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FUNCTIONAL MICROBIAL PATHWAYS LINKING GUT DYSBIOSIS TO IMMUNE ACTIVATION IN INFLAMMATORY BOWEL DISEASE: A REVIEW

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory condition marked by persistent immune activation and disruption of intestinal homeostasis. Although gut dysbiosis is a consistent feature of IBD, the specific microbial species involved vary widely across patients and cohorts. In contrast, microbial functional pathways show greater consistency and represent the components of the microbiome most directly sensed by the host immune system. This review integrates findings from published experimental, clinical, and multi-omics studies investigating microbial functional pathways and immune activation in IBD. Accumulating evidence indicates that IBD is associated with increased pro-inflammatory microbial functions alongside a reduction in regulatory metabolites, particularly short-chain fatty acids (SCFAs) such as butyrate. This review emphasizes that concentrating on microbial functional pathways elucidates how diverse microbial communities can induce analogous inflammatory responses in IBD. Understanding these conserved microbial functions may help explain the biological basis of persistent inflammation in IBD.

Keywords: *inflammatory bowel disease; gut microbiota; microbial functional pathways; lipopolysaccharide.*

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1. INTRODUCTION

IBD is a chronic inflammatory condition in which intestinal homeostasis fails. This disease is defined by loss of regulatory mechanisms, leading to persistent inflammation, accompanied with immune activation within the intestinal environment. This persistent inflammatory condition indicates defects in regulatory mechanisms rather than dysregulation in balanced immune pathways alone [1,6].

The gut microbiota is crucially responsible for preserving intestinal homeostasis and immune balance in the healthy gut. In IBD, microbial dysbiosis is persistently observed across patients and different disease stages, including active disease and remission. The change in bacterial composition is closely connected with immune activation, barrier dysfunction, and immune signaling. Multi-omics studies explicitly show that microbial alterations in the gut not only cause inflammation but also influence immune responses [3].

Gut dysbiosis is commonly reported in IBD, but the specific microbial species associated with the disease differ widely between patients and cohorts. Nonetheless, the inflammatory processes and disease behavior remain generally identical. This indicates that immune responses in IBD are primarily influenced by microbial functions and the signals they generate, rather than the presence of specific microbial taxa. Because early microbiome studies mostly focused on identifying disease-associated microbial species, most IBD research initially relied on taxonomic descriptions of the gut microbiota [2,3].

Although gut dysbiosis has been extensively studied in relation to inflammatory bowel disease, inconsistencies between taxonomic findings and clinical implications, including disease behavior, relapse, and response to therapy, persists largely due to marked inter-individual variability. As a result, consistent associations between specific microbial taxa and disease-related outcomes have remained difficult to establish. Considering microbial functions from a pathway-based perspective provides an alternative framework by focusing on activities that directly affect intestinal barrier integrity and immune regulation. Identifying conserved functional shifts that sustain immune activation may therefore help explain disease persistence and highlight how microbial functions act as integrative drivers of inflammation in IBD [2,3,10].

2. LIMITATIONS OF TAXONOMIC APPROACHES IN UNDERSTANDING IBD-ASSOCIATED DYSBIOSIS

2.1 Taxonomic variability and functional redundancy

In IBD, microbial activity, function, and metabolism are observed alongside differences in microbial composition. Microbial species composition differs between individuals and varies with disease severity. During flares and remission, patient-to-patient composition changes despite similar clinical conditions, as observed across multiple cohort studies. Dysbiosis features functional signaling changes irrespective of taxonomic inconsistency, which triggers immune activation [3].

Functional redundancy means many microbial species in one IBD patient perform the same biological function, so loss or gain does not depend on specific bacteria. In dysbiotic patients, microbial communities appear, vanish, and reappear dynamically; taxonomy alone misses this erratic behavior [3,8].

2.2 Functional profiling: moving beyond microbial species

Although microbial species composition differs across IBD cohorts, functional profiles remain consistent when disease-associated features are examined. Functional profiling targets metabolic pathways, enzymatic capacities, and metabolite production, focusing on what communities do, not their taxonomy or identity of individual species [3].

Species loss does not necessarily lead to community dysfunction, because microbial functions and metabolism are more conserved than taxonomic composition. Inflammation alters the gut (nutrients, oxygen), stressing microbes; only those with key metabolic capabilities persist. Immune cells respond to microbial products, not specific microbes, and these functional changes correlate more closely with inflammation than the taxonomy of species [3,9].

3. PRO-INFLAMMATORY MICROBIAL FUNCTIONS IN IBD

3.1 Role of LPS in gut inflammation

Lipopolysaccharide (LPS) is not an external pathogen; it is a gut microbiota-derived molecular signal present in normal physiological conditions. In IBD, LPS is continuously produced by endogenous gut microbiota, and it is a structural component of the outer membrane of gram-negative bacteria. LPS-producing taxa are constantly present but in a controlled manner. However, in IBD, increases in LPS-related biosynthesis and inflammatory functions occur even if taxonomical composition changes between IBD patients and endotoxin-associated microbial activity become more prominent. Inflammation that occurs due to LPS exposure in IBD is at a chronic low level over an extended period of time [4,6].

3.2 Dysbiosis Effects

The loss of beneficial microbes, reduction in metabolically active taxa, decreased microbial diversity, and expansion of pro-inflammatory signals are defined as gut dysbiosis in IBD. Dysbiosis reduces protective metabolites and increases inflammatory signals, shifting microbial functional capacity. These functional changes affect intestinal inflammation and barrier integrity [3,8].

3.3 Barrier Layers

Gut microbiota and barrier integrity are closely interconnected. Dysbiosis triggers intestinal barrier dysfunction due to damage occurring across three barrier layers. The first one is the chemical barrier, which consists of a mucous layer, antimicrobial substances, and metabolites produced through microbes. The intestinal mucus layer acts as a protective shield that keeps bacteria away from gut cells. In dysbiosis, mucous thickness reduces while beneficial microbes decrease, increasing separation between microbes and epithelium. This allows microbes and microbial metabolites to easily approach the epithelium wall [6,10].

3.4 Mechanical Shield

The second shield is a mechanical barrier that depends on epithelial cell integrity and tight junction proteins that glue cells together, but in dysbiosis, the loss of SCFA-producing microbes, mainly butyrate, leads to reduced tight junction protein expression, increased harmful microbes, and increased epithelial apoptosis. These effects result in increased gut permeability; therefore, harmful microbes and their products disrupt tight junctions and invade epithelial cells [6,11].

3.5 Immune Dysregulation

The third shield is the immune barrier, which contains immune cells like macrophages in the lamina propria. The chemical and mechanical leaky gut barrier allows continuous translocation of microbial components to cross the epithelium. Immune cells remain activated, thus leading to chronic immune activation. As a result, inflammation constantly increases. Hence, the main aim of the immune system as a protective immune tolerance is replaced by persistent immune activation, eventually leading to immune dysregulation [4,6].

3.6 Vicious Cycle

The dysbiosis creates intestinal permeability, which leads to immune activation, and this incessant interaction leads to inflammatory cytokine production. Inflammation further damages epithelial cells and worsens dysbiosis. This interconnected system emphasizes a self-reinforcing inflammation loop, and together, these processes form a vicious cycle that perpetuates chronic inflammation [4,10].

While pro-inflammatory microbial functions drive immune activation in IBD, the persistence of inflammation also reflects the loss of microbial-derived regulatory metabolites that normally maintain gut homeostasis [4,6,11,12].

These interconnected processes collectively form a self-reinforcing inflammatory loop in IBD (Fig. 1).

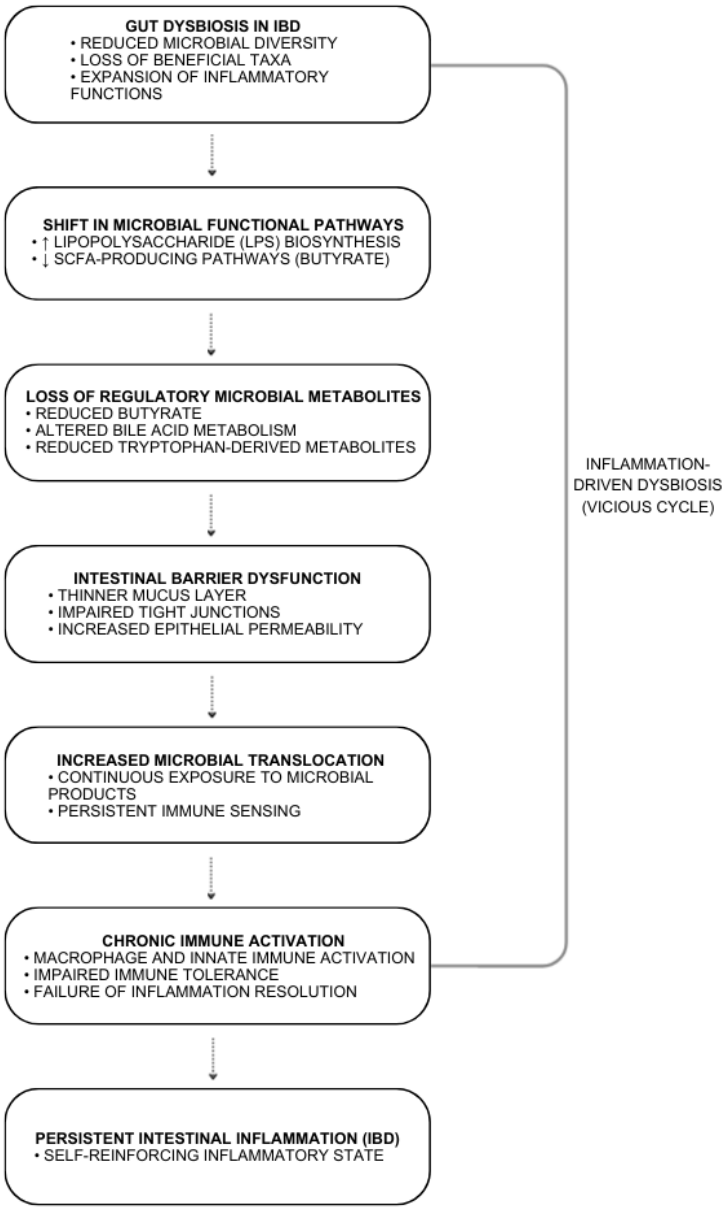

Figure 1. Functional microbial pathways linking gut dysbiosis to persistent immune activation in IBD.

Gut dysbiosis in IBD is characterized by increased pro-inflammatory pathways such as LPS biosynthesis and reduced production of regulatory metabolites, particularly SCFAs such as butyrate. Loss of microbial-derived regulatory metabolites impairs intestinal barrier integrity, increases epithelial permeability, and promotes microbial translocation. Continuous immune sensing of microbial products sustains chronic immune activation, establishing a self-reinforcing inflammatory cycle in IBD.

4. ANTI-INFLAMMATORY MICROBIAL METABOLITES AND GUT HOMEOSTASIS

4.1 Metabolite Dysregulation in IBD

Across many IBD patient cohorts, studies indicate that a disturbed gut microbiome displays a reduction in beneficial metabolites, and this results in inflammation. In IBD, many useful metabolites decrease and fundamentally affect the gut's health at a functional level. Among these, SCFAs are mainly vital for maintaining good gut health [11,12].

4.2 SCFAs Types and Functions

Furthermore, in IBD, fiber-fermenting pathways collapse and SCFAs-producing pathways weaken. SCFAs are divided into three types: acetate, propionate, and butyrate. Acetate is produced by gut bacteria, and it enters into systemic circulation, while propionate is absorbed and metabolized in the liver, but butyrate is one of the essential dominant SCFAs because it is consumed by colon epithelial cells (colonocytes). Butyrate is used as an energy source for colonocytes and supports epithelial health and is considered an anti-inflammatory signal in the gut. The reason is that it reduces the pro-inflammatory activity of LPS and intestinal macrophages and also enhances the activity of the generation and function of Treg cells; this maintains immune tolerance of gut microbiota [11,12].

4.3 Consequences of SCFA Reduction

If such fundamental SCFAs as butyrate are reduced, the main energy source for colon epithelial cells is lost, weakening the epithelial barrier, disrupting tight junctions, and impairing immune tolerance, causing the barrier to become leaky. As a result, chronic intestinal inflammation conditions occur relevant to IBD [11,12].

4.4 Other Decreased Metabolites

Along with SCFAs, other beneficial metabolites also decrease; one major group includes secondary bile acids (SBAs) like deoxycholic acid (DCA) and lithocholic acid (LCA). The function of SBAs in the gut is to control inflammation, maintain epithelial stability, and activate receptors to prevent bacterial overgrowth. Another group includes tryptophan-derived microbial metabolites such as indole-3-acetic acid and indole-3-propionic acid. These metabolites are essential because they bind to host receptors that protect epithelial cells and regulate immune balance; therefore, loss of such metabolites disturbs protective signaling. The third group is amino acids and derivatives; those are arginine and citrulline. In active IBD, arginine levels in gut tissue are reduced, which helps epithelial repair and immune regulation, while citrulline is also reduced and is linked with disease activity [12].

4.5 Increased Metabolites in IBD

There are some metabolites that increase in IBD, but all increased metabolites are not uniformly inflammatory. Some of the metabolites that go up are primary bile acids, kynurenine pathway metabolites, butyric acid, cadaverine (polyamines), and taurine. However, their effects depend on the situation [12].

4.6 Butyrate's Protective Roles

Beyond being an energy source, butyrate acts as a signaling molecule that connects microbial metabolism with host immune regulation, linking microbial functional output directly to epithelial and immune homeostasis [5,11,12].

Butyrate presence indicates that gut lining cells are healthier and the barrier is stronger. Strengthening barriers lowers microbial translocation, which means that immune cells are less likely to come into contact with PAMPs and activate the immune system inappropriately. SCFAs promote immune tolerance, support regulatory immune responses, and provide counterbalance to pro-inflammatory signaling. They promote anti-inflammatory immune phenotype and maintain immune homeostasis by limiting excessive activation. In addition, butyrate promotes the generation of Treg cells, which help to limit inflammation [5].

Thus, intestinal inflammation in IBD cannot be explained by inflammatory signals alone but by the combined loss of regulatory microbial functions [5,6,12].

5. FUNCTIONAL IMBALANCE DRIVING PERSISTENT INFLAMMATION

In IBD, intestinal inflammation is recurring; this persistent inflammation is caused by continuous production of LPS through gut microbiota. This gut microbiota-derived LPS is chronic and present in low dosage, but LPS production is repeatedly generated over time, and due to the ongoing generation of LPS, the LPS-related signaling pathway remains active [4,7].

In a healthy gut, inflammation pathways are counterbalanced with regulatory mechanisms, but in IBD dysbiosis, this counter-regulation fails, and this creates pro-inflammatory signals that remain active over time. In normal conditions, gut microbiota produces metabolites such as SCFAs, particularly butyrate, which suppress unnecessary immune signaling. But in IBD, fewer beneficial metabolites are generated, and therefore the anti-inflammatory metabolites required for inflammation resolution are reduced [11,10,13].

6. LONG-TERM IMMUNE EFFECTS OF MICROBIAL IMBALANCE

Loss of microbial regulatory metabolites does not initiate immune activation but prevents responses from returning to baseline, resulting in persistently active immune behavior over time [5].

The immune system in a healthy gut has continuous contact with gut-derived microbial metabolites, so the immune system is not exposed to gut microbiota only during sepsis. In IBD, this interaction is long-term and persistent, so immune responses are not just short-term reactions [13,8].

Due to continuous microbiota signal changes, they alter the host immune system response. These microbial products not only act on single immune cells, but they also influence many parts of the immune system, including both innate and adaptive immunity [8].

In IBD, gut immune health becomes imbalanced when there is a loss of regulatory control, allowing inflammatory activity to keep going rather than resolve. These inflammatory conditions stay active for a long time even though the immune pathways themselves are normal [10].

The immune system response to gut microbial products is not limited to recognizing microbes alone; these products directly activate immune cells. Changes in microbial metabolites alter immune behavior, and over time the immune system gradually shifts toward inflammation or impaired regulatory responses [5, 14].

7. DISCUSSION AND FUTURE DIRECTIONS

These long-term, function-driven changes in immune behavior show that future microbiome research should focus less on which microbes are present and more on what metabolic pathways they use to drive or resolve inflammation in IBD [9,15,16].

Microbial functions show more similarity across individual and cohort studies than microbial species composition. These observations suggest that

conserved microbial functions may represent key biological drivers of immune dysregulation in IBD. Different microbial species can perform the same metabolic pathway, so their overall functional activity remains stable even if there are differences in taxonomy [15].

Instead of focusing on marker-based taxonomic composition, shotgun metagenomics studies microbial communities based on their genes, pathways, and functions carried out by the microbiome. This is essential because different species carry the same biological pathways; hence, functioning patterns can remain constant even when microbial species differ. The limitations of taxonomy representation for robust inference are highlighted by the fact that model choice has less impact on predictive performance in microbiome studies than the definition of microbial features [9,16].

8. CONCLUSION

Chronic immune activation in IBD is closely linked to changes in the gut microbiome. Although gut dysbiosis is continuously seen in IBD, differences in microbial species alone cannot explain why disease behavior remains similar across patients. Instead, changes in microbial functions provide a clearer explanation for sustained inflammation. Increased pro-inflammatory microbial signals along with reduced regulatory metabolites such as butyrate contribute to persistent immune activation. So, concentrating on microbial metabolic pathways rather than microbial taxa helps better to explain how different microbial communities can lead to similar inflammatory responses in IBD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

Not applicable, as this study is a review article.

ETHICAL STATEMENT

Not applicable, as the study is based on previously published literature.

AUTHOR CONTRIBUTIONS

Mihika Kenavdekar: Conceptualization, literature review, analysis, manuscript drafting, and editing. Elamathi Natarajan: Supervision, critical review, validation, and final approval of the manuscript.

Kindly proceed with the publication process. Please let us know if any further information is required.

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