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Effects of The Intestinal Microbiota on Host Immunity

Review

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Abstract – The human gut is a complex microbiota that harbors thousands of microbial species that play an important role in supporting the well-being of its hosts. The composition of the gut microbiota varies with age, from childhood to adulthood, and is influenced by dietary habits, environment and genetics. Recent advances in methods that do not rely on culture and nucleic acid methods have improved our understanding of the diversity of the gut microbiota. Microbial species in the gut release short-chain fatty acids (SCFAs), which have anti-inflammatory properties. The gut microbiota also plays an important role in modulating the immune system, promoting immunity and maintaining homeostasis. The impact of gut microbiota on host health is well-known, since gut dysbiosis has been linked to various diseases, including metabolic disorders, autoimmune diseases, allergies, and inflammatory heart disease. Gut microbiota communicate bidirectionally with the respiratory system, creating a gut-lung axis, which is associated with various respiratory diseases. Treatments targeting the gut microbiota, such as probiotics, prebiotics, nutritional supplements, and fecal microbiota transplantation (FMT), aim to restore the microbial balance and promote the growth of beneficial bacteria in the gut. Nevertheless, it is important to gain knowledge about the complex relationship between the gut microbiota and the host in order to develop personalized therapies and microbiota-based therapies for various diseases. This review summarizes studies on the role of the microbiota on host immunity.

Keywords – Microbiota, Immune System, IBD, Host-Derived Mirnas, Therapeutics, Fecal Microbiota Transplantation.

I. Introduction

Billions of microbial species colonize the human body, their genes and their secreted metabolites, collectively known as the human microbiome [1]. The gut microbes represent more than 95% of the entire human microbiota, representing the most abundant microbial organisms in the body [2,3]. This dynamic microbial community provides many of the metabolic and molecular signaling functions necessary for healthy tolerance. One of the main functions of gut microbes is the maturation of the immune system of the gut and the maintenance of local immune homeostasis. While a healthy microbial community is essential for gut health, disruption of this balance, called dysbiosis, has been linked to a variety of diseases such as IBD [4], a disease characterized by inflammation of the intestinal mucosa, leading to symptoms such as abdominal pain, severe diarrhea, fatigue, weight gain, and malnutrition. IBD is a focus of microbiome research, although its heterogeneity makes it difficult to understand how microbiome dysbiosis affects disease etiology and progression [5]. Many studies have revealed that the intestinal tract in IBD does not contain a variety of bacteria such as Faecalibacterium prausnitzi, Akkermansia muciniphila, Clostridium buytricum, Roseburia, Bifidobacterium and Lactobacillus [6,7,8]. Other research has provided a systematic look at how these microbes contribute to gut health. For example, these microbes contribute to the production of anti-inflammatory metabolites such as butyrate. Another step is to modulate the host's

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immune response through the induction of Treg cells and anti-inflammatory cytokines. In addition, gut microbes are important for maintaining the integrity of the intestinal mucosal barrier, preventing the absorption of toxins and pro-inflammatory metabolites [8,9].

Given the critical role of gut microbes in human health and, in particular, in local inflammatory conditions of the gut, there is a significant increase in interest in modifying the gut microbiome using either live or synthetic or through dietary modification. . As the interactions, functions, and phenotypes of the gut microbiome have emerged, it has become a target for new treatments and research that leads to precision medicine, especially when combined with other multiomics data [10]. Emerging research focuses on modifying the microbiome to manage IBD by altering the host's immune response. Another exciting development is the development of targeted approaches to restore dysbiosis through the correct adjustment of the gut microbial community. In this review, we discuss and summarize recent knowledge about the role of the gut microbiome and progress in the treatment of IBD. We review the progress and development of microbiome-based therapies and biomarkers and discuss the gaps and challenges in this field.

1.The early interactions between gut microbes and the immune system

We better understand how the immune system accepts or ignores billions of microbial cells, which outnumber human cells [11,12]. It is logical that the immune system began to accept commensal microbes to maintain their incredible function, which leads to dependence. Microbes in the gut are recognized by the immune system through dendritic cells (DCs) and Toll-like receptors (TLRs) [13]. The binding of microbes to the intestinal lumen, or adhesion to the outer mucosal layer and TLRs expressed on intestinal epithelial cells, induce Dendritic cells (DCs) to enter intestinal epithelial cells (IECs) through tight junctions with the sampled microbes [13,14]. After that, DCs deliver antigens from microbes that represent them to host immune cells, leading to the induction of immunity [14].

Gut microbes are important for the development and maturation of the mucosal barrier and maintain intestinal homeostasis [13]. A key component of the immune system is the gut-associated lymphoid tissue (GALT), which is responsible for detecting and response to antigens in the gastrointestinal tract, distinguishing. between harmful and acceptable antigens or self-antigens [15]. In addition to their role in regulating the mucosal immune response and homeostasis in inflammatory diseases such as IBD, GALTs have important tissue connections including (1) Peyer's patches, located in the ileum, which are clusters of lymphoid follicles rich in B and T lymphocytes, (2) lamina propria, a layer of connective tissue beneath the epithelium containing macrophages and dendritic cells; (3) intraepithelial lymphocytes, T cells within the intestinal epithelium that help maintain immunity and control inflammation (4) mesenteric lymph nodes and surrounding connective tissue, which monitor lymphatic drainage and regulate the immune response [16]. Gut microbial colonization soon after birth is essential for proper development and maturation of the GALT. They stimulate the growth and differentiation of immune cells in the GALT, including T cells, B cells, and antigen-presenting cells, by exposing them to microbial antigens. This exposure contributes to the protection and maturation of the immune response, making the defence more effective against pathogens and maintaining tolerance to harmless antigens from commensal microbes. Gut microbes modulate GALT through epigenetic markers to promote their tolerance.

The gut microbiome contributes to the maturation of the immune system of the gut. Microbial antigens are recognized by dendritic cells, which migrate to the mesenteric lymph nodes and transform T cells into specialized subtypes such as Th1, Th17, and regulatory T cells (Treg cells). These T cells are the source of various cytokines such as anti-inflammatory IL-10, which helps prevent inflammation, and pro-inflammatory IL-17, which promotes rapid defence against pathogens. In addition, viral antigens, such as lipopolysaccharides, activate ILC3 cells, causing the release of GM-CSF and IL-22, which recruit neutrophils for additional protection against viruses. In addition, the gut microbiome encourages B cells to become IgA-secreting cells. Secretory IgA is another defence mechanism. Many species in the microbiome are known to produce antimicrobial peptides (AMPs) that inhibit harmful bacteria in the gut. Beneficial metabolites also contribute to intestinal homeostasis and improve intestinal barrier function by increasing the expression of tight junction proteins, while side-chain fatty acids (SCFAs) bind to G protein-coupled receptors (GPRs), thereby promoting anti-inflammatory activity. SCFAs directly induce Treg cells to produce IL-10 and inhibit NF-κB signaling and histone deacetylase (HDAC) activity, thereby reducing the expression of pro-inflammatory genes. In addition, the

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SCFA-producing bacteria Akkermansia mucinipila promotes the production of mucin, which is the main substance in the mucus layer.

2. Gut microbes are responsible for modulating the local immune response

Maintaining cytokine balance, primarily by maintaining Treg and Th1/Th17 cells in a stable state, is important for the regulation of mucosal homeostasis [17]. Some bacteria such as F. prauznitsii induce Treg differentiation, leading to increased production of the anti-inflammatory cytokine, IL-10 [14]. Other microbes stimulate the production of IgA, which protects against invading pathogens while stimulating Treg cell proliferation and promoting IL-10 production to prevent inflammation [18].Small intestine bacteria interact with immune cells through their secreted metabolites such as short-chain fatty acids (SCFAs), which modulate inflammation. For example, butyrate is an SCFA produced by beneficial bacteria such as Bacteroides thetaiotaomicron and F. prausnitsii [19], which exerts anti-inflammatory activity through several mechanisms, including the induction of Treg cell differentiation and the production of anti-inflammatory cytokines such as IL-10 and IL-18 [20,21]. A decrease in short-chain fatty acids is common in IBD [22]. Butyrate works by binding to G protein-coupled receptors (GPCRs) and as a histone deacetylase (HDAC) inhibitor [20]. Other bacterial factors involved in the immune response are bile acid metabolites that can regulate the expression of genes related to T helper cell differentiation . Some microbes convert lithocholic acid to isolithocholic acid (isoLCA) and 3-oxolithocholic acid (3-oxoLCA) through the enzymatic activity of the enzyme 3a-hydroxysteroid dehydrogenase . These two bile acid metabolites inhibit the orphan nuclear receptor γt associated with the retinoic acid receptor, causing the destruction of Th17 differentiation and a corresponding decrease in the pro-inflammatory interleukin, IL-17 . Interestingly, it was found that the gene that encodes the enzyme 3a-hydroxysteroid dehydrogenase in IBD patients is overexpressed [23]. Tryptophan metabolites are microbial products that interact with and activate the aryl hydrocarbon receptor (AhR), inducing CD4+ T cells and innate lymphoid cells in the gut [24]. IBD patients exhibit reduced production of microbiome-derived AhR ligands due to altered microbiome composition.

3. The small intestine supports homeostasis

One of the strategies developed by intestinal microbes to modify the local mucosal barrier and maintain homeostasis is to maintain the integrity of the mucosal barrier and its function [13]. Data from germ-free (GF) mice show that inoculation with B. thetaiotaomicron alters the expression of several genes, including those involved in mucosal immunity, postnatal intestinal maturation, and xenobiotic degradation. [25]. Bacteria stimulate mucin production by intestinal goblet cells. Mucin forms a protective layer on intestinal cells, acting as a barrier to reduce direct exposure to microbes or their metabolites, thereby reducing inflammation [26]. Microbial metabolites such as butyrate promote mucin production and stimulate the growth and repair of colonocytes that line the intestine. One study showed that bacteria can enter the IEC of mucin-deficient mice, causing inflammation and cancer [27]. In addition, mucin concentrates on microbial metabolites, thereby facilitating communication between microbes and hosts. The small intestine induces the expression of tight junction proteins, preventing the release of metabolites and microbes from the intestine into the systemic circulation, which can cause systemic inflammation [28]. In addition, some intestinal microbes such as Escherichia coli metabolize tryptophan and produce indole, which promotes the development of tight junctions in the intestine and reduces the permeability of the epithelial layer [29,30]. The ability of the intestinal bacteria to compete against the invading bacteria also contributes to the integrity of the barrier, which will be exposed if it breaks the barrier and damage from viruses. The small intestine stimulates the host to produce antimicrobial peptides, which are absorbed into the intestine and enter the mucosal layer, making it almost useless [31].

4. Gut microbes modulate host immune responses

Gut microbes can modulate the host's immune response through miRNA. For example, one study showed that mice with colitis had reduced expression of miRNA-10a which corresponds to high levels of pro-inflammatory cytokines such as IL-12/IL-23p40 [32]. Furthermore, microbial inhibition of miR-375-3p promotes the proliferation of IEC [33], while microbial stimulation of miR-21-5p increases IEC capacity, leading to inflammation [34]. The effect of commensal microbes on host gene expression may also be mediated by microbial metabolites such as lipopolysaccharides (LPS) and SCFAs [35]. One study showed that butyrate changes the expression of 44 miRNAs in HCT-116 colon cancer cells [35]. For example, miR-106b affects the expression of the p21 gene that

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mediates the anti-inflammatory effects of microbial short-chain fatty acids [35]. Maintaining control of host miRNAs is important for regulating intestinal immune function, influencing susceptibility to inflammatory diseases. Germ-free (GF) mice show differential expression in 16 miRNA genes compared to mice [36]. These genes regulate immune function and intestinal homeostasis through regulation of the intestinal barrier [36]. muciniphila and its membrane protein Amuc_1100 promote intestinal epithelial cell proliferation and support immune function by upregulating the expression of miR-143/145 in the gut, which activates the insulin-like growth factor-1 (IGF-1) signaling pathway. [37]. Some probiotics such as L. salivarius and L. fermentum exhibit anti-inflammatory activity by increasing the expression of miRNA-150 and miRNA-143 in a murine model of colitis [38]. Other microbial enemies such as Fusobacterium nucleatum increase resistance to chemotherapeutic agents by reducing the expression of miRNA-18a and miRNA-4802, leading to involvement in the autophagy pathway [2]. Other studies have reported that F. nucleatum can inhibit anti-tumor T cell responses, leading to cancer progression through a modulatory effect on miRNA-21, which increases the levels of prostaglandin E2 and IL-10; however, the exact mechanism is unknown [39]. Furthermore, F. nucleatum uses miRNA to stimulate NF-κB (NF-κB) gene expression, causing inflammation [39]. On the other hand, F. prausnitzii suppresses NF-κB gene expression through hyperacetylation [40]. Some species of E. *coli* . The bacterium E. coli is involved in the development of colorectal cancer (CRC) by increasing the expression of miR-20a-5p, which increases the expression of some growth factors leading to cancer [41].

Although the mechanism is not fully understood, some data suggest a possible role for colibactin, a microbial metabolite secreted by E. coli. coli Nissle 1917, and the development of colorectal cancer through direct DNA damage [41]. A recent study found that colibactin can awaken latent bacteriophage in response to DNA damage, causing indirect and specific killing against microbes, which thus affects the structure and the activity of gut microbes [42]. Many miRNAs control cellular functions such as the immune response by controlling cell differentiation, while negative miRNAs are associated with autoimmune diseases [43]. For example, commensal microbes can suppress the expression of miR-10a in dendritic cells targeting IL-12/IL-23p40, thereby contributing to immune homeostasis [32]. Some microbial infections affect the expression of miRNAs, leading to changes in the immune response of the host in the disease state. For example, Mycobacterium tuberculosis reduces miR-let 7f in infected macrophages, leading to reduced production of tumor necrosis factor (TNF) and IL-1β which inhibits the immune system by affecting inflammatory response of NF-κB [44]. A similar effect was observed for Helicobacter pylori [45]. MiRNAs from the gut microbiota are secreted into extracellular vesicles (EVs) that regulate the expression of target genes by binding to mRNA. In addition, microbe-derived metabolites and pathogens can also affect host miRNA expression, mainly through the Toll-like receptor (TLR)/MyD88 pathway. On the other hand, miRNAs released by the host in gallbladders and feces are picked up by the gut microbiome, changing their abundance, activity and growth. (2,3)

Role of microbiome-miRNA axis against IBD; (2) A. muciniphila promotes intestinal epithelial cell (IEC) proliferation by upregulating cAMP-responsive element-binding protein (CREBH), a transcription factor known for its anti-inflammatory activity. Increased CREBH expression leads to the restoration of host miR-143 and miR-145, which activates insulin-like growth factor (IGF), a stimulator of intestinal proliferation and recovery from injury, by inhibiting the endogenous IGF inhibitor, IGFBP5. (3) Host-derived miR-193a-3p also suppresses inflammation. miR-193a-3p inhibits PepT1 transporter activity. Because of this inhibition, no part of the bacterial products that promote inflammation, such as N-Formyl-Methionyl-Leucyl-Phenylalanine (fMLF) or muramyl dipeptide (MDP), is released. (4,5) The role of the microbiome-miRNA axis in the development of IBD. (4) Microbial stimulation of Toll-like receptors (TLRs) increases the expression of miR-21-5P in IECs. miR-21-5P inhibits phosphatase and tensin homolog (PTEN) and programmed cell death 4 (PDCD4). This deletion increases ADP ribosylation factor 4 (ARF4), a GTPase that inhibits the tight junction protein claudin-4 from binding to the occluded endometrium, thereby increasing intestinal permeability. (5) Adherent invasive Escherichia coli (AIEC) inhibits let-7b expression in the setting of Crohn's disease. This activates TLR4, which increases the release of pro-inflammatory cytokines, promoting mucosal inflammation and immune response against the gut microbiota.

Several miRNAs are known to regulate microbes and gut homeostasis by modulating the expression of Treg cells and T helper cells such as Th1, Th2, and Th17 [46]. Th1 is thought to cause Crohn's disease, while Th2 causes ulcerative colitis and Th17 is involved in multiple sclerosis [46].Differentiation of naïve CD4+ T cells into Th17 and Treg is tightly regulated by the host, gut microbes,

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Vol. 47 No. 2 November 2024, pp. 535-549

microbial metabolites, and miRNAs. Th17/Treg imbalance is a major contributor to autoimmune diseases, especially gastric cancer and multiple sclerosis (MS) [46,47]. One study identified miRNA-141 and miRNA-200a as stimulators of Th17 differentiation and repressors of Tregs, leading to MS progression [48]. The study suggests that miRNA-141 and miRNA-200a can inhibit the regulatory proteins for Th17 differentiation, leading to the production of Th17 [48]. Another example is miRNA-155, which regulates the Th17/Treg balance through TLRs [47]. Expression of miR-155 enhances Th17 immunogenic activity and suppresses Treg cells, while suppression of miR-155 results in reduced inflammation [49]. The same effect is also observed for some intestinal microbes or their LPS. Research shows that L. salivarius and L. fermentum restored the normal level of miR-155, maintaining the Th17/Treg balance and reducing inflammation associated with colitis in mice, mainly by restoring intestinal immune function [38]. Other examples of miRNAs that modulate intestinal barrier function include miR-18b, miR-363-3p, and miR-106a [50]. These miRNAs inhibit Th17 differentiation and the production of the pro-inflammatory interleukin IL17 [50]. A computational analysis was performed to predict the effects of 64 miRNAs on Th17 based on their interactions with gene transcription. 11 miRNAs could modulate Th17 differentiation as both suppressors and effectors [51]. The inhibitory miRNAs included miR-1, miR-27a, miR-27b, miR-30c, and miR-141, while the modulatory miRNAs included miR-20a, miR-20b, miR-21, miR-93, miR-106a, and miR-152 [51]. There is growing interest in identifying microbes or miRNAs that inhibit Th17 production and alter the balance to reduce autoimmune inflammation. Controlling the interaction between miRNAs and microbes appears to be an exciting advance in the treatment or prevention of inflammatory and autoimmune diseases [52].

5. Intestinal microbial dysbiosis disrupts homeostasis and promotes IBD

Microbiome dysbiosis disrupts the immune balance, leading to autoimmune diseases and inflammation [53,54]. IBD is a heterogeneous disease of various etiologies depending on their location in the gastrointestinal tract and includes Crohn's disease (CD), ulcerative colitis (UC) and microscopic colitis (MC) [55,56]. Several studies have supported the key role of intestinal microbes in IBD [57]. Differences in microbial composition result in different levels of pro-inflammatory and anti-inflammatory mediators that can trigger IBD or keep it under control. For example, several studies have reported a strong reduction of F. prausnitsii in IBD patients [58]. F. prausnitsii is a known producer of butyrate and other proteins that inhibit the production of pro-inflammatory cytokines [6]. Another study showed that healthy controls with a genetic risk for developing IBD had a significant microbial composition characterized by a decrease in the genus Roseburia [59], which converts acetate to butyrate. Segmented filamentous bacteria (SFB) induce Th17 differentiation, leading to overproduction of IL-17 and IL-22 [60]. In general, this effect results in higher levels of inflammation and stronger immune responses in mice [60].

Furthermore, reduced SFB is associated with reduced Th17 numbers and, consequently, lower IL-17 levels [61], while high SFB abundance is associated with autoimmune diseases such as rheumatoid arthritis. resulting in the production of autoantibodies [62]. DNA from some small bacteria inhibits Treg differentiation through stimulation of TLR9, which disrupts intestinal homeostasis [63]. Microbial dysbiosis results in the release of microbial toxins and metabolites such as bacterial lipopolysaccharides (LPS) that cause inflammation and immune system hyperactivity [64]. During homeostasis (left), the intestine maintains a state of eubiosis that is abundant in various types of bacteria such as Bifidobacterium spp., Akkermansia spp.,etc. This health condition supports the immune system, in which a balance is maintained between Th cells, Treg cells and their associated cytokines. In the healthy intestine, M2 macrophages, known for their anti-inflammatory activity, constitute the predominant macrophage phenotype. The immune system is also protected by B cells, which secrete IgA antibodies that target harmful bacteria and avoid the resident microbiome. In addition, the nasal layer works as a protective barrier. Bacterial metabolites, such as short-chain fatty acids (SCFAs), help maintain a healthy intestinal barrier, while other useful species stimulate the production of mucin, the main defence against colds. mucous membranes. Meanwhile, in IBD patients (right), disruption of the gut microbiome community leads to a state of dysbiosis, and many SCFA producers are depleted, while others that promote inflammation increase. Due to this imbalance, a high level of inflammatory cytokines is secreted, which is aggravated by the loss of the mucous and the change in the integrity of the mucosal layer, which leads to bacterial migration works on the recruitment of new immune cells such as neutrophils while inhibiting anti-inflammatory activity of Treg cells. In addition, M1 macrophages, associated with intestinal inflammation, proliferate and secrete inflammatory cytokines. In contrast to a healthy intestine, high levels of reactive oxygen species (ROS) and other mediators of intestinal toxicity, such as nitric oxide, both exacerbate toxicity, and define the light source.

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Several studies found that the cluster of differentiation (CD) patients, in particular, had lower microbial abundance than Ulcerative colitis (UC) patients. Both systems contain high levels of Firmicutes and Actinobacteria, while Enterobacteriaceae are abundant in CD, but lower levels are found in UC [65]. In a study that used gene-level metagenomic mapping to identify diagnostic microbiome signatures [66], Solobacterium moorei F0204 was identified as a marker of inflammatory bowel disease [66]. Other data have shown that CD patients adherent-invasive *E. coli* (AIEC), which is thought to cause inflammation by irritating the intestinal mucosa [67]. AIEC also produces propionates, stimulating the production of IL-1β, part of the inflammasomes that increase the production of IL-18, a pro-inflammatory interleukin. The inflammatory factor is a multiprotein complex that induces the production of pro-inflammatory cytokines, causing severe inflammation [68]. A recent study showed that the administration of genetically modified AIEC, without the enzyme necessary for propionate synthesis, resulted in a lower rate of inflammation in mice with Crohn's symptoms like [69] . Another study reported that AIEC caused a strong immune response to inflammation in CD patients by inhibiting the expression of let-7b miRNA, which led to the production of pro-inflammatory cytokines [70].

6. Abnormal expression of host-derived miRNAs

The use of miRNAs is one of the possible mechanisms by which host genes affect the dynamics of microbial pathogens and their gene expression, resulting in a balanced or altered microbiome [71]. Negative miRNA expression alters the abundance of microbes and their metabolites, causing disease [46,71]. Fecal miRNA can be used as a biomarker of microbial fluctuation in the initiation and progression of intestinal diseases such as IBD and Colorectal cancer (CRC) [4]. One study showed that mice deficient in miRNA production had poor growth of gut microbes associated with increased intestinal inflammation. Interestingly, administration of fecal supplements with miRNAs from wild-type mice to diseased mice restored normal microflora and markers of inflammation [52]. In addition, miRNAs secreted by intestinal epithelial cells influence the expression of mucosal-associated genes, which ultimately influence microbial colonization [46].Several examples of specific miRN As regulating microbial abundance and subsequent host function have been identified [46]. Growth of F. nucleatum and E . coli, two bacterial strains implicated in IBD and CRC, are regulated by miR-515-5p and miR-1226-5p [2,4]. miR-21, a miRNA overexpressed in inflammatory bowel disease, is increased in animal models of colitis by control of intestinal microbes [72].In addition to directly controlling microbial growth, some miRNAs affect the ability of intestinal cells to absorb microbial metabolites. For example, miR-193a-3p reduces the ability of intestinal cells to absorb microbial pro-inflammatory tripeptides (L-Ala-γ-D-Glu-meso-DAP), which cause inflammation. miR-193a-3p exerts its function by suppressing the expression of PepT1 which facilitates the uptake of this metabolite [74]. Interestingly, PepT1 is overexpressed in colitis and data show that antibiotic treatment abrogates its effects due to the lack of microbial products [73].

7. Targeted therapies for the gut microbiota

Current treatment for IBD mainly focuses on controlling inflammation with drugs, including corticosteroids, aminosalicylates, immunomodulators, and biologics [75]. Corticosteroids (e.g., prednisone) and aminosalicylates (e.g., 5-aminosalicylic acid) help to reduce inflammation by inhibiting the release of pro-inflammatory mediators such as prostaglandins and leukotrienes [76,77]. Immunomodulators (e.g., azathioprine) inhibit the proliferation of inflammatory cells and are often used clinically to induce or maintain remission, especially in patients with steroid-dependent CD. , which is difficult to manage. Despite their effectiveness in relieving IBD symptoms, aminosalicylates, corticosteroids, and immunomodulators have limitations, including high relapses after treatment discontinuation and poor patient compliance with long-term use. Biological products, which are now widely used in clinical practice, usually stimulate the immune system with different goals. For example, TNF blockers antagonize TNF-α, eliminating its biological activity and reducing inflammation. Integrin inhibitors, on the other hand, inhibit the binding of integrin α4β7 to its ligand, preventing lymphocyte migration to the inflamed intestinal mucosa and suppressing the local immune response [78]. Although biotherapy is effective for most patients, up to 30% of individuals show no response to initial treatment and up to 50% experience failure of response over time [79].

Patients with IBD are at increased risk of developing opportunistic infections. Studies have shown that the use of corticosteroids, immunomodulators, and biologics can compromise the immune system in patients with IBD, leading to an increased risk of infections and a higher incidence of malignancies [80]. As a result, current drugs often do not treat the causes of IBD, such as disruption of the intestinal barrier and dysbiosis of the gut microbiota [81], which can cause adverse effects. In some cases, many

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Vol. 47 No. 2 November 2024, pp. 535-549

patients may need surgery. With the emergence and development of the dysbiosis theory regarding the gut microbiota, research into protecting the microbiota in the treatment of IBD has greatly increased. This treatment aims to restore gut health, reduce inflammation and improve symptoms by changing the structure and function of the microbiota. These may include interventions such as enteral nutrition (EN), the use of probiotics or fecal microbiota transplantation (FMT), among others, to control the gut microbial community. These new therapeutic approaches may be beneficial for patients who respond poorly to traditional therapies or experience adverse reactions. Figure 2. Therapeutic approaches targeting the gut microbiota. (1) EN is administered to IBD patients via oral administration or nasogastric tube. (2) FMT involves introducing the fecal microbiota of healthy individuals into the patient's gut. (3) Oral probiotics induce positive changes in the composition of the intestinal microbiota.

7.1. Enteral Nutrition

A nutritional diet is recommended for IBD patients who are malnourished or at risk of malnutrition, according to the consensus of experts in nutritional support therapy for IBD [82]. Enteral nutrition is a special diet in which the liquid food system is delivered orally or through a nasogastric tube. The duration of treatment is usually 6 to 8 weeks [83,84]. Not only does it provide essential nutrients, but also fits into the physiological digestive system, thus preserving the integrity of the intestinal mucosal barrier. Its effectiveness is similar to that of corticosteroids, but it causes less side effects. In pediatric and adolescent patients with CD, EN is the most effective treatment to initiate remission [85]. The mechanisms used by EN are poorly understood. However, it is thought that EN can reduce the production of inflammatory molecules in the intestinal mucosa and correct the imbalance in the intestinal microbiota. In addition, it induces a positive change in the microbiota from an initial pro-inflammatory state to an anti-inflammatory state. These actions can lead to an increase in intestinal inflammation and support the healing of the intestinal mucosa [86].

Studies have shown that EN treatment leads to a positive change in the gut microbiota, changing from a pro-inflammatory to an anti-inflammatory state, thus promoting disease remission. In people with CD receiving treatment with EN, an imbalance in the intestinal microbiota includes a marked decrease in the phyla Bacteroidetes and Firmicutes, associated with an increase in Enterobacteriaceae. In a prospective clinical study of pediatric patients with CD, changes in the fecal bacterial community as determined by 16S rRNA sequencing after two weeks of EN were indicative of an increase in Bacteroidites and restoration of microbial balance [87]. Interestingly, Gerasimidis et al. found that patients with remission on EN treatment had an increase in sulfur content and a decrease in butyrate salts in their stool, leading to a decrease in bacterial diversity. The abnormal environmental conditions in the intestine are associated with the healing of the intestinal mucosa and the reduction of clinical symptoms of the disease, which is contrary to previous research [88]. Future research efforts aim to study the mechanisms by which NE affects the microbiota with the aim of devising appropriate strategies to manage changes in the intestinal microenvironment.

7.2. Fecal microbiota transplantation

Faecal microbiota transplantation is a therapeutic technique that involves introducing faecal microbiota obtained from healthy donors into the intestines of patients to restore the normal microbial composition of the intestines [89]. Different methods can be administered to patients, including colonoscopy, enema, upper gastrointestinal tract, or oral administration using frozen capsules. Studies have shown the effectiveness of the delivery methods mentioned above [90]. The success of FMT depends on its ability to restore the healthy microbial community in the patient's gut to a healthy state. In 1989, FMT was used in patients with UC. Long-term follow-up showed that the first patient treated remained disease-free for over 20 years [91]. A meta-analysis combining 23 studies including 319 patients with varying degrees of disease severity who received FMT therapy found that 93 patients achieved clinical remission. Clinical remission rates are 20% for mild IBD and 30% for severe IBD. Studies show that patients with moderate or severe IBD may benefit from FMT more than those with mild disease [92]. Imdad A et al. also summarized four large randomized studies, showing a significant improvement in clinical remission rates in IBD patients after FMT. The remission rate was twice as high as in the control group [93]. Interestingly, the effectiveness of FMT in the treatment of IBD currently appears to be controversial. A prospective study by Vaughn et al. evaluated the clinical response to FMT in 19 patients with CD. Results showed that 58% of patients achieved clinical remission. Analysis of samples before and after FMT in 15 of these subjects showed a significant increase in gut microbiota diversity after FMT.

However, the study also reported adverse effects. One patient developed urticaria and the other experienced worsening clinical symptoms. The latter patient had multiple chronic diseases and eventually required surgery [94]. In summary, FMT has a good safety profile in IBD. The most commonly reported adverse reactions are abdominal pain, constipation, nausea, upper respiratory tract infections, headache, dizziness and fever [95]. The effects of serious adverse reactions such as exacerbation of ulcerative colitis, sepsis, small bowel problems and pneumonia are low. However, current research related to fecal changes in IBD is limited to clinical studies. These tests are not accurate or reliable due to the influence of many factors. Additionally, there are no standardized guidelines for donor selection, stool preparation methods, or stool culture frequency, making this trial a clinical trial. The incidence of serious adverse reactions is still uncertain, as is its effectiveness, which allows for more multicenter controlled trials to demonstrate its effectiveness and safety.

7.3. Probiotics

Probiotics are beneficial microorganisms found in the gut that have been used to treat various diseases, including inflammation, tumors, obesity, diabetes, and others [96,97,98,99]. First, they produce specific antimicrobial effects in the human body by producing substances such as bacteriocins, hydrogen peroxide and defensins. Second, they improve intestinal barrier function by increasing mucus production and promoting the formation of tight junctions, which reduce the resistance of the intestinal mucosa [100]. In addition, they regulate the immune response by modulating the production of immunoglobulins and the generation of pro-inflammatory cytokines. By regulating the NF-κB pathway, they reduce the production of pro-inflammatory cytokines (e.g., IL-8, TNF-α, IFN-γ) and increase the production of pro-inflammatory cytokines, such as IL-10 and TGF-β. [101]. In recent years, probiotics have shown potential as a treatment modality in IBD clinical trials. For example, Ballini et al. conducted a study in which 40 IBD patients were randomly assigned to receive either probiotics or a placebo for 90 days. Results showed that oral probiotics effectively and independently controlled oxidative stress levels and intestinal inflammation in IBD patients [102]. Currently, commonly used probiotics include Lactococcus, Lactobacillus, Bifidobacterium, and Escherichia coli Nissle 1917.

Lactobacillus plantarum can reduce the production of pro-inflammatory cytokines and prevent bacteria from entering the intestinal wall. Bifidobacterium helps prevent the breakdown of the barrier and promotes the repair of damaged cells, thus maintaining the stability of the intestinal barrier. Specifically, the BGN4-SK strain of Bifidobacterium bifidum alleviates DSS-induced colitis by producing antioxidant enzymes, increasing the expression of related genes, and reducing pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α [103].Escherichia coli Nissle 1917 is a well-known immunomodulator that can increase the production of anti-inflammatory cytokines, such as IL-10, and induce IgA antibody responses. Lactobacillus plantarum, on the other hand, can reduce the production of pro-inflammatory cytokines and prevent pathogens from adhering to the intestinal epithelium [104]. VSL #3 is a highly concentrated mixture containing 8 microbial species that is considered a promising probiotic [105]. Sood et al. conducted a multicenter, double-blind, controlled study demonstrating the beneficial effects of VSL #3. Treatment outcomes were measured using the Ulcerative Colitis Disease Activity Index (UCDAI). Study results showed that patients in the VSL #3 group had significantly reduced UCDAI scores and better mucosal healing compared to the placebo group [106].

Researchers confirmed that VSL #3 regulates the host response and enhances the epithelial defence function by increasing the anti-inflammatory cytokine IL-10 and inhibiting the secretion of pro-inflammatory cytokines such as TNF-α and IFN-γ [107]. Interestingly, VSL #3 showed a synergistic effect when used in combination with drugs. For example, when combined with 5-aminosalicylic acid, it can enhance anti-inflammatory effects and inhibit the production of leukotrienes and IL-1. Furthermore, when used in combination with balsalazide, it is more effective in preventing UC than balsalazide alone [101]. In addition, VSL #3 can also prevent pouchitis, a complication in patients with UC [108]. In general, long-term treatment with VSL #3 in patients with IBD can lead to improvement. Therefore, probiotics play an important role in regulating the intestinal microbiota and intestinal barrier, thus helping to fill the gaps in healthy nutrition. By modulating the immune response, protecting the integrity of the intestinal barrier and reducing inflammation, probiotics can complement traditional therapies, providing a comprehensive approach to the management of intestinal disorders such as IBD. However, patient and therapeutic response is influenced by a variety of factors, such as host genetics, lifestyle, dietary habits, and the composition of the endogenous microbiota [109]. Furthermore, maintaining the efficacy of probiotics represents a major technical challenge. Many probiotic strains can perish during storage and transportation, rendering them ineffective before patients can reap their full health benefits. We are planning future research examining the

characteristics and interactions of different probiotic strains to determine their synergistic effects. This will allow the creation of personalized and individualized treatment plans based on the IBD phenotype. By optimizing the selection of probiotic strains based on each patient's unique microbiome composition and immune response, it will be possible to improve treatment outcomes, support traditional therapies, and provide effective and efficient care.

II. Conclusion

Based on the above, we believe that we can try to use the characteristics of the gut microbiota as a therapeutic and prognostic biomarker for IBD. For example, some studies show an increase in Firmicutes in UC patients responding to mesalazine [110]. Furthermore, CD patients whose gut microbiota composition was similar to that of healthy controls had fewer relapses than patients with dysbiosis [111]. Based on these results, future medical advances may focus on using gut microbiota characteristics for self-medication. This may include the use of targeted therapies to protect the microbiota, correct microbial metabolic activity and restore the immune system, helping IBD patients manage their disease effectively and safely. Personalized therapy promises to be a major innovation in the medical field in the future, providing better treatment outcomes for IBD patients. However, this area requires further research to confirm and refine these concepts, translating them into therapeutic strategies suitable for clinical practice.

Abbreviations

Chronic inflammatory bowel disease: IBD

Crohn's disease: CD

Ulcerative colitis: UC

Faecalibacterium prausnitsii: F. prausnitsii

Microbial anti-inflammatory molecule: MAM

Short-chain fatty acids: SCFA

Regulatory T cells: Treg

Lithocholic acid: LCA

Reactive oxygen species: ROS

Adherent-invasive Escherichia coli: AIEC

Sulfate-reducing bacteria: SRB

Enteral nutrition: EN

Faecal microbiota transplantation: FMT

ulcerative colitis activity index: UCDAI

Pattern recognition receptors: PRR

Toll-like receptors: TLR

Molecular models associated with microbes: MAMPs.

Conflict of interest

All authors declare no conflicts of interest.

Author contribution

Authors have equally participated and shared every item of the work.

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