

Review

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Review

The Dynamic Crosstalk between Gut Microbiota, Immune System, and Autophagy in the Onset of Inflammatory Bowel Disease: Molecular Mechanisms and Current Therapeutic Approaches

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Abstract: The crosstalk between gut microbiota, intestinal epithelial cells, and innate and adaptive immune system governs the maintenance of the intestinal homeostasis. Any interference in this tight dialogue and in the processes preserving cellular homeostasis (e.g., autophagy) may dysregulate the immune response and impair the clearance of harmful bacteria favoring the dysbiotic alteration of the microbic flora that leads to chronic inflammation. Gut dysbiosis is strongly associated with gastrointestinal inflammatory disorders, among them the inflammatory bowel disease (IBD). This review discusses the current knowledge on IBD, from the genetic background of high-risk patients to the molecular mechanisms underlying the disease, the contribution of the microbic flora, and the role of autophagy in intestinal epithelial cells and provides the state of art regarding the targeted-nutritional approaches aimed to restore the beneficial crosstalk between an “anti-inflammatory” microbiota and the host. Analysis of the molecular pathogenesis of IBD will help identify genetic and diet-associated risk factors and thus suggest personalized strategies to prevent and manage the disease to improve quality of life with long-term maintenance of the remission phase.

Keywords: IBD; Crohn's disease; ulcerative colitis; inflammation; immune system; autophagy; microbiota; probiotics; fecal microbiota transplantation

1. Introduction

The inflammatory bowel disease (IBD) comprises a variety of widespread gastrointestinal diseases whose incidence has been increasing in recent decades, especially in industrialized countries [1]. Epidemiologic data reporting the increased incidence of IBD are supported by the view that the worldwide adoption of a Western lifestyle may increase the occurrence of the disease [2].

IBD includes chronic inflammatory idiopathic disorders within the gastrointestinal tract, such as Crohn's disease (CD) and ulcerative colitis (UC), characterized by the alternation of exacerbation and remission phases. CD and UC share the symptoms and the chronic inflammatory state, yet they differ in that CD may involve the whole gastrointestinal tract displaying a discontinuous pattern with the inflamed tissues alternated with non-inflamed tissues, whereas UC is localized in the mucosa and submucosa of the colonic region, partially or entirely, with a continuous inflamed pattern [3]. Both CD and UC may lead to the obstruction of the gastrointestinal tract and cause nausea, diarrhea with bleeding, vomiting, fever, fatigue and weakness, loss of weight, abdominal pain, cramps, as well as intestinal perforation, bloody ulceration, and crypt abscesses [4].

Although the etiopathogenesis is not fully understood, IBD is a multifactorial disease whose rise and progress rely on a complex interplay between genetic, environmental, and microbiological

factors that leads to an uncontrolled immune system activation [5]. About 300 genes directly associated with IBD have been emerged by genome wide association studies (GWAS) and meta-analysis, and their polymorphisms may expose people to a high risk of developing the disease [6].

Recent GWAS have identified novel single nucleotide polymorphisms (SNPs) whose genetic variants may disrupt the intestinal homeostasis and increase host genetic susceptibility [7]. Of note, genetic variants in autophagy-related genes results in impaired clearance of intercellular bacteria and an increase in the release of inflammatory cytokines, promoting the onset of inflammatory chronic disease. This highlights how autophagy serves as a key mechanism in preventing the development of IBD, by modulating immune system functions, production of cytokines, and participating in pathogen clearance [8]. Besides, also epigenetic mechanisms may contribute to IBD development and progression. DNA methylation and miRNAs interfere in T-cell differentiation, cytokines regulation, Th17 molecular signaling, and autophagy [9].

Metagenomic studies reported that patients suffering from IBD present an altered balance in gut bacteria function and composition, a condition known as dysbiosis, compared to the healthy group. The composition of commensal bacteria results in a reduced bacterial biodiversity with a decrease of anaerobic strains, such as *Firmicutes* and *Bacteroides*, and predominant facultative anaerobic strains, such as *Proteobacteria* [10]. This may trigger primary inflammation that, if exacerbated, may evolve in chronic inflammation and impact on the permeability of intestinal epithelial barrier compromising gut mucosa structure [11].

2. The Intestinal Epithelial Barrier

The intestinal epithelial barrier plays a pivotal role in preserving the delicate balance between defense mechanisms and symbiotic interaction within the gut. Beyond its primary role in processing and absorbing food and nutrients, the intestinal epithelial barrier acts as biochemical and physical barrier against pathogens, toxins, and dietary antigens, establishing a primary defense line from the contents of the bowel lumen [12,13]. Simultaneously, it creates the proper microenvironment, preventing excessive colonization of commensal bacteria in the luminal compartment and facilitating the harmonious interaction between the host and the microbiota [14] (Figure 1).

The intestinal epithelium, composed of a single layer of columnar polarized cells, undergoes a self-renewal process approximately every 5-7 days. This renewal is facilitated by a population of intestinal pluripotent stem cells residing in specific niches within the inner part of the epithelium, called Lieberkühn crypts [15]. These stem cells actively proliferate, migrate to the upper surface along the crypt-luminal axis, differentiate into specialized cells and undergo apoptosis within a few days. The coordinated presence and activity of these stem cells ensures the continuous regeneration of columnar polarized cells, maintaining the structural integrity of the gut [16].

The differentiated cells deriving from intestinal stem cells (ISC) include enterocytes, Paneth cells, enteroendocrine cells, and goblet cells. Enterocytes, comprising approximately 80% of specialized cell types, play a crucial role in the absorption of dietary compounds by enhancing their adsorptive area with microvilli, particularly pronounced in the small intestine. Paneth cells support the intestinal stem cell population through signaling molecule secretion and regulate microbial flora with antimicrobial peptides and immunomodulating signals. A decreased expression of Paneth cell-derived α -defensins and defective anti-microbial peptides have been observed in patients with CD [17,18]. Enteroendocrine cells produce hormones governing food digestion, absorption, and appetite, also acting as communication molecules with the immune system [16,19]. Goblet cells, the specialized entities responsible for secretion, release a glycoprotein network which composes the mucus layer that covers the intestinal epithelium [20]. Mucin proteins produced by these cells create a gel-like structure that prevents the direct contact between the bowel lumen and epithelial cells representing the first barrier of defense against bacteria and inflammation in the intestine. This structure not only provides an adhesion substrate for the microbiota niche but also simultaneously impedes the transepithelial invasion of microorganisms into the systemic circulation [21]. The mucus layer exhibits antimicrobial properties by releasing secretory immunoglobulin A and antimicrobial molecules targeting viruses, fungi, and bacteria. The structural characteristics of the mucus, including

its composition and thickness, maintain intestinal health. Several factors, including microbes, growth factors, neuropeptides, pro-inflammatory cytokines, and toxins, may affect the production of mucins and the architecture of mucus layer disrupting gut homeostasis and triggering an inflammatory response [22].

In the subepithelial layer, the gastrointestinal tract holds the gut-associated lymphoid tissue (GALT), which includes Peyer's patches and specialized immune cells such as macrophages, dendritic cells, plasma cells, and lymphocytes. These cells ensure the integrity of the intestinal barrier and trigger immune responses in the presence of luminal antigens [23]. Intestinal macrophages, despite the diminished inflammatory activity in response to microbial antigens or host cytokines, promote the differentiation of regulatory T-cells. They also limit the Th1 and Th17 responses, while preserve their phagocytic and bactericidal functions [24]. Dendritic cells actively monitor the intestinal microenvironment and initiate adaptive immune responses through the release of molecular signals [25].

Adjacent epithelial cells are firmly connected to the apical surface through tight junctions, a transmembrane protein family that includes claudins and occluding. The multiprotein complexes, interacting with the actin-myosin cytoskeleton via scaffold molecules [26], maintains cell polarity and ensure the integrity of gut epithelial. Tight junctions also regulate paracellular transport by creating pores in the intercellular spaces, facilitating the transport of selected small molecules from the apical to the basolateral side [27]. Claudins are divided in two categories based on their function: some create pores facilitating selective ion passage, while others contribute to enhance barrier tightness. This dual functionality results in a distinctive expression pattern not only in the crypt and luminal surface, but also throughout the entire gastrointestinal tract [28]. Occludin is a component of the intracellular domain of tight junctions and is necessary for their assembly. The phosphorylation of specific residues affects occludin localization: low phosphorylation levels lead to cytoplasmic accumulation, while high phosphorylation levels induce positioning within the tight junction complex [29].

The integrity of intestinal epithelial barrier is guaranteed not only by tight junctions but also by anchoring junctions. Adherens junctions, a key component of anchoring junctions, participate in cell adhesion. They facilitate the connection between adjacent cells by engaging in cytoskeleton interaction through transmembrane adhesion molecules. The main actor in adherens junctions family is E-cadherin, which provides a calcium-dependent intercellular adhesion. On the cytoplasmic side, E-cadherin forms multiprotein complexes with members of the catenin superfamily fixing to the actin cytoskeleton [30,31]. Defective epithelial junctions and alterations in the genes encoding epithelial junctions have been identified as a significant cause of IBD. For instance, SNPs in *CDH1*, which encodes for E-cadherin, have been associated with UC [32]. Certain pro-inflammatory cytokines, such as TNF- α and IFN- γ , have been found to raise the permeability of tight junctions leading to the breakdown of the epithelial barrier function, pathogens entry and sustained inflammation associated with IBD [33,34].

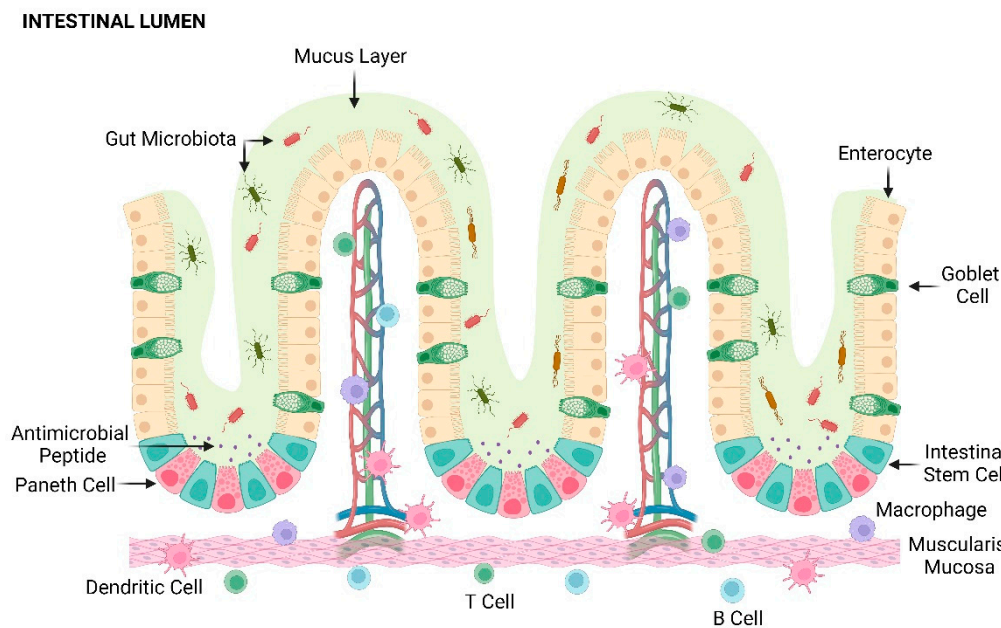


Figure 1. *Intestinal epithelial barrier.* The intestinal epithelial barrier is constituted by a single layer of specialized cells (enterocytes, goblet cells, Paneth cells, and intestinal stem cells) that create a physical wall against the external microenvironment. The covering mucus layer provides the adhesion substrate for the microbiota and prevents the transepithelial invasion of microorganisms in the systemic circulation. Immune cells (macrophages, dendritic cells, plasma cells, and lymphocytes) reside in the subepithelial layer and trigger the immune response in the presence of luminal antigen (created with BioRender).

3. Gut Microbiota

Human gut microbiota actively regulates host health, physiology, metabolism, and immune system, and prevents pathogens colonization by establishing a mutualistic relationship with the host, effectively overseeing the health status of the organism [35].

Microbiota includes up to 1000 different microbic species and the genomic material of these microorganisms, called microbiome, is one hundred times greater than human genome [36]. The composition and the abundance of commensal microorganisms is highly variable in term of species and is based on the anatomical location along the gastrointestinal tract. Microbiota population changes in each human and the biodiversity creates a unique microbiome profile that is considered a typical feature of each individual [37].

The microbic flora definition begins during childbirth and the natural or cesarean delivery, and its composition is further influenced by breast feeding or formula feeding [38]. Since the first years of age, commensal bacteria establish a relationship with the immune system enabling the maintenance of homeostasis with the host. This equilibrium remains stable unless external disturbances (e.g., aging, diet, antibiotics, and illnesses) disrupts this balance [39].

In healthy individuals, the intestinal microbiota consists of a large community of microbial species, represented by *Bacteroidetes* and *Firmicutes* as predominant *phyla* [36]. Commensal bacteria accomplish the fermentation of non-digestible carbohydrates from the diet producing short-chain fatty acids (SCFAs) that are then transported into the intestinal epithelial cells [40]. The SCFA butyrate is the most absorbed microbiota metabolite and represents the main source of energy for colonocytes, helping the proliferation and the differentiation of intestinal epithelial cells [41]. SCFAs possess anti-inflammatory properties by promoting T-cell differentiation, exert an anti-carcinogenic role, decrease oxidative stress, and participate in the maintenance of intestinal mucosa integrity and gut permeability. Collectively, they show the ability to modulate gene expression through the

activation of G-protein coupled receptors (GPR41, GPR43, and GPR109a) and the inhibition of the histone deacetylase [42–46].

Within the intestinal microenvironment, the SCFAs decrease the release of pro-inflammatory cytokines, such as IL-13, IL-6, IL-12, and TNF- α , preventing interference with the expression of tight junction, consequently improving the permeability of the gut barrier [47]. The anti-inflammatory properties of SCFAs are mediated by the binding with GPR109a in the dendritic cells and macrophages. The activation of this receptor mediates the expansion of Treg cells with the increase of IL-10 and the reduction of Th17 and IL-6 [48]. The activation of GPR43 attenuates NLRP3 response and the consequent IL-18 secretion [49]. Through the inhibition of HDACs, commensal bacteria interfere with T-cell chemotaxis in the microenvironment and create an immunological tolerance that leads to an anti-inflammatory phenotype balancing immune homeostasis [50]. Mouse models lacking a eubiotic gut microbiota display immature lymphoid structures, low lymphocyte population, and reduced production of antimicrobial peptides [51].

Gut microbiota represents a natural defense barrier against pathogens infection [52]. Commensal microorganisms prevent pathogens invasion competing for nutrients within the microbial niche of the gastrointestinal tract. The fermentation of *Bifidobacteria* decreases the pH of the microenvironment and prevents the colonization of *E. coli* [53]. In addition, gut flora counteracts bacterial invasion through the release of molecules, such as lipopolysaccharides and flagellin, that stimulate the Toll-like receptor signaling triggering immune system activation [54].

Dietary habits considerably influence the composition of intestinal microbiota [55]. In addition to diet, the premature and excessive use of antibiotics contributes to intestinal dysbiosis, and this has been recognized over a long period to increase the risk of intestinal diseases [56].

Intestinal dysbiosis is defined as a pathogenic change in the functions and composition of gut microflora and is associated with intestinal inflammatory diseases [57,58]. A dysbiotic microbiota can overwhelm self-defense mechanisms, resulting in excessive oxidative stress and inflammasome formation. Through the release of toxins, the reduced production of beneficial metabolites, and the disruption of epithelial integrity, intestinal pathogens hyper-activate the immune system and stimulate a chronic inflammatory status that may evolve in a high-grade dysplasia. Long-standing colitis in IBD patients can lead to a particular subtype of colorectal cancer known as colitis-associated colorectal cancer (CAC) [59].

4. Inflammatory and Molecular Mechanisms in IBD

Despite the pathogenesis of IBD is not yet fully understood, it is thought to result from abnormal immune reactions towards microorganisms in genetically susceptible individuals [60]. The immune system in the intestine has a hard responsibility of rapidly and efficiently responding to harmful bacteria, while also tolerating beneficial microbes and food antigens.

The dynamic crosstalk between microbiota, intestinal epithelial cells, and local immune cells represents one of the fundamental features for maintaining intestinal homeostasis and for mounting protective immunity to pathogens [61]. Perturbations in this fine balance, due to genetic and/or external factors (e.g., lifestyle, diet, stress, anxiety, and depression) [62], may result in aberrant and chronic intestinal inflammation, tissue damage, and ultimately in the onset of IBD [63,64].

Several evidence indicates that the development of IBD is influenced by both dysfunctional innate and adaptive immune pathways within the intestine.

The innate immune response represents the primary defense mechanism against harmful microorganisms (Figure 2). Defective intestinal epithelial barrier and increased permeability are two of the major causes of intestinal inflammation and have long been observed in patients with both CD and UC [65,66].

Innate immune cells, such as macrophages, dendritic cells (DCs), neutrophils, natural killer (NK) cells, and innate lymphoid cells (ILCs), as well as epithelial cells, detect bacterial antigens by their pattern recognition receptors (PRRs) expressed both extra- and intra-cellularly [67]. PRRs include Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), and RIC-1-like receptors (RLRs) [61]. These receptors, by recognizing conserved structural motifs on

microorganisms (known as pathogen-associated molecular patterns (PAMPs) lead to the activation of several signaling pathways and the production of pro-inflammatory cytokines, chemokines, and antimicrobial ensuring an effective innate response against pathogens [68]. Innate immune cells also activate effector cells, such as T helper lymphocytes, and inhibit the activation of T regulatory cells [69].

In the healthy intestine, basal PRR activation maintains barrier function and commensal composition, but aberrant PRR signaling may contribute to the pathophysiology of IBD.

Evidence suggests that the over-expression of certain TLRs and down-regulation of TLR antagonists may lead to an improper reaction to commensal bacteria playing a part in the predisposition and perpetuation of IBD [70]. For instance, TLR4 expression was reported to be elevated in colonic tissue of UC and CD patients [71]. The genetic polymorphism in the *NOD2* gene determines a significantly higher incidence of CD associated with decreased functional integrity of the epithelium [72]. Other evidence suggests that loss-of-function mutations of *NOD2* lead to reduced NF- κ B activation and inadequate response which might result in reduced antibacterial agent production and pathogenic microbial invasion [73]. Loss-of-function in *NOD2* may also results in the lack of inhibition of TLR2 stimulation, leading to the activation of inflammatory pathways and excessive Th-1 responses [74].

The inflammasome is considered one of the prominent mediators of innate immunity and recent studies have demonstrated that its activation plays an essential role in the pathogenesis of IBD. Inflammasome processes the precursor of IL-1 β and IL-18 which regulate Th17 and Th1 cells, respectively, amplifying the immune response [75].

A significant increased activation of the IL-1 system was found in the intestinal mucosa of CD and UC patients compared with control group [76]. IL-1 β is a pro-inflammatory cytokine mainly secreted by macrophages, which synergistically acts with TNF- α and IL-6, to induce intestinal inflammation [77].

IL-18 results overexpressed in intestinal lesions of patients with CD. IL-18 facilitates IFN- γ production by Th1 cells and Th2 cytokines, in conjunction with IL-12 and IL-2, respectively [78].

Some studies provide evidence that loss or over-activation of NLRP3, one of the most studied NOD-like receptors that form an inflammasome, may break down the immune balance leading to the onset of intestinal inflammation. Over-activation of NLRP3 caused by various genetic abnormalities lead to development of colitis [79], whereas deficiency of NLRP3 and inflammasome related genes may induce more severe colitis in mice [80]. The inflamed intestinal mucosa recruits a large number of activated M1 macrophages characterized by secreting IL-1, IL-6, TNF- α , IL-12, and IL-23, as well as producing reactive oxygen species (ROS), and proteases that could degrade the extracellular matrix, triggering dramatic inflammation and phagocytosis of pathogens [61]. M1 macrophages also induce tight junction break down, epithelial barrier damage, epithelial cell apoptosis, and T helper responses, causing tissue damage and aggravating the inflammatory response [81].

The modulation of macrophage polarization by inhibiting the pro-inflammatory M1 subset and/or inducing the anti-inflammatory M2 subset may attenuate IBD. M2 macrophages promote resolving inflammation and remodeling tissue by producing several factors, especially IL-10 [82]. The lack of macrophage-derived IL-10 or inhibition of M2-like phenotype may result in macrophage hyper-responsiveness and in the exacerbation of colitis [83].

Gut DCs are activated with high levels of specific TLRs in IBD patients and lead to the production of high levels of IL-12 and IL-6, altering the mucosa and triggering inflammation. They further promote the inflammatory state by migrating to peripheral lymphoid tissue, where they generate antigen-specific T-cell responses [84].

ILCs are involved in the first line of immune response via the instant release of huge amounts of effector cytokines that orchestrate further immune reactions [85]. ILCs can be categorized into three main subgroups: ILC1s, ILC2s, and ILC3s. ILC1s, including cytotoxic NK cells, amplify immune responses against intracellular pathogens, via an extensive release of IFN- γ and TNF- α , whereas ILC2s and ILC3s are characterized by the secretion of effector cytokines IL-5, IL-13, IL-9 and IL-17A, IL-22, respectively. Tight control of ILCs number and their activation status guarantee barrier

integrity and tissue homeostasis without the induction of chronic immune responses. Remarkable numerical changes in ILC populations have been found in inflamed intestine tissues. In particular, ILC1s are increased at sites of active inflammation in patients suffering from IBD [86].

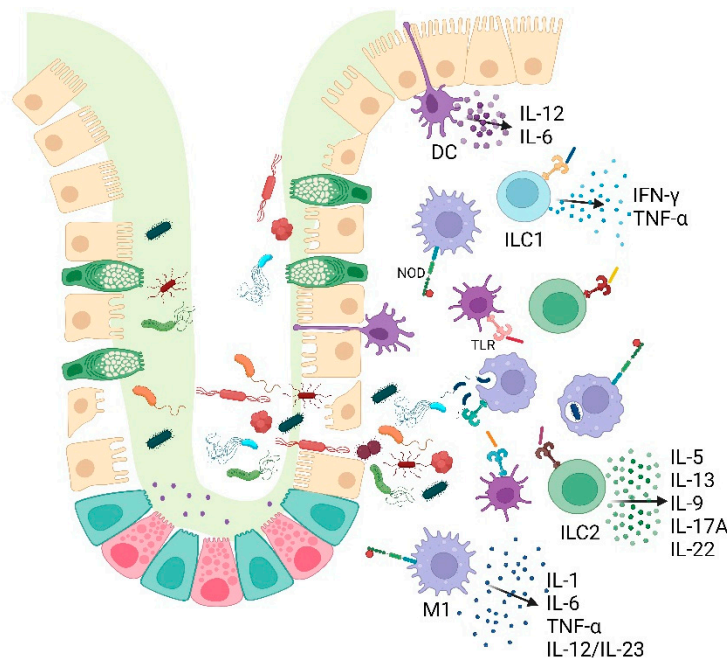


Figure 2. *Innate immune system.* Macrophages, neutrophils, dendritic cells, natural killer, and innate lymphoid cells are the main actors of innate immunity. Innate immune response is fast and non-specific and provides an initial defense against infections after the recognition of non-self-components by the PRRs presenting on the membrane of the specialized cells. This leads to the neutralization or disruption of external antigens and to the activation of the adaptive immune system (created with BioRender).

Innate immune cells also promote antigen presentation and T cell activation participating in the crosstalk between innate and adaptive immune response [69] (Figure 3).

CD4⁺ T cells are the key players of the adaptive immune response, and they cooperate with the molecules and cells of the innate immune system to mount an effective immune response. The activation and the differentiation of Th0 cells into Th1, Th2 or Th17 is essential for the clearance of specific pathogens. IL-12/23 group is produced by activated antigen-presenting cells and promotes IBD by driving pathogenic T cell responses. In particular, IL-12 may promote the differentiation of naive CD4⁺ T cells into IFN- γ producing Th1 cells and the proliferation and effector functions of NK cells and cytotoxic T cells [87], whereas IL-23 reinforce Th17 cell response and antagonizes the anti-inflammatory responses of Treg cell responses to promote [88].

Abnormal development of activated T cells may lead to the onset of inflammation by an excessive release of cytokines and chemokines. Increased activity of Th1 producing higher amounts of IL-2, TNF- α and IFN- γ and Th2 characterized by an excessive production of IL-4, IL-5 and IL-13 have been observed in CD and UC, respectively [89,90]. Cytokines released by activated Th1 and Th2 are considered mediators of the lesions in inflamed mucosa of IBD patients. Th1 cells accumulate in the intestinal tract of individuals with CD and are directly associated with disease. Th1 cytokines activate the transcription factor STAT1 leading to up-regulation of transcription factor T- β , and recruitment of macrophages, NK cells, and CD8⁺ T cells and thus the release of multiple downstream inflammatory cytokines, such as IL-6. In particular, IFN- γ is considered one of the major drivers of excessive immune response which leads to massive leukocyte infiltration and mucosal damage by inducing enterocyte apoptosis [89]. TNF- α , which level correlates with the clinical disease activity of

CD patients, promotes the secretions of IL-1 and IL-6, and activates apoptosis pathway, JNK pathway, and NF- κ B pathway stimulating the acute phase response [91,92].

IL-6 has been found increased in CD and UC patients. Augmented IL-6 levels are related to frequency of relapses and the severity of inflammation [93]. After binding to its receptor, IL-6 promotes the increased expression and nuclear translocation of STAT3, which results in the intestinal T-cell resistance to apoptosis through induction of the anti-apoptotic genes Bcl-2 and Bcl-xl [94]. The released IL-6 also results in the expression of some adhesion molecules and chemokines involved in neutrophils recruitment [95], in the differentiation of Th17 cells [96], and in the prevention of Treg differentiation, leading to chronic intestinal inflammation [97].

IL-13 released by Th2 cells has been shown to increase intestinal permeability and induce enterocyte differentiation and apoptosis [90,98].

Th17 cells are characterized by the production of IL-17A, IL-21, and IL-22 which exert an inflammatory role by activating STAT3. Clinical studies have found that the intestinal mucosa and lamina propria of IBD patients contain much higher levels of Th17 cells and IL-17 compared with the healthy controls [99,100]. The expression of IL-17 in peripheral blood mononuclear cells (PBMCs) of subjects with UC has been shown to correlate with the severity of the disease [101]. IL-17A induces neutrophil recruitment to the inflammatory site and mediates pro-inflammatory cytokine production by macrophages [102].

The activation and the effector function of Th cells is prevented by regulatory T (Treg) cells. Treg cells play a negative immunomodulatory role in immune tolerance and are involved in the maintenance of gut mucosal homeostasis by suppressing abnormal immune responses through the production of anti-inflammatory cytokines, such as IL-10 and TGF- β [103]. IL10 influences the renewal of intestinal stem cells and the regulation of the intestinal microflora promoting the proper functioning of the intestinal epithelial barrier [104], whereas TGF- β regulates immunological homeostasis [105].

IL-10 affects the activity of Th17 and inhibits the antigen presenting cells by reducing the expression of MHC. In particular, IL-10 inhibits the synthesis of pro-inflammatory cytokines, such as IL-1 β , TNF- α , IL-6, and the Th2 cell-derived cytokines, chemokine release, as well as the expression of inflammatory enzymes in macrophages and the proliferation of CD4⁺ T. In addition, IL-10 increases the expression of several anti-inflammatory proteins, including IL-1 receptor antagonist, soluble TNF- α receptor, and tissue inhibitor of matrix metalloproteinases [104]. Loss-of-function mutations in the genes encoding for IL-10 and IL-10 receptors have been associated with a very early-onset form of IBD [106].

A main function of TGF- β signaling in T-cells is to suppress T-cell proliferation and activation through Treg differentiation. Impairment of TGF- β signaling increased colitis progression [107].

Unfortunately, Treg cells are depleted in peripheral blood of patients with active IBD compared to control group [108]. Therefore, the decrease in anti-inflammatory activity of Treg may be an important mechanism in contributing to IBD pathogenesis. Of note, it has been observed that Treg stimulated with IL-6 can express IL-17, thus acquiring the Th17-like cells phenotype. This phenomenon seems to be irreversible and could be important during the onset of chronic mucosal inflammation [109].

The study of interactions between cells and products of the innate and adaptive immune systems and their relationship with the intestinal microbiota, has led to new advancements in the development of novel strategies for the treatment of IBD. Given the fundamental role of cytokines in controlling mucosal inflammation in IBD, the utilization of recombinant anti-inflammatory cytokines or antibodies specific for pro-inflammatory cytokines [110,111], as well as the use of specific neutralizing antibody [112,113], may be an effective method for suppressing chronic intestinal inflammation in IBD suppressing patients.

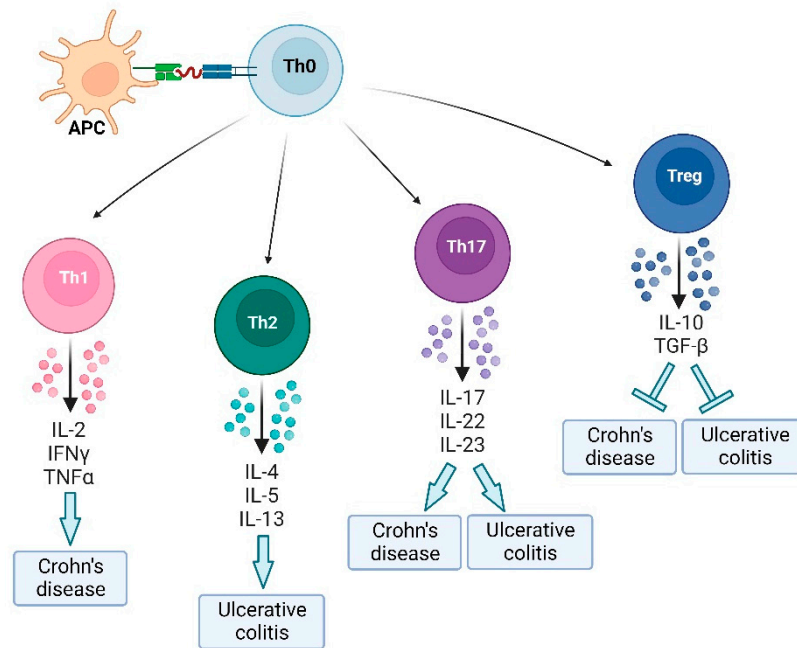


Figure 3. Adaptive immune system. Adaptive immune response is secondary to the innate response and requires the activation of lymphocytes. The activation and the differentiation of Th0 cells into Th1, Th2 or Th17 is essential for the clearance of specific pathogens through the release cytokines and chemokines. Abnormal expansion of activated T cells is found in IBD patients (created with BioRender).

5. Autophagy and the Maintenance of Intestinal Epithelial Barrier

Autophagy is deregulated in several diseases, including neurodegenerative and metabolic disorders, cancer, and inflammatory diseases, and contributes to the pathogenesis and disease progression [114]. Of note, autophagy may prevent the onset of the inflammatory chronic disease by modulating the immune system functions, the inflammasome formation and production of cytokines, and participating in pathogen clearance [115,116].

Autophagy is a highly conserved catabolic process in eukaryotic cells that physiologically participates in the maintenance of cell homeostasis through the lysosome-mediated degradation of damaged, aged, or redundant cellular components, as well as the destruction of intracellular pathogens. In response to several stress conditions, such as lack of nutrients, growth factor deprivation, infections, and hypoxia, cells induce autophagy as an adaptive mechanism to obtain amino acids during challenging environmental conditions. By contrast, growth factors, insulin, and amino acids induce the activation of the master negative regulator of autophagy, the mammalian target of rapamycin (mTOR), whose activation stimulates protein synthesis, cell survival, proliferation, and growth by inhibiting autophagy pathway.

Several studies have extensively reported the role of autophagy in the regulation of innate and adaptive immune cells, as well as in stromal cells. Recently, a new involvement of autophagy has been emerging in intestinal epithelial cells (Figure 4). *In vivo* and *in vitro* results, and clinical studies, show that autophagy is fundamental for intestinal homeostasis, immune response, and prevention from pathogen colonization.

GWAS found that SNPs in autophagy-related genes have been associated to genetic susceptibilities in developing inflammatory disease and, at last, colorectal cancer [117,118].

Paneth cells are considered the origin site of intestinal inflammation [119]. During pathogen infection in a cell where the Golgi apparatus is impaired in packaging and transporting vesicles containing antimicrobial peptides, Paneth cells trigger secretory autophagy as an alternative mechanism for the release of the lysozyme. *ATG16L1* deficiency in intestinal epithelial cells, typical of CD patients, results in a defective morphology of Paneth cells, which fail in the release of

antimicrobial peptides and in the mucin production [120,121]. Polymorphic variants in *ATG16L1* sequence reduce the ability of dendritic cells to process antigens in the luminal compartment of gut and induce the expression of a pro-inflammatory phenotype in these cells [122].

Nucleotide binding oligomerization domain containing protein 2 (NOD2) induces autophagy by sequestering ATG16L1 on cell membrane. *NOD2* frameshift mutations interfere with the homeostasis of the intestinal microbiota and excessively stimulate inflammatory responses in the gut. *NOD2* polymorphisms prevent protein interaction with ATG16L1 in the plasma membrane, increasing susceptibilities to CD. This results in an impaired clearance of intercellular bacteria and increases the release of inflammatory cytokines [121]. *NOD2* loss-of-function mutations hamper the activation of NF- κ B against pathogens recognized by PRRs, leading to an exacerbated Th1 response [74].

Autophagy dysregulation in Paneth cells also affects the function of the whole intestinal cell populations. Paneth cells contribute, at least in part, to the molecular signals required for maintaining the stemness behavior of ISCs. Stem cells utilize the ATP generated through the oxidative phosphorylation, and autophagy in Paneth cells serves as protection mechanism against oxidative stress resulting from ROS production [123]. In case of chronic inflammation, defective Paneth cells are inefficient in supporting ISCs, making them more susceptible to ROS and lacking the proliferative response crucial for intestinal epithelial regeneration [124].

Crohn's disease-associated polymorphisms in the sequence of *MTMR3* (myotubularin related protein 3) and *PTPN2* (protein tyrosine phosphatase, non-receptor type 2) genes compromise autophagy by interfering with autophagosome formation and exacerbate the secretion of inflammatory cytokines [125,126].

Besides polymorphic variants and mutations, also miRNAs participate in the regulation of autophagy-related genes [127–130]. miR-106b and miR-93 interfere with the clearance of Crohn's disease-associated bacteria by contrasting the formation of autophagosome [130].

Autophagy is also involved in the occurrence of UC, although to a lesser extent than what has been observed in CD. Genomic analysis of patients with UC reveals a reduced expression of the autophagy-related protein activating transcription factor 4 (ATF4) in the intestinal inflamed mucosa compared to the mucosa of the normal counterpart [131].

The anti-inflammatory role of autophagy is related to its interaction with the inflammasome complex, the central player in inflammation. As described above, NLRP3 stands out as the most studied multi-protein complex that takes charge of triggering inflammatory responses. NLRP3 function is connected to CASP1 activity, leading to the release of IL-1 β and IL-18. In the inflammatory process, NLRP3 interacts with mTOR promoting its phosphorylation and subsequent activation. The accumulation of pro-inflammatory cytokines and mediators, due to NLRP3 inhibition of autophagy, intensifies inflammatory response. The accumulation of damaged mitochondria releasing NLRP3-activating signals, coupled with ROS production and Th17 responses, amplifies aberrant inflammasome activation thereby contributing to chronic inflammation [132]. To prevent the exacerbation of the inflammatory response, cells autonomously activate autophagy, promoting the NLRP3 autolysosome inclusion, and subsequent autophagic degradation [133]. Autophagy may degrade ubiquitinated inflammasome and the inactive precursor of IL-1 β [134]. *ATG16L1* deficiency impairs autophagy and results in the accumulation of IL-1 β and IL-18 in serum under the stimulation with lipopolysaccharide in colitis-exposed mice [135].

The targeted deletion of the gene encoding the autophagy adaptor SQSTM1/p62, specifically in macrophages, results in the accumulation of damaged mitochondria, excessive inflammasome activation, accumulation of IL-1 β , and macrophage death [136].

Autophagy regulates tight junction expression. Its induction induces the degradation of claudin 2 (CLDN2) allowing the selective cation passage. The lysosomal degradation of this tight junction reduces cell permeability in intestinal epithelial barrier. TNF positively regulated the turnover of claudin 2, increasing epithelial permeability and contributing to the onset of intestinal inflammatory disease [137,138]. The intestinal barrier permeability is regulated also by the interaction between occludin and BECLIN1. Their interaction on the plasma membrane leads to occludin endocytic

internalization reducing the integrity of the intestinal barrier. The interaction between BECLIN1 and occludin occurs independently of autophagy. However, when autophagy is induced, it interferes with BECLIN1-occludin interaction. This interference restores the localization of occludin in plasma membrane and re-establishes the barrier integrity [139].

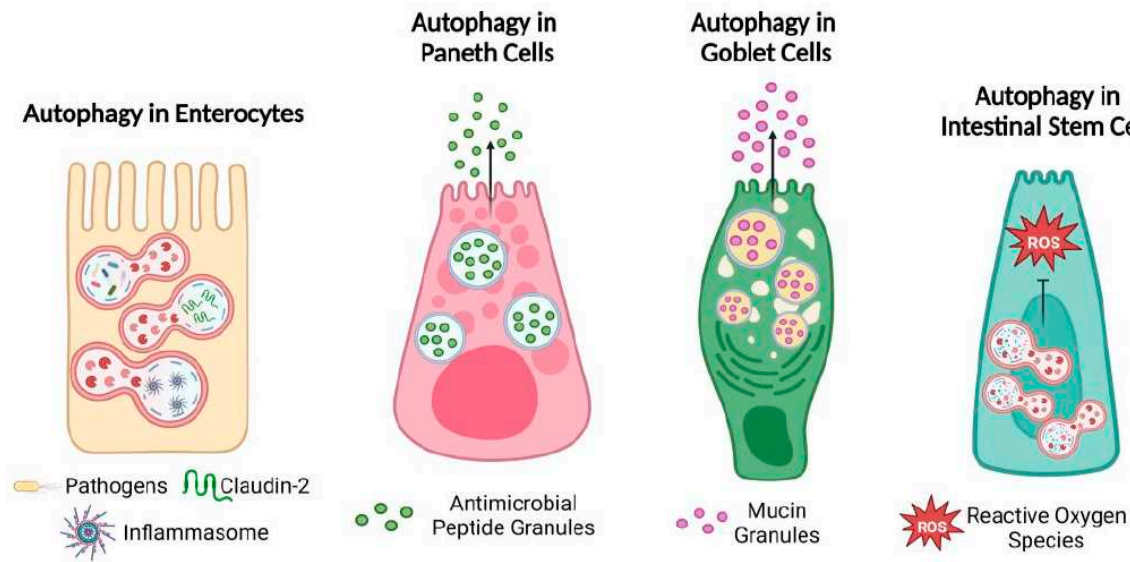


Figure 4. Role of autophagy in the maintenance of the correct function of intestinal epithelial cells. In enterocytes, autophagy limits pathogen invasion and proliferation, enhances barrier integrity, and modulates the inflammatory response through the degradation of inflammasome complex. In Paneth cells and goblet cells, autophagy regulates the formation and the secretion of antimicrobial peptide and mucin granules, respectively. In intestinal stem cells, autophagy maintains stemness properties and protects the cells from oxidative stress (created with BioRender).

6. Gut Dysbiosis in the Inflamed Gut Microenvironment

The intestinal epithelial barrier constitutes the first line defense mechanism against external agents. Compromising this physical wall means mucosal layer reduction, increase of intestinal permeability, dysregulation of immune response, and gut translocation of microbial molecules and pathogens that overall lead to a systemic inflammatory status.

A growing body of evidence suggest a correlation between the composition of intestinal microbiota and the chronic intestinal inflammation. This emphasizes that the intestinal dysbiosis may act as both the cause and outcome of chronic inflammation [140]. Microbiome analysis report that the dysbiotic gut microbiota in IBD patients triggers chronic immune activation and inflammation in colon. However, the colonization of the intestinal mucosa of IBD patients by microbiota from healthy donors prevents colitis. This suggests that the occurrence of a dysbiotic microenvironment is a fundamental aspect of IBD pathogenesis [141] (Figure 5).

To examine the gut microflora in individuals potentially affected by IBD, microbiome studies focus on α and β diversity parameters. These parameters relate to the variety of bacterial species in the same sample or across different samples, respectively. The main difference in the microbiota between IBD patients and the healthy group results in the reduction of biodiversity [142]. Microbiome sequencing of CD- and UC-affected patients revealed an increase of *Proteobacteria*, *Ruminococcus*, and pro-inflammatory strains, including species from *Enterobacteriaceae*, particularly *E. coli*. Conversely, there is a reduction in butyrate-producing *Firmicutes*, *Bacteroidetes*, *Lactobacillus*, *Eubacterium*, *Roseburia*, and *Faecalibacterium* species, all of which are involved in the production of butyrate, along with a decrease of anti-inflammatory bacteria (e.g., *Faecalibacterium prausnitzii*) [143–148]. Specifically, in individuals with CD, there is a reported increase in *Enterobacteriaceae*, including *E. coli* and

Fusobacterium, as well as *Ruminococcus gnavus*, accompanied by a decrease in *Bifidobacterium adolescentis*, *Dialister invisus*, and *Faecalibacterium prausnitzii* [149,150].

The gut microenvironment is influenced by the availability of nutrients and oxygen, determining the growth of various bacteria species. During inflammation, pathogenic bacteria take advantage from the condition, engaging in competition with commensal bacteria for the mucosal compartment. *Salmonella typhimurium* and *Citrobacter jejuni* are two of the main pathogens associated with infection and inflammation in human [151,152]. The initiation of inflammation raises the level of oxygen in the gut, favoring the colonization and the proliferation of facultative anaerobes strains (*E. coli*, *Salmonella*, *Shigella*, *Proteus*, and *Klebsiella*), even though the obligate anaerobic bacteria are still producing butyrate [153]. This metabolic shift amplifies the gut oxygenation and increase the lactate level in the intestinal lumen [154]. When the commensal microbial flora decreases, impairing butyrate production, colonocytes fail to utilize SCFAs as their primary fuel source and to maintain normal levels of ATP necessary for the maintenance of the intestinal epithelial barrier. The absence of butyrate also favors the expression of the “leaky” tight junction protein Claudin-2 and the downregulation of the “tight” one [155]. This outcome creates an energy-deficient mucosa, defined as “starved”, which promotes bacterial translocation in the lamina propria and entry in the systemic circulation [156,157]. This observation is supported by serum analysis revealing that IBD patients display elevated levels of lipopolysaccharide compared to their healthy counterparts. Importantly, this condition persists even when symptoms are in remission among patients with inactive CD, suggesting a compromised intestinal homeostasis [158].

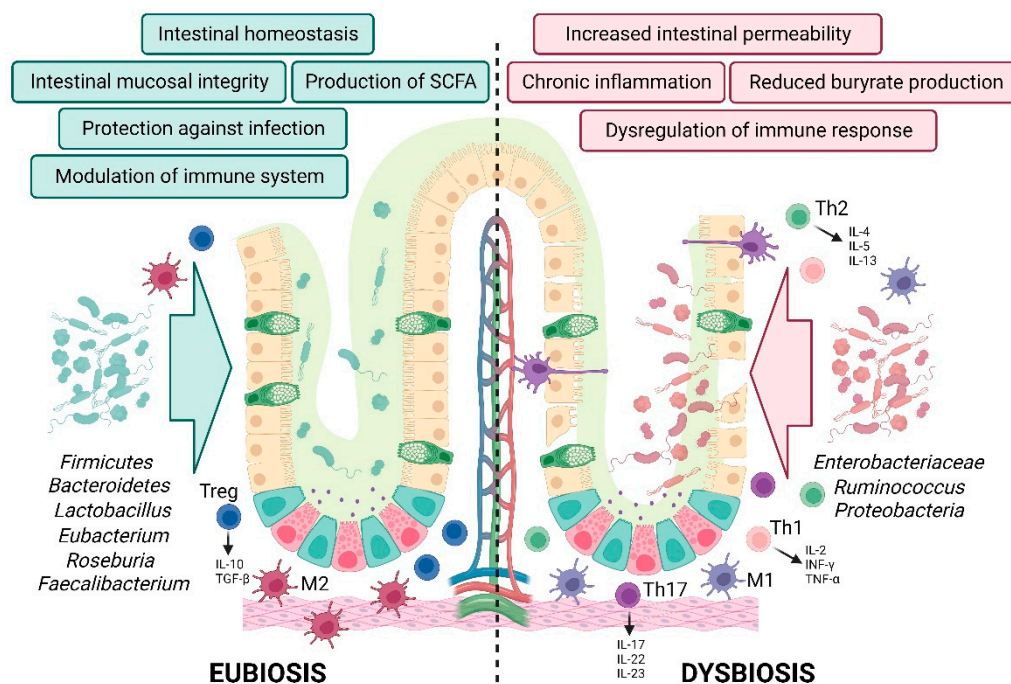


Figure 5. The relationship between gut dysbiosis and inflammatory bowel disease. The condition of eubiosis, which defines the balance between the host and bacteria, is essential for proper intestinal homeostasis and host health. Alteration in the function and composition of gut microbiota due to environmental changes results in a condition defined as dysbiosis, which leads to the onset of IBD (created with BioRender).

7. Therapeutic Strategies for Manipulating Intestinal Microbiota

The therapeutic protocols for managing IBD are designed to extend the remission phase and involve medical and surgical interventions focused on addressing symptoms. Pharmacological treatments for patients suffering from IBD include corticosteroids, immunosuppressant agents,

antibiotics, monoclonal antibodies, and biologic therapies [159]. Clinical trials suggesting the potential use of current small molecules and biological drugs, such as interleukin inhibitors, integrin inhibitors, modulator of sphingosine-1 phosphate, and JAK inhibitors, have been recently presented in [160]. However, the effectiveness of these treatments differs among patients, and their prolonged administration is associated with a high risk of developing drug tolerance and side effects.

Given the recognized role of gut microbiota in preserving intestinal homeostasis, treatments aiming to induce or sustain remission in IBD patients by restoring a healthy microbial environment have been proposed and are still ongoing, showing promising success [161]. Manipulating the gut microbiota may be the best choice proposed as a weapon in the challenge of IBD. Current strategies include fecal microbiota transplantation (FMT) and the administration of living bacteria capable of re-colonizing the intestinal mucosa and restoring gut homeostasis balance.

7.1. Therapeutic Strategies for Manipulating Intestinal Microbiota

Fecal microbiota transplantation (FMT) is a procedure involving the transplantation of healthy donor feces into the gastrointestinal tract of patients with chronic intestinal diseases, aiming to reverse microbiota dysbiosis. This can be carried out through i) enema or endoscopy, both of which are invasive approaches often poorly tolerated by patients, or alternatively, through ii) the oral delivery of lyophilized and stable bacteria in capsules, a method that is more favored by the recipients [162,163].

The FMT approach is currently utilized for treating *Clostridium difficile* infections, which arise after prolonged use of antibiotics against this microorganism and result in disruptions to gut microbiota homeostasis [164].

Despite variations in FMT protocols across different clinical trials, including differences in donor selection criteria, patient treatment, and therapy administration, the success of the interventions is reported in more than 90% of cases [165]. This highlights the promising outcome of these therapies, suggesting the potential application of FMT in the management of other diseases associated with dysbiosis, addressing the attention on IBD. Recently, a large body of evidence has demonstrated that patients with IBD who undergo FMT exhibit positive clinical outcome with an increase in microbiota composition and biodiversity. Notably, the microbiome of the recipients closely resembles the donor microbiome profile [166]. These findings support the consideration of FMT as a primary treatment of IBD [167–170].

Studies conducted on IBD patients report that recipients of FMT exhibit a higher remission rate compared to the placebo group [171,172]. Specifically, in UC patients, FMT induces remission within 8 weeks of the intervention [173] and prevents relapse [166]. Additionally, FMT is linked to an increase in butyrate production [174]. Clinical symptoms are alleviated and lesions in the colonic mucosa decreased [175]. For CD patients, the transplantation reduces the severity of the disease and the expression of inflammatory markers, along with an improvement in symptoms such as diarrhea, fever, and abdominal pain. This results in significant changes in gut microbiota composition, with qualitative and quantitative modifications in the microbiome profile [176,177]. FMT appears to be a promising strategy in the challenge for IBD treatment, though further investigations and extensive studies on safety and long-term effects are needed.

7.2. Probiotic Supplementation

The employment of bacterial strains that modulate the composition of gut microbiota and restore homeostasis in host-microbe interactions holds potential in the management of IBD, similar to the FMT approach. The beneficial effects mediated by commensal bacteria on the intestinal mucosa and microenvironment are achieved through the administration of probiotics, defined by the Food and Drug Administration as “live microorganisms that confer a health benefit to the host when administered in adequate amounts” [178].

For the past three decades, probiotics have been utilized in the treatment of IBD [179]. Probiotics exhibit beneficial properties in murine and rat models of colitis. Several strains of *Bifidobacterium*, *E. coli*, and *Lactobacillus* demonstrate anti-inflammatory effects [180] and reduce the outgrowth of

pathogens by competing for nutrients [181]. Supplementation with *Bifidobacterium*, *Lactococcus acidophilus*, and *Enterococcus* in mouse models of colitis positively regulates the expression of tight junctions and influences the T cells population, particularly increasing Treg cells [182].

Patients affected by UC and treated with supplementation of *Bifidobacterium longum* and *Escherichia coli* Nissle 1917, display improved outcome, and the probiotics acts as well as the therapy with mesalazina in keeping the remission of the disease [183,184]. *Propionibacterium freudenreichii* modulates host inflammation by regulating the release of the anti-inflammatory cytokine IL-10, similar to engineered *Lactococcus lactis* which shows protective in murine models of colitis [185,186]. Children and adolescents with mild or moderate-grade UC treated with supplementation of *Lactobacillus lactis* show improvements in the restoration of intestinal mucosa compared to the control group [187].

The use of a probiotic mixture containing strains of *Lactobacillus*, *Bifidobacteria*, and *Streptococcus*, known as VSL#3, has demonstrated the induction and the maintenance of disease remission in UC patients [188]. VSL#3 is employed either as adjuvant therapy or as monotherapy [189]. This mixture reduced the expression of inflammatory cytokines by inhibiting the signaling of TLR4/NF- κ B and downregulating the expression of NF- κ B and TNF- α [180]. In UC patients, *Lactobacillus rhamnosus*, either as monotherapy or in combination with mesalazine, has shown a safer and more effective effect than the administration of mesalazine alone, maintaining remission from the disease [190].

Different outcomes have been reported in clinical trials conducted on CD patients, suggesting the need for well-designed trials to assess the efficacy of probiotics in the treatment of CD [191]. *Lactobacillus rhamnosus* does not demonstrate any beneficial effect on children with CD, and in some case, it may lead to the relapse; similarly, VSL#3 has shown a loss of effectiveness [192]. Other trials are exploring the role of non-bacterial probiotics, including the use of yeast, such as *Saccharomyces boulardii*, which reduces exacerbation in CD patients and improves intestinal barrier permeability when combined with other therapy [193,194].

Given their role in immune system modulation, probiotics may open up new therapeutic possibilities for IBD patients [195]. However, severe intestinal damage may not be reversible and the use of probiotics as a tool for gastrointestinal diseases could be associated with the risk of significant side effects (i.e., bacteremia or sepsis) in patients with compromised immune defenses. After 13 days of oral probiotics administration, a UC adult patient experienced a worsening in health status due to bacteremia [196]. Therefore, the therapy should be considered individually for each patient. Only specific probiotic strains that have been well-tested and administered in proper doses should be employed for managing patients.

8. Conclusions

Crohn's disease and ulcerative colitis are chronic inflammatory disorders that increase the risk of colitis-associated colorectal cancer two to three times more than in healthy individuals. Due to the complexity and the heterogeneity of the disease, fully understanding the pathogenetic mechanisms is challenging. Existing therapeutic approaches focus on symptoms management to enhance and sustain the remission phase rather than targeting the removal of triggering event.

The manipulation of the gut microbiota through fecal microbiota transplantation or the administration of bacterial strains that restore and maintain intestinal microbiota homeostasis, has proven to be a beneficial strategy for treating IBD. This primarily involves modulating inflammatory pathways and promoting mucosal healing through the synergistic action of different strains. Probiotic therapy has demonstrated effectiveness in rat and mouse models, as well as in clinical trials, either in monotherapy or in combination with the current drugs. Probiotics restore the population of commensal bacteria and appear to have a protective role in patients, showing promise as a therapeutic strategy. However, additional studies are needed to confirm the safety and the effectiveness of this novel approach in the management of IBD. The current findings present some limitations that should not go unnoticed: i) the widely used in vivo models do not entirely replicate the human disease due to the distinct organization of the gastrointestinal tract; ii) the key players involved in the pathogenesis cannot be artificially reproduced; iii) potential side effects arising from

the compromise immune system of IBD patients need to be considered. To overcome this last limit, one solution may be to exploit post-biotics (microbial components and metabolites released by live bacteria) as a mixture in combination with probiotics, which could be safer than living microorganism. Taken together, the future of gut bacteria-based therapy must be improved, further developed, and confirmed to clarify whether this approach may be an option in the treatment and resolution of IBD.

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