MICROBIAL PATHOGENESIS OF ULCERATIVE COLITIS

Abstract

Global increase in inflammatory bowel disease (IBD) may be due to alteration of gut microbiota, changing environmental pattern and its impact, role of genetics and immune response towards foreign bodies. Ulcerative colitis (UC) may be a chronic illness that includes perennial inflammation of the colonic mucous membrane. UC is an inflammatory gastrointestinal disease usually associated with the inner lining of large intestine due to microbial dysbiosis, including bacteria, viruses and fungi. Several major factors are responsible for inducing gut dysbiosis, immune dysregulation which exaggerate the severity of infection. The therapeutic approach of probiotics, prebiotics and antibiotics will be beneficial for the efficacious microbiome manipulation in ulcerative colitis. The treatment goal is to induce a steroid-free recurrence also to prevent complications of the disease at the same time. The treatment depends on the level of severity, localization and the course of the disease. Aminosalicylic acid (5-ASA) compounds are used as first line of treatment. More severe disease should be treated with oral and local application of amino salicylic acid compound; immune modulators and steroidal therapy has been proved more efficacious.

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

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I. INTRODUCTION

Inflammatory bowel disease (IBD) is an inflammatory gastrointestinal tract disease and can be classified into two main clinical phenomenon namely Crohn's disease (CD) and ulcerative colitis (UC).Inappropriate immune response to gut microbes in a genetically susceptible host is one of the important causes. Uncontrolled inflammation of the colon in ulcerative colitis is has been noticed, it is a chronic and recurrent disease. The innermost lining of large intestine (colon) and rectum are mainly affected by it and spread from the distal to the proximal colonic segments, the rectum is generally affected and get inflamed easily. In this chapter, we will discuss several factors responsible for the development of UC, its clinical manifestations, pathogenic role of gut microbiome, and immune dysregulation. Intestinal epithelial cells are mainly the target site of the UC in contrast, granulomatous cellular infiltration observed in Crohn's diseases. Ulcerative colitis can be complicated and sometimes may become fatal, 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 in the gut microbial profile including a decrease 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

Table 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. **Symptoms:** Diarrhoea is one of the most common symptoms of ulcerative colitis often streaked with blood or pus, occasionally cramping and pain in abdomen, rectal bleeding

(stool with blood)frequent urge to defecate. Other symptoms may include fever, anaemia, weight loss and fatigue.

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

- **Classification on the basis of location:** The rectum and sigmoid are the distal segments of the large bowel which is generally affected in UC. Considering its location it can be classified, into following three groups known as Montreal Classification(Table 2)

Table 2: **Montreal Classification (2006)**

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

- **Classification on the basis of severity**

On the basis of severity level it can be classified accordingly [2]

- Remission (S0)-less than 3 stools per day with the presence of blood, with increased urge to defecate.
- Mild (S1) –passage of stool up to 4 per day streaked with blood, with no change observed in body temperature and heart rate.
- Moderate (S2) - at least 4 - 6 bloody stools per day, with no systemic involvement.
- Severe (S3) –passage of more than 6 bloody stools per day, with systemic involvement (with higher body temperature, heart rate above 90/min, decreased hemoglobin concentration lower than 10.5 g/dL, or ESR higher than 30 mm/h).

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

- **Dysbiosis in Ulcerative Colitis:** Dysbiosis, defined as imbalance in the gut microbiome community, is one of the major contributing factors to intestinal inflammation. The most common bacterial pathogen responsible to cause enteric infection is *Campylobacter spp.*, followed by enteric bacteria i.e, *Salmonella spp.* and *Shigella spp.* [3, 4].The four major phyla comprising the human gut microbiota. 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* both the species helps in facilitating, internalization and migration of commensal like noninvasive *Escherichia coli* strains and forms the basis to create equilibrium in gut microbiota[7, 8].*Campylobacter spp.* may involve in inducing inflammatory cascade with frequent occurrence of acute gastroenteritis is at early stage.To maintain the intestinal innate and adaptive immune response the colonic microflora plays several major roles like providing short chain fatty acids and the synthesis of essential vitamins B and K [9], 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.

  - **Gut 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]. There are number of factors have been shown to weaken the normal gut microbiota functioning including age, genetic make-up, food habit, living standard and drugs [15-17]. *Fusobacterium* the most common obligate anaerobic bacteria colonizes both the buccal 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 are known for its protective functioning to prevent the host from mucosal inflammation via several mechanisms, down-regulation of cytokine causing inflammation and the stimulation of the anti-inflammatory cytokine IL-10, *Faecalibacterium prausnitzii* itself has an anti-inflammatory property [22-23]. In addition, little variation in the diversity of gut microbiota the alteration of intestinal mucosal immune response can be seen. Many bacterial communities shown that are (*Clostridium* and *Bacteroides spp.)* responsible for inducing the expansion of regulatory Tcells (Treg) and cause alleviation of inflammation *[*24]

Alteration inmicrobiota is responsible for changing the gut equilibria and respond accordingly to invading pathogen.(Table 3)

Helicobacter pylori are a microaerophillic, spiral shaped Gram-negative bacillus. The microaerobic metabolism, its anti-acid activity and specific motility helps to colonize the bacteria in gastric mucosa[25]. The mechanism of action of *H. Pylori* includes secretion of several cytotoxins and other virulence factors to induce the inflammatory response by TH1. *H. pylori* produces cytotoxin associated gene A antigen (CagA) which act as a strong virulent factor in progression of diseases one of the potent carcinogenic factor causing gastric cancer if the strain carrying CagA positive gene. Other cytotoxin produce by *H. pylori known as* vacuolating cytotoxin (VacA) which stimulates the signalling pathways. Once the *H. pylori* has been eradicated from the gastric mucosa the inflammatory response gets slower down. [26].

On contrary to this, animal experiments and epidemiologic studies [27] found that H. *pylori* infection is inversely related to the progression of the disease, this correlation suggesting that as the *H. pylori* colonizing itself might induce some protective sheath to gut environment by suppressing inflammatory responses and inducing systemic immunity. Eradication of *H. pylori* the most important organism to cause peptic ulcer has increased the incidence of inflammatory bowel diseases[28]. The mechanism to provide the shielding environment of Helicobacter species on inflammatory bowel diseases will be helpful to manage the infection and can provide platform for disease prevention and treatment. E.coli makes the the conversion of dendritic cells (DCs) into mature DCs so that these cells can express high levels of MHC II, CD80, CD86, and CD40 to produce numerous pro-inflammatory 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 and reduced level of pro-inflammatory factors, while increased levels of IL-10, TGF-β, and IL-18 causes 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 under the influence of IL-10 and TGF-β secretion. Through lymphocyte recirculation mechanisms, Tregs produced in the gastric mucosa and induces as immunoregulatory effect systemically and influences the pathogenesis of inflammatory bowel diseases[29](Figure 1)

- **Fungal Microbiota (Mycobiota):** Fungi constitute the major portion in humans at different body sites[30]. Most predominating fungal infections caused by different *Candida* species then, *Histoplasma capsulatum* found exclusively in most studies followed by *Pneumocystis jirovecii* , and *Cryptococcus neoformans* [31,32]. Candida, Saccharomyces and *Cladosporium* species are the most predominating genera, in healthy person [33]. Taxa belongs to *Basidiomycota, Ascomycota,* and *Candida albicans* have a significant role in increasing inflammatory bowel diseases, whereas in mucosa of healthy individual *Saccharomycetes* and *Tremellomycetes* classes, are found in abundant [34, 35]. The innate immune response are induced by many components like glycoprotein

cell wall of fungi (chitin, β-glucans), through lectin receptor such as dectin-1, components of the complement system Toll-like receptors(TLR2 and TLR4).These compounds get activated and expedite downstream immune cascades by engaging different molecules such as interleukins, neuclear factors and other adapter proteins involve in assembly of multifunctional signalling complexes like CARD9 (Caspase recruitment domain-containing protein 9), IL-17 and IL-22, ITAM (Immunoreceptor Tyrosine-based Activation Motif) [36]. The intestinal epithelial cells which act as a barrier to prevent from foreign bodies loses its integrity on prolonged inflammation along with the disruption of tight junction (TJ).Therefore, foreign invaders and pathogens can easily penetrate the mucosal barrier and activates the inflammatory response by several Pattern Recognition Receptor like Toll Like Receptors and Dectin-1 [37- 38].

- **Viral Microbiota (Virobiota):** Virobiota comprises both eukaryotic viruses as well as bacteriophages. In healthy individuals the gut virome is mainly predominated by the bacteriophages ds-DNA *Caudovirales* and ss-DNA *Microviridae.* Under stress Bacteriophages, infect their bacterial hosts and kill other bacteria by newly formed progenies [39-42] As a result, the major proportion of bacteriophages community get altered and disrupt the ecology of gut microbiota where bacterial diversity are vastly dependent on it [43] also causes disturbances in the horizontal transfer of genetic elements and resistant gene between bacterial populations.

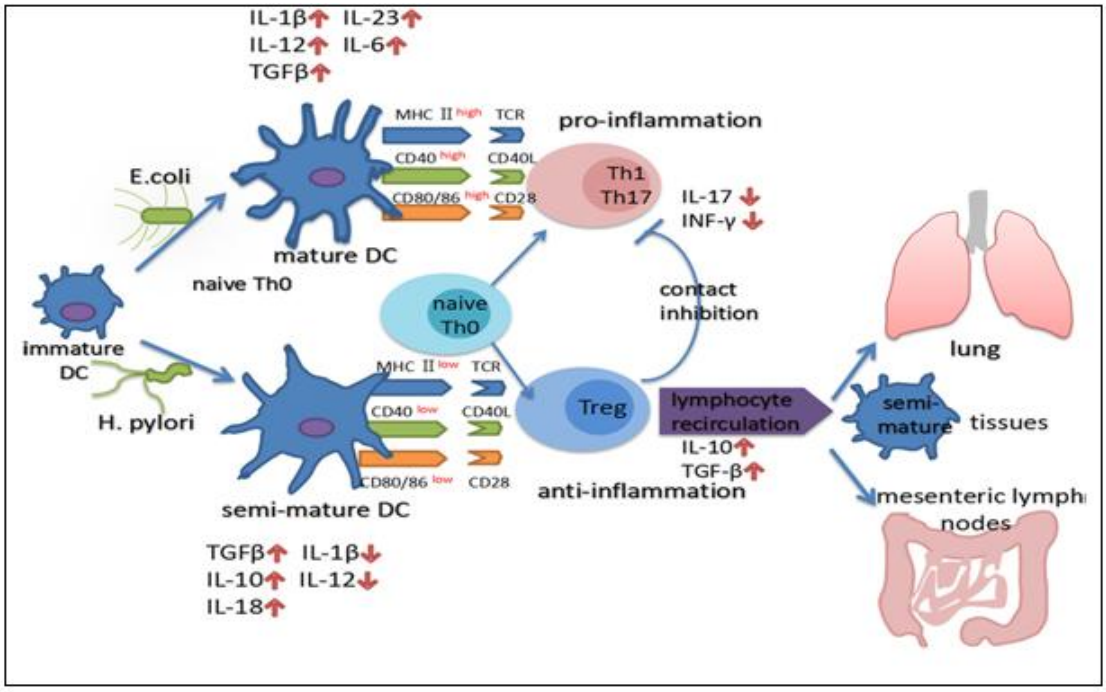

Figure 1: Protective effect of *Helicobacter pylori* infection by inducing Dendritic cells (DCs) and immunosuppressive T regulatory (Tregs)

The stimulation of DCs with 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 and exerts a systematic immunoregulators effect that influences the pathogenesis of inflammatory bowel diseases (Picture courtesy Yu et al. [29]

[44-46]. Thus bacteriophages bring the alteration in gut microbiome and can also induce humoral immune responses [47]. Thus, bacteriophages plays important role as immune ligands and also boost host immunity as well as inflammation. Intestinal abnormalities get ameliorated by viruses, such as Norovirus, that can affect the functioning and beneficial effect of commensal bacteria [48]. Viruses attached to the mucosa 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].

Table 3: Difference in gut microbiota in UC compared to healthy individuals

	Lower in number in Ulcerative colitis	**Higher in number in Ulcerative colitis**
Microbial Communities	*Bifidobacterium spp.* *Clostridium spp.* *Bacteroides spp.* *Saccharomyces cerevisiae* *Faecalibacterium prausnitzii* *Fusobacterium spp.* *Roseburia spp.* *Suterella spp.*	*Proteobacteria spp.* *Escherichia coli,* *Pasteurellaceae* *Veillonellaceae* *Ruminococcus gnavusa* *Pasteurellaceae* *Veillonellaceae* *Caudovirales* *Clavisporalusitaniae* . *Candida albicans* . *Candida tropicalis*

The combinatorial effect of susceptible gene of gut Norovirus infection led to the manifestation of the disease, suggesting its role in pathogenesis and/or progression of the disease. Gut viruses provides protection synergistically by the Toll like receptors to the gut environment(TLR3 and TLR7). It has been observed that if the patient carrying mutation in both the TLRs the rate of hospitalization get increased in comparison with UC patient without mutations [50].

- **Helminths:** Helminths, the worm like parasites, 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]. Production of mucus and water secretion get increases into the gut lumen under the influence of Helminths[55-56].The efficacy of *Trichiuris suis* or pig whip

worm often shown in patients with ulcerative colitis[57-60].The mechanism of protection provided by Helminths includes the induction of dendritic cells, which controls the growth of regulatory T cell (Treg cell) and production of anti-inflammatory IL-10 it also promotes the growth of IL4-producing, Th2 cells, Th2 cells induced by worm have the capacity to produce cytokines for disease control. Thus,the re-infection can be greatly reduced through the induction of regulatory T cells which has been activated by stimulation of Th2 response, [61,62].There are certain important parasites available which can produce disease preventing factors such as *Necator americanus* [63] or *Trichurisuis*, *Trichuris muris, Trichuris trichiura* ova [64,65] and *Heligmosomoides polygyrus bakeri* [66].

- **ImmuneDysregulation:** Despite of having complicated etiology of ulcerative colitis, several studies have illustrated that certain cytokines and chemokine has immunoregulatory role and initiates the inflammation of bowel and causes excessive destruction of the colon tissues. In stable environment, gut microbes produce an immune tolerance in the host, while having inflammation like UC, antigens from gut microbiome activate certain pro-inflammatory components like Th1 and Th17 cells, causes increased penetration by persisting microbes in colon [68](Figure 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 intake of microbial antigens,Toll Like Receptor substrate, and microbes that bolster the immune responses to initiate the inflammation[66].

  - **Cytokines:** Cytokines stimulates immune cells and causes the progression of the disease. For example, interleukin belongs to the family of cytokine has its own role in the pathogenesis of ulcerative colitis, IL-1β promotes inflammation and active IL-1β express itself in mucosa of colon.[69-70] Due to the impact of Th2 response member of IL-1 family which is IL-33 promote the mucus secretion to protect the epithelium and also helps in up-regulation of the expression of IL-5 and IL-13 takes place.[71] Increased expression of IL-33 and its receptor ST2 found in patient with UC [72,73].There is evidence of response of IL-6, that may activates Signal Transducer and Activator of Transcription3 (STAT3), marked increased in the production of IL-6 and its soluble IL-6 receptor also act as carcinogen of colorectal cancer related to ulcerative colitis. [74-76] other important factor belongs to cytokine i.e, Tumour necrosis factor α (TNF-α) plays a significant role in pathogenesis, because it increase the expression of IL-1β, IL-6, and IL-33. [77-78] The TNF-α level are correlated clinically with the intensity of ulcerative colitis[79]. Transforming growth factor β (TGF-β) has dual role in the pathogenesis of bowel diseases. It causes destruction of epithelial cells and stimulation of fibrosis and also induces tolerance and homeostasis [80].In mononuclear cells, the increased level of TGF-β1 found in lamina propria of ulcerative colitis, which is unlikely to Crohn's disease where decreased level of TGF-β1 is found [81]. TGF-α and TGF-β both are having opposite response where former enhances the severity of the diseases while later helps in reducing the intestinal inflammation by increased expression of IL-33 [82].Pro-inflammatory cytokine IL-17 activates the STAT3 pathways along with IL-6 and stimulates chronic inflammatory immune response [83-85].

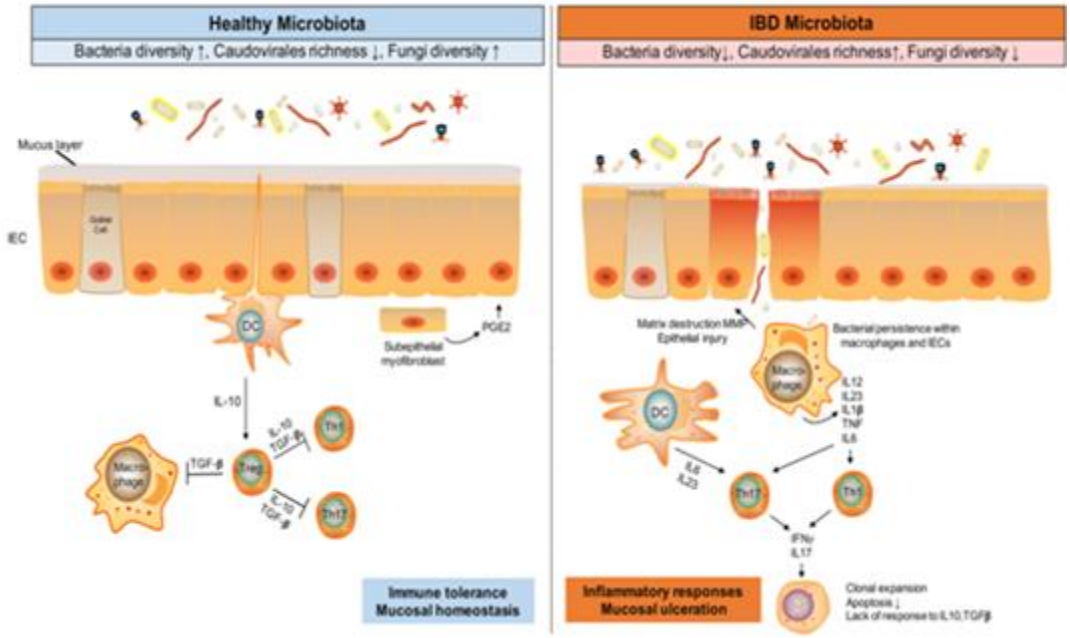

Figure 2: Alteration in Gut microbiota and immune responses in Ulcerative colitis.

Microbial dysbiosis causes tissue destruction by excessive production of IL17 by Th17 cells and Th1 response, by activated dendritic cells, whereas in healthy individuals the maintenance of mucosal homeostasis and differentiation of regulatory T cells (Treg)is controlled by TGF-β and IL10 it also pave the way to immune tolerance (Picture courtesy- Zuo T et al. [68])

- **Chemokine:** The increased production of IL-8 is found in tissues of ulcerative colitis patients in comparison to normal individuals. It acts as a leucocyte chemo-attractant that induces the migration of neutrophils to the site of inflammation. [86].

- **Th17 cells:** Th17 cells are actively involved in pathogenesis of ulcerative colitis,[87] by producing the strong pro-inflammatory IL-17. Several studies have revealed that there is increased expression of IL-17and IL-17A and IL-7F found in the mucosa of patients of ulcerative colitis [85,88]It is documented well that increased expression of IL-7 has observed in inflamed colon [89](Figure 3 A & B). Thus, the current focus based on the theory of blocking IL-17A and IL-17F in treating Inflammatory Bowel Diseases concentrating[90].

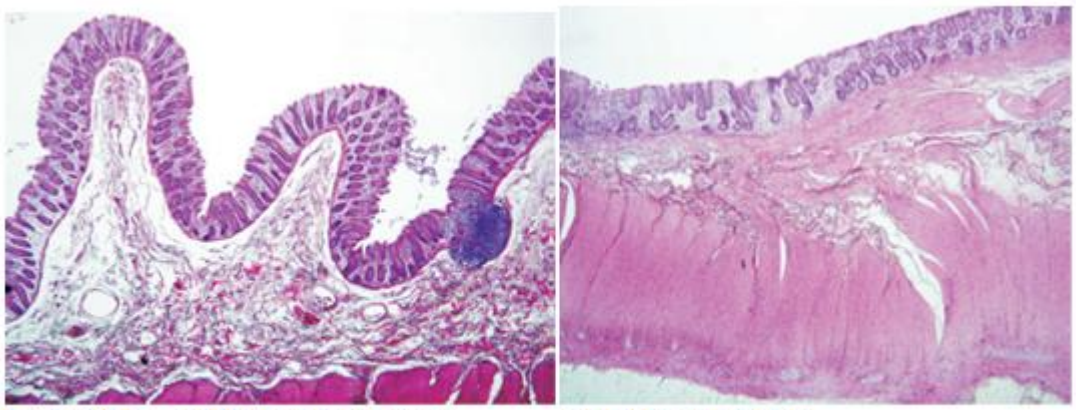

Figure 3 A: a) Un-inflamed colon b) Inflamed colon

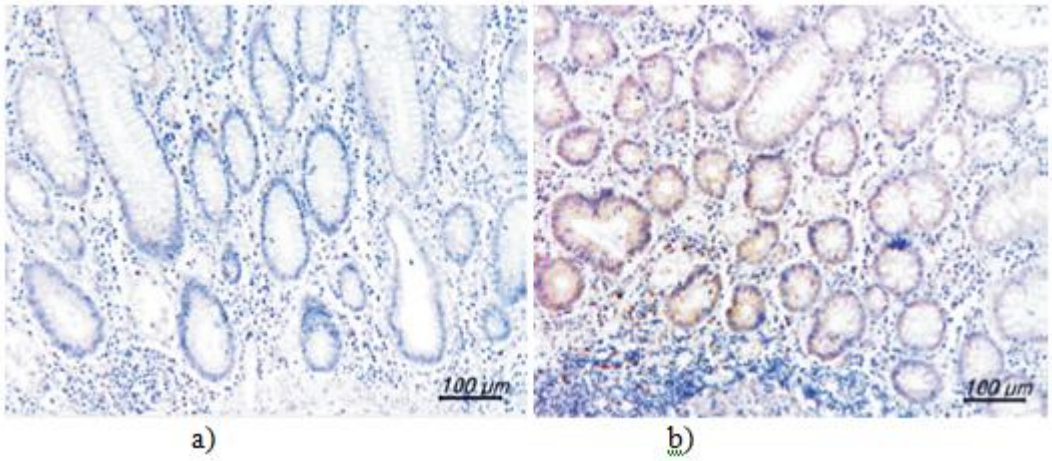

Figure 3 B: Difference in Histology of colon tissue from healthy and ulcerative colitis- a) colon tissue in healthy individual b) interleukin 17 (IL-17) expression in colon tissue from UC patient. (Picture courtesy- Lee et al. [89])

- **Treg Cells (Regulatory T cells):** Regulatory T cells (Treg) are mainly associated with the pathogenesis of inflammatory bowel diseases, in ulcerative colitis the immune response is mediated by stimulated T-cell[91]. Cellular immune homeostasis is maintained by Treg cells, it establishes the inflammatory response to foreign invaders or non-pathogenic antigens such as commensal bacteria. The differentiation of Treg cells are dependent on several factors like cluster of differentiation (CDs) and interleukin like CD25 and IL-10 thus, alteration in components of these genes making them to deviate from proper functioning of Treg cell, so that poorly performing Treg cells induces inflammatory disorder. Moreover, individual lacking receptor of IL-10 on Treg cells are more susceptible to colitis and intestinal inflammation [92-94].

- **Diet and the Gut microbiome:** Gut microbiota largely depend on the diet we intake and influence the environment 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, high blood sugar, increase in weight (obesity), hypercholesterolemia, and cardiovascular disease [96-97] and is associated with a decreased ratio of

commensal bacteria like *Bacteroides* and *Firmicutes* and making them more susceptible to an increased invasive E. coli infection [98]. Consumption of pineapple and coffee products has increased incidence of ulcerative colitis [99].Low fiber diet is very much responsible in causing depletion of normal commensal bacteria, this brings the change in proportion of microbial ecosystem and gradually become aggressive and irreversible over the generation [98], these data imply that improper balanced diet causes the microbial dysbiosis. In humans,high consumption of carbohydrate rich diet causes the abundance of *Candida spp.*, but no effect has been noticed with diet high in protein, fatty acids and amino acids [33].However, lesser number of *Candida spp.* has been found in fecal samples of those subjects consuming animal-based diet rather than plant-based diet, thus the variation in *Candida spp.* depends on our food we take [100].Overall, what we consume 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.

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

    - Blood tests
    - Stool sample- Increased number of White blood cells (WBC) is indicative of ulcerative colitis.
    - Colonoscopy- It is a flexible tube with attached camera inserted though the anus into the colon to get small samples of tissue (biopsy) for laboratory analysis and may also give visual image of any ulceration. It is used to examine the whole picture of colon.
    - Flexible sigmoidoscopy- A slender flexible tube inserted into the colon, unlike the colonoscopy it allows the examination of only distal part of colon.
    - X-ray - whole abdomen X-ray is required to find any perforation or severe complication in the colon.
    - CT scan- A CT scan has been emerged as one of the important tool to examine the abdomen or pelvis to reveal the complications and extent of severity of colon.
    - Computerized tomography (CT) and magnetic resonance (MR) enterography- These are considered as non-invasive test includes examination of colon by CT. The sensitivity rate of these tests is higher than the conventional imaging test in locating the site of inflammation within the gut.

5. **Treatment:** Treatment of ulcerative colitis includes the therapy by aminosalycylate compound as first line drug, as a second line drug corticosteroid therapy included to induce the remission. Excessive and long term use of steroids causes toxicity. The patients with refractory diseases or those who remains unresponsive for the first or second line therapy the immunomodulators are recommended which acts by suppressing the immune response [101].

6. **15-Aminosalicylate(5-ASA):** Mesalamine also called as 5-aminosalicylate (5-ASA), the first-line therapy for ulcerative colitis. It is helpful in achieving and maintaining the remission. The mechanism of functioning of 5-ASA is not well understood, it is believed that it function by blocking the transcription factors directly within the colonic mucosa so that it inhibit the inflammatory mediators [102].It has found that it may activate the nuclear Peroxisome proliferator-activated receptor (PPAR) [103] and act topically on the

mucosa to reduce inflammation. Rectal therapy includes the direct delivery of 5-ASA 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 amount of mesalamine at the site of inflammation is directly correlated to achieve the remission. Other medications with similar properties include sulfasalazine (Azulfidine), mesalamine, balsalazide, andolsalazine. Route of administration (mouth or enema)is entirely dependent on the area of affected colon.

- **Corticosteroid Drugs:** Prednisone and budesonide are generally most common corticosteroid used to treat the moderate to severe UC. Due to its side effect, clinicians are reluctant of recommending it. In cases of refractoriness (unresponsiveness to treatment) immunomodulators (aza-thioprine, 6-mercaptopurine) can be another option[104].

- **Immunomodulators Drugs:** An Immunomodulator drug reduces inflammation by repressing the immune response. Azathioprine, to facitinib, cyclosporine are few of the important immunomodulators or immunosuppressant used in clinical practice. Its acts by inhibiting thepurine formation thus, the synthesis of DNA and RNA get affected. Lesser number of geneticmaterial in proliferating cells like T and B cells, thus causing immunosuppression.[105-106].

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 prepared by including several species of lyophilised bacterial species like *Lactobacillus casei, Lactobacillus delbrueckii sub spp. Bulgaricus, Lactobacillusa cidophilus, 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 immunosuppressive SCFAs (Short Chain Fatty Acids) stimulating regulatory T cell to produce IL-10 thereby inhibiting exaggerated immune responses. *F. prausnitzii*, *Clostridia spp.*, and *Bacteroides. Fragilis* inducing anti-inflammatory milieu and thereby reducing the symptom and severity of colitis [24,110,111].Although the idea of providing prebiotic (oligosaccharides and fibres)as dietary substrates, increases the plethora of SCFA producing commensals remained unsatisfactory [112].

II. CONCLUSION

The most studied bacterial microbiota is gut, but still the understanding of pathogenesis of ulcerative colitisis less and more complicated, much more direction is needed to know about the mechanism of other gut microbiome like virobiota and mycobiota,. To understand the complexity of gut ecosystem more thorough and mechanistic studies are required. By implementing the various newer molecular and microbiological techniques will be needed to crack the mechanism of the host-microbes interaction, evolution of new strain,its role in differentiation of other gut microbes and its tendency to cause diseases. The pathogenesis of inflammatory bowel diseases involves not only the gut microbes but also

several pro-inflammatory mediators, like chemokine and cytokines and number of effector cells. Alteration in gene of these components brings significant change in the gut environment under the influence of it the gut microbiome get altered and become more prone to inflammatory diseases. Balanced diet is required to maintain the colonic homeostasis; minor changes in the gut microbiome may sometimes induce chronic intestinal inflammation in UC patients. Therefore, we need to focus on the newer technologies to diagnose it properly at early stage and to develop effective therapy with lesser number of side effects. To maintain the equilibrium inside the gut is the key to prevention of 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 orcampylobacter gastroenteritis. Gastroenterology. 2009; vol. 137: no. 2, pp. 495–501.
[4] A. Ternhag, A. Torner, A. Svensson*etal.*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.ProcNatlAcadSci 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 nutrientmetabolism. 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., *etal*.. 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.EMBORep. 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.
[17] Extensive impact of non-antibiotic drugs on human gut bacteria.Nature. 2018;555: 623–628.
[18] Zuo T., KammM. 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.
[19] 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.
[20] Castellarin M., Warren R. L., Freeman J. D.et al.Fusobacteriumnucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012; 22: 299–306.
[21] 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.
[22] Yu, T., Guo, F., Yu, Y., Sun, T., Ma, D., Han, J., et al. Fusobacteriumnucleatum promotes chemoresistance to colorectal cancer by modulating autophagy. Cell. 2017; 170: 548–563.e16

[23] Sokol H., Pigneur B., Watterlot L., Lakhdari O., et al. Faecalibacteriumprausnitzii 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.
[24] Llopis M., Antolin M., Carol M., Borruel N., et al. Lactobacilluscaseidownregulates commensals inflammatory signals in Crohn's disease mucosa.Inflamm. Bowel Dis. 2009;15: 275–283.
[25] 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.
[26] Dunn, B. E., Cohen, H. &BlaserM. J. Helicobacter pylori. Clin. Microbiol. Rev. 1997;10:720–741
[27] Marshall, B. J. & Warren, J. R.Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration Lancet 1984; 1: 1311
[28] Arnold, I. C., Iris, H. & Anne, M.Theimmunomodulatory properties of Helicobacter pylori confer protection against allergic and chronic inflammatory disorders.Front. Cell. Infect. Microbiol.2012; 2, 10
[29] Thia K. T. et al. An update on the epidemiology of inflammatory bowel disease in Asia. Am. J. Gastroenterol. 2008;103, 3167–3182
[30] 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.
[31] 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.
[32] 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
[33] Toruner M, Loftus EV, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology. 2008;134:929–936.
[34] Hoffmann C., Dollive S., Grunberg S., et al. Archaea and fungi of the human gut microbiome: correlations with diet andbacterial residents. 2013;PLoS ONE 8:e66019.
[35] 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.
[36] Sokol H., Leducq V, Aschard H., Pham H. P., et al. Fungal microbiotadysbiosis in IBD.Gut. 2017; 66: 1039–1048.
[37] 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.
[38] Brun P, Castagliuolo I., Di Leo V., Buda A., et al. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholicsteatohepatitis.Am. J. Physiol. Gastr. L. 2007; 292:G518–G525.
[39] 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.
[40] 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.
[41] 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.
[42] 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.
[43] 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.
[44] 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.
[45] Maiques E., Ubeda C., Campoy S., Salvador N., et al. Beta-lactamantibiotics induce the SOS response and horizontal transfer of virulence factors in Staphylococcus aureus. J. Bacteriol.2006; 188: 2726–2729.
[46] Zhang Y. F., and LeJeune 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.
[47] 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.
[48] 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.
[49] Kernbauer E., Ding Y., and Cadwell K. An enteric virus can replace the beneficial function of commensal bacteria.Nature2014;516: 94–98.
[50] 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.

[51] 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.
[52] 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.
[53] Weinstock J. V., and Elliott D. E. Helminths and the IBD hygiene hypothesis.Inflamm. Bowel Dis. 2009; 15: 128–133.
[54] 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.
[55] 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.
[56] Stepek G., Auchie M., Tate R., Watson K., et al. Expression of the filarial nematode phosphorylcholine containing glycoprotein, ES62, is stage specific.Parasitology2002;125: 155–164.
[57] 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.
[58] Summers R. W., Elliott D. E., Urban J. F., et al. Trichurissuis therapy in Crohn'sdisease.Gut2005a; 54: 87–90.
[59] Summers R. W., Elliott D. E., Urban J. F., Thompson R. A., et al. Trichurissuis therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology.2005b; 128: 825–832.
[60] Velthuis J. H., Unger W.W., Abreu J. R., Duinkerke, G., et al. Simultaneous detection of circulating autoreactiveCD8(+) T-cells specific for different islet cell-associated epitopes using combinatorial MHC multimers. Diabetes 2010; 59: 1721–1730.
[61] Helmby, H. (2015). Human helminth therapy to treat inflammatory disorders where do we stand?BMCImmunol. 2015;26:16:12.
[62] Whelan RA K, Hartmann S, Rausch S. Nematode modulation of inflammatory bowel disease. Protoplasma. 2012;249:871–86.
[63] Wang L.J, Cao Y., and Mizoguchi H.N.S. Helminth infections and intestinal inflammation. World J Gastroenterol. 2008;14:5125–32.
[64] Croese J, O'neil J, Masson J, Cooke S, Melrose W, Pritchard D, et al. A proof of concept study establishing Necatoramericanus in Crohn's patients and reservoir donors. Gut. 2006;55:136–37.
[65] Artis D, Potten CS, Else KJ. *Trichurismuris*: host intestinal epithelial cell hyperproliferation during chronic infection is regulated by interferon-γ Experiment Parasitol. 1999;92:144–53.
[66] Blum AM, Hang L, Setiawan T. Heligmosomoidespolygyrusbakeri induces tolerogenic dendritic cells that block colitis and prevent antigen-specific gut T cell responses. J Immunol. 2012;189:2512–20.
[67] Broadhurst MJ, Leung JM, Kashyap V, McCune JM, Mahadevan U, McKerrow JH, et al. IL-22± CD4± T cells are associated with therapeutic Trichuristrichiura infection in an ulcerative colitis patient. Sci Trans Med. 2010;2:60–88.
[68] Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature 1996; 383:787-93.
[69] Zuo T and Ng SC. The Gut Microbiota in the Pathogenesis and Therapeutics of Inflammatory Bowel Disease. *Front. Microbiol*. 2018; 9:2247.
[70] Dinarello CA. Interleukin-1beta and the autoinflammatory diseases. N Engl J Med 2009;360:2467-2470.
[71] 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.
[72] 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.
[73] 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.
[74] 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.
[75] 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.
[76] 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.
[77] 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.

[78] 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.
[79] Sanchez-Munoz F, Dominguez-Lopez A, Yamamoto-Furusho JK. Role of cytokines in inflammatory bowel disease. World J Gastroenterol 2008;14:4280-4288.
[80] Li MC, He SH. IL-10 and its related cytokines for treatment of inflammatory bowel disease. World J Gastroenterol 2004;10:620-625.
[81] Li MO, Flavell RA. TGF-beta: a master of all T cell trades. Cell 2008;134:392-404.
[82] Del Zotto B, Mumolo G, Pronio AM, Montesani C, TersigniR,Boirivant M. TGF-beta1 production in inflammatory bowel disease: differing production patterns in Crohn's disease and ulcerative colitis. ClinExpImmunol 2003;134:120-126.
[83] 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.
[84] 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.
[85] 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.
[86] Fujino S, Andoh A, Bamba S, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003;52:65-70.
[87] 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. ClinSci (Lond) 1992;82:273-275.
[88] Murphy KM, Stockinger B. Effector T cell plasticity: flexibility in the face of changing circumstances. Nat Immunol 2010;11:674-680.
[89] 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.
[90] Lee SN, Kwon J, Cho ML.Immunological pathogenesis of inflammatory bowel diseases. Intest Res 2018;16(1):26-42.
[91] 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.
[92] 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.
[93] Boden EK, Snapper SB. Regulatory T cells in inflammatory bowel disease. CurrOpinGastroenterol 2008;24:733-741.
[94] Wirtz S, Neurath MF. Mouse models of inflammatory bowel disease. Adv Drug Deliv Rev 2007;59:1073-1083.
[95] 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.
[96] 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.
[97] Conlon M. A., and Bird A. R. The impact of diet and lifestyle on gut microbiota and human health. Nutrients 2015; 7, 17–44.
[98] 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.
[99] 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.
[100] 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.
[101] 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.
[102] 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
[103] Bantel H, Berg C, Vieth M, et al. Mesalazine inhibits activation of transcription factor NF-kappaB in inflamed mucosa of patients with ulcerative colitis. Am J Gastroenterol.2000;95:3452-3457.
[104] 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.

[105] Travis SPL, Stange EF, Lémann M, Øresland T, BemelmanWA,Chowers Y, et al. European evidence-based consensus on themanagement of ulcerative colitis: current management. JCrohn's Colitis.2008;2:24–62.
[106] Timmer A, McDonald JW, Tsoulis DJ, Macdonald JK.Azathioprine and 6-mercaptopurine for maintenance ofremission in ulcerative colitis. Cochrane Database Syst Rev.2012;12:9.
[107] Kennedy NA, Rhatigan E, ArnottID, Noble CL, ShandAG,Satsangi J, et al. A trial of mercaptopurine is a safe strategy inpatients with inflammatory bowel disease intolerant toazathioprine: an observational study, systematic review andmeta-analysis. Aliment PharmacolTher. 2013;38:1255–66.
[108] 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.
[109] 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.
[110] 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.
[111] Round, J. L., Lee, S.M., Li, J., Tran, G., Jabri, B., Chatila, T. A., et al. The tollLikereceptor 2 pathway establishes colonization by a commensal of the human microbiota. Science.2011; 332: 974–977.
[112] Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermudez-Humaran, L. G., Gratadoux, J. J., et al. Faecalibacteriumprausnitzii 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.
[113] 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.

