Microbiome-Immune Interactions in Ulcerative Colitis

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Inflammatory bowel disease (IBD) is a chronic autoimmune condition affecting the gastrointestinal (GI) tract. IBD includes Crohn's disease (CD) and ulcerative colitis (UC), with UC characterized by inflammation of colonic mucosa and submucosa starting at the rectum and extending through the colon. The precise etiology of UC is unknown but is thought to involve a combination of environmental and genetic factors. Chief among these is the intestinal microbiome, which has been extensively studied both for its role in disease pathogenesis and possible treatment. In this review, we will discuss the microbial changes that have been described in UC, its interplay with host immune function, and evidence supporting its role as a potential therapeutic. We will also discuss parallels between UC, the microbiome and colitis-associated cancer (CAC).

Keywords: ulcerative colitis ; UC ; inflammatory bowel diseases ; IBD ; pediatrics ; paediatrics ; probiotics ; prebiotics ; synbiotics ; antibiotics ; fecal microbiota transplant ; faecal microbiota transplant ; FMT ; colitis-associated cancer ; CAC ; colorectal cancer ; CRC ; dysbiosis

1. Background

Inflammatory bowel disease (IBD) is a chronic autoimmune condition affecting the gastrointestinal (GI) tract. It comprises Crohn's disease (CD) and ulcerative colitis (UC), and generally presents as a progressive inflammatory condition. UC is characterized by inflammation of colonic mucosa and submucosa starting at the rectum and extending through the colon. Typical symptoms of UC flares include abdominal pain, hematochezia, tenesmus, and loose stools. Extraintestinal manifestations may also present, including ocular pathologies, arthropathies, liver disease such as primary sclerosing cholangitis, and dermatological manifestations [1].

Various genetic and environmental factors have been implicated in UC susceptibility [2]. To date, over 200 single nucleotide polymorphisms (SNPs) have been associated with the risk of developing UC [3]. Epidemiological studies have shown a higher incidence of UC among populations adopting Western diets rich in refined sugars, dairy, protein, and animal fat, and low in dietary fiber including wholegrains, fruits, and vegetables [4]. The role of environmental influences aligns with the hygiene hypothesis, which states that limited exposure to microorganisms during infancy and childhood may impair appropriate priming and development of the immune system, thus promoting autoimmunity [5]. Exposure to antibiotics during gestation and childhood, psychological stress, and family history also affect the risk of developing UC [6]. These factors profoundly alter the intestinal microbiome but may also provide opportunities for new treatment options.

2. Microbiome-Immune Interactions in UC

2.1. Immune System Perturbations in UC

Perturbations in intestinal microbiota and immune dysregulation are key features of UC pathogenesis (**Figure 1**). Colonization is largely believed to commence during parturition, although limited evidence suggests that some microbial cells might be present in utero during the prenatal period [7]. The largest contributors to intestinal microbiota composition constitute mode of childbirth and feeding during infancy. Subsequent expansion and diversification of the intestinal microbiome continues throughout childhood and adolescence until a relatively stable composition is achieved in adulthood [8].

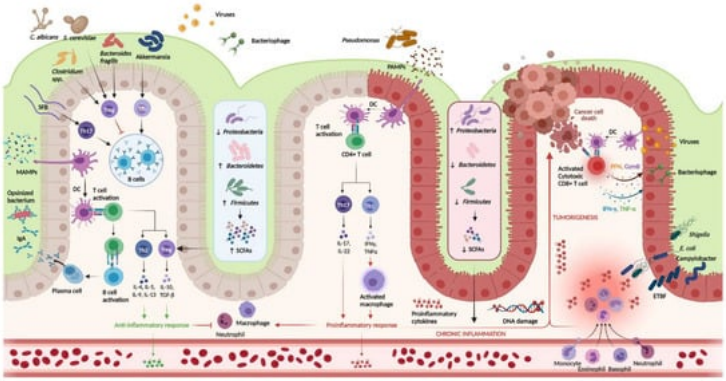

Figure 1. Host-immune interactions in ulcerative colitis. Intestinal microbiota interact with the immune system through various pathways. In the healthy colon, DCs sample MAMPs and present antigens on major histocompatibility complex class II to naive CD4+ T cells. Naive CD4+ T cells become activated and differentiate into various T cell subtypes depending on the presence of specific cytokines within the local microenvironment. Anti-inflammatory Th subtypes comprise Th2 and Treg cells. CD4+ T cells also activate plasma cells which secrete immunoglobulin A (IgA) which is essential for microbial opsonization. Proinflammatory Th subtypes consist of Th1 cells and Th17 cells, which are upregulated in the diseased colon via interactions between DCs and PAMPs. Chronic inflammation contributes to DNA damage and tumorigenesis. Invading viruses stimulate CD8+ cytotoxic T cell activation via antigen-MHC I interactions. However, CD8+ T cells can also assist in cancer cell death. Disruptions in the mucosal barrier provides avenues for microbial translocation, including ETBF, which has been implicated in colitis-associated cancer. Finally, the production of SCFA is increased in the healthy colon (mediated by increased density of Firmicutes and Bacteroidetes phyla), while increased density of the Proteobacterium phylum is associated with lower concentrations of SCFA and colonic inflammation. DC, dendritic cell; DNA, deoxyribonucleic acid; ETBF, enterotoxigenic *Bacteroides fragilis*; IFN-γ, interferon-gamma; IgA, immunoglobulin A; MAMPs, microbe-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; SCFAs, short chain fatty acids; SFB, segmented filamentous bacteria; Th, T helper; Treg, T regulatory; TNF-α, tumor necrosis factor-alpha. Created in Biorender.com (accessed: 1 August 2021) [9].

Early life may be considered a common denominator between intestinal microbiota development and susceptibility to UC, as perturbations in early microbial colonization such as caesarean section delivery, dietary changes, exposure to antibiotics, systemic stressors, and infection constitute the same environmental factors associated with the risk of developing UC [10][11][12].

The microbiome plays an important role in maintaining intestinal homeostasis by training the innate and adaptive immune systems to tolerate commensal microbes, while offering protection against harmful pathogens [13][14][15]. Tolerance towards commensal microorganisms is mediated via: (1) reducing contact between luminal microbes and the intestinal mucosa through physical barriers [16], and (2) development of immune hyporesponsiveness [17].

The intestinal mucosal barrier serves as the first line of defense against bacterial translocation into systemic circulation and is composed of physical and immunological elements working together to maintain intestinal health. Alterations in the physiological composition of gut microbes in early life disrupt tolerance to commensals, permit translocation of pathogens, and result in dysregulation of host immune function through various signaling cascades [18]. Microbial dysbiosis, intestinal barrier defects, and alterations in mucin secretion may occur even in the absence of active inflammation, including outside of the colon in UC. This suggests that disruptions to normal intestinal physiology are primary contributors to UC pathogenesis and likely predate inflammation [19].

2.1.1. Physical Barrier

A mucus blanket composed of heavily glycosylated mucins serves as the first physical element of the intestinal mucosal barrier. Mucins may be membrane tethered, secretory, or non-gel forming. Their production and secretion are principally mediated by goblet cells and may be influenced by nonspecific factors such as immune system interactions with microbiota and dietary factors, and specific modulators including epigenetics and transcriptional factors [20]. Among the various pathogen recognition receptor (PRR) ligands, toll-like receptor (TLR) ligands serve as particularly powerful stimuli for goblet cell production of mucins [21]. Intestinal microorganisms synthesize a variety of conserved structural components which act as ligands for PRRs termed microbe-associated molecular patterns (MAMPs), which are expressed by commensals and enteropathogens. In the context of pathobionts, MAMPs are typically referred to as pathogen-associated molecular patterns (PAMPs) [22]. Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* produce PAMPs, lipopolysaccharide (LPS) and flagellin, which bind TLR4 and TLR5, respectively, to alter mucin production and activate inflammatory pathways such as the nuclear factor-κB (NF-κB) cascade. While goblet cells are found throughout the GI tract, they are most concentrated in the colon and rectum where they form a thick mucin bilayer [17][23]. Notably, this increasing density gradient of goblet cells correlates with the density and diversity of gut microbes from proximal to distal aspects of the GI tract [24].

The mucous bilayer in the colon consists of a loosely arranged outer layer (ranging in thickness from 100 to 400 µm in the small bowel, to ~700 µm in the colon) which interacts with microbes, and a dense, impenetrable inner layer (ranging in thickness from 15 to 30 µm in the small bowel, to ~100 µm in the colon) rich in antimicrobial peptides [20][25]. This mucin meshwork allows for selective diffusion of nutrients and oxygen while limiting microbial contact with the underlying epithelium. Glycosylation of mucins is essential for maintaining intestinal homeostasis and involves either *O*-glycosylation or *N*-glycosylation. *O*-glycans act as important food sources for intestinal microbiota, while *N*-glycans maintain the mucosal barrier. Together, these carbohydrate moieties influence the composition of the intestinal microbiota and protect against intestinal inflammation and disease susceptibility [20]. For example, increased glycosylation of *N*-glycans via overexpression of the enzyme β-1,4-galactosyltransferase I (βGalT1) results in a higher Firmicutes to Bacteroidetes ratio, protection against tumor necrosis factor-α (TNF-α) induced inflammation, and decreased susceptibility to dextran sulfate sodium (DSS)-induced colitis [26]. In contrast, reductions in goblet cell densities [27], alterations in mucin production, and discontinuity of the mucous blanket layer have been implicated in UC pathophysiology. Specifically, reduced expression of MUC9 and MUC20, and increases in MUCH16 have been reported across UC patients irrespective of disease activity,

while increases in MUC1 and decreases in MUC2 expression appear to be limited to regions of ulceration [1][28][29]. Decreases in mucin glycosylation and sulphation and increases in sialylation impair barrier function and are well described features of UC [30].

Below the mucin layer, the GI tract is lined by a monolayer of intestinal epithelial cells (IECs) connected via junctional complexes, forming villi and crypts. The IECs form the largest physical barrier of the GI tract and are the strongest determinants of protection against the external environment. They physically separate the products of the intestinal lumen from the underlying lamina propria, thereby maintaining intestinal homeostasis. The junctional complexes which connect the IECs are vital in regulating selective transportation of water and nutrients and preventing penetration of the intestinal mucosa by commensals and enteropathogens [31]. These protein complexes are composed of tight junctions, adherens junctions, and desmosomes. The IECs comprise five distinct cell types, including enterocytes, enteroendocrine cells, tuft cells, Paneth cells, and microfold (M) cells [21], which are regenerated by pluripotent stem cells residing within the intestinal crypts [32]. While IECs exhibit primarily protective functions, defects in this barrier layer have been associated with increased susceptibility to gastrointestinal disease. For example, alterations in deoxyribonucleic acid (DNA) methylation and transcriptome patterns have been implicated in UC pathogenesis. Several of the affected pathways include innate immune system function including cytokine signaling and complement activation, as well as extracellular matrix composition including collagen, laminin, and fibril synthesis and degradation [33]. Many of these epigenetic alterations in methylation patterns appear to be independent of microscopic mucosal inflammation and remain stable over time in UC patients. IECs harvested from inflamed mucosa of UC patients exhibit alterations in molecular signaling cascades, including enhanced Notch signaling and TNF-α induced NF-κB signaling [34]. Furthermore, IECs harvested from patients with active UC exhibit higher apoptotic indices which contributes to impaired barrier function and permits translocation of commensal and enteropathogenic microorganisms, resulting in higher levels of proinflammatory cytokines including TNF-α [35]. Increases in TNF-α result in impairment of the mucosal barrier by inducing caspase-dependent apoptosis and caspase-independent necroptosis of multiple IECs [36]. This, in part, explains the therapeutic success of antibodies targeting TNF-α in select patients. However, a subgroup of patients demonstrates little to no response despite adequate dosing and duration of anti-TNF-α treatment, suggesting that intestinal inflammation independent of TNF-α signaling may be involved in certain subgroups of UC patients [37].

2.1.2. Immunoglobulin A

Within the mucus layer reside additional components of the host defense system including antibacterial peptides and secretory immunoglobulin-A (IgA). The gut mucosa harbors the largest concentration of IgA in the human body, which can be produced in a T-cell dependent or T-cell independent manner [38]. Plasma cells within the lamina propria produce dimeric IgA which is shuttled from the basolateral membrane to the apical surface of IECs via the polymeric immunoglobulin receptor (pIgR) [39]. At the apical surface of IECs, the pIgR-Ig complex is cleaved to produce secretory IgA. Once secreted, IgA can mediate its physiological functions including neutralizing bacterial toxins, inhibiting epithelial translocation of PAMPs such as *Shigella* LPS, coating microorganisms to reduce their immunogenicity, and facilitating the uptake of organisms (such as non-invasive *Salmonella*) to stimulate stronger adaptive immune responses [40]. Secretory IgA is essential for protecting against microbial invasion, influencing the composition of intestinal microbiota and protecting against intestinal inflammation [39].

The expression of IgA and pIgR can be altered by the intestinal microbiota. Upregulation can be achieved via activation of the NF-κB signaling cascade through commensal bacteria including *Bacteroides thetaiotaomicron* and certain strains belonging to the *Enterobacteriaceae* family [41][42]. This upregulation is presumably mediated via direct interactions between commensal MAMPs and TLRs, which stimulate myeloid differentiation factor 88 (MyD88) signaling and increase transcription of pIgR [43]. While proinflammatory cytokines such as interferon (IFN)-γ, TNF-α, interleukin (IL)-1, and IL-4 induce pIgR transcription, paradoxically, intestinal inflammation associated with UC causes downregulation of pIgR expression by IECs [44]. In addition to downregulating pIgR expression, UC is associated with lower concentrations of secretory IgA in the intestinal lumen, higher concentrations of IgA in the serum, decreased transcytosis of dimeric IgA across IECs, and accumulation of IgA within the lamina propria [44].

Crosslinking of IgA with its cognate transmembrane receptor on neutrophils, i.e., FcαRI, stimulates neutrophil recruitment to inflamed tissues and stimulates the release of leukotriene B4 (LTB4), a potent neutrophil chemoattractant [45]. In this manner, a sustained inflammatory loop can be maintained leading to excessive tissue damage. In addition to increased IgA–FcαRI interactions, UC disease activity is also associated with increased neutrophil uptake of IgA-opsonized bacteria within the intestinal mucosa [45]. This contributes to lower concentrations of IgA within the intestinal lumen, diminished immune protection against enteropathogenic invasion, increasing patient susceptibility to inflammation mediated by microbes, and worsened disease activity. Downregulation of pIgR and somatic mutations in IL-17 signaling have been reported in sporadic CRC, which may be driven by particular members of colonic microbiota [46][47]. The influence of microbiota on tumorigenesis is discussed further below.

2.1.3. Innate and Adaptive Immunity

Within the lamina propria are additional bacterial defenses belonging to innate and adaptive immunity. Innate immunity comprises antibacterial peptides, lysozymes, macrophages, and dendritic cells, while adaptive immunity includes T and B

cells, which are concentrated within highly organized lymphoid follicles known as Peyer's patches [48]. Dendritic cells extend their cytoplasmic projections into the intestinal lumen, where they sample intestinal contents and present antigens to T cells within the Peyer's patches [49]. These dendritic cells are a heterogenous group of antigen-presenting cells with unique biological function that are primarily focused on maintaining a balance between proinflammatory and tolerogenic responses [50].

Genome-wide association studies have identified over 200 loci specifically associated with increased risk of developing UC [3]. Many of these genes have been implicated in innate and adaptive immune system function and impaired autophagy, including specific defects in extracellular matrix protein 1 (ECM1), IL-10, and IL-23R [51].This impaired clearance of microbes causes persistent stimulation of the innate immunity system, prolonged stimulation of the adaptive immune system and chronic inflammation [52]. Inflamed mucosa exhibits upregulation of TLR2 and TLR4 in dendritic cells, which contributes to increased expression of proinflammatory cytokine IL-12 and alterations in microbial interactions [53]. Activated dendritic cells initiate and perpetuate inflammation alone or in combination with adaptive immune cells [50]. Upregulation of IL-13 receptor subunit α-2 (IL-13Rα2) has also been described in intestinal epithelial cells during active UC, which appears to impair goblet cell function, inhibit mucosal regeneration, and alter IL-13 signaling [54]. While low levels of IL-13 are secreted by natural killer cells and macrophages in non-inflamed colonic mucosa, increased release of IL-13 by mononuclear cells in active UC has been implicated in epithelial cell apoptosis and impairment of tight junctions, subsequently producing conduits for microbial translocation and perpetuation of intestinal inflammation [55].

Commensal microorganisms also produce an abundance of PRR ligands which shape homeostatic immune function. IL-17-producing CD4+ Th17 cells are concentrated within the lamina propria and their immunomodulatory role is highly influenced by commensal bacteria, such as segmented filamentous bacteria (SFB) and *Bifidobacterium adolescentis* [56]. *Bacteroides fragilis*, which is another commensal bacterium, synthesizes a capsular polysaccharide A (PSA) with potent immunomodulatory roles. This PSA contributes to the activation of the phosphoinositide 3-kinase (PI3K) pathway and downstream cAMP response element-binding protein (CREB)-dependent transcription of anti-inflammatory genes [57]. This supports the priming of CD4+ regulatory T (Treg) cells, production of anti-inflammatory IL-10, immune system maturation, and maintenance of Th1/Th2 balance [58]. These host–microbial interactions underscore how early life exposure to microorganisms is critical for shaping host immune interactions, establishing immunoregulatory networks, and influencing susceptibility to inflammatory diseases in later life.

2.2. Intestinal Microbiota Composition in Ulcerative Colitis

The vast majority of commensal microbiota are found within the GI tract [59]. Alterations in the structure or function of one or multiple classes of microbes, a condition called microbial dysbiosis, may significantly impact host health and has been implicated in various acute and chronic intestinal disorders such as UC [60].

Gut microbes are uniquely distributed across the GI tract with abundance and composition reflecting varying physiologic conditions. Factors such as pH, luminal transit time, nutritional substrates, and mucus layer composition impact microbial colonization and proliferation [13]. Intestinal microbiota are also fundamental for nutrient extraction, complementing host metabolism, supporting host nutrition and growth, and promoting intestinal cell proliferation by providing a unique enzymatic pool to digest macromolecules derived from dietary sources. Among these, the generation of key metabolites such as short-chain fatty acids (SCFAs), vitamins (i.e., vitamin K, B12), folate and bile acids rely on bacterial metabolism [13]. Several gut microbes possess enzymatic machinery to synthesize or modify host neurotransmitters and hormones [61].

The intestinal epithelium represents a key host-microbe interface in UC. Several studies have demonstrated that the inflammatory processes triggering UC are caused by direct contact of dysbiotic microbes with the intestinal mucosa [62]. To better understand the role of the intestinal microbiota in driving inflammatory processes in UC, the bacterial taxonomic profiles and fungi of stool samples and mucosal biopsies of UC patients have been sequenced [63]. While this phylogenetic analysis presents some limitations due to the intra- and interindividual variability of intestinal microbial communities, multiple studies have reported consistent alterations in the intestinal microbiota of UC patients as compared with healthy controls (**Table 1**). For example, the microbiome in UC is characterized by reduced bacterial α-diversity, reflecting species richness and evenness, and β-diversity (variability) in community composition between UC and healthy subjects [64][65]. UC is associated with a decrease in the number of bacterial taxa from the Firmicutes and Bacteroidetes phyla and a significant increase in bacterial communities from the Proteobacteria phylum [64][65][66][67][68]. These changes are collectively described as a state of bacterial dysbiosis. This dysbiosis could explain the presence of inflammation in the colon of UC patients, as the increased abundance of Gram-negative taxa such as *Escherichia-Shigella*, *Fusobacterium*, *Actinobacillus*, *Streptococcus,* and *Campylobacter* shift the host-microbe equilibrium towards a proinflammatory phenotype, supported by evidence of altered expression of several TLRs in subjects with UC [69][70][71]. TLR4 recognizes molecular profiles derived from Gram-negative bacteria (i.e., lipopolysaccharide), thus, playing a key role in limiting their invasion when the intestinal barrier is disrupted during inflammation [68]. Conversely, the depletion of members from the *Clostridiaceae* family (phylum Firmicutes), such as *Faecalibacterium prausnitzii* and other species from the genera *Clostridium*, *Ruminococcus*, *Eubacterium*, *Roseburia*, and *Akkermansia* significantly lower production of butyrate, propionate, and acetate, and thus impair epithelial barrier function by reducing colonocyte proliferation and affecting Treg cells' maturation through abnormal production of proinflammatory markers [13][64][65][72][73][74].

TABLE 1. Intestinal microbiota alterations in ulcerative colitis and impacts on host immune, intestinal function.

Gut Microbiota Alterations in UC				Consequences for Mammalia
Life Domain	**Taxonomic Classification**	**Compositional Changes of Gut Microbiota**	**Functional Changes of Gut Microbiota**	**Impact on Host Immune Function**
Bacteria	Phyla	16S ribosomal RNA gene sequencing ↓α- diversity in UC as compared with HC [63][71] ↑β-diversity in UC (UC bacteriome clusters differently form HC) [63][71] ↓relative abundance of Firmicutes and Bacteroidetes [13][63][64][67][74]	shotgun metagenomics sequencing ↑l-arginine biosynthesis (I, IV), biotin biosynthesis II, transfer RNA charging [71]	
	Families	↑Proteobacteria [13][63][64][65][68] ↓*Clostridiaceae* [64][65] ↑*Enterobacteriaceae* [79]	Super pathway of polyamine biosynthesis in patients with risk factors for developing UC as compared with HC [71] ↑amino acid and protein metabolism (in UC as compared with HC): l-lysine fermentation to acetate and butanoate, creatinine degradation II, ketogenesis, protein *N*-glycosylation [70]	*Ruminococcus, Eubacterium, Akkermansia, Anaerostipes h* ↓butyrate production = ↓Treg ↓maturation of Treg cells in th epithelium increased levels o cytokines [64][65][71][72][76]
	Genera	↓*Clostridium clusters IV, XIVa* [65] ↓*Ruminococcus, Eubacterium, Roseburia, Akkermansia* [64][71] ↓*Adlercreutzia, Bilophila, Bifidobacterium* [71] ↓*Bacteroides, Lachnospira, Phascolarctobacterium, Coprococcus, Odoribacter, Butyricimonas* [68][79] ↑*Escherichia-Shigella, Fusobacterium, Campylobacter, Helicobacter* [64][68][71] ↑*Actinobacillus* [71] ↑*Streptococcus, Anaerostipes Enterococcus, Actyinomyces, Lactobacillus, Acetobacter, Rothia, Pseudomonas, Collinsella* [68]	↑proteolytic and elastase activity in pre- and post-UC as compared with HC Correlated with the protease-producing bacterial species altered in UC- *Proteobacteria* and *Bacteroides*- ↑elastase from *B. vulgatus*) [71] ↓glycerol and glycerophospholipids in UC as compared with HC Positive correlation between bacterial species and carbohydrate-degradation pathways [75]	*Enterobacteriaceae* ↑colonic epithelial cells invas ↑levels of proinflammatory cy TNF-α [77] *Fusobacteria* ↑tumorigenesis in the colon [*Faecalibacterium prausnitzii* ↑production of IL-12, IFNγ an levels in blood cells [78] *Adlercreutzia* ↓synthesis of isoflavones, ph with antimicrobial and anti-in properties [71]
	Species	↓*Faecalibacterium prausnitzii* [65][76][80] ↓*Anaerostipes hadrus* [72] ↑*Flavonifractor plautii, Coprococcus catus, Parabacteroides merdae* [71]		
Fungi	Phyla	Stool ITS2 gene sequencing ↓α-diversity in UC (not in CD) [63] ↑β-diversity between UC in flare as compared with UC in remission and to HC [63] ↑ ratio of Basidiomycota/Ascomycota in UC in flare as compared with UC in remission and to HC [63] ↑correlation between fungi and bacteria in UC as compared with CD and HC [63] Colonic mucosa: ↓fungi load in UC as compared with HC No significant changes in α-diversity UC mycobiota clusters differently from HC No changes in the ratio of Basidiomycota/Ascomycota [81]	N/A	*Saccharomyces cerevisiae* ar *Albicans* = ↑IL-6 production [6 ↓*Saccharomyces cerevisiae* = (anti-inflammatory cytokine) [*Aspergillus* ↑aflatoxin production, a carci [81] Positive correlation between *Wickerhamomyces* a the expression of TNF-α and I (in colonic mucosa) [81] Negative correlation between *Sporobolomyces* an between *Trametes* and IL-1β ([81]
	Genera	↓*Saccharomyces* in UC fecal samples [63] ↑*Aspergillus* in UC mucosa specimen [81]		
	Species	↓*Saccharomyces cerevisiae* in UC fecal samples [63] ↑*Candida albicans* in UC fecal samples [63] Trend toward an increase in mucosal specimen [82]		

Gut Microbiota Alterations in UC				Consequences for Mammalia
Life Domain	**Taxonomic Classification**	**Compositional Changes of Gut Microbiota**	**Functional Changes of Gut Microbiota**	**Impact on Host Immune Function**
Virus	**Orders**	**Metagenomics sequencing of viral-like particles** **↓α-diversity (virome species richness and evenness) in UC mucosal samples** [83] **↑abundance Caudovirales bacteriophages in UC mucosal samples** [83] **↑β-diversity; UC mucosal virome clusters differently from HC** [83] **↑virome dissimilarity between UC subjects (not observed in HC subjects)** [83]	**↓integral component of membrane, DNA binding, ATP-binding cassette (ABC) transporter and integrase core domain in UC as compared with HC** [83] **↑Pathways related to the phage lysis of bacteria:** **DNA template negative regulation of transcription, beta-lactamase, glutamine amidotransferase, glycosal hydrolases, type II/IV secretion system and multicopper oxidase in UC as compared with HC** [83]	**↑bacteriophage = ↑bacterial ly production, TLRs overstimula inflammation** [83] **↑transfer of bacterial genetic antibiotic resistance genes)** [8 **↑phages can stimulate IFN-γ v sensing receptor TLR9** [84]
	Families	**↓*Anelloviridae* (eukaryotic virus)** [83] **↑*Microviridae* (single-stranded DNA phage), *Myoviridae, Podoviridae* (double-stranded DNA phages)** [83] ***Pneumoviridae* (eukaryotic virus)** [83]		
	Genera	**↓*Coccolithovirus*, *Minivirus* *Orthopoxvirus* (vertebrate-infecting virus) (all eukaryotic viruses)** [83] **↑*Phix174microvirus*, *P1virus, Lambdavirus*, *T4virus,* *P22virus* (all *Caudovirales* bacteriophages) *Orthopneumovirus*** [83]		
	Species	**↓α-diversity of *Caudovirales* species in UC mucosal samples** [83] **↑*Escherichia* and *Enterobacteria* bacteriophages** [83] ***Lactobacillus,* *Escherichia,* and *Bacteroides* bacteriophages** [84]		

UC, ulcerative colitis; HC, healthy controls; CD, Crohn's disease; IL, interleukin; CAC, colitis-associated cancer; IFN, interferon; TNF, tumor necrosis factor-α; Treg, regulatory T-cell.

Enterobacteriaceae (phylum Proteobacteria) uptake carbohydrates from the mucus layer, expanding their colonization and abundance while impairing mucosal integrity [13]. Increased *Enterobacteriaceae* and a lower concentration of *Bacteroides* observed in colonic or rectal UC-biopsies have been associated with inflammation severity and outcomes of relapse and remission [79]. *Bacteroides* suppress inflammation mediated by Th1 and Th2 immune cell activity, whereas the abnormal interaction between *Enterobacteriaceae* or their metabolites with the colonic epithelial cells stimulates the production of proinflammatory cytokines and induces the immune response [79]. Pathogen-induced acute enteritis has also been associated with risk of developing UC. For instance, it has been shown that specific strains of *Campylobacter jejuni* can cause the translocation of non-pathogenic commensal microbes across the intestinal epithelium by disrupting the integrity of the tight junctions. The passage of commensals through the intestinal barrier can increase the number of interactions between such microbes and host immune receptors, including TLRs, resulting in chronic inflammation [85].

In addition to bacterial dysbiosis, UC has also been associated with its own microbiome changes, highlighting the complexity of untangling microbial crosstalk in the pathogenesis of the disease [63][82]. This also extends to the intestinal (fungal) mycobiome. UC patients during active disease show an increase in the Basidiomycota/Ascomycota ratio as compared with those in remission and healthy controls. Sokol et al. found changes in the abundance of *Saccharomyces cerevisiae* and *Candida albicans* in stool samples from UC subjects. The authors also described the ability of *Saccharomyces cerevisiae* to produce anti-inflammatory IL-10, suggesting a role for this yeast in the pathogenesis of gut inflammation. Interestingly, this study reported the presence of strong correlations between fungi and bacteria only in UC and not in CD subjects, highlighting how such interkingdom interactions can enhance and contribute to the inflammatory phenotype of UC [63]. Subsequently, Qiu et al. showed an increase of *Aspergillus* in colonic mucosa specimens from UC subjects. Although this study did not find the same changes in the fungal population observed by Sokol et al., it reported positive correlations between *Wickerhamomyces*, *Penicillium*, and proinflammatory markers. Our knowledge of the host-fungi relationship in inflammation continues to develop [81].

A metagenomic analysis may provide more reliable information regarding the functional role of the intestinal microbiota in UC than taxonomic profiling, as the functional potential of the microbial genome is more stable and conserved [71][76]. Shotgun metagenomics have identified more than 20,000 gene families and up to 15 metabolic pathways altered in UC subjects (**Table 1**) [71]. UC is associated with a significant increase in protease and peptidase activity, suggesting a bacterial proteolytic signature involved in driving inflammation. Hence, elastase activity negatively correlates with beneficial bacteria such as *Adlercreutzia* and *Akkermansia*, but positively correlates with *Bacteroides vulgatus*, a bacterial species known for its proteolytic functional profile. These findings suggest that fecal proteolytic activity might be predictive of disease outcomes in UC [71].

Recent advances that have allowed sequencing of whole DNA of intestinal microorganisms have also facilitated the exploration of the virus kingdom within the human microbiome. In line with previous findings, UC is associated with compositional and functional changes of the mucosal virobiota [83][86]. In healthy conditions, the intestinal mucosal layer has a relatively low viral load, composed of a diverse viral population that is relatively stable over time. In contrast, UC-colonic biopsies show an expansion of viral abundance and reduced α-diversity of the viral population, which is mainly enriched by Gram-negative bacteriophages, mostly from the Caudovirales order [83]. The parallel viral and bacterial dysbiosis in UC suggest the presence of functional inter-kingdom crosstalk in sustaining inflammatory processes. The enrichment of Gram-negative bacterial taxa observed in UC could potentially stimulate the expansion of bacteriophages against such bacteria, resulting in bacteriolysis and subsequent release of PAMPs that could trigger inflammatory responses [13][83][84].

Despite recent advances in sequencing technologies, further studies are needed to elucidate the causal role of the intestinal microbiota in modulating the inflammatory processes in UC. This may occur by integrating microbiome sciences with metabolomics and epigenetics [76][87]. Understanding the contribution of each microbial kingdom to host–microbe interactions could significantly improve the management of UC and support opportunities for personalized medicine [88].

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