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The role of gut microbiota, immune system, and autophagy in the pathogenesis of inflammatory bowel disease: Molecular mechanisms and 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 microbial 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 microbial flora, and the role of autophagy in intestinal epithelia homeostasis. Further, we illustrate 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.

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 where the Western diet and lifestyle are being adopted (Kaplan and Windsor, 2021; Sugihara and Kamada, 2021).

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 (Maaser et al., 2019). 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 (Khor et al., 2011).

Although the etiopathogenesis is not fully understood, IBD is a multifactorial disease whose rise and progression rely on a complex

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colites; GWAS, genome wide association study; SNP, single nucleotide polymorphism; ISC, intestinal stem cell; GALT, gut-associated lymphoid tissue; SCFA, short-chain fatty acid; IEC, intestinal epithelial cell; HDAC, histone deacetylase; CAC, colitis-associated colorectal cancer; DC, dendritic cell; NK, natural killer; MC, mast cell; ILC, innate lymphoid cell; PRR, pattern recognition receptor; TLR, Toll-like receptor; CLR, C-type lectin receptor; NLR, NOD-like receptor; RLR, RIC-1-like receptor; PAMP, pathogen-associated molecular pattern; ROS, reactive oxygen species; PBMC, peripheral blood mononuclear cell; FMT, fecal microbiota transplantation.

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interplay between genetic, environmental, and microbiological factors that leads to an uncontrolled immune system activation (Ko et al., 2014). About 300 genes directly associated with IBD have emerged by genome wide association studies (GWAS) and meta-analysis, and their polymorphisms may expose people to a high risk of developing the disease (Jostins et al., 2012).

Recent GWAS have identified novel single nucleotide polymorphisms (SNPs) whose genetic variants may increase the patient's genetic susceptibility to loss of intestinal homeostasis (Zhang and Li, 2014). Of note, genetic variants in autophagy-related genes result 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 (Larabi et al., 2020). Besides, epigenetic mechanisms (such as DNA methylation and miRNAs) may contribute to IBD development and progression by interfering with T-cell differentiation, cytokines regulation, Th17 molecular signaling, and autophagy (Annese, 2020).

Metagenomic studies reported that patients suffering from IBD present an altered balance in gut bacteria function and composition, a condition referred to as dysbiosis, compared to the healthy group. The composition of commensal bacteria results in a reduced bacterial biodiversity with a decrease of obligate anaerobic strains, such as *Firmicutes* and *Bacteroides*, and predominant facultative anaerobic strains, such as *Proteobacteria* (Liu et al., 2021). 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 (Kostic et al., 2014).

Here, we present an overview of the current knowledge on the molecular mechanism underlying the pathogenesis and progression of IBD, with a particular focus on the role of autophagy in dampening inflammation and preserving the immune homeostasis in the intestine. We also mention the novel therapeutic strategies based on the fecal microbiota transplantation and probiotics strain supplementation that aim to restore the beneficial crosstalk between the microbiota and the host.

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 gut lumen. 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 (Peterson and Artis, 2014) (Fig. 1).

The intestinal epithelium, composed of a single layer of columnar polarized cells, undergoes a self-renewal process approximately every 5–7 days. The intestinal epithelium renews through pluripotent intestinal stem cells (ISCs) in Lieberkühn crypts (Barker, 2014). These cells proliferate, migrate to the upper surface, differentiate, and undergo apoptosis within a few days, ensuring continuous regeneration and structural integrity of the gut (van der Flier and Clevers, 2009).

The differentiated cells deriving from ISCs include enterocytes, Paneth cells, enteroendocrine cells, goblet cells, and tuft 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 the secretion of signaling molecules and regulate the microbial flora with antimicrobial peptides and immunomodulatory signals. A decreased expression of Paneth cell-derived α-defensins and defective anti-microbial peptides have been observed in patients with CD (Wehkamp et al., 2005; Arijs et al., 2009). Enteroendocrine cells produce hormones governing food digestion, absorption, and appetite, also acting as communication molecules with the immune system (van der Flier and Clevers, 2009; Salzman et al., 2007). Goblet cells, the specialized entities responsible for secretion, release a glycoprotein network that composes the mucus layer covering the intestinal epithelium (Johansson et al., 2011). Mucin proteins produced by these cells create a gel-like structure that serves as the first line of defense against bacteria and inflammation in the intestine, preventing direct contact between the gut lumen and epithelial cells. This structure provides an adhesion substrate for the microbiota niche and simultaneously impedes the transepithelial invasion of microorganisms into the systemic circulation (Schroeder, 2019). The mucus layer exhibits antimicrobial properties by releasing secretory immunoglobulin A and antimicrobial

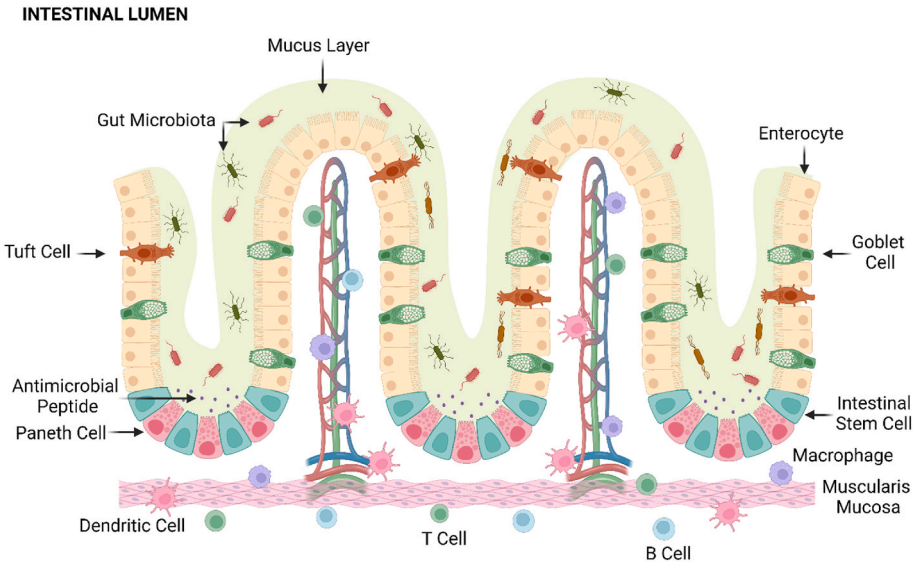

Fig. 1. *Intestinal epithelial barrier.* The intestinal epithelial barrier is constituted by a single layer of specialized cells (enterocytes, goblet cells, Paneth cells, intestinal stem cells, and tuft cells) that create a physical wall against the external microenvironment. The covering mucus layer 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 orchestrate the immune or tolerant response toward microbes and luminal antigen (created with BioRender).

molecules targeting viruses, fungi, and bacteria. The structural characteristics of the mucus, including its composition and thickness, maintain intestinal health. Several factors, including pro-inflammatory cytokines, growth factors, neuropeptides, microbes, and toxins, can influence mucins production and mucus layer architecture, ultimately disrupting gut homeostasis and triggering an inflammatory response (Kebouchi et al., 2020). Tuft cells are secretory epithelial cells involved in type II immune response acting as immune sentinels for parasitic infections. These cells release IL-25, which stimulates innate lymphoid cells to produce IL-4 and IL-13, which in turn stimulate the differentiation and the increased activity of tuft cells, as well as mucus production by goblet cells. This positive feedback results in the removal of parasites (Hendel et al., 2022; von Moltke et al., 2016).

A recent study has demonstrated that the lack of tuft cells in mice, due to the knock-down of *Pou2f3* transcription factor, results in a late immune response against helminths. The treatment with recombinant IL-25 restores an immune response comparable to that observed in control mice, highlighting the driving role of IL-25 in the immune response type II mediated by tuft cells (Gerbe et al., 2016).

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 (Mörbe et al., 2021). Intestinal macrophages remain essentially anergic in response to TLR stimulation despite their phagocytic and bactericidal activity (Smythies et al., 2005). In the lamina propria, the macrophages release large quantities of IL-10 to inhibit the differentiation of Th1 and Th17 and promote the differentiation of anti-inflammatory Treg cells, whereas dendritic cells tend to promote the formation of pro-inflammatory Th17 (Denning et al., 2007). These two activities maintain the equilibrium between protective immunity against harmful bacteria and immune tolerance toward commensal microbes and food antigen and prevent intestinal inflammation.

Adjacent epithelial cells are firmly connected to the apical surface through tight junctions that are formed by transmembrane proteins, including claudins and occludins. The multiprotein complexes, interacting with the actin-myosin cytoskeleton via scaffold molecules (Balda and Matter, 2016), maintain cell polarity and ensure the integrity of the intestinal epithelium. 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 (Schulzke and Fromm, 2009). Claudins are classified 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 in the crypt and luminal surface, and throughout the entire gastrointestinal tract (Tsukita et al., 2019). Occludin is a component of the intracellular domain of tight junctions and is necessary for their assembly. The phosphorylation of specific residues influences occludin localization: low phosphorylation leads to cytoplasmic accumulation, while high phosphorylation induces relocation within the tight junction complex (Dörfel and Huber, 2012).

The integrity of intestinal epithelial barrier is guaranteed also by adherens junctions. 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 (Niessen and Gottardi, 2008; Hartsock and Nelson, 2008). Defective epithelial junctions and alterations in the genes encoding for epithelial junction proteins have been identified as a significant cause of IBD. For instance, SNPs in *CDH1*, which encodes for E-cadherin, have been associated with UC (Anderson et al., 2011). 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 (Su et al., 2013; Ma et al., 2005).

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 (Chen et al., 2021). Though the human microbiota comprises bacteria, fungi and virus, this review focuses on bacteria only since these microbes are the major contributors in IBD pathogenesis, as it will appear evident in the next paragraphs. It has been estimated that the human intestine hosts up to ~39 trillion bacteria (which is very close to the number of cells in a 70 kg body) belonging to > 4500 different microbial species (Sender et al., 2016; Nayfach et al., 2019). The genomic material of these microorganisms, called microbiome, is one hundred times greater than the human genome (Qin et al., 2010). The composition and the abundance of commensal microorganisms is highly variable in terms of species and is based on the anatomical location along the gastrointestinal tract. Microbiota population is different and changes continuously in each human, contributing to the development of a distinctive microbiome profile (Faith et al., 2013). This profile is established early, beginning during childbirth, and is further influenced by breastfeeding or formula feeding (Penders et al., 2006). 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, drugs, and illnesses) disrupt this balance (Rinninella et al., 2019).

In healthy individuals, the intestinal microbiota can be categorized into four *phyla*: *Actinobacteria*, *Proteobacteria*, *Firmicutes*, and *Bacteroidetes*. Notably, the latter two constitute approximately 90% of human microbiota (Qin et al., 2010). Through the fermentation of non-digestible carbohydrates from the diet, commensal bacteria produce short-chain fatty acids (SCFAs) that are then transported into the intestinal epithelial cells (IECs) (Morrison and Preston, 2016). 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 IECs (Panebianco et al., 2018). 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 (HDAC) (Carlsson et al., 2013; Laval et al., 2015; Basso et al., 2019; Khan et al., 2019; van der Beek et al., 2017).

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 integrity of the gut barrier (Parada Venegas et al., 2019). 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 (Singh et al., 2014). The activation of GPR43 attenuates NLRP3 (Nod-Like Receptor Protein 3) response and the consequent IL-18 secretion (Swanson et al., 2019). By inhibiting HDACs, butyrate from *Clostridium* was shown to increase the expression of TGF-β1 in intestinal cells, which then promotes Treg maturation (Martin-Gallausiaux et al., 2018).

Taken together, the SCFAs produced by commensal bacteria activate biochemical pathways and epigenetic mechanisms that lead to the secretion of cytokines and mediators that ultimately preserve the intestinal integrity and dampen the inflammation, thus restoring immune homeostasis (Zhang et al., 2019). Mouse models lacking a eubiotic gut microbiota display immature lymphoid structures, low lymphocyte

population, and reduced production of antimicrobial peptides (Chung et al., 2012).

Gut microbiota represents a natural defense barrier against pathogens infection (Gagnière et al., 2016). 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 *Escherichia coli* (Maslowski et al., 2009). 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 (Panwar et al., 2021).

Dietary habits considerably influence the composition of intestinal microbiota (Hold, 2014). 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 (Becattini et al., 2016).

Intestinal dysbiosis is defined as a pathogenic change in the functions and composition of gut microflora and is associated with intestinal inflammatory diseases (Gomaa, 2020; Glassner et al., 2020). A dysbiotic microbiota can overwhelm self-defense mechanisms, resulting in excessive oxidative stress and inflammasome activation. 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) (Keller et al., 2019).

4. Inflammatory molecular mechanisms in IBD

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.

Although the pathogenesis of IBD is not yet fully understood, it is thought to result from abnormal immune reactions towards microorganisms in genetically susceptible individuals. Several evidence indicate that the development of IBD is influenced by both dysfunctional innate and adaptive immune systems within the intestine (Strober et al., 2007).

The innate immune response represents the primary defense mechanism against harmful microorganisms (Fig. 2). The key components of this response in the intestine include mucus, bactericidal antigens, tight junctions crucial for barrier integrity, and innate immune cells. 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 (Odenwald and Turner, 2017; Salim and Söderholm, 2011).

Innate immune cells, such as macrophages, dendritic cells (DCs), neutrophils, natural killer (NK) cells, mast cells (MCs), 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 (Rakoff-Nahoum et al., 2004). PRRs include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), and RIC-1-like receptors (RLRs) (Maloy and Powrie, 2011). These receptors recognize conserved structural motifs on microorganisms, known as pathogen-associated molecular patterns (PAMPs), triggering the activation of several signaling pathways. This activation leads to the production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides, ensuring an effective innate response against pathogens (Wallace et al., 2014). Innate immune cells also activate effector cells, such as T helper lymphocytes, and inhibit the activation of T regulatory cells (Holleran et al., 2017).

Normal activation of PRRs in the healthy intestine preserves barrier function and microbiota composition, but their persistent activation 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 aberrant response to commensal bacteria playing a part in the predisposition and perpetuation of IBD (Kordjazy et al., 2018). TLRs are expressed by IECs and stromal cells of the intestine and when activated they induce the transcriptional activity of NF-kB triggering the release of several pro-inflammatory cytokines, including IL-6, IL-12, IL-1, and TNF-α. These secreted cytokines promote the differentiation of Th1 and Th2, as well as dendritic cells (Lu et al., 2018). It has been reported that patients with UC show an increased gene expression of *TLR 2*, *4*, *8*, and *9*

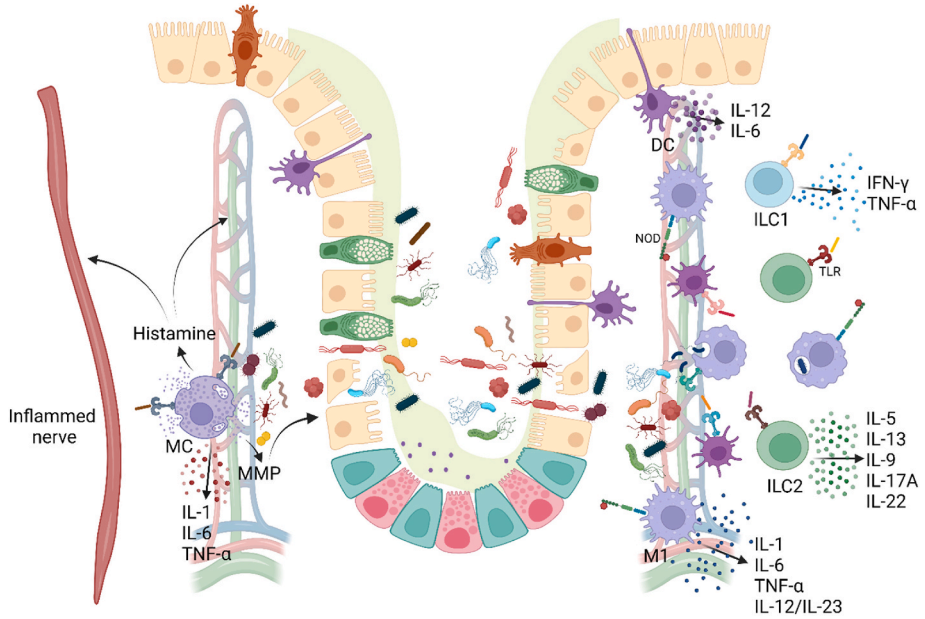

Fig. 2. *Innate immune system.* Macrophages, neutrophils, dendritic cells, natural killer, mast cells, and innate lymphoid cells are the main actors of innate immunity. Innate immune response is fast and non-specific and provides an initial defense against infections after the recognition of non-self-components by the PRRs present 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. DC, dendritic cell; ILC1, innate lymphoid cell 1; ILC2, innate lymphoid cell 2; M1, classically activated M1 macrophages; MC, mast cell; NOD, nucleotide-binding oligomerization domain; TLR, toll-like receptor (created with BioRender).

(Sánchez-Muñoz et al., 2011). Of note, increased *TLR9* gene expression results as a consequence of polymorphic variants, intestinal inflammation, dysbiosis, and neutrophil infiltration in patients with UC. This up-regulation of TLR9, responsible for recognizing bacterial DNA, positively correlates with IL-6 and TNF-α contributing to the increase of UC severity (Sánchez-Muñoz et al., 2010). Various studies have reported an association between *TLR4* SNPs with both CD and UC (Oostenbrug et al., 2005; Brand et al., 2005; Török et al., 2004; Shen et al., 2010). Compared to control group, where TLR4 is either low expressed or absent, IBD patients show high expression of TLR4 in intestinal mucosa that, like TLR9, correlates with pro-inflammatory cytokines secretion and chronic inflammation (Sánchez-Muñoz et al., 2010).

NOD2 polymorphisms are associated with an increased incidence of CD along with an increased epithelium permeability (Inohara et al., 2003). Additional findings demonstrated that *NOD2* loss-of-function prevents NF-κB activation resulting in impaired antibacterial agent production and the subsequent increase of pathogenic microbial invasion (Abraham and Cho, 2006). Lack of *NOD2* may also stimulate TLR2 activation, promoting pro-inflammatory pathways and exacerbating Th1 response (Watanabe et al., 2004).

The inflammasome is considered one of the prominent mediators of innate immunity, and recent evidence shows that its activation plays an essential role in the pathogenesis of IBD. Inflammasome processes the precursors of IL-1β and IL-18, which respectively regulate Th17 and Th1 cells, amplifying the immune response (van de Veerdonk et al., 2011). A significant increased activation of the IL-1 system was found in the intestinal mucosa of CD and UC patients compared with the control group (Strober et al., 2002). The pro-inflammatory IL-1β is mainly secreted by macrophages and synergizes with IL-6 and TNF-α to trigger intestinal inflammation (Ligumsky et al., 1990). IL-18 is hyper-expressed in intestinal lesions of CD patients. IL-18 together with IL-12 facilitates IFN-γ production by Th1, whereas together with IL-2 stimulates a type 2 immune response (Nakanishi, 2018).

Some studies provide evidence that loss or over-activation of NLRP3, the NOD-like receptor that forms the inflammasome, may break down the immune balance leading to the onset of intestinal inflammation. Several genetic alterations resulting in the over-activation of NLRP3 have been associated with the development of colitis (Liu et al., 2017), whereas the lack of inflammasome-related genes, including *NLRP3*, may increase the severity of colitis in mice (Zaki et al., 2010).

The inflamed intestinal mucosa recruits a large number of activated M1 macrophages that produce reactive oxygen species (ROS), and secrete IL-12, IL-23, IL-6, IL-1, and TNF-α, as well as proteases. This triggers dramatic inflammation, remodeling of the extracellular matrix, and phagocytosis of pathogens (Maloy and Powrie, 2011). M1 macrophages also induce tight junction breakdown, epithelial barrier damage, epithelial cell apoptosis, and T helper responses, causing tissue damage and aggravating the inflammatory response (Lissner et al., 2015).

The inhibition of the pro-inflammatory M1-like phenotype and/or the induction of the anti-inflammatory M2 subset may attenuate IBD. M2 macrophages are involved in the resolution of inflammation and in tissue regeneration through the release of anti-inflammatory cytokines, particularly IL-10 (Martinez et al., 2009). 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 (Zhu et al., 2014).

Gut DCs present specific TLRs that once activated lead to the release of elevated levels of IL-6 and IL-12, causing mucosa alteration and inflammation in IBD patients. These cytokines further migrate to the peripheral lymphoid tissue, promoting the inflammatory state and generating the antigen-specific response of T cells (Hart et al., 2005).

ILCs participate in the first line of immune response through the secretion of huge amounts of cytokines that furtherly drive the immune response (Britanova and Diefenbach, 2017). ILCs can be classified into three subtypes: ILC1s, ILC2s, and ILC3s. ILC1s, including cytotoxic NK cells, intensify the immune reaction toward intracellular pathogens by excessively releasing TNF-α and IFN-γ, whereas ILC2s and ILC3s secrete effector cytokines IL-5, IL-13, IL-9, and IL-17A, IL-22, respectively. Tight control of ILC number and activation ensures the integrity of the barrier and tissue homeostasis preventing chronic immune reactions. Remarkable variations in the number of ILC populations have been reported in inflamed tissue of the intestine. In particular, ILC1 infiltration is increased in active inflammation regions in IBD patients (Forkel et al., 2019).

Other important players in the immune and inflammatory response associated with IBD are the MCs, which are well represented in the lamina and the muscular and serous layers (Boeckxstaens, 2015; Panarelli, 2023). In response to altered epithelial permeability, mucosal MCs release histamine, tryptase, metalloproteases, and pro-inflammatory cytokines (including TNF-α, IL-6, and IL-1β) that further sustain local inflammation, increase epithelial permeability, induce peristalsis, and provoke pain by stimulating the nociceptive receptors (He, 2004; Theoharides, 2014). Consistently, increased levels of histamine have been reported in duodenum, colon, and rectum biopsy of IBD patients (Ahn et al., 2014).

Innate immune cells also promote antigen presentation and T cell activation participating in the communication between innate and adaptive immune responses (Holleran et al., 2017) (Fig. 3).

$CD4^+$ T cells are the main actors of the adaptive immune response, as they collaborate with the cells and molecules of the innate immune system to generate an effective response. The activation and the differentiation of T helper (Th) 0 cells into Th1, Th2 or Th17 is essential for the clearance of specific pathogens.

IL-12/23 group is released by activated antigen-presenting cells and promotes IBD by driving pathogenic T cell responses. In particular, IL-12 may induce the differentiation of naive $CD4^+$ T cells into Th1 cells releasing IFN-γ and the proliferation and activation of natural killer (NK) and cytotoxic T cells (Trinchieri, 2003), whereas IL-23 reinforce the response of Th17 cells and decreases the Treg cell anti-inflammatory response (Teng et al., 2015).

The persistent activation of T cells leads to an excessive release of chemokines and cytokines that contribute to the initiation of inflammation. Cytokines released by activated Th1 and Th2 mediate the lesions in inflamed mucosa of IBD patients. Increased amounts of IL-2, TNF-α, and IFN-γ (released by Th1) and of IL-4, IL-5, and IL-13 (released by Th2) have been observed in CD and UC, respectively (Raphael et al., 2015; Heller et al., 2005). The accumulation of Th1 cells in the intestinal tract of CD patients directly correlates with the disease. Th1 cytokines activate the transcription factor STAT1 promoting the over-expression of transcription factor T-β, and recruitment of $CD8^+$ T cells, NK cells, and macrophages, and thus the secretion of the downstream inflammatory cytokines.

IFN-γ is the leading driver of excessive immune response leading to massive leukocyte infiltration and mucosal damage by inducing enterocyte apoptosis (Raphael et al., 2015).

TNF-α, whose level correlates with the clinical disease activity of CD patients, induces the release of IL-6 and IL-1 and activates NF-κB, and JNK pathways, finally stimulating the acute phase response (Aardoom et al., 2019; Armuzzi et al., 2020).

IL-6 has been found increased in CD and UC patients. Augmented IL-6 levels are related to an increase in the severity of inflammation and frequent recurrence (Pawłowska-Kamieniak et al., 2021). After binding to its receptor, IL-6 promotes the increased expression and nuclear translocation of STAT3, which results in the apoptosis resistance of T-cells in the intestine through the induction of Bcl-xl and Bcl-2 anti--apoptotic genes (Atreya et al., 2000). The release of IL-6 also results in the expression of some chemokines and adhesion molecules involved in neutrophils recruitment (Fielding et al., 2008), in the differentiation of Th17 cells (Chonov et al., 2019), and in the prevention of Treg differentiation, leading to chronic intestinal inflammation (Bettelli et al., 2006).

IL-13 released by Th2 cells enhances intestinal permeability and

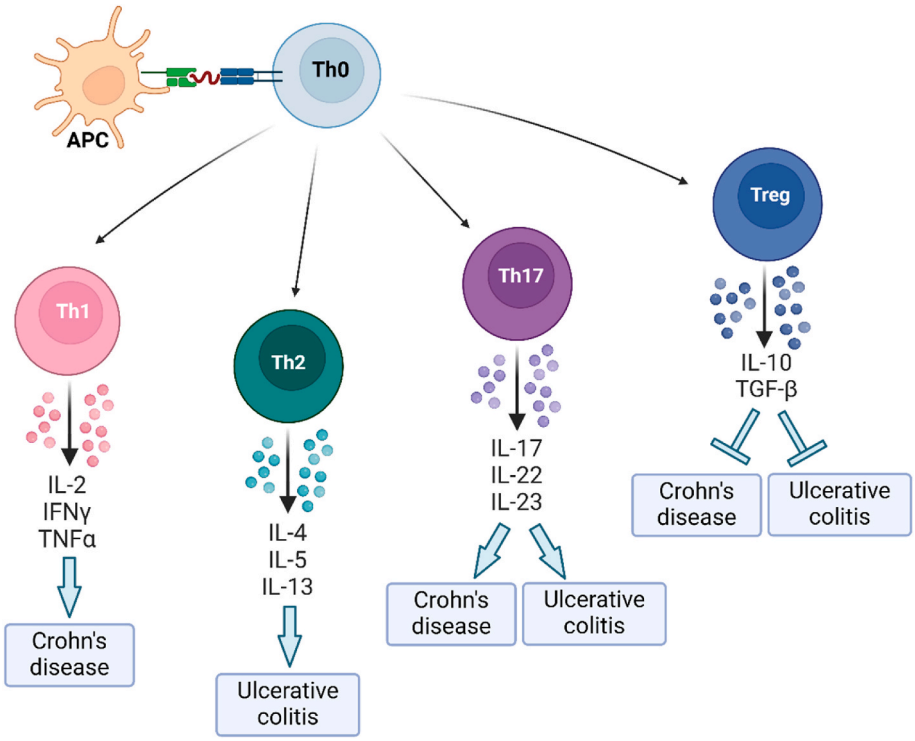

Fig. 3. *Adaptive immune system.* Adaptive immune response is secondary to the innate response and requires the activation of lymphocytes. The activation and differentiation of Th0 cells into Th1, Th2 or Th17 in response to specific pathogens participate to onset of IBDs through the release of pro-inflammatory cytokines and chemokines. The presence of anti-inflammatory Tregs is essential to maintain the correct balance between immune and tolerogenic reactions, thus preventing the progression of IBD. APC, antigen presenting cell; Th, helper T-cells; Treg, regulatory T-cells (created with BioRender).

induces enterocyte differentiation and apoptosis (Heller et al., 2005; Ceponis et al., 2000).

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 observed a higher infiltration of Th17 cells and IL-17 in the intestinal mucosa and lamina propria of IBD-affected patients, compared to healthy individuals (Kobayashi et al., 2008; Rovedatti et al., 2009). 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 (Lee et al., 2018). IL-17A recruits neutrophils in the inflamed tissue and mediates pro-inflammatory cytokine production by macrophages (Kolls and Lindén, 2004).

The activation and the effector function of Th cells is prevented by regulatory T (Treg) cells. Treg cells abolish abnormal immune responses through the production of anti-inflammatory cytokines, including TGF-β and IL-10, resulting in immune tolerance and maintenance of the homeostasis of the gut mucosa (Valencia et al., 2006). IL-10 influences stem cells intestinal renewal and the regulation of the intestinal microflora promoting the proper functioning of the intestinal epithelial barrier (Neumann et al., 2019), whereas TGF-β regulates immunological homeostasis (Marek et al., 2002). 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 proliferation of $CD4^+$ T cells, the synthesis and the release of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6) and chemokines by Th2, and the production of inflammatory enzymes by macrophages. Besides, IL-10 stimulates the production of anti-inflammatory proteins, including matrix metalloproteinases tissue inhibitors, soluble TNF-α receptor, and antagonists of IL-1 receptor (Neumann et al., 2019). 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 (Glocker et al., 2011).

A main effect of TGF-β signaling is the suppression of T-cell proliferation and activation through Treg differentiation. Impairment of TGF-β signaling increased colitis progression (Ihara et al., 2017).

The decrease of anti-inflammatory Tregs may be crucial for IBD pathogenesis. Consistently, it has been reported a strong depletion of Treg cells in peripheral blood of patients with IBD compared to the control group (Singh et al., 2001). Of note, Treg cells express IL-17 upon stimulation with IL-6, thus acquiring a Th17-like cell phenotype. This phenomenon seems to be irreversible and could drive the onset of chronic mucosal inflammation (Lee et al., 2009).

The dynamic interaction between microbiota, epithelial cells, and immune cells in the intestine represents one of the fundamental features for maintaining intestinal homeostasis and for activating effective immune responses against pathogens (Maloy and Powrie, 2011). Perturbations in this fine balance, due to genetic and/or external factors (e.g., lifestyle, diet, drugs, stress, anxiety, and depression) (Ananthakrishnan et al., 2013), may result in aberrant and chronic intestinal inflammation, tissue damage, and ultimately in the onset of IBD (Schett and Neurath, 2018; Graham and Xavier, 2020).

Understanding the interactions between cells and products of innate and adaptive immunity and their relationship with the intestinal microbiota may lead to new advancements in the development of novel strategies for the treatment of IBD.

5. Autophagy and the maintenance of intestinal epithelial barrier

In vivo and *in vitro* results and clinical studies show that autophagy may prevent the onset of the IBD by preserving the homeostasis and integrity of the intestinal barrier, regulating the inflammatory pathways and immune system function, and providing protection against infection and cell death (Hooper et al., 2019; Iida et al., 2017). The close association between autophagy and intestinal homeostasis is evident in the strong correlation observed between genes involved in the autophagy pathway and susceptibility to IBD (Foerster et al., 2022).

Briefly, 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 activate autophagy as an adaptive mechanism to obtain amino acids and energy to face 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 while inhibiting the autophagy pathway.

The role of autophagy in the various IECs has clearly emerged from recent studies (Fig. 4). GWAS found that certain SNPs in autophagy-related genes are associated with genetic susceptibilities in developing inflammatory intestinal diseases (Franke et al., 2010).

Interestingly, autophagy-related 16-like 1 (*ATG16L1*), the nucleotide binding oligomerization domain containing protein 2 (*NOD2*), and vitamin D receptor (*VDR*) are the best representative IBD-related gene variants involved in Paneth cell autophagy.

It has been reported that the Thr300Ala polymorphism in the *ATG16L1* gene increases the risk of developing CD. A mouse model of this polymorphism revealed important morpho-functional dysfunction of the Paneth cells which lost the ability to utilize autophagy for the engulfment of microbes and release of antimicrobial peptides (Lassen et al., 2014). Moreover, polymorphic variants in *ATG16L1* sequence reduce the ability of DCs to process antigens in the luminal compartment of the gut and favor a pro-inflammatory phenotype in these cells (Nguyen et al., 2013).

NOD2, constitutively expressed in myeloid cells and in the Paneth cells, induces autophagy by recruiting the autophagy protein ATG16L1 to the plasma membrane at the bacterial entry site. *NOD2* frameshift mutations result in the encoding of a shortened protein that fails to localize to the plasma membrane, thus retaining ATG16L1 in the cytosol and preventing its membrane localization. This impairment leads to compromised clearance of intracellular bacteria and elevated release of inflammatory cytokines, increasing susceptibilities to CD (Lassen et al., 2014). Upon activation, NOD2 leads to the activation of NF-κB and of mitogen-activated protein kinase (MAPK), resulting in the subsequent induction of pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6 (Hsu et al., 2007). *NOD2* loss-of-function mutations hamper the activation of NF-κB against pathogens recognized by PRRs, leading to an exacerbated Th1 response (Watanabe et al., 2004).

The activation of VDR in the intestine may downregulate intestinal inflammation by inducing the autophagic degradation of the inflammasome (Karimi et al., 2019). Low expression of VDR leads to a reduced ATG16L1 expression, thus hampering the antimicrobial capabilities of Paneth cells and resulting in elevated bacterial loads within the intestinal mucosa. This scenario is believed to contribute to the initiation of IBD (Wu et al., 2015).

Paneth cells are considered the origin site of intestinal inflammation (Adolph et al., 2013), and autophagy plays a role in their secretion of lysozyme in response to intestinal infection (Bel et al., 2017). Autophagy dysregulation in Paneth cells also affects the function of the whole intestinal cell populations. In addition, Paneth cells contribute to the molecular signals required for maintaining the stemness behavior of ISCs. Stem cells utilize the ATP generated through oxidative

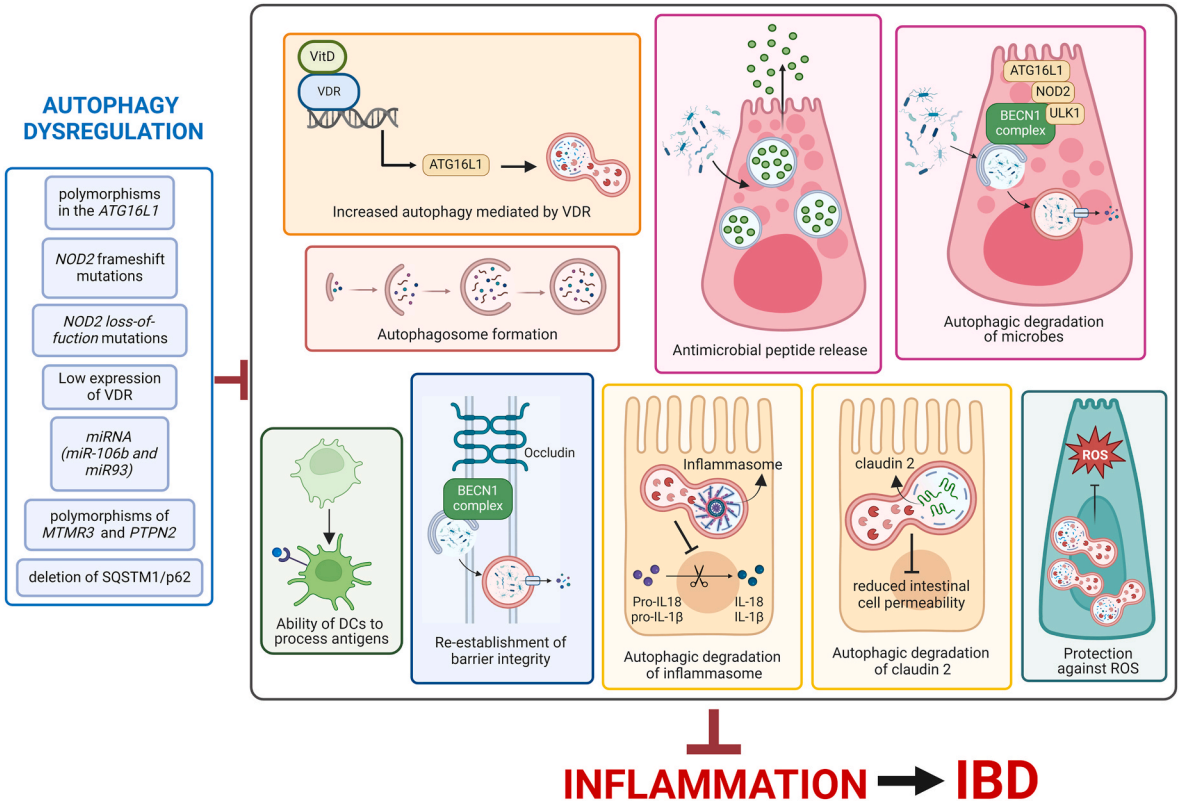

Fig. 4. *Role of autophagy in the maintenance of the correct function of intestinal epithelial cells.* Autophagy dysregulation contributes to the development of inflammatory bowel disease (IBD). Genetic mutations, such as those in *ATG16L1*, *NOD2*, and *VDR*, impair autophagic functions in Paneth cells, leading to reduced antimicrobial peptide release and inefficient degradation of microbes. In intestinal epithelial cells, autophagy plays a role in degrading the inflammasome and claudin 2, thereby reducing inflammation and intestinal permeability. It also provides protection against reactive oxygen species (ROS) and helps restore intestinal barrier integrity by regulating occludin localization. Additionally, autophagy affects the ability of dendritic cells to process antigens, influencing immune responses and contributing to the maintenance of intestinal homeostasis (created with BioRender).

phosphorylation, and autophagy (particularly, mitophagy) in Paneth cells serves as a protection mechanism against oxidative stress (Pickles et al., 2018; Levy et al., 2020).

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 (Lahiri et al., 2015; Scharl et al., 2012).

Besides polymorphic variants and mutations, also miRNAs participate in the regulation of autophagy-related genes (Vidoni et al., 2020; Vidoni et al., 2021; Vallino et al., 2020; Lu et al., 2014). miR-106b and miR-93 interfere with the clearance of Crohn's disease-associated bacteria by contrasting the formation of the autophagosome (Lu et al., 2014).

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 (Hu et al., 2019).

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. 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 (Cosin-Roger et al., 2017). NLRP3 function is connected to CASP1 activity, leading to the release of IL-1β and IL-18. In the inflammatory process, NLRP3 interacts with mTOR promoting its phosphorylation and activation with consequent inhibition of autophagy and exacerbation of the release of pro-inflammatory cytokines. To prevent the exacerbation of the inflammatory response, the cell autonomously activates the autophagic degradation of NLRP3 (Deretic and Levine, 2018). Autophagy may degrade ubiquitinated inflammasome and the inactive precursors of IL-1β and IL-18 (Shi et al., 2012). *ATG16L1* deficiency impairs autophagy and results in the accumulation of IL-1β and IL-18 in serum under the stimulation with lipopolysaccharide in colitis-exposed mice (Saitoh et al., 2008).

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-1β, and macrophage death (Zhong et al., 2016).

Autophagy also regulates the tight junctions between IECs. Its induction induces the degradation of claudin 2 (CLDN2) allowing the selective cation passage. The lysosomal degradation of this tight junction protein reduces cell permeability in intestinal epithelial barrier. TNF-α positively regulates the turnover of claudin 2, increasing epithelial permeability and contributing to the onset of intestinal inflammatory disease (Nighot et al., 2015; Zhang et al., 2017). 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 and consequent loss of 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 (Wong et al., 2019).

6. Gut dysbiosis in the inflamed gut microenvironment

A growing body of evidence suggests a correlation between the composition of intestinal microbiota and chronic intestinal inflammation (Fig. 5). Despite the role of the dysbiotic microbiota in the immune system activation, chronic inflammation reciprocally molds the gut microbiota, participating in the development of dysbiosis. This emphasizes that the intestinal dysbiosis may act as both the cause and the outcome of chronic inflammation (Guan, 2019). However, establishing a definitive cause-and-effect relationship between intestinal microbiota and IBD is challenging (Ni et al., 2017), especially considering the lack of information in several studies about the timing of dysbiosis relative to disease onset.

To examine the gut microflora in individuals potentially affected by IBD, microbiome studies focus on α and β diversity measures. These measures examine the number and/or distribution 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 is the reduced biodiversity (Derwa et al., 2017). Microbiome sequencing

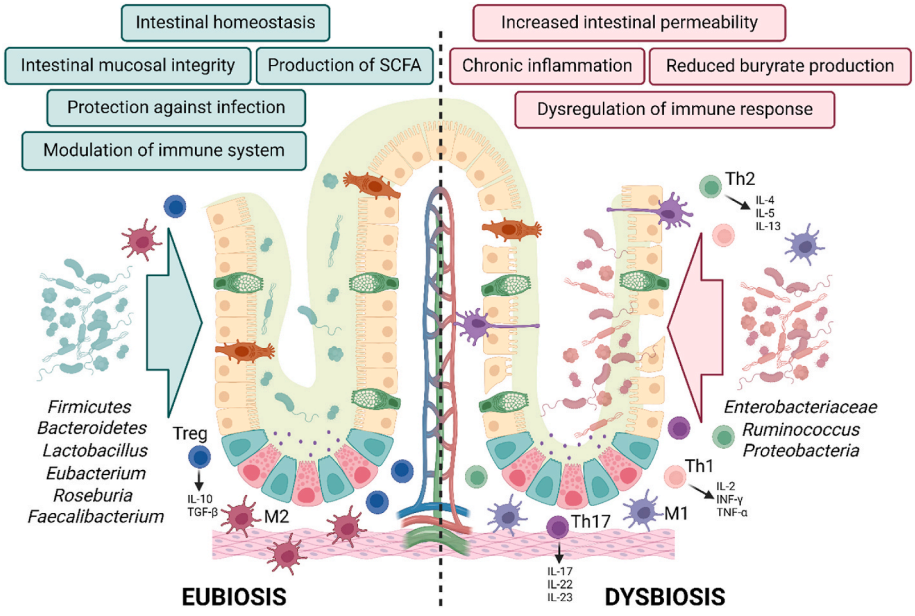

Fig. 5. *The relationship between gut dysbiosis and inflammatory bowel disease.* The condition of eubiosis, which defines the balance between the host and bacteria, is essential for proper intestinal homeostasis and host health. Alteration in the function and composition of gut microbiota due to environmental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

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, along with a decrease of anti-inflammatory bacteria (e.g., *Faecalibacterium prausnitzii*) (Vester-Andersen et al., 2019; Lopez-Siles et al., 2015; Martinez-Medina et al., 2009; Nishino et al., 2018; Frank et al., 2007; Ott et al., 2004). Specifically in individuals with CD, an increase in *Enterobacteriaceae*, including *E. coli* and *Fusobacterium*, has been reported, accompanied by a decrease in *Bifidobacterium adolescentis*, *Dialister invisus*, and *Faecalibacterium prausnitzii* (Lupp et al., 2007; Joossens et al., 2011). UC patients exhibit an increase in *Mycobacterium avium paratuberculosis*, *E. coli*, *Clostridium difficile*, *Helicobacter*, *Salmonella*, *Yersinia*, *Fusobacterium*, and *Listeria* species, along with a decrease in *Firmicutes* and *Bacteroidetes* (Shen et al., 2018).

The gut microenvironment is influenced by the availability of nutrients and oxygen, determining the growth of various bacteria species. Notably, microbiota-derived butyrate serves as a vital energy source for colon enterocytes. The metabolic process involves the oxidation of butyrate, resulting in the production of carbon dioxide (CO_2). This metabolic activity consumes significant amounts of oxygen, leading to a hypoxic state in surface colonocytes which favors the proliferation of commensal anaerobic bacteria species. During inflammation, pathogenic bacteria limit the availability of butyrate. When the butyrate is lacking, mature colonocytes ferment glucose into lactate to obtain ATP, thereby increasing oxygenation of the epithelial surface which ultimately favors the colonization and the expansion of facultative anaerobes strains (*E. coli*, *Salmonella*, *Shigella*, *Proteus*, and *Klebsiella*) into the intestinal lumen (Nagao-Kitamoto et al., 2016; Rivera-Chávez et al., 2017). The absence of butyrate also favors the expression of the "leaky" tight junction protein Claudin-2 and the downregulation of the "tight" one (Saeedi et al., 2015). This outcome creates an energy-deficient mucosa, defined as "starved", which promotes bacterial translocation in the lamina propria and entry in the systemic circulation (Donohoe et al., 2011; Gassler et al., 2001). 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 (Pastor Rojo et al., 2007).

This evidence suggests that the occurrence of a dysbiotic microenvironment is a fundamental aspect of IBD pathogenesis. Interestingly, the colonization of the intestinal mucosa of IBD patients by microbiota from healthy donors prevents colitis.

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. Pharmacological treatments for patients suffering from IBD include corticosteroids, immunosuppressant agents, antibiotics, monoclonal antibodies, and biological therapies (Neurath, 2017). Clinical trials suggesting the potential use of current small molecules and biological drugs, such as interleukin inhibitors, integrin inhibitors, modulators of sphingosine-1 phosphate, and JAK inhibitors, have been recently presented (Bretto et al., 2023). 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, such as fever, nausea, vomiting, fatigue, headache, yeast and virus infections, and even malignancy (McLean and Cross, 2014).

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 (Lê et al., 2022). 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. Fecal microbiota transplantation

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 (Gupta and Khanna, 2017; Bajaj et al., 2019).

FMT has become a standard treatment for *Clostridium difficile* infections, which often occur after prolonged antibiotic use and disrupt gut microbiota balance (Wortelboer et al., 2019). Recently, the use of FMT has increased significantly, drawing considerable attention from medical professionals and the FDA. Initially, all FMT procedures required an Investigational New Drug application, a common requirement for experimental therapies. However, due to concerns raised by gastrointestinal societies, the FDA issued guidance in 2014 allowing discretion for FMT when treating *Clostridium difficile* infections, as long as patient consent, thorough donor screening, and physician oversight were in place (US Food and Drug Administration). Despite these changes, an Investigational New Drug application remains mandatory for other uses, such as treating IBD. As FMT becomes more widely accepted, regulatory oversight continues to adapt (Gerding and Lessa, 2015).

Selecting appropriate donors is a significant challenge in the implementation of FMT. Ideal candidates are generally young individuals with normal BMI, as advancing age is associated with alterations in gut microbiota that may negatively affect the recipient's inflammatory state (Kim and Gluck, 2019; Odamaki et al., 2016). Donors are rigorously screened for parasitic, viral, and bacterial infections, through both serological and stool analyses to minimize the risk of transmissible infections (Kim and Gluck, 2019; Cammarota et al., 2019). Blood tests should assess complete blood cell count, liver enzymes, creatinine, C-reactive protein, and serology for hepatitis viruses and HIV (Cammarota et al., 2019). Stool testing should screen for common enteric pathogens, including *Clostridium difficile*, parasites, and *Helicobacter pylori* antigen (Zboromyrska and Vila, 2016). Additionally, screening for antibiotic-resistant bacteria is essential due to the risks posed by gastrointestinal carriage in asymptomatic individuals (Cammarota et al., 2019). Only after all tests return negative can a candidate be accepted as a stool donor. Individuals who have recently taken antibiotics, are on immunosuppressants or chemotherapy, or have a history of malignancies or autoimmune diseases are excluded from donation (Cammarota et al., 2019).

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 (Quraishi et al., 2017). 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 reported that patients with IBD who undergo FMT demonstrated improvements in IBD-related symptoms, such as abdominal pain, frequency of diarrhea, and rectal bleeding. This positive clinical outcome is paralleled by the promotion of mucosal healing and changes in the microbial composition (Tian et al., 2019). Notably, the microbiome of the recipients closely resembles the donor microbiome profile (Sood et al., 2019). These findings may support the consideration of FMT as a primary treatment of IBD (Lopez and Grinspan, 2016; Costello et al., 2017; Caldeira et al., 2020; Kong et al., 2020).

Studies conducted on IBD patients report that recipients of FMT exhibit a higher remission rate compared to the placebo group (Moayyedi et al., 2015; Costello et al., 2019). Specifically, in UC patients, FMT induces remission within 8 weeks of the intervention (Wang et al., 2018) and prevents relapse (Sood et al., 2019). The microbiome analysis of patients in remission phase reported an enrichment in *Eubacterium* and *Roseburia* bacteria, as well as an increase in SCFAs production. Moreover, the presence of *Bacteroides* in donor stool were predictive of the remission phase in the FMT recipient patients, whereas the lack of remission phase was related to the presence of *Streptococcus* species (Paramsothy et al., 2019). Additionally, the increased butyrate production is a potential indicator of FMT efficacy (Xu et al., 2021). For CD patients, the transplantation reduces the severity of the disease and the expression of inflammatory markers, along with an improvement in symptoms. This results in significant changes in gut microbiota composition, with qualitative and quantitative modifications in the microbiome profile (Fehily et al., 2021; Paramsothy et al., 2017). Despite the promising results from FMT, further investigations and extensive studies are needed to evaluate its safety and long-term effects, particularly considering the potential for rare but severe side effects.

7.2. Probiotic supplementation

The employment of bacterial strains that modulate the composition of gut microbiota and restore homeostasis in host-microbe interactions holds significant potential in the management of IBD, similar to the FMT approach. The beneficial effects of 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" (Food and Agriculture Organization and of the United Nations/World Health Organization, 2002). Probiotics modulate the microbial flora by releasing antimicrobial agents or metabolites that hampers the colonization of pathogens, as well as by competing for receptors and binding sites with other microorganisms in the microbial niche (Hemarajata and Versalovic, 2013).

Interestingly, probiotics have been shown to positively influence autophagy, a crucial process for maintaining cellular homeostasis, as discussed above. Recent studies reveal that certain strains of probiotic lactic acid bacteria (*Lactobacillus*) enhance the expression of the vitamin D receptor (VDR) and key autophagy-related proteins, such as BECLIN1 and ATG16L1. The upregulation of VDR and autophagic markers is essential for the anti-inflammatory effects of these probiotics and their ability to protect against infections, as demonstrated in both *in vitro* and *in vivo* models of IBD (Lu et al., 2020). Additionally, recent research has shown that *Bifidobacterium* significantly increases the expression of autophagy-related genes, such as *PIK3C3*, *ATG7*, *ATG5*, and *ATG16*, particularly during inflammation. This suggests that *Bifidobacterium* can regulate autophagy throughout different stages of inflammation, contributing to its protective role in inflammatory diseases like IBD (Torkamaneh et al., 2023). Moreover, *Bifidobacterium dentium* has been found to enhance mucus production and secretion in the gut through autophagy and calcium signaling. Specifically, this probiotic stimulates the expression of autophagy-related genes such as *ATG16L*, *ATG5*, *BECLIN1*, and *LC3*, which improve calcium signaling and mucin release from goblet cells, thereby strengthening the intestinal mucus barrier. These findings highlight the potential of probiotics to positively impact gut health, particularly in conditions like IBD, by modulating mucin production and secretion (Engevik et al., 2019).

For over three decades, probiotics have been used in the treatment of IBD, demonstrating beneficial effects in murine and rat models of colitis (Coqueiro et al., 2019). Various strains, including s *Bifidobacterium*, *E. coli*, and *Lactobacillus* demonstrate anti-inflammatory effects (Jakubczyk et al., 2020; Manna et al., 2023) and reduce the outgrowth of pathogens by competing for nutrients (Deriu et al., 2013). The supplementation of *Bifidobacterium*, *Lactococcus acidophilus*, and *Enterococcus* in mouse models of colitis has been shown to positively regulates the expression of tight junctions and influences the T cells population, particularly increasing Treg cells (Zhang et al., 2018).

Clinical studies have demostrated that patients with UC treated with *Bifidobacterium longum* and *Escherichia coli* Nissle 1917, display improved outcome, with probiotics acting as well as mesalazine in maintaining the remission of the disease (Tamaki et al., 2016; Kruis et al., 2004). Additionally, *Propionibacterium freudenreichii* modulates host inflammation by regulating the release of the anti-inflammatory cytokine IL-10, similar to engineered *Lactoccoccus lactis* which shows protection in murine models of colitis (Deutsch et al., 2017; Steidler et al., 2000). Children and adolescents with mild or moderate-grade UC treated with *Lactobacillus lactis* supplementation show improvements in the restoration of intestinal mucosa compared to the control group (Oliva et al., 2012). UC patients treated with *Bifidobacterium longum* show reduced rectal bleeding and achieved clinical remission (Tamaki et al., 2016). Moreover, combining probiotics with standard anti-inflammatory drugs for IBD elicit a synergistic effect. For example, in UC patients, combining mesalazine with cocktail of probiotic containing *Lactobacillus* and *Bifidobacterium* has been shown to decrease disease severity and reduced recovery time (Palumbo et al., 2016).

Supplementation with the commercial probiotic blend VSL#3, either as monotherapy or in combination with conventional medications, has been shown to improve symptoms and induce and maintain remission in patients with UC (Cheng et al., 2020; Sood et al., 2009; Tursi et al., 2010), although it appears less effective in CD (Cabré and Gassull, 2007). This mixture contains various strains of lactic acid-producing bacteria including *Lactobacillus*, *Bifidobacteria*, and *Streptococcus*, and has been shown to promote intestinal barrier integrity and reduce the secretion of inflammatory cytokines (Sood et al., 2009). As per the mechanisms, this mixture of bacteria reduces the expression of inflammatory cytokines IL-6 and TNF-α by inhibiting TLR4/NF-κB signaling, as well as reducing IL-23, STAT3, iNOS (inducible nitric oxide synthase), and COX-2 (cyclooxygenase-2) expression, while up-regulating TGF-β in UC models (Cheng et al., 2020; Wang et al., 2019).

It is known that *Streptococcus thermophilus* and *Bifidobacterium infantis* induce the remission phase in UC by colonizing the affected bowel area (Bibiloni et al., 2005). In UC patients, *Lactobacillus rhamnosus*, either as monotherapy or in combination with mesalazine, has been shown to be safer and more effective in maintaining disease remission compared to mesalazine alone (Zocco et al., 2006). Although CD patients typically exhibit reduced levels of *Bifidobacterium* strains, supplementation with *Faecalibacterium prausnitzii* results more effective than *Bifidobacterium* in inducing remission phase (Sokol et al., 2008).

Recent trials have also explored the potential role of non-bacterial probiotics, including the use of yeast, such as *Saccharomyces boulardii*. This approach has shown promise in reducing exacerbation and sustaining remission in CD patients by improving intestinal barrier permeability, particularly when used in combination with other therapy (Bousvaros et al., 2005; Garcia Vilela et al., 2008).

Given their role in immune system modulation, probiotics may open up new therapeutic possibilities for IBD patients (Hansen and Sartor, 2015). However, it is important to note that in case of severe intestinal damage, probiotics may not be able to reverse the condition, and their use could elicit unwanted side effects (i.e., bacteremia or sepsis) in patients with compromised immune defenses. As a warning example, a UC adult patient experienced a worsening in health status due to bacteremia after 13 days of oral probiotics administration (Meini et al., 2015). Therefore, it is essential to tailor probiotic therapy to individual patients, taking into account factors such as the type and severity of inflammatory changes, microbiota composition, and environmental and genetic aspects. The efficacy of a specific living strain can vary among patients, so it is essential to use only thoroughly tested probiotic strains in appropriate doses to ensure effective management.

8. Conclusion

Due to the complexity and the heterogeneity of IBDs, fully understanding the pathogenetic mechanisms is challenging. Autophagy, as a homeostatic regulator of the inflammasome, plays an important role in maintaining a balanced immune system in the intestine. SCFAs (particularly butyrate) produced by commensal bacteria contribute to dampen inflammation, thus preventing from IBD onset and progression. It has been reported that CD and UC increase the risk of colitis-associated colorectal cancer because of the protracted inflammation. Interestingly, butyrate was shown to elicit anticancer effects in colorectal cancer cells through induction of autophagy (Garavaglia et al., 2022; Vallino et al., 2023; Luo et al., 2023). This suggests that probiotics not only contribute to gut microbiota balance but also modulate autophagy, offering a dual mechanism of action in the treatment of IBD. Existing therapeutic approaches focus on symptom management to enhance and sustain the remission phase rather than targeting the removal of triggering events.

Microbiota-based therapies have demonstrated effectiveness in rat and mouse models, as well as in clinical trials, either in monotherapy or in combination with the current drugs. These therapies aim to restore the population of commensal bacteria by either supplementation of probiotic mixture or by FMT. The latter shows a better clinical profile because it has a higher microbial density and diversity that accelerates the normalization of the microbiome but is the least preferred option by patients (Khoruts, 2018). A Cochrane review of the available clinical trials for inducing remission in CD patients with probiotics did not conclude for a certain effect versus placebo, suggesting the need for well-designed trials (Butterworth et al., 2008).

Additional studies are needed to confirm the safety and the effectiveness of these novel approaches 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 reproduce the human disease due to the distinct organization of the gastrointestinal tract; ii) the key pathways involved in the pathogenesis cannot be artificially reproduced *in vitro*; 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 microorganisms. 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.

CRediT authorship contribution statement

Beatrice Garavaglia: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Letizia Vallino:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Angela Amoruso:** Writing – review & editing. **Marco Pane:** Writing – review & editing. **Alessandra Ferraresi:** Writing – review & editing, Visualization. **Ciro Isidoro:** Writing – review & editing, Visualization, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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