitivity of 82%.

Immunity-oriented diagnostic tools have considerable potential, as evidenced by the multi-kingdom antibody profiling approach based on flow cytometry, which uses microbial epitopes from fecal samples (identified by cell size and chitin content) to directly and reliably detect patient antibody responses against gut microbes [43,44]. Importantly, IBD patients exhibit elevated anti-C. albicans hyphae IgA and anti-AIEC IgG antibodies, and this method can therefore differentiate CD from UC with a specificity of 83%.

Antigen-reactive T cell enrichment technology utilizes magnetic beads to enrich $CD154^+$ cells, thereby efficiently isolating blood antigen-specific T cells directed against gut microbes. Importantly, patients with Crohn's disease (CD) have a significant enrichment of cytotoxic Th1 cells specific for Candida albicans and Saccharomyces cerevisiae, whose abundance is positively correlated with the extent of intestinal inflammation and thus can be reliably used as a marker for disease activity [45].

Because IBD patients with persistently low Prevotella abundance or AIEC colonization have a 2.3 - fold increased relapse risk, it is now well established that a fecal Candida/Bifidobacterium ratio>1.5 greatly increases the likelihood of complications such as strictures and fistulas in CD patients.

The available data on treatment response prediction are very clear and well organized: patients with higher baseline abundance of R. inulinivorans and Burkholderiales have a 67% response rate to anti - integrin therapy [46], whereas anti - TNF therapy responders have significantly greater gut abundance of Bifidobacterium and Eubacterium rectale than non - responders [47]. UC patients with moderate pre - FMT C. albicans abundance (10^3–10^4 CFU/g feces) attain 53% remission, in contrast to <20% for those with too high or too low abundance [48].

Since machine learning classification models based on gut microbiota features have already become important tools for IBD prediction and auxiliary diagnosis, it is natural and proper to point out that their fundamental approach is to integrate microbial markers with clinical data for disease classification and prognosis.

From the results of marker screening and model construction, it is clear that the screening dimensions considered are taxa abundance (e. g., P. copri, Enterobacteriaceae, SCFA producers), functional genes (e. g., SCFA synthesis, LPS synthesis genes), and metabolites (e. g., fecal P. vulgatus protease, SCFA concentration) as determined by metagenomic analysis. The data integration step then systematically combines microbial markers with patient clinical features (age, disease subtype, CRP) and lifestyle factors (diet, antibiotic history) to form multi-dimensional datasets.

Core classification models and application scenarios include:

Disease diagnosis models make use of Random Forest, support vector machines, and deep learning algorithms to discriminate IBD patients from healthy controls on the basis of microbial features, hence obtaining area under the curve values between 0. 75 and 0. 85, and as a result they perform very well in identifying ulcerative colitis and Crohn ' s disease, as well as distinguishing

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active from remission phases.the authors used Phocaeicola vulgatus protease abundance, specific Phocaeicola copri strain abundance, and the Enterobacteriaceae ratio to predict progression free survival and inflammation relapse risk [49,50], and nicely demonstrated that ulcerative colitis patients with elevated fecal P. vulgatus protease levels have greater epithelial barrier damage and a much higher risk of disease worsening.Treatment response prediction models use pre-treatment gut microbiota features to predict how patients will respond to immunosuppressants, fecal microbiota transplantation, or probiotics, and a clear, reproducible finding is that patients with higher pre-treatment microbial diversity and higher abundance of short-chain fatty acid producers have higher fecal microbiota transplantation response rates and better sustained inflammation remission.

The predictive power of the models arises directly from the well-established links between microbial features and IBD pathophysiology (P. copri pro - inflammatory strains associate with inflammation, P. vulgatus protease relates to epithelial barrier disruption), hence they have strong clinical interpretability. But it is also important to recognize key limitations of current models: geographic variability (different microbiota compositions across regions), confounding by diet/lifestyle factors, lack of unified detection standards and reference ranges, all of which limit cross - cohort applicability. Furthermore, functional heterogeneity at the strain level (e. g.,P. copri with bidirectional effects) makes marker screening challenging, so precise functional strain identification via single - cell sequencing is essential.

3.2. Microbial modulation strategies in treatment

The present established framework for microbiota-targeted intervention in IBD can quite naturally be summarized as transplantation and engineered application of beneficial microbes from healthy individuals, targeted eradication of pathogens, combined regulatory strategies, and exploitation of synergistic mechanistic pathways.

Supplementing beneficial microbes from healthy sources by means of Fecal Microbiota Transplantation (FMT) or synthetic microbial communities composed of Bifidobacterium, Lactobacillus, A. muciniphila, Blautia spp., F. prausnitzii, etc., is a well-established way to restore gut microbiota diversity and functional balance in IBD patients. Importantly, engineered strains such as Bifidobacterium e.the expression of glutamate decarboxylase (GadB), oxygen-tolerant F. prausnitzii, or engineered probiotics expressing IL - 22 or having enhanced glycan metabolism capacity all lead to production of GABA and SCFAs, repair of the intestinal barrier, modulation of immune responses, and importantly, anti - inflammatory and analgesic effects via activation of the GPR41/FFAR3,GPR43,PPARγ ,and STAT3 signaling pathways [32].

Precise intervention strategies for pathogenic bacteria enriched in IBD patients' guts (e. g., AIEC, Klebsiella pneumoniae, C. difficile, C. albicans) have been well explored and include the use of narrow-spectrum antibiotics (e. g., rifaximin, fidaxomicin) [51], specific phage cocktails, and antimicrobial peptides (e. g., peptide YY expressed by engineered Lactobacillus) [52]. The unifying goal of these approaches is to eradicate pathogens while preserving beneficial microbiota, thereby avoiding the dysbiosis typically induced by broad-spectrum antibiotics [53,54].

The combined use of different intervention strategies has clear, well-documented synergistic effects: synthetic microbial communities paired with high-fiber diets promote SCFA production and favor beneficial colonization, probiotics combined with anti-inflammatory drugs improve the intestinal microenvironment, thereby greatly enhancing microbiota intervention efficacy. More importantly, supplementation with N - acetylglucosamine (GlcNAc) or human milk oligosaccharides (HMOs, such as 2′-fucosyllactose) indirectly promotes beneficial bacterial proliferation and inhibits pathogen colonization by modulating host glycan metabolism.

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These strategies collectively act on four key mechanistic pathways:

The short-chain fatty acid mediated pain modulation pathway activates the GPR41 receptor, thereby inhibiting TRPV1 channel sensitization and reducing visceral hypersensitivity. In contrast, the GABA mediated neural inhibition pathway inhibits sensory neuron excitability via GABAA and GABAB receptors, which directly alleviates abdominal pain. The microbiota immune neural axis pathway also modulates the rel.because pro - inflammatory cytokines such as TNF -α,IL - 1β,and IL - 6 are easy to block, and blocking them effectively inhibits their sensitizing effects on ion channels and receptors TRPA1,Nav1. 8,and PAR2, the 5 - HT mediated pain signaling pathway has a clear and logical mechanism: it restores microbiota stability, suppresses aberrant 5-HT secretion by enterochromaffin cells, and thereby decreases mechanical sensitivity caused by 5-HT3 receptor activation.

The Delphi expert consensus clearly and unambiguously supports (90%– 95%) the combination of microbiota intervention with validation in Human Microbiota - Associated (HMA) animal models and clinical research, and it logically and systematically outlines future directions: optimize donor screening, improve engineered bacterial colonization stability, develop more precise targeted eradication tools (e. g., CRISPR - based bactericidal technology), and investigate the diet - microbiota - neuro - immune multidimensional regulatory network to ultimately achieve individualized, safe, and durable microecological therapy for IBD.

4. Conclusion

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease whose pathogenesis is best understood as a systemic imbalance process centered on "dysbiosis," given its multifactorial nature involving genetics, environment, immunity, and the gut microbial community. Therefore, this review very logically and clearly presents the evidence that the intestinal microbiome of IBD patients shows characteristic disturbances across several kingdoms, including bacteria.the fungi and viruses under consideration exhibit not only a marked reduction in α - diversity and loss of beneficial commensals (e. g.,F. prausnitzii, Blautia spp.,bifidobacteria) ,but also abnormal enrichment of pro - inflammatory pathogens (e. g.,AIEC, C. albicans). More importantly, this structural imbalance has direct and profound consequences for microbial metabolic function: it is associated with greatly reduced production of key metabolites.the abolition of intestinal barrier integrity is due to the combined actions of short-chain fatty acids (SCFAs), γ - aminobutyric acid (GABA), and secondary bile acids, together with the accumulation of pro - inflammatory or toxic substances such as hydrogen sulfide and branched - chain amino acids, which in turn activate aberrant immune responses and thereby contribute to the development of neuropathic symptoms like abdominal pain via the gut - brain axis.

Current literature has made a clear and important shift from "compositional description" to a functional output - oriented, multi - omics integrated perspective, and hence classification models based on metagenomic, metabolomic, and serum anti - glycan antibody profiles have shown tremendous promise for early prediction, subtype differentiation, activity assessment, and treatment response prediction in IBD. More intriguingly, the microbe - host - glycan tripartite interaction network has emerged as a central and novel focus for understanding IBD pathogenesis: pathogens use glycan mimicry or host mucosal glycans to colonize and trigger autoimmunity, while aberrant host glycan modifications (e. g.,N - glycosylation defects) expose immunogenic epitopes, creating a classic vicious cycle.

Targeted gut microbiota intervention strategies are clearly moving from empirical approaches toward precise regulation, and recent advances such as FMT, synthetic microbial communities,

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engineered probiotics, and phage therapy all aim not merely to restore microbial structure but also to repair the barrier, inhibit inflammation, and relieve pain by directly modulating SCFA/GABA/5-HT metabolic pathways. Therefore, the future of microecological therapy for IBD lies in establishing individualized microbiota profiles, delivering functional strains with precision, and designing a multidimensional synergistic intervention system that integrates diet, microbiota, neural, and immune components.

An exhaustive analysis of the dynamic changes in the trans-kingdom microbiome in IBD and its interactions with host physiology and pathology not only clarifies the disease essence but also directly provides a theoretical basis and clear translational pathway for developing non-invasive diagnostic tools, preventive interventions, and safe, effective microecological therapies. More importantly, advances in technology combined with multicenter validation studies have made the new generation of microbiota-centric IBD diagnosis and treatment paradigms extremely promising for reshaping clinical practice.

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