CHAPTER- Microbial Pathogenesis of Ulcerative Colitis

Dr. Ruchi Mishra

Abstract: The Inflammatory bowel disease (IBD) increasing globally, due to altered gut microbiota, changing pattern and adverse effect of environmental factors, human immune responses and genetics. Ulcerative colitis (UC) may be a chronic illness that includes perennial inflammation of the colonic mucous membrane. UC is a gastrointestinal disease associated with a gut microbial dysbiosis, including an expansion of bacteria, viruses and fungi. Several major factors are responsible for inducing gut dysbiosis, immune dysregulation which exaggerate the severity of infection.The therapeutic strategy of antibiotics, probiotics and prebiotics will be beneficial for the effective microbiome manipulation in ulcerative colitis.The goal of medical treatment is to rapidly induce a steroid-free remission while at the same time preventing complications of the disease.The choice of treatment depends on severity, localization and the course of the disease.5-aminosalicylic acid (5-ASA) compounds is used as first line of treatment. More extensive or severe disease should be treated with oral and local 5-ASA compounds, immunomodulators and corticosteroids to induce remission.

Keywords: Ulcerative colitis, Inflammatory bowel disease, gut microbiota, gut microbial dysbiosis, diet, inflammatory bowel disease, immunomodulators, corticosteroids.

1.1 INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract and can be classified into two main clinical phenomenon namely Crohn's disease (CD) and ulcerative colitis (UC).The main cause of UC are due to inappropriate immune response to gut microbes in a genetically susceptible host. Uncontrolled inflammation of the colon in ulcerative colitis has been noticed, it is a chronic and recurrent disease. It affects mainly the innermost lining of large intestine (colon) and rectum.It spreads from the distal to the proximal colonic segments, the rectum is generally affected and get inflamed easily. In this chapter, we will discuss several major factors responsible for the development of UC, including its major clinical manifestations, pathogenesis its association to gut microbiome, and immune dysregulation. UC differs by the fact that, it is a more superficial bowel inflammation targeting epithelial cell damage, in contrast, bowel wall granulomatous cellular infiltration observed in Crohn's diseases. Ulcerative colitis can sometimes lead to life-threatening complications if it remained undiagnosed or left untreated. The gastrointestinal tract is oftenly loaded with large number of the microbiome, which is responsible for maintaining gut homeostasis and act as a digestive organ, regulates the

immune system, and a guardian of harmful infections [1]. In UC patients, many alterations (dysbiosis) have been found inthe gut microbial profile including adecrease in diversity, of *Bacteroides, Firmicutes, Clostridia, Bifidobacterium and Lactobacillus*an increase in class of Gammaproteobacteria especially*E. coli* and *Fusobacterium* [2]. The different intestinal floras have their own role in maintaining gut environment, few microbiome along with its role are enlisted in Table 1.1

Table 1.1: List of enteric bacteria and their role to intestinal inflammation in Ulcerative Colitis.

Role in Ulcerative Colitis	Bacterial species
Initiating agents of inflammation	*Campylobacter spp.* *Salmonella spp.* *Shigella spp.*
Proinflammation	*Campylobacter spp.* *Escherichia coli* *Rhodococcus spp.* *Stenotrophomonas spp.* Enterohepatic *Helicobacter* *Bacteroides ovatus* *Fusobacterium varium*
Bacteria secreting anti-inflammatory factors	*Bacteroides spp.* *Firmicutes* *Faecalibacterium prausnitzii* *Lactobacillus spp.*

1.2 Symptoms

Symptoms of ulcerative colitis includes diarrhea often streaked with blood or pus, occasionally abdominal pain and cramping, rectal pain, rectal bleeding (stool with blood), urgency to defecate. Other symptoms may include fever, anaemia, weight loss and fatigue.

1.3 Classification of Ulcerative colitis

Ulcerative colitis has been classified on the basis of severity, location and extent of the disease.

1.3.1 Classification on the basis of location

The distal segments of the large bowel (rectum and sigmoid), is generally affected in UC. Considering its location it can be classified, into 3 groups known as Montreal Classification (Table 1.2)

Table 1.2: **Montreal Classification (2006)**

Ulcerative colitis	Classification of Montreal	Symptoms
E 1 – Proctitis	Inflammation confined to the rectum.	Rectal bleeding
E 2 – Left Sided Colitis	Inflammation extends from the rectum through the sigmoid and descending colon and left colon.	Bloody diarrhea, abdominal cramp and pain on the left side
E 3 – Pancolitis (Extensive colitis)	Affects the entire colon (proximal to the splenic angle)	Severe bloody diarrhea, abdominal cramps, pain and fatigue with significant weight loss

1.3.2 Classification on the basis of severity

The disease can be classified according to the severity or the clinical picture [2]

1. Remission (S0)-presence of blood in stool 3 or less stool per day, with increased urge to defecate.

2. Mild (S1)- up to 4 stools per day streaked with blood, with normal body temperature and heart rate.

3. Moderate (S2)- 4 to 6 bloody stools per day, no systemic involvement.

4. Severe (S3)- more than 6 bloody stools per day, with systemic involvement (with higher body temperature, heart rate above 90/min, decreased hemoglobin concentration below 10.5 g/dL, or ESR above 30 mm/h).

1.4 Pathogenesis

The pathogenesis of ulcerative colitis, involves multitude of factors such as abnormal gut microbiota, immune response dysregulation, importance of environmental stimuli, imbalance diet and exaggeration of inflammation by certain food material has centered role in disease pathogenesis.

1.4.1 Dysbiosis in Ulcerative Colitis

Dysbiosis, defined as quantitative and qualitative microbial imbalance in the gut, is one of the major factor contributing to intestinal inflammation.The most commonly identified bacterial pathogen as cause of enteric infection is *Campylobacter spp.*, followed by *Salmonella spp.* and *Shigella spp.* [3, 4].The human gut microbiota is mainly composed of four major phyla. The most dominating Firmicutes phyla composed of *Clostridium* XIV and IV groups then, Bacteroidetes phyla having *Bacteroides*, followed by the Proteobacteria including *Campylobacter, Salmonella, Shigella* etc. and phyla Actinobacteria are Gram positive bacteria with extensive mycelial like growth that is Actinomycetales [5, 6]. *Campylobacter ureolyticus* and *Campylobacter jejuni* are found to facilitate internalization and translocation of commensal, noninvasive *Escherichia coli* strains and forms the basis to create in equilibrium in gut microbiota[7, 8].These findings might indicate that in UC, *Campylobacter spp.* induce an inflammatory cascade that starts with an episode of acute gastroenteritis. The colonic microflora provide short chain fatty acids and the synthesis of essential vitamins B and K [9], and maintenance of intestinal innate and adaptive immune response, in return host provide residence and nutrient rich environment to these bacteria [10]. This shift in gut microbiota, known as dysbiosis and it is important to cause ulcerative colitis.

1.4.1.1 Bacterial Microbiota

Bacterial microbiota, the most widely studied component of the gut environ, which inhabit its host in variable concentrations. The gut microbiome performs several important functions in the host, it acts as an organ to educate the immune system[11], secreting beneficial enzymes for digestion of complex substrate into simpler one, to make it more accessible for the host [12], and supressing noxious microorganisms [13]. The phyla Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria and Verrucomicrobia are the predominant constituents in the healthy gut microbiota [14]. A multitude of factors have been shown to impair the normal gut functioning including age, genetics, diet, living standard and drugs [15-17]. *Fusobacterium* principally colonize both the oral cavity and the gut and it has been found abundantly in mucosa of ulcerative colitis as compared to healthy

controls [18]. *Fusobacterium spp*.found in colorectal tumour than in adjacent normal tissues [19-21].*Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium*, belongs to the genera of bacterial community which have been shown to be protective of the hostfrom mucosal inflammation via several mechanisms, down-regulation of inflammatory cytokines andthe stimulation of the anti-inflammatory cytokine IL-10, *Faecalibacterium prausnitzii* itself has an anti-inflammatory property [22-23]. In addition, the change in the diversity of gut microbiota can alter the host mucosal immune response. *Clostridium* and *Bacteroides spp.* could induce the expansion of regulatory Tcells (Treg) and cause alleviation of intestinal inflammation [24] Alteration in microbiota is responsible for changing the gut equilibria and respond accordingly to invading pathogen.(Table 1.3)

Helicobacter pylori is a, spiral-shaped Gram-negative bacillus. The microaerobic metabolism, its anti-acid activity and specific motility helps to colonize the bacteria in gastric mucosa[25]. *H. pylori* pathogenic mechanism includes the secretion of vacuolating cytotoxin (VacA) and cytotoxin associated gene A antigen (CagA) proteins and other virulence factors to induce inflammatory response dominated by TH1. The inflammatory response is reduced once the *H. pylori* has been eradicated from the gastric mucosa. Several studies revealed that *H. pylori* is one of the potent carcinogenic factor to cause the chronic gastritis and may lead to gastric cancer [26].

On contrary to this, animal experiments and epidemiologic studies[27] revealed an inverse correlation between *H. pylori* infection and progression of the disease, suggesting that *H. pylori* colonization induces a special protective environ in gut to prevent it from several autoimmune disorders by inducing systematic immune tolerance and suppressing inflammatory responses. Eradication of *H. pylori* for peptic ulcer has increased the incidence of Inflammatory bowel diseases[28]. The mechanism to provide the protective environment of *H. pylori* on inflammatory bowel diseases will be helpful to manage the infection and can provide platform for disease prevention and treatment.The transformation of Dendritic cells (DCs) into mature DCs by E.coli making them to express high levels of MHC II, CD80, CD86, and CD40 that produce numerous proinflammatory factors, such as IL-12, IL-1β, IL-6, and IL-23, in contrast to *H. pylori* stimulated DCs which retain a semi-mature structure with low production of MHC II, CD80, CD86, and CD40 expression and decreased level of pro-inflammatory factor secretion, increased levels of IL-10, TGF-β, and IL-18, is required for the differentiation of immunosuppressive regulatory T cells (Tregs) rather than differentiating into Th1 or Th17 cells from naive Th0 cells. Thus, Tregs inhibit the transformation of Th0 and maintaining the immature status of DCs by direct contact and IL-10 and TGF-β secretion. Through lymphocyte recirculation mechanisms, Tregs produced in the gastric mucosa and exert a systematic immunoregulatory effect that influences the pathogenesis of various autoimmune and inflammatory bowel diseases [29](Fig. 1.1)

1.4.1.2 Fungal Microbiota (Mycobiota)

Fungi constitutes the major portion in humans at different body sites [30]. Most predominating fungal infections caused by *Candida* species (*C. albicans, C. tropicalis* and *C. glabrata*) then, *Histoplasma capsulatum* found exclusively in most studies followed by *Pneumocystis jirovecii* , and *Cryptococcus neoformans* [31,32]. *Saccharomyces, Candida,* and *Cladosporium* are the most predominating genera, in healthy person [33]. Taxa belongs to *Basidiomycota*, *Ascomycot*a, and *Candida albicans* have been shown to be significantly raised in inflammatory bowel diseases, whereas *Saccharomycetes* and *Tremellomycetes* classes, are the most abundant taxa in the mucosal samples from healthy individuals[34,35]. The glycoprotein cell wallcomponents of the fungi, chitin, β-glucans and mannans can induce the innate immune response, through lectin receptor such as dectin-1 (C-type), components of the complement system Toll-like receptors (TLR2 andTLR4), and membersof the scavenger receptor family (CD5, SCARF1, and CD36).Activation of these molecules leads to downstream immunecascades engaging molecules, such as CARD 9 (Caspase recruitment domain-containing protein 9), IL-17, IL-22,ITAM (Immunoreceptor Tyrosine-based Activation Motif), NFAT (Nuclear factor of activated T-cells), and NF-kB [36]. Prolonged inflammation along with the disruption of tight junction (TJ) occludin and ZO-1, leads to the loss of integrityof intestinalepithelial cells (IECs) which act as a physical barrier to prevent from foreign invaders.Therefore, pathogens like fungi and bacteria can penetrate the mucosal barrier and activate TLRs, Dectin-1 and CARD 9 in the lamina propria and concluding into a more severe inflammatory response [37- 38].

1.4.1.3 Viral Microbiota (Virobiota)

The viral component of the microbiota comprises both eukaryotic viruses and prokaryotic bacteriophages together known as virobiota. In healthy individuals the gut virome is characterized predominantly by the bacteriophages temperate ds-DNA *Caudovirales* and ss-DNA *Microviridae.* Bacteriophages, latently infect their bacterial hosts and kill other bacteria under stress by newly formed progenies [39-42] Alteration in bacteriophage proportion might have further impact on the bacterial microbiota ecology. Bacterial fitness and diversity are vastly dependent on bacteriophages community in gut. [43] In the gastrointestinal tract, bacteriophages engage in the horizontal transfer of genetic elements between bacterial populations, including those for antibiotic resistance and disease.

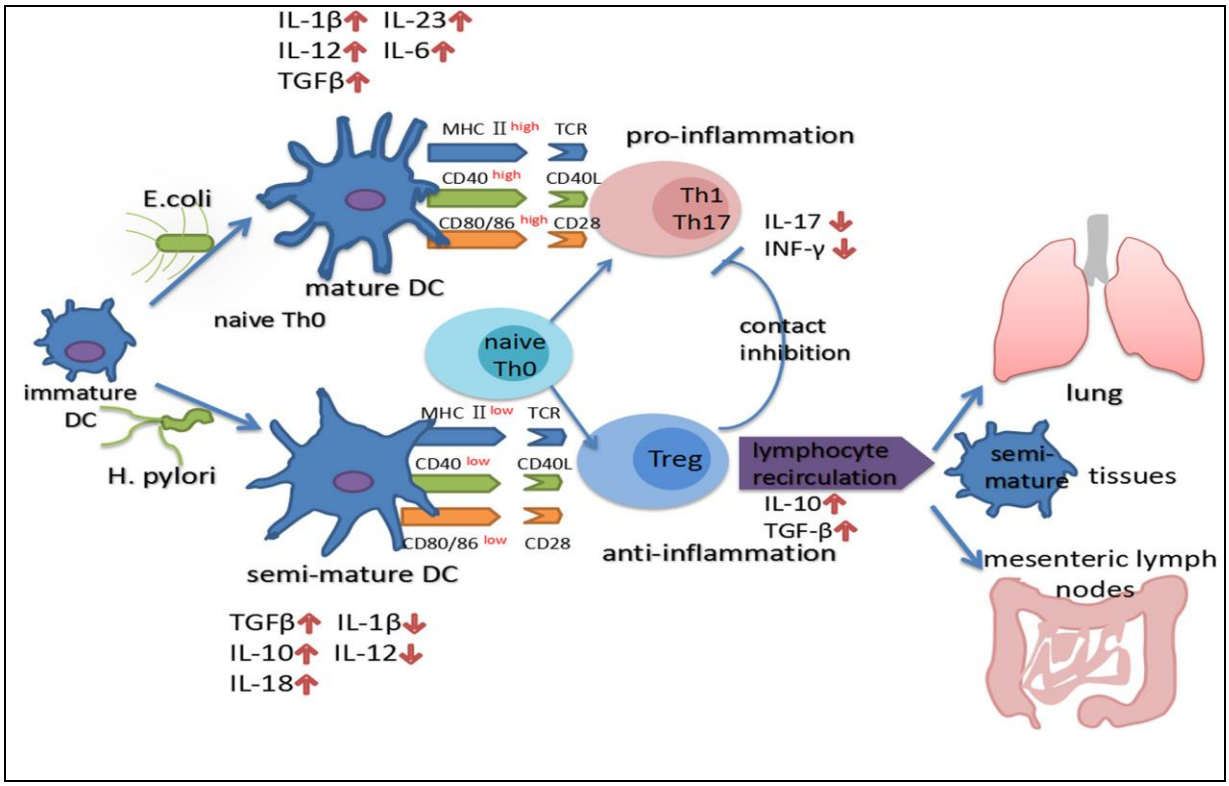


Fig. 1.1 Protective effect of H. pylori infection induce tolerogenic Dendritic cells (DCs) and immunosuppressive T regulatory (Tregs) *H. pylori* stimulated DCs which retain a semi-mature structure with low production of immunoregulators and decreased level of pro-inflammatory factors, which is required for the differentiation of regulatory T cells (Tregs) rather than differentiating into Th1 or Th17 cells from naive Th0 cells. Thus, Tregs inhibit the transformation of Th0 and maintaining the immature status of DCs by direct contact and IL-10 and TGF-β secretion. Through lymphocyte recirculation mechanisms, Tregs produced in the gastric mucosa and exert a systematic immunoregulatory effect that influences the pathogenesis of various autoimmune and inflammatory bowel diseases (Picture courtesy Yu et al. [29]

[44-46]. Thus bacteriophages brings the alteration in gut microbiome. They can also induce humoral immune responses [47]. Thus, bacteriophages could act as immune ligands that boost host immunity as well as inflammation. Viruses, such as Norovirus, can functionally replace the beneficial effect ofcommensal bacteria, ameliorating intestinal abnormalities [48]. Viruses attached to themucosa could protect the epithelium against bacterial invasion,by binding through the immunoglobulin like protein on the phage capsid and mucin glycoproteins on the mucosal surface [49]. The combinatorial effect of susceptible gene of

Table 1.3: Altered gut microbiota in UC compared to healthy individuals in humans.

	Decreased in Ulcerative colitis	**Increased in Ulcerative colitis**
Microbial Composition	1. *Bifidobacterium spp.* 2. *Clostridium spp.* 3. *Bacteroides spp.* 4. *Saccharomyces cerevisiae* 5. *Faecalibacterium prausnitzii* 6. *Fusobacterium spp.* 7. *Roseburia spp.* 8. *Suterella spp.*	1. *Proteobacteria spp.* 2. *Escherichia coli,* 3. *Pasteurellaceae* 4. *Veillonellaceae* 5. *Ruminococcus gnavusa* 6. *Pasteurellaceae* 7. *Veillonellaceae* 8. *Caudovirales* 9. *Clavisporalusitaniae* 10. *Candida albicans* 11. *Candida tropicalis*

gut Norovirus infection led to the manifestation of the disease,suggesting its role in pathogenesis and/or progression of the disease. The protective effects of the gut viruses were mediated synergistically by toll like receptors (TLR3 and TLR7). Higher rates of hospitalization have been observed if patients carrying mutation in both TLR3 and TLR7 when compared with UC patients without mutations [50].

1.4.1.4 Helminths

Helminths, the worm like parasites, have the potential to inhabit the gastrointestinal tract. The changing pattern of environment and living standard, has drastically reduced the exposure to helminths during early childhood thus, causing least number of individuals getting infected by parasites in twenty first century[51]. Lack of helminths is associated with inflammatory bowel diseases,as they are important immune-regulatory component known to prevent the host from infection. [52-54].Helminths causes increases in mucus and water secretion into the gut lumen, as measures for anti-inflammatoryresponses in the host [55-56].The efficacy of *Trichiuris suis* or pig whip worm shown in patients with ulcerative colitis[57-60].Helminths enhances the induction of dendritic cells,which controls the growth of regulatory T cell (Treg cell) populations and production of anti-inflammatory IL-10 in the intestine.The mechanism of providing protection by helminths includes the promotion of the growth of IL4-producing, Th2 cells, worm induced Th2 cells produce cytokines for disease control. StimulatedTh2 response, causes induction of regulatory T cells (Tregs), which may

control re-infection through their potent immune regulatory system[61,62].There are certain important parasites available which can produce disease preventing factors such as *Necator americanus* [63] or *Trichuri ssuis*, *Trichuris muris* ova or larvae [64] or inoculation with *Trichuris trichiura* ova [65] and *Heligmosomoides polygyrus bakeri* [66].

1.4.2 Immune Dysregulation

Even though the complicated pathogenesis of ulcerative colitis, several studies have demonstrated that certain cytokines and chemokine has immunoregulatory role and initiates the inflammation of bowel and causes excessive destruction of the colon tissues.At equilibrium, gut microbes induce an immune tolerance in the host, while in inflammatory condition like UC, antigens from dysbiotic microbes activate certain proinflammatory components like Th1 and Th17 cells, causes increased penetration by persisting microbes in colon [68](Figure 1.2) Th1 mediated immune response characterizes the inflammatory infiltration and leads to tissue injury, whereas Th2 mediated immune response are anti-inflammatory in action [67].This mucosal injury end up in further uptake of microbial antigens,Toll Like Receptor ligands, and microbes that perpetuate the immune responses to initiate the inflammation[66].

1.4.2.1 Cytokines

Cytokines stimulates immune cells and causes the progression of the disease. For example, the IL-1 family of cytokine plays important role in the pathogenesis of ulcerative colitis, IL-1β promotes inflammation and active IL-1β is expressed in the colonic mucosa.[69-70] IL-33 belongs to IL-1 family, stimulates mucus secretion to protect the epithelium and upregulates the expression of IL-5 and IL-13 as part of the Th2 response.[71] Ulcerative colitis patients having increased expression of IL-33 and its receptor ST2 [72,73].There is evidence of response of IL-6, which activates Signal Transducer and Activator of Transcription3 (STAT3), marked increased in the production of IL-6 and its soluble IL-6receptor also act as carcinogen of colorectal cancer related to ulcerative colitis. [74-76] Tumour necrosis factor α (TNF-α) has a significant function in pathogenesis, because it increase the expression of IL-1β, IL-6, and IL-33. [77-78] TheTNF-α levels are correlated clinically with the severity of ulcerative colitis[79]. Transforming growth factor β (TGF-β) has dual role in the pathogenesis of bowel diseases. It stimulates epithelial distruction and fibrosis and induces tolerance and homeostasis [80].In mononuclear cells, the enhanced level of TGF-β1 found in lamina propria of ulcerative colitis, unlike Crohn's disease where it is in decreased level [81]. TGF-β improved intestinal inflammation by reducing the expression of IL-33, in contrast to TGF-α which enhance the severity of disease [82].IL-17 is a pro-inflammatory cytokine that activates STAT3, along with IL-6 which stimulates a strong chronic immune inflammatory response [83-85].

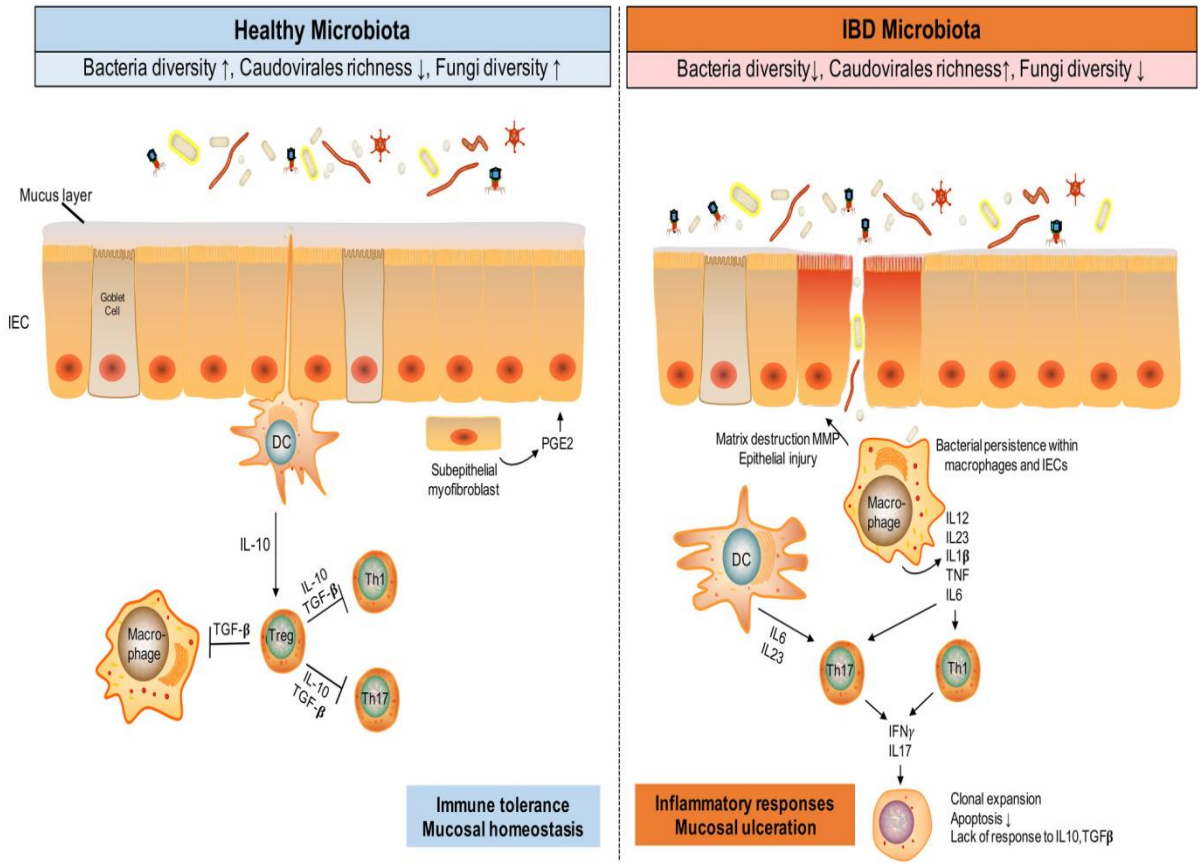


Figure 1.2: Alteration in Gut microbiota and immune responses in Ulcerative colitis. Microbial dysbiosis causes tissue destruction by excessive production of IL17 by Th17 cells and Th1 response, by activated dendritic cells, whereas in healthy individuals TGF-β and IL10 controls the differentiation of regulatory T cells (Treg) and maintain immune tolerance and mucosal homeostasis (Picture courtesy- Zuo T et al. [68])

1.4.2.2 Chemokine

IL-8 is especially a leucocyte chemoattractant that induces the migration of neutrophils to inflamed tissue. The increased production of IL-8, is found in tissues of ulcerative colitis patients in comparison to normal individuals [86].

1.4.2.3 Th17 cells

Th17 cells are relevant to the pathogenesis of ulcerative colitis, [87] IL-17 are strong pro-inflammatory interleukin released by Th17 cells. In contrast to healthy individual IL-17

expression and IL-17A and IL-17F mRNA levels found higher in the mucosal and serum of patients of ulcerative colitis [85,88] It is documented well that increased expression of IL-7 has observed in inflamed colon [89] (Fig. 1.3 A & B). Thus, the current focus on IBD therapies is on blocking IL-17A and IL-17F [90].

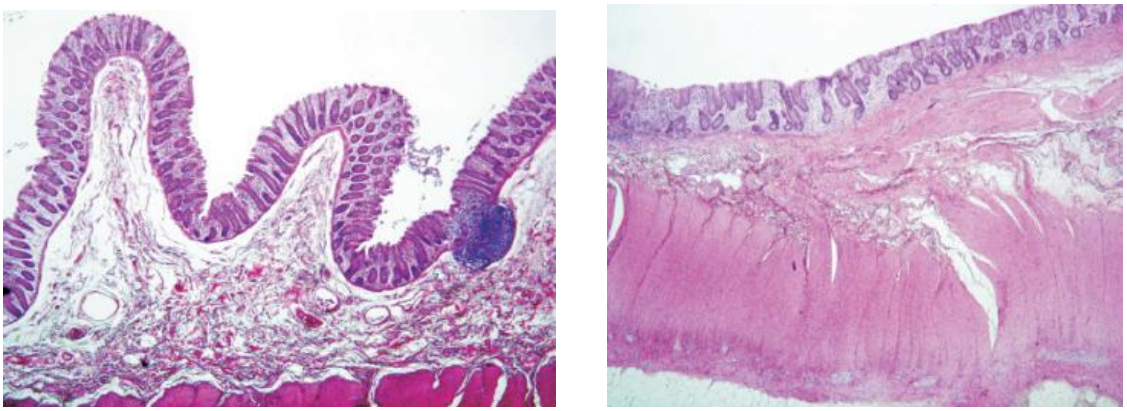
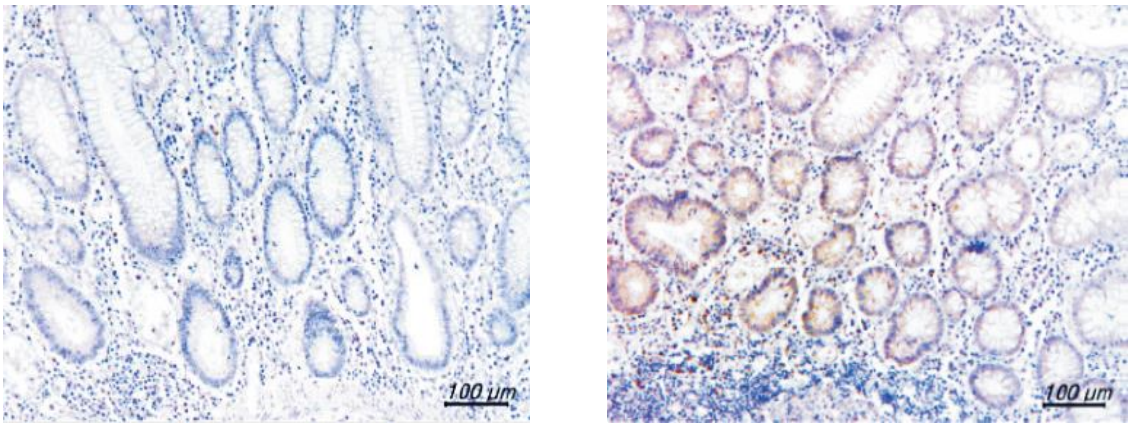


Figure 1.3 A: a) Un-inflamed colon b) Inflamed colon



a) b)

Figure 1.3 B: Histology of colon tissue a) H&E of colon tissue in healthy individual b) interleukin 17 (IL-17) expression in colon tissue from UC patient. (Picture courtesy- Lee et al. [89])

1.4.2.4 Treg Cells (Regulatory T cells)

The intestinal inflammatory response in ulcerative colitis is mainly mediated by the T-cell response thus, Treg cells are associated with the pathogenesis of inflammatory bowel diseases [91].Treg cells helps in maintenance of immune homeostasis and establishing

inflammation in response to foreign or non-pathogenic antigens such as commensal bacteria, thus, poorly performing Treg cell leads to an inflammatory disorder. CD25 and IL-10, which are responsible for Treg cell differentiation, mutation in these components causing them deviated from proper functioning. Moreover, loss of IL-10 results in intestinal inflammation, and Treg cells lacking the IL-10 receptor are more susceptible to colitis [92-94].

1.4.3 Diet and the Gut microbiome

Gut microbiota largely depend on the diet we intake and influence the environ of the gut [95].Diet (junk food, rich diet) predisposes the individuals to diseases and making them more prone to diseases like inflammatory bowel diseases, diabetes, obesity, hypercholesterolemia, and cardiovascular disease [96-97] and is associated with a decreased ratio of *Bacteroides* to *Firmicutes* and making them more susceptible to anincreased presence of Adherent-Invasive E. coli (AIEC) infection [98]. Consumption of pineapple and coffee products has increased incidence of ulcerative colitis [99].Low fiber diet is shown to be associated witha depletion of the microbial ecosystem, this microbial extinction became irreversible and aggressive over the generations [98], these data imply that improper balanced diet causes the microbial dysbiosis. In humans, carbohydrate rich diet is associated with abundance of*Candida spp.*, but no effect has been noticed with diet high in protein, fatty acids and amino acids [33]. Number of *Candida spp.* in fecal samples were reduced in subjects consuming an animal-based diet andincreased on a plant-based diet, thus the variation in *Candida spp*. depends on the food we intake and bring changes in the gut mycobiota. [100]. Overall, diet has an impact on the gut microbiota. However, data shows the strong association of diet with the microbial dysbiosis but still mechanistic study are much needed.

1.5 Diagnosis

Ulcerative colitis can be diagnosed in one or several ways according to the severity and extent of the disease.

1. Blood tests

2. Stool sample- Increased number of White blood cells (WBC) is indicative of ulcerative colitis.

3. Colonoscopy- A thin, flexible, lighted tube with an attached camera inserted into the colon to get small samples of tissue (biopsy) for laboratory analysis.

4. Flexible sigmoidoscopy- By using a slender, flexible, lighted tube to examine the rectum and sigmoid segment of the colon.

5. X-ray- whole abdomen X-ray is required to rule out serious complications, such as a perforated colon.

6. CT scan- A CT scan of abdomen or pelvis may be performed to reveal the complications and extent of severity of colon.

7. Computerized tomography (CT) enterography and magnetic resonance (MR) enterography- The non-invasive test includes examination of colon by CT. These tests are more sensitive for locating inflammation with in the gut than conventional or standard imaging tests.

1.6 Treatment

Treatment includes 5-ASA therapy as first line therapy, corticosteroids are considered a second-line therapy option for the induction of remission. The major drawback of using steroids are its high toxicity, particularly when used for longer term. The immunomodulators, 6-mercaptopurine (6-MP) and azathioprine are recommended for patients with refractory disease who fail to improve on 5-ASAs or steroids [101].

1.6.1 5-Aminosalicylate(5-ASA)

Mesalamine, or 5-aminosalicylate (5-ASA), is the first-line therapy for achievingand maintaining remission in ulcerative colitis and ulcerative proctitis. The mechanism of 5-ASA is not fullyunderstood, it is believe that it inhibit inflammatory mediators by blocking transcriptionfactors directly within the colonic mucosa [102]. 5-ASA is thought to activate the nuclear Peroxisome proliferator-activated receptor (PPAR) [103].It acts topically on the mucosa to reduce inflammation. Rectal therapy deliver mesalamine directly to the rectum and colon, while oral therapy, the drug are prevented from being absorbed systemically by coating systems which delayed the release of active drug to reach the siteof inflammation. The percentage of achieving remission depends on the amount of active mesalamine that reaches the site of inflammation. 5-aminosalicylic acid (5-ASA) is oftenly the first line of treatment, other medications with similar properties include sulfasalazine (Azulfidine), mesalamine, balsalazide andolsalazine. Taking it by mouth or enema depends on the area of your colon that is affected.

1.6.2 Corticosteroids

It includes prednisone and budesonide are generally reserved for moderate to severe ulcerative colitis.Due to its side effect, they are not frequently in use, in cases of refractoriness (no response to treatment with prednisone therapy) the clinicians may suggest the use of immunomodulators (aza-thioprine, 6-mercaptopurine) [104].

1.6.3 Immunomodulator drugs

These drugs reduces inflammation, by suppressing the immune response, which initiated the process of inflammation. Examples include azathioprine, tofacitinib, cyclosporine is the main immunomodulator or immunosuppressant used in clinical practice. Azathioprine is a synthetic analog of purine and it acts by inhibiting DNA synthesis in proliferating cells, for instance, B and T lymphocytes [105-106].

1.7 Antibiotics, Probiotics and Prebiotics

Antibiotics, probiotics and prebiotics have shown promise in treating inflammatory bowel diseases with varying results. Combinations therapy of antibiotics found useful and improved the outcome [107-108] but, it may induce antibiotic resistance in gut microbes.The probiotic combination (aprobiotic preparation of eight live freeze-dried bacterial species, including *Lactobacillus casei, Lactobacillus delbrueckii subspp. Bulgaricus, Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium breve, and Streptococcus salivarius subsp. Thermophiles*) may have shown marked effect in clinical severity [109]. *Faecalibacterium prausnitzii* having tendency to produce barrier-enhancing and immuno suppressive SCFAs (Short Chain Fatty Acids) stimulating regulatory T cell to produce IL-10 thereby inhibitingexaggerated immune responses. *F. prausnitzii, Clostridia spp.*, and *Bacteroides .fragilis* inducing anti-inflammatory milieu and thereby reducing the symptom andseverity of colitis [24,110,111].Although the idea of providing prebiotic (oligosaccharides and fibers) as dietary substrates, to selectively increase the abundance of SCFA-producing commensals remained unsatisfactory [112].

1.8 Conclusion

The pathogenesis of ulcerative colitis is complicated, bacterial microbiota is the most studied gut microbiota component but still much needed to know about the mechanism of other gut microbiome like virobiota and mycobiota, these are still in infancy. Understanding the complexity of gut ecosystem will require thorough mechanistic studies involving molecular and microbiological techniques to determine the mechanism of the host-microbes interaction,the role of different gut microbes in disease pathogenesis and evolution. It also involves many pro-inflammatory mediators, like chemokines and several cytokines which play a central role in the induction and maintenance of chronic intestinal inflammation in UC patients, however, there is still much needed to focused on. Therefore,these components needs to study thoroughly, that could be targeted and give way to the development of an effective ulcerative colitis therapy. Number of effector cells involved in the pathogenesis of UC, it is required to maintain the balance of immune cells in preventing the inflammatory bowel diseases.

REFERENCES

1. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-amino- salicylic acid therapy for mildly to moderatelyactive ulcerative colitis. A randomized study. N Engl J Med.1987; 317:1625–9.

2. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. Gastroenterology 2014; 146: 1489-1499.

3. K. O. Gradel, H. L. Nielsen, H. C. Schønheyder *et al*. Increased short- and long term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. Gastroenterology. 2009; vol. 137: no. 2, pp. 495–501.

4. A. Ternhag, A. Torner, A. Svensson *et al.* Short- and long-term effects of bacterial gastrointestinal infections. Emerging Infectious Diseases. 2008; vol. 14: no. 1, pp. 143– 148,

5. Eckburg P.B, Bik E.M, Bernstein C.N, et al. Science. 2005; Jun 10; 308(5728):1635-8.

6. Frank D.N, St. Amand A.L, Feldman R.A, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A. 2007; Aug 21; 104(34):13780-5.

7. Kalischuk L. D, Inglis G. D, and Buret A. G. Campylobacter jejuni induces transcellular translocation of commensal bacteria via lipid rafts. Gut Pathogens, 2009;vol 1, p. 2.

8. Lamb-Rosteski J. M., Kalischuk L. D, Inglis G. D *et al*. Epidermal growth factor inhibits Campylobacter jejuni-induced claudin-4 disruption, loss of epithelial barrier function, and Escherichia coli translocation. Infection and Immunity. 2008; vol. 76: no. 8, pp. 3390–3398.

9. Cummings J. H. and Macfarlane G. T. Collaborative JPEN Clinical Nutrition Scientific Publications role of intestinal bacteria in nutrient metabolism. Journal of Parenteral and Enteral Nutrition.1997; vol. 21: no. 6, pp. 357–365.

10. Sears C. L. A dynamic partnership: celebrating our gut flora. Anaerobe.2005; vol 11: no. 5, pp. 247–251.

11. Round, J. L., and Mazmanian, S. K. The gut microbiota shapes intestinal immune responses during health and disease. Nat. Rev. Immunol.2009; 9: 313–323.

12. El Kaoutari A., Armougom F., Gordon J. I., *et al*.. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. Nat. Rev. Microbiol. 2013; 11: 497–504.

13. O'Hara, A.M., and Shanahan, F. The gut flora as a forgotten organ. EMBO Rep. 2006; 7: 688–693.

14. Jandhyala S. M., Talukdar R., Subramanyam C., *et al.* Role of the normal gut microbiota. World J. Gastroenterol. 2015; 21: 8787–8803.

15. Yatsunenko T., Rey F. E., Manary M. J., *et al*. Human gut microbiome viewed across age and geography. Nature. 2012; 486: 222–227.

16. Maier, L., Pruteanu, M., Kuhn, M., Zeller, G., Telzerow, A., Anderson, E. E., et al. Extensive impact of non-antibiotic drugs on human gut bacteria.Nature. 2018;555: 623–628.

17. Zuo T., Kamm M. A., Colombel J.-F., and Ng S. C. Urbanization and the gut microbiota in health and inflammatory bowel disease. Nat. Rev. Gastro. Hepat. 2018; 15: 440–452.

18. Ohkusa T., Yoshida T., Sato N., *et al*. Commensal bacteria can enter colonic epithelial cells and induce proinflammatory cytokine secretion: a possible pathogenic mechanism of ulcerative colitis. J. Med. Microbiol. 2009; 58: 535–545.

19. Castellarin M., Warren R. L., Freeman J. D.et al.Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012; 22: 299–306.

20. Kostic A. D., Gevers D., Pedamallu C. S., Michaud M., et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res. 2012; 22: 292–298.

21. Yu, T., Guo, F., Yu, Y., Sun, T., Ma, D., Han, J., et al. Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy. Cell. 2017; 170: 548–563.e16.

22. Sokol H., Pigneur B., Watterlot L., Lakhdari O., et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn's disease patients. Proc. Natl. Acad. Sci. U.S.A. 2008;105: 16731–16736.

23. Llopis M., Antolin M., Carol M., Borruel N., et al. Lactobacillus casei downregulates commensals inflammatory signals in Crohn's disease mucosa. Inflamm. Bowel Dis. 2009;15: 275–283.

24. Atarashi K., Tanoue T., Oshima K., Suda W., et al. T-reg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature.2013; 500: 232–236.

25. Dunn, B. E., Cohen, H. & Blaser M. J. Helicobacter pylori. Clin. Microbiol. Rev. 1997;10:720–741

26. Marshall, B. J. & Warren, J. R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration Lancet 1984; 1: 1311

27. Arnold, I. C., Iris, H. & Anne, M.The immunomodulatory properties of Helicobacter pylori confer protection against allergic and chronic inflammatory disorders. Front. Cell. Infect. Microbiol.2012; 2, 10

28. Thia K. T. et al. An update on the epidemiology of inflammatory bowel disease in Asia. Am. J. Gastroenterol. 2008;103, 3167–3182

29. Yu Y., Zhu S., Li P. *et al. Helicobacter pylori* infection and inflammatory bowel disease: a crosstalk between upper and lower digestive tract. *Cell Death Dis* 2018 Oct; 9(10): 961.

30. Underhill D. M., and Iliev I. D. The mycobiota: interactions between commensal fungi and the host immune system. Nat. Rev. Immunol. 2014; 14, 405–416.

31. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol. 2012;107:1409–1422

32. Toruner M, Loftus EV, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology. 2008;134: 929–936.

33. Hoffmann C., Dollive S., Grunberg S., et al. Archaea and fungi of the human gut microbiome: correlations with diet and bacterial residents. 2013;PLoS ONE 8:e66019.

34. Ott S. J., Kuhbacher T, Musfeldt, M., Rosenstiel P., et al. Fungi and inflammatory bowel diseases: alterations of composition and diversity. Scand. J. Gastroentero. 2008;43: 831–841.

35. Sokol H., Leducq V, Aschard H., Pham H. P., et al. Fungal microbiota dysbiosis in IBD. Gut. 2017; 66: 1039–1048.

36. Sartor, R. B., and Wu, G. D. Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. Gastroenterology. 2017;152: 327–339.

37. Brun P, Castagliuolo I., Di Leo V., Buda A., et al. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of non alcoholic steatohepatitis. Am. J. Physiol. Gastr. L. 2007; 292:G518–G525.

38. Iliev I. D., Funari V. A., Taylor K. D., et al. Interactions between commensal fungi and the C-type lectin receptor dectin-1 influence colitis. Science.2012; 336: 1314–1317.

39. Reyes A., Haynes M., Hanson N., Angly F. E., et al. Viruses in the faecal microbiota of monozygotic twins and their mothers. Nature 2010; 466: 334–338.

40. Minot S., Bryson A., Chehoud C., et al. Rapid evolution of the human gut virome. Proc. Natl. Acad. Sci. U.S.A. 2013;110: 12450–12455.

41. Minot S., Grunberg S., Wu G. D., Lewis J. D., et al. Hypervariable loci in the human gut virome.Proc. Natl. Acad. Sci. U.S.A. 2012; 109: 3962–3966.

42. Waller A. S., Yamada T., Kristensen D. M., Kultima J. R., et al. Classification and quantification of bacteriophage taxa in human gut metagenomes. ISME J. 2014; 8: 1391–1402.

43. Brüssow H., Canchaya C., and Hardt W. D. Phages and the evolution of bacterial pathogens: From genomic rearrangements to lysogenic conversion. Microbiol. Mol. Biol. R. 2004; 68: 560-602.

44. Maiques E., Ubeda C., Campoy S., Salvador N., et al. Beta-lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in Staphylococcus aureus. J. Bacteriol.2006; 188: 2726–2729.

45. Zhang Y. F., and Le Jeune J. T. Transduction of bla (CMY-2), tet (A), and tet (B) from Salmonella enterica subspecies entericaserovar Heidelberg to S-Typhimurium. Vet. Microbiol.2008; 129: 418–425.

46. Reyes A., Wu M., McNulty N. P., Rohwer F. L., et al. Gnotobiotic mouse model of phage-bacterial host dynamics in the human gut.Proc. Natl. Acad. Sci. U.S.A.2013; 110: 20236–20241.

47. Uhr J. W., Dancis J., Franklin E. C., et al. The antibody response to bacteriophage phi-X 174 in newborn premature infants. J. Clin. Invest. 1962; 41: 1509–1513.

48. Kernbauer E., Ding Y., and Cadwell K. An enteric virus can replace the beneficial function of commensal bacteria.Nature2014; 516: 94–98.

49. Barr J. J., Auro R., Furlan M., et al. Bacteriophage adhering to mucus provide a non-host-derived immunity. Proc. Natl. Acad. Sci. U.S.A.2013; 110: 10771–10776.

50. Yang YJ., Kim M.-S., Kim E., et al. Enteric viruses ameliorate gut inflammation via toll-like receptor 3 and tolllike receptor 7-mediated interferon-b production. Immunity 2016; 44: 889–900.

51. Elliott D. E, and Weinstock J. V. Helminth-host immunological interactions: prevention and control of immune-mediated diseases.Ann. N. Y. Acad. Sci. 2012;1247: 83–96.

52. Weinstock J. V., and Elliott D. E. Helminths and the IBD hygiene hypothesis. Inflamm. Bowel Dis. 2009; 15: 128–133.

53. Weinstock J. V., Summers R. W., Elliot D. E., etal.The possible link between de-worming and the emergence of immunological disease. J. Lab. Clin. Med.2002; 139: 334–338.

54. Ramanan D., Bowcutt R., Lee S. C., Tang M. S., et al. Helminth infection promotes colonization resistance via type 2 immunity. Science. 2016; 352:608–612.

55. Stepek G., Auchie M., Tate R., Watson K., et al. Expression of the filarial nematode phosphorylcholine containing glycoprotein, ES62, is stage specific. Parasitology 2002;125: 155–164.

56. HarnettW., and Harnett M. M. Filarial nematode secreted product ES-62 is an anti-inflammatory agent: therapeutic potential of small molecule derivatives and ES-62 peptide mimetics. Clin. Exp. Pharmacol. Physiol.2006; 33: 511–518.

57. Summers R. W., Elliott D. E., Urban J. F., et al. Trichuris suis therapy in Crohn's disease.Gu t2005a; 54: 87–90.

58. Summers R. W., Elliott D. E., Urban J. F., Thompson R. A., et al. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology.2005b; 128: 825–832.

59. Velthuis J. H., Unger W.W., Abreu J. R., Duinkerke, G., et al. Simultaneous detection of circulating auto reactive CD8(+) T-cells specific for different islet cell-associated epitopes using combinatorial MHC multimers. Diabetes 2010; 59: 1721–1730.

60. Helmby, H. (2015). Human helminth therapy to treat inflammatory disorders where do we stand? BMC Immunol. 2015;26:16:12.

61. Whelan RA K, Hartmann S, Rausch S. Nematode modulation of inflammatory bowel disease. Protoplasma. 2012; 249: 871–86.

62. Wang L.J, Cao Y., and Mizoguchi H.N.S. Helminth infections and intestinal inflammation. World J Gastroenterol. 2008; 14: 5125–32.

63. Croese J, O'neil J, Masson J, Cooke S, Melrose W, Pritchard D, et al. A proof of concept study establishing Necator americanus in Crohn's patients and reservoir donors. Gut. 2006; 55: 136–37.

64. Artis D, Potten CS, Else KJ. *Trichuris muris*: host intestinal epithelial cell hyperproliferation during chronic infection is regulated by interferon-γ Experiment Parasitol. 1999; 92:144–53.

65. Blum AM, Hang L, Setiawan T. Heligmosomoides polygyrus bakeri induces tolerogenic dendritic cells that block colitis and prevent antigen-specific gut T cell responses. J Immunol. 2012;189: 2512–20.

66. Broadhurst MJ, Leung JM, Kashyap V, McCune JM, Mahadevan U, McKerrow JH, et al. IL-22± CD4± T cells are associated with therapeutic Trichuris trichiura infection in an ulcerative colitis patient. Sci Trans Med. 2010; 2:60–88.

67. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature 1996; 383:787-93.

68. Zuo T and Ng SC. The Gut Microbiota in the Pathogenesis and Therapeutics of Inflammatory Bowel Disease. *Front. Microbiol*. 2018; 9:2247.

69. Dinarello CA. Interleukin-1beta and the autoinflammatory diseases. N Engl J Med 2009; 360: 2467-2470.

70. McAlindon ME, Hawkey CJ, Mahida YR. Expression of interleukin 1 beta and interleukin 1 beta converting enzyme by intestinal macrophages in health and inflammatory bowel disease. Gut 1998; 42: 214-219.

71. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin- 1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 2005; 23:479-490.

72. Beltran CJ, Nunez LE, Diaz-Jimenez D, et al. Characterization of the novel ST2/IL-33 system in patients with inflammatory bowel disease. Inflamm Bowel Dis 2010; 16: 1097-1107.

73. Kobori A, Yagi Y, Imaeda H, et al. Interleukin-33 expression is specifically enhanced in inflamed mucosa of ulcerative colitis. J Gastroenterol 2010; 45:999-1007.

74. Mitsuyama K, Toyonaga A, Sasaki E, et al. Soluble interleukin-6 receptors in inflammatory bowel disease: relation to circulating interleukin-6. Gut 1995; 36:45-49.

75. Reinisch W, Gasché C, Tillinger W, et al. Clinical relevance of serum interleukin-6 in Crohn's disease: single point measurements, therapy monitoring, and prediction of clinical relapse. Am J Gastroenterol 1999; 94: 2156-2164.

76. Li Y, de Haar C, Chen M, et al. Disease-related expression of the IL6/STAT3/SOCS3 signalling pathway in ulcerative colitis and ulcerative colitis-related carcinogenesis. Gut 2010; 59: 227-235.

77. Murch SH, Braegger CP, Walker-Smith JA, MacDonald TT. Location of tumour necrosis factor alpha by immunohistochemistry in chronic inflammatory bowel disease. Gut 1993; 34: 1705-1709.

78. Sanchez-Munoz F, Dominguez-Lopez A, Yamamoto-Furusho JK. Role of cytokines in inflammatory bowel disease. World J Gastroenterol 2008; 14: 4280-4288.

79. Li MC, He SH. IL-10 and its related cytokines for treatment of inflammatory bowel disease. World J Gastroenterol 2004;10: 620-625.

80. Li MO, Flavell RA. TGF-beta: a master of all T cell trades. Cell 2008; 134: 392-404.

81. Del Zotto B, Mumolo G, Pronio AM, Montesani C, Tersigni R, Boirivant M. TGF-beta1 production in inflammatory bowel disease: differing production patterns in Crohn's disease and ulcerative colitis. Clin Exp Immunol 2003; 134: 120-126.

82. Rani R, Smulian AG, Greaves DR, Hogan SP, Herbert DR. TGF-beta limits IL-33 production and promotes the resolution of colitis through regulation of macrophage function..Eur J Immunol 2011; 41:2000-2009.

83. Gu FM, Li QL, Gao Q, et al. IL-17 induces AKT-dependent IL-6/JAK2/STAT3 activation and tumor progression in hepatocellular carcinoma. Mol Cancer 2011; 10:150.

84. Wruck CJ, Fragoulis A, Gurzynski A, et al. Role of oxidative stress in rheumatoid arthritis: insights from the Nrf2-knockout mice. Ann Rheum Dis 2011;70: 844-850.

85. Fujino S, Andoh A, Bamba S, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003; 52:65-70.

86. Mahida YR, Ceska M, Effenberger F, Kurlak L, Lindley I, Hawkey CJ. Enhanced synthesis of neutrophil-activating peptide-1/interleukin-8 in active ulcerative colitis. Clin Sci (Lond) 1992;82:273-275.

87. Murphy KM, Stockinger B. Effector T cell plasticity: flexibility in the face of changing circumstances. Nat Immunol 2010;11:674-680.

88. Seiderer J, Elben I, Diegelmann J, et al. Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD. Inflamm Bowel Dis 2008;14:437-445.

89. Lee SN, Kwon J, Cho ML. Immunological pathogenesis of inflammatory bowel diseases. Intest Res 2018;16(1):26-42.

90. Wedebye Schmidt EG, Larsen HL, Kristensen NN, et al. TH17 cell induction and effects of IL-17A and IL-17F blockade in experimental colitis. Inflamm Bowel Dis 2013; 19:1567-1576.

91. Brand S. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. Gut 2009;58:1152-1167.

92. Boden EK, Snapper SB. Regulatory T cells in inflammatory bowel disease. Curr Opin Gastroenterol 2008;24:733-741.

93. Wirtz S, Neurath MF. Mouse models of inflammatory bowel disease. Adv Drug Deliv Rev 2007; 59:1073-1083.

94. Chaudhry A, Samstein RM, Treuting P, et al. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. Immunity 2011;34: 566-578.

95. Albenberg, L. G., and Wu, G. D. Diet and the intestinal microbiome: associations, functions, and implications for health and disease. Gastroenterology.2014;146, 1564–1572.

96. Conlon M. A., and Bird A. R. The impact of diet and lifestyle on gut microbiota and human health. Nutrients 2015; 7, 17–44.

97. Carrillo-Larco, R. M., Bernabé-Ortiz, A., Pillay, T. D., Gilman, R. H., Sanchez, J. F.,Poterico, J. A., et al. Obesity risk in rural, urban and rural-to-urban migrants: prospective results of the PERU MIGRANT study. Int. J. Obes. 2016; 40: 181–185.

98. Agus A., Denizot J., Thevenot J., Martinez-Medina M., et al. Western diet induces a shift in microbiota composition enhancing susceptibility to Adherent-Invasive, E. coli infection and intestinal inflammation. Sci. Rep. 2016; 6:19032.

99. Shivashankar R., Beauvais J. C., and Lewis J. D. The relationship of regional diets with global incidence rates of inflammatory bowel disease. Gastroenterology. 2017; 152: S975–S976.

100. David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E, Wolfe, B. E., et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014; 505, 559-563.

101. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American college of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2004; 99: 1371-1385

102. Bantel H, Berg C, Vieth M, et al. Mesalazine inhibits activation of transcription factor NF-kappa B in inflamed mucosa of patients with ulcerative colitis. Am J Gastroenterol. 2000; 95:3452-3457.

103. Rousseaux C, Lefebvre B, Dubuquoy L, et al. Intestinal anti-inflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. J Ex Med. 2005; 201(8):1205-1215.

104. Travis S P L, Stange E F, Lémann M, Øresland T, BemelmanW A, Chowers Y, et al. European evidence-based consensus on the management of ulcerative colitis: current management. J Crohn's Colitis. 2008; 2: 24–62.

105. Timmer A, McDonald J W, Tsoulis D J, Macdonald J K. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev.2012; 12:9.

106. Kennedy N A, Rhatigan E, Arnott I D, Noble CL, Shand A G, Satsangi J, et al. A trial of mercaptopurine is a safe strategy inpatients with inflammatory bowel disease intolerant to azathioprine: an observational study, systematic review and meta-analysis. Aliment Pharmacol Ther. 2013; 38:1255–66.

107. Ohkusa, T., Kato, K., Terao, S., Chiba, T., Mabe, K., Murakami, K., et al. Newly developed antibiotic combination therapy for ulcerative colitis: a double-blind placebo-controlled multicenter trial. Am. J. Gastroenterol. 2010; 105: 1820–1829.

108. Turner, D., Levine, A., Kolho, K. L., Shaoul, R., and Ledder, O. Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: a preliminary report. J. Crohns Colitis. 2014; 8: 1464–1470.

109. Bibiloni, R., Fedorak, R. N., Tannock, G. W., Madsen, K. L., Gionchetti, P., Campieri, M., e al. VSL# 3 probiotic-mixture induces remission in patients with active ulcerative colitis. Am. J. Gastroenterol. 2005; 100: 1539–1546.

110. Round, J. L., Lee, S.M., Li, J., Tran, G., Jabri, B., Chatila, T. A., et al. The toll Like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science. 2011; 332: 974–977.

111. Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermudez-Humaran, L. G., Gratadoux, J. J., et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc. Natl. Acad. Sci. U.S.A. 2008; 105: 16731–16736.

112. Sartor, R. B., and Wu G. D. Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. Gastroenterology.2017; 152: 327–339.