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Review article

NOVEL PERSPECTIVES ON THE CONTRIBUTORS TO INFLAMMATORY BOWEL DISEASE DEVELOPMENT

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Abstract: *Irritable bowel disease (IBD), commonly referred to as Crohn's disease (CD) and ulcerative colitis (UC), is a persistent and recurring inflammation of the gastrointestinal tract (GIT). Despite the increasing prevalence of IBD globally, its precise aetiology remains unidentified, and no definitive treatment or cure has been established. The intricate interplay among environmental influences, genetics, and the host's immune system is believed to be the primary aetiology of IBD. Recent advancements in next-generation sequencing technologies indicate that IBD is linked to alterations in the function and composition of the gut microbiota, called dysbiosis. Experimental and clinical evidence suggests that dysbiosis plays a crucial part in the onset of IBD. Despite extensive investigations aimed at identifying new pathogenic factors related to IBD, encompassing environmental, genetic, microbial, and immune response elements, a comprehensive knowledge of IBD aetiology still needs to be identified as the treatment for IBD patients requires improved outcomes. A more profound comprehension of the disease's aetiology may yield distinctive insights applicable to developing therapeutic strategies for IBD. Recent research has markedly enhanced our understanding of the pathobiology of IBD, resulting in substantial progress in its diagnosis and treatment. We have emphasized current advancements and discoveries about emerging elements that contribute to disease pathogenesis, such as gut microbiota, which significantly influence the aetiology of IBD and may serve as prospective targets for innovative therapeutics in IBD patients.*

Keywords: Inflammatory bowel disease; gut microbiome; Crohn's disease: ulcerative colitis.

Background

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC) is a persistent, recurrent provocative disorder of the intestines (1, 2). Chronic gastrointestinal inflammation is a characteristic feature of inflammatory bowel diseases (IBDs). Patients with IBD suffer from diarrhoea, abdominal pain, hematochezia, weight reduction, and infiltration of neutrophils and macrophages, which induce inflammation and ulceration by the secretion of cytokines, proteolytic enzymes, and free radicals (3). The group of chronic bowel diseases encompasses CD and UC, both of which are systemic conditions characterized by common extraintestinal manifestations, such as arthralgia/arthritis and anaemia (4). A dysbiotic gut microbiota, host genetic predispositions, environmental stressors, and immune-mediated chronic inflammation of the gastrointestinal tract (GIT) intricately interact to induce IBD. The molecular pathways linking the gut microbiota and the intestinal mucosa still need to be examined despite efforts using metagenomic approaches to delineate the dysbiosis associated with IBD (5). IBD is increasingly prevalent globally. However, its precise aetiology remains unidentified. CD and UC therapy are centred on proinflammatory pathways.

Evidence substantiating the contribution of lymphoid organs in the pathogenesis of IBD has expanded significantly in recent decades (6). Bile acids have emerged as a notable category of metabolites linked to the altered microbiota in patients with IBD (5, 7). The predominant idea of the aetiology of IBD posits that anomalous immune responses and persistent bowel inflammation result from a multifaceted interaction among genetic predispositions, environmental influences, and the host immune system (8). IBD is a widespread condition with significant incidence in Western countries; nevertheless, it has swiftly escalated in newly commercialized nations in the Middle East, Africa, Asia and South America (9). Chronic inflammation and a dysregulated immune inflammatory response are common characteristics of both subtypes; hence, the immune system has been the focus of extensive study on the pathophysiology of IBD. Despite the intricate pathophysiology of IBD), many studies indicate that elevated interleukin (IL)-17 production has a role in the progression of IBD (10). The gut-brain axis is a meticulously organized communication system significantly influencing higher cognitive functions, emotions, and neurological and behavioural disorders. It also preserves homeostasis (11). These pathways may facilitate the commencement of IBD, with some data indicating their influence on the incidence, recurrence, and clinical progression (12).

According to Nikolakis et al. (6), lymphatic system mechanisms are usually connected with immune responses and possibly contribute to the pathogenesis of inflammatory

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illnesses. Due to the ineffectiveness or lack of efficacy of the medications, individuals with IBD continue to have a lower quality of life, even if there are more therapeutic alternatives available for treating the illness. There may be new ways to approach treating IBD if we investigate innovative options focusing on the aetiology of the disease. For more comprehension and progress towards better treatment options and adapted medicine, our current knowledge of IBD pathophysiology must be upgraded. Alterations in gut microbiota are the nascent contributors to disease aetiology, and this review emphasized the latest research on the microbiome. This could be an essential target for the development of new therapeutics for IBD and a key player in the disease's aetiology.

The microbiome of the bowel in the development of IBD

The bacteria in the intestine are a varied and abundant group known as the gut microbiota. The gut microbiota carries out physiological functions linked to host defence, immunity, and digestion. Researchers have recently used next-generation sequencing technology to coin the term "dysbiosis," which describes a shift in the composition and function of the gut microbiota in IBD. The pathogenesis of IBD may be significantly influenced by dysbiosis, according to Nishida et al. (8). According to Liu et al. (13), genome-wide association studies have identified over 200 genes linked to IBD, some of which are known to be involved in or implicated in modifying host responses to gut microbiota. According to several theories, the gut microbiota may have a role in the pathophysiology of IBD (14, 15). There are 100 trillion microorganisms in the human gut, including viruses, bacteria, fungi, and protozoa. Comprise the microbial flora, or microbiota, as a whole (16). Healthy individuals' gut microbiota is known to benefit the host in several ways, including immunity, nutrition, metabolism, and pathogen defence (8). As people and the gut microbiota co-evolve, symbiotic interactions are necessary to maintain human health. A negative shift in the gut microbiota's makeup and function that impacts the interaction between bacteria and the host immune system is known as dysbiosis. Growing evidence links gut microbial dysbiosis to human conditions such as irritable bowel syndrome, allergies, asthma, metabolic syndrome, and cardiovascular disease.

Research has demonstrated that the microbiome of individuals with inflammatory bowel disease (IBD) is distinct from that of healthy individuals (17, 18). Nutrition, an environmental component, and intestinal microbiota may influence the aetiology of IBD, as indicated by the increasing prevalence of sick individuals. This review examines the latest studies on the function of gut microbiota in the development of inflammatory bowel disease (IBD). It explores potential therapeutic strategies aimed at targeting the gut microbiota.

Functions of gut microbiota

The physiological functions of gut microbiota in host biology can be classified into three primary categories: energy production, immune system modulation, and pathogen protection (19).

Energy Production:

The host derives nutrients and energy from the gut microbiota. Human commensal bacteria can synthesize and provide vitamin K and water-soluble B vitamins, including Bifidobacterium (20). Short-chain fatty acids (SCFAs; C2-C6) are also synthesised by gut bacteria via the fermentation of resistant starch or indigestible carbohydrates (dietary fibre). The phylum Firmicutes and Bacteroidetes cooperate with species proficient in oligosaccharide fermentation, such as Bifidobacteria, to produce short-chain fatty acids from indigestible carbohydrates. Acetate, propionate, and butyrate are the colon's primary short-chain fatty acid anions (21). The principal energy source for colonic epithelial cells is butyrate. Acetate and propionate are systemically available due to butyrate, predominantly absorbed by the intestinal epithelium (22). In IBD, there is a substantial reduction in SCFA levels, which may be a critical factor jeopardizing intestinal and immunological homeostasis.

Immune system regulation

The gut microbiota significantly impacts the development of the host's immune system (23, 24). The configuration and function of the gut microbiota are, in turn, affected by the host immune system (25). Germ-free mice, devoid of gut microbiota, exhibit inadequate immunological development, evidenced by underdeveloped lymphoid tissues, a reduced number of intestinal lymphocytes, and diminished levels of immunoglobulin A and antimicrobial peptides (26, 27). Reintroducing gut microbiota into germ-free mice effectively rectifies immune system deficiencies and anomalies (28). Candidatus Arthromitis, a species of segmented filamentous bacteria, is classified as one of these specific bacteria (SFB). SFB colonization alone facilitates the development of the mucosal immune system (29). The maturation of the host immune system in germ-free mice colonized with human microbiota is contingent upon host-specific microbiota (30). Furthermore, the gut microbiota regulates the T helper (Th) cell profile and T-cell repertoires (31). Regulatory T cells, or Tregs, are CD4+ T cells that modulate or suppress the activity of other immune system cells (32, 33). Mice reared on antibiotics or in a sterile environment exhibit significantly reduced Th17 cell populations in the stomach mucosa. This discovery indicates that gut microbiota plays a role in the maturation of Th17 cells. A recent study indicates intestinal epithelial cells capable of adhering to pathogens such as Citrobacter rodentium and Escherichia coli (EHEC) O157 promote the generation of Th17 cells (34).

Protection from pathogens

The host's defence against pathogens is partially reliant on the gut microbiota. Animals in germ-free conditions are susceptible to infections from intestinal pathogens. This vulnerability may come from an abnormality in the mucosal immune system. Deficiencies in the physical and nutritional environments of the gastrointestinal tract, which are competitively occupied by commensal microbiota and hinder pathogen colonization, constitute an additional defence mechanism against infections (35). "Colonisation resistance" denotes the mechanism by which commensal microorganisms competitively inhibit the invasion of pathogens (36). The gut microbiota enhances colonisation resistance to intestinal illnesses via direct and indirect mechanisms. Certain commensal bacteria actively prevent gut infections by competing for resources or facilitating the production of inhibitory substances. The prolific colonic anaerobe Bacteroides (B.) thetaiotaomicron metabolizes the carbohydrates required by C. rodentium, facilitating the competitive exclusion of pathogens from the intestinal lumen (37). A bacteriocin produced by B. thuringiensis preferentially targets Bacilli and Clostridia, including spore-forming species like Clostridium difficile (38). Commensal microbiota and microbial compounds indirectly protect against illnesses by eliciting immune responses. Lipopolysaccharides and flagellin produced by the gut microbiota enhance the expression of antimicrobial peptides and RegIII in epithelial cells by activating Toll-like receptor 4+ stromal cells and TLR5+ CD103+ dendritic cells (39, 40). SFB stimulates the generation of antimicrobial peptides, the secretion of IgA from B cells, and the growth of Th17 cells in the intestinal mucosa (41).

Alteration of gut microbiota in the pathogenesis of IBD

Compared to healthy individuals, patients with inflammatory bowel disease have reduced levels of bacteria with anti-inflammatory characteristics and elevated levels associated with inflammation (42, 43). The variety of gut microbiota is diminishing, with a notable reduction in Firmicutes being the most consistent change (15). Proteobacteria and Bacteroidetes have been noted to exhibit increased abundance, whereas reductions have also been documented (44). Reports indicate that the Clostridium cluster IV member F. Prausnitzii mitigates inflammation through butyrate production. Patients with CD exhibit reduced amounts of Clostridium lavalense, Ruminococcus torques, Blautia faecis, Roseburia inulinivorans, and F. Prausnitzii when contrasted with healthy people (18). F. Prausitzii has been linked to an increased incidence of relapse of ileal Crohn's disease post-surgery. In UC patients experiencing remission, F. prausnitzii colonization was impaired and sustained clinical remission was associated with the resurgence of F. prausnitzii following return (45). In healthy individuals with a heightened genetic predisposition for IBD, the gut microbiota notably reduced Roseburia spp. Nonetheless, Crohn's disease patients exhibited a relative augmentation of Proteobacteria, particularly E. coli, compared to faecal samples from mucosa-associated microbiota (46). Adhesion-invasive E. coli (AIEC), first identified in adult Crohn's disease patients, is a strain of E. coli exhibiting proinflammatory features associated with Crohn's disease (47). Reports indicate that the prevalence of AIEC increased to approximately 38% in patients with active CD, in contrast to 6% in healthy individuals (48). Intestinal inflammation is induced by an increase in pathogenic bacteria that adhere to the intestinal epithelium, altering the diversity and composition of the gut microbiota and eliciting inflammatory responses by regulating the expression of inflammatory genes (49). Fluorescence in situ hybridization studies indicate that patients with inflammatory bowel disease exhibit more mucosa-associated bacteria (50). This may be attributable to elevated levels of mucolytic bacteria in patients with inflammatory bowel disease, such as Ruminococcus gnavus and Ruminococcus torques (51). The pathogenesis of inflammatory bowel disease (IBD) is associated with the production of metabolites influenced by the disruption of gut microbiota. It has been noted that butyrate-producing bacteria, including F. prausnitzii and Clostridium clusters IV, XIVa, and XVIII, contribute to a reduction in SCFA levels in individuals with IBD (18). The diminished production of SCFAs adversely affects the proliferation of epithelial cells and the differentiation and expansion of Treg cells, both essential for maintaining intestinal homeostasis (52). IBD patients exhibit an increased presence of sulfate-reducing bacteria, particularly Desulfovibrio, resulting in hydrogen-sulfate production that damages intestinal epithelial cells and induces mucosal inflammation (53-55). These findings conclusively indicate a connection between changed gut microbiota and inflammatory bowel disease (IBD) pathogenesis.

Dysbiosis as a Potential Therapeutic Target in IBD

One new target for treating inflammatory bowel disease is dysbiosis manipulation. Some possible approaches are as follows:

Modulation of Intestinal Microbiota by Probiotics

Probiotics, or live bacteria, benefit the host by influencing the gut microbiota (56). The usefulness of several probiotics in controlling the microbiota and treating intestinal dysbiosis in IBD has been investigated. Clinical studies have demonstrated the influence of specific bacteria on gastrointestinal inflammation, such as Streptococcus, Bifidobacterium, and Lactobacillus. A large clinical experiment looked at how well the nonpathogenic strain of E. coli Nissle 1917 maintained UC remission. In UC patients in remission, salicylate and E. coli Nissle 1917 were equally safe and efficacious (57). Studies employing VSL#3, a probiotic that contains four Lactobacilli (L. et al. acidophilus, L. delbrueckii subsp., Bulgaricus), three Bifidobacteria (B. et al. breve, and B. infantis), and one Streptococcus (Streptococcussalivarius subsp. thermophiles), have provided the majority of the data currently available on IBD patients. In a clinical trial, VSL#3 effectively caused remission in patients with mild-

to-moderately active ulcerative colitis (58, 59). According to a small cohort trial, VSL#3 also benefited and maintained remission (59). According to a recent meta-analysis, regular treatment + VSL#3 produced better remission induction and response results than standard treatment alone (58). A randomized trial investigated the efficacy of Lactobacillus GG in dormant UC. Lactobacillus GG fared better in safety and efficacy than conventional mesalazine therapy to maintain UC patients in remission (60). According to Cochrane research, probiotics did not help UC go into remission more than a placebo or conventional therapy. The role of probiotics in UC has been the subject of numerous systematic reviews and meta-analyses, but no definitive findings have been found (61). On the other hand, there is minimal evidence to support the efficacy of probiotics in CD patients. A randomized, double-anonymized, placebo-controlled study looked at the efficacy of L. johnsonii in CD patients who had intestinal resection surgery; nevertheless, L. johnsonii did not significantly affect the suppression of recurrence rate (62). When evaluated in dormant UC, other probiotics, including Saccharomyces boulardi and E. coli Nissle 1917 had no discernible effect on Lactobacillus GG's effectiveness (63, 64). Lactobacillus GG fared better in safety and efficacy than conventional mesalazine therapy to maintain UC patients in remission (60). A Cochrane analysis found that probiotics did not improve CD induction or maintenance over a placebo. Well-designed randomized clinical trials (RCTs) should be conducted to ascertain whether probiotics are beneficial in treating CD (65).

Modulation of Intestinal Microbiota by Fecal Microbiota Transplantation

Faecal microbiota transplantation (FMT) attempts to repair the intestinal microbiota in unwell individuals by transferring the intestinal microbiota of healthy donors. FMT has been therapeutically adapted to treat recurrent Clostridium difficile infection (CDI), and it has been demonstrated to be effective in treating CDI, with a high cure rate of >90% in clinical investigations (66). Because FMT effectively treats CDI, it may also help treat other dysbiosis-related illnesses. Recently, FMT has drawn interest as a novel treatment strategy for IBD. In 2017, Paramsothy et al. conducted a meta-analysis of 11 studies on FMT for CD, including 83 CD patients (seven prospective uncontrolled cohort studies and four case reports). A 50.5% clinical remission rate was seen (42/83). According to the authors, there were indications of publication bias in this meta-analysis. Future RCTs should be conducted to evaluate FMT's efficacy in CD patients. Compared to CDI, FMT is less effective in IBD. CDI is the outcome of an overgrowth of Clostridium difficil after antibiotic use disturbs the gut flora. Accordingly, FMT treatment demonstrated respectable cure rates for recurrent CDI, irrespective of the donor, recipient, or delivery method (66). However, several factors, including microbial, genetic, immunologic, and environmental, influence the pathogenesis of IBD. The host and gut microbiota interact more intricately in IBD than in CDI. Furthermore, each clinical trial has a different FMT approach, which results in different outcomes. This includes standards for donor selection, patient pre-treatment, and administration route. The biggest issue, though, is that dysbiosis is connected to the pathophysiology of IBD, albeit it is not clear if this is a result of the inflammatory process or its cause. Each of these factors contributes to the lower clinical effectiveness of FMT for IBD compared to FMT for CDI.

Concluding Remarks

In summary, intestinal homeostasis and the development and activation of the host immune system depend on the gut microbiota. The immune system and the gut bacteria influence one another in a feedback loop. The gut bacteria also influence the host's metabolic efficiency and disease resistance. These novel understandings of the gut microbiota demonstrate a strong correlation between the development of inflammatory bowel disease and dysbiosis, a detrimental alteration of the gut microbiota. Additionally, they have contributed to developing innovative therapies for inflammatory bowel disease (IBD) that specifically target dysbiosis. For instance, FMT is receiving much interest as a possible novel treatment for inflammatory bowel disease. Determining whether or not FMT is beneficial for inflammatory bowel disease (IBD), one of the most prevalent gastrointestinal illnesses, requires considering the gut microbiota and gut virome. Future findings in gut microbiota research will undoubtedly lead to new treatment strategies for inflammatory bowel disease (IBD). Recent developments in human organoid technology and cutting-edge bioinformatics techniques have created an intriguing opportunity to learn more about the role of gut bacteria in IBD. This might open the door to innovative therapeutic strategies, such as changing gut flora.

Declarations

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All data generated or analysed during the study are included in the manuscript.

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