



Microorganisms in Pathogenesis and Management of Ulcerative Colitis (UC)

12

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Abstract

With the global rise in incidences of ulcerative colitis and various dysbiosis in the gut microbiota, there has been a growing demand to understand the development and cause behind this disease. Numerous findings have been predicted that gut microbiome is involved in the development of the ulcerative colitis and could also delay the healing process. Studies suggest that the penetration of gut bacteria inside the intestinal wall cause the release of interferon gamma, tumor necrotic factors, interleukins-1 and 6 (IFN- γ , TNF- α , IL-1, and IL-6) that produce reactive oxygen species which further damages the intestinal lining and at the top delays the healing process. The major role is played by the regulatory T cells (Tregs) and the formation of interleukin-10 (IL-10) via GPR43. The Treg cells are stimulated by IL-10 that causes activation of macrophages. Many pro-inflammatory mediators such as Th-1 and Th-17 are produced in response to invasive gut microorganisms (e.g., TNF- α , IFN- γ) by enhancing the transcription of significant genes. This chapter focuses on all the alternative pathophysiology and pathogenesis and management related to ulcerative colitis.

Keywords

Ulcerative colitis · Epithelial restitution · Intestinal wound healing · Pathophysiology · *H. pylori* · *Mycobacterium avium* complex · TNF- α · Treg cells

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241

12.1 Introduction

Ulcerative colitis is a very common inflammatory disease (long lasting); it is characterized by non-infectious inflammation that affects the colon and rectum. The condition is characterized by continuous inflammation that causes deep ulcerations on the rectum. Several factors can elicit ulcerative colitis—gut bacteria, immune system, genetic factors, and eating habits. The pathogenesis of ulcerative colitis is not very clearly understood, but new techniques and research over the intestinal microbiota have revealed a lot of information (Shen et al. 2018; Ohkusa and Koido 2015; Thoreson and Cullen 2007). To take a deep dive into this topic, we tried to get all the recent data and clinical trials to come up with a solid conclusion. Ulcerative colitis comes under the umbrella of inflammatory disease—chronic condition, idiopathy inflammatory disease. With all the latest research and data, it is quite clear that thickness of mucus and any alteration in its composition cause stress and can misfold the mucus associated with the protein. Any irregularities in the immune response involving the innate as well as the adaptive immunity can cause macroscopic lesions (Ordás et al. 2012; Keshteli et al. 2019). Ulcerative colitis can be characterized by the presence of pANCA (primary sclerosing cholangitis) antibodies and the isoform of 1 and 5 human tropomyosin or a bloody diarrhea. That include mycobacterium avium complex or its subspecies paratuberculosis aka MAP (Fries and Comunale 2011).

Other factors that play the major roles are diet and sucrose intake which maximize the risk of ulcerative colitis (UC). However, a diet rich in PUFA (polyunsaturated fatty acids) and vitamins/minerals has shown to surely reduce the chance of ulcerative colitis. Various reasonable theories for the etiology of gastrointestinal microbiota, microbiota metabolites formation, immune system changes, and gastric mucosal integrity have also been postulated (Kapel 1950; Gitter et al. 2001). The local complication of ulcerative colitis is colon cancer, rupture of the bowel, and massive hemorrhage. Many studies have confirmed that any inflammation can happen due to malfunctioning of M-cells. M-cells can cause antigen sampling that further lead to translocation of microbial peptide. Microbial peptide then further stimulate the immune cells to release interferon gamma, tumor necrotic factors, interleukins-1 and 6 (IFN- γ , TNF- α , IL-1 & IL-6), which produces reactive oxygen species, that involved in the ill effect of ulcerative colitis. Ulcerative colitis (UC) (Fig. 12.1) (Kevans et al. 2016; Martinez et al. 2008). The products of anaerobic respiration are thought to be produced by reactive oxygen species. In the course of interaction between the colon/rectum and the pathogen, the inflammation is limited to the mucosa and submucosa levels only. Neutrophils accumulated can be found infiltrating the crypts, forming crypt abscesses, and also the accumulation of phagocytes in the lamina propria, most notably neutrophilic granulocytes, which upon activation release large quantities of reactive oxygen species (ROS) that are cytotoxic to the mucosal cells as well as epithelial cells (Zhang et al. 2017; Nemoto et al. 2012; Angelberger et al. 2013). These compounds could be utilized by

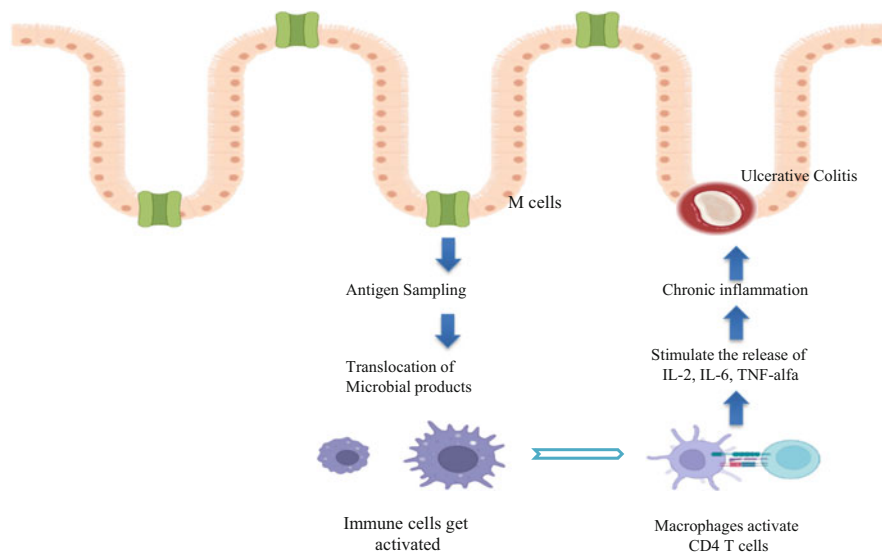


Fig. 12.1 Role of antigen (microorganism) in cytokine production in UC

facultative anaerobes to overrun, resulting in microbial populations being reduced. This dysbiosis microbiome could promote the formation of fungus which aggravate inflammatory response by activating the type-I T helper (TH1) pathway through chitin and glucan antigen-presenting cells (APCs). In addition, microorganism dysbiosis has been linked to an increase in bacteriophage species and activity, which can affect the overall microbiome through elevated levels of dimethyl sulfoxide, tetramethyl ammonium oxalate, and trimethylamine N-oxide (Sun et al. 2016; Paramsothy et al. 2019).

Potential significance of short-chain fatty acids (SCFAs) produced from fiber in maintaining gut microflora has been established, and SCFA acts as an energy source for intestinal mucosa. In addition, SCFAs also control the functioning of the gut wall as well as the immune response by signaling through G-protein-coupled receptors (GPCRs). Through the GPR43 receptor, SCFAs induce the development of regulatory T cells (Treg), stimulating the formation of cytokines (IL)-10. In addition, SCFA also stimulate IL-18 synthesis, which is important for anti-inflammation as well as epithelium healing, by facilitating upregulation in intestinal cells via GPR43. SCFAs potentially influence the functioning of the gut wall by inducing the expression of adhesion molecules as well as promoting the mucin production (MUC2) (Byndloss et al. 2019; De Leon et al. 2013; Bjerrum et al. 2010). The systemic complications that are caused by the ulcerative colitis are conjunctivitis, mouth ulcer, fatty liver, large joint arthritis, venous thrombosis, etc.

12.2 Role of Microorganism in the Pathophysiology of Ulcerative Colitis

Bacteria in the gut are more than important as ever, based on our limited diet we get. The intestinal lining especially of colon and rectum need to regenerate more quickly than any other cells or tissues in our body; the gut bacteria will produce different amino acid vitamins and proteins that will help repair these intestinal linings. The gastrointestinal microbiome plays an important mechanism in strengthening the gut immunity as along the way it also stimulates the lymphocytes for the expansion of colon, and it also prevents lymphocyte apoptosis. Studies show that with the lack of these bacteria in the intestine, the healing process is strongly hampered, which will further cause ulcer or inflammation to enhance (Fig. 12.2).

Some bacteria will selectively stimulate interleukin-12 productions like the Gram-positive bacteria, whereas some will induce interleukin-4 production like the Gram-negative bacteria (Marteau et al. 2004; Hendrickson et al. 2002). Mostly in small intestinal samples from patient populations with ulcerative colitis, Gram-negative anaerobic bacteria, particularly *Escherichia coli* and *Fusobacterium varium*, also with the existence of *Peptostreptococcus* encroachment, the

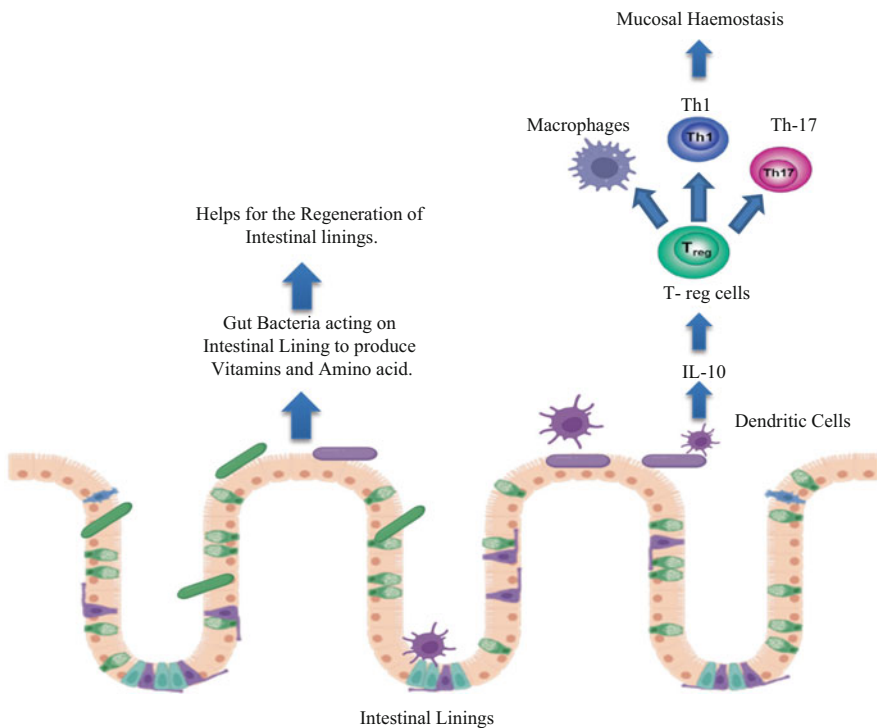


Fig. 12.2 Representation of action of gut bacteria on the intestinal linings. A healthy microbiota can help with immune tolerance and also cause mucosal hemostasis

possibilities of inflammatory response would also significantly raise, and so will drastic microorganism invasions of the mucous membranes, in contrast to healthy individuals (Macfarlane et al. 2004; Tamboli et al. 2004; Ohkusa et al. 2002). The relationships between respiratory epithelium as well as native microbial species (flora) are the focus of the emerging techniques. A few of them can now be used to identify ulcerative colitis from other conditions (e.g., anti-*Peptostreptococcus anaerobius* Ab-antibody) as well as colitis (e.g., anti I2-from *Pseudomonas fluorescens* antibody or antibody to an outer membrane porin of *E. coli*—anti-ompC) (Martinez et al. 2008). The bacterium composition of a gut activates epithelium and lymphatic tissues inside the gastrointestinal among both systemic and local immune function. MAP is eliminated from the feces of sick animals and released in their milk. Thus, there are two ways for MAP to cause infection: fecal contamination transfer via contaminated water and intake of infected breastmilk or items manufactured from contaminated milk (Head and Jurenka 2003; Hindryckx et al. 2016; Bjerrum et al. 2010).

One other possible way of inflammation and an early onset of ulcerative colitis is through the impairment of metabolism of epithelial cells (Borruel et al. 2002). The way it happens is that the anaerobic bacteria by the fermentation process ingest the carbohydrates and proteins to a SCFA which acts as a main source of energy for them. This fatty acid also works as an energy source for intestinal cells, and any variation in this energy can cause ulcerative colitis. The bacteria *Desulfovibrio desulfuricans* can cause an excess of hydrogen sulfide that acts as a toxin and leads to ulcerative colitis (Roediger 1980; Guo et al. 2020). Many RT-PCR assessments employing 16S rRNA-based species PCR primers revealed that *Rhodococcus erythropolis*, *Clostridium*, *Methanobrevibacter smithii*, *Desulfovibrio* (sulfate-reducing bacteria, SRB), Enterobacteria, type E *Clostridium perfringens*, *Enterococcus faecalis*, and enterohepatic *Helicobacter* species were substantially enhanced throughout UC (Frank et al. 2007) (Table 12.1).

1. ***Helicobacter pylori***: It is a common bacterium that can elicit ulcerative colitis. It is a Gram-negative microaerophilic bacteria with curved or spiral flagellated flagella. Although the mechanism is not clear, some consider it to be due to the immune regulation caused by *H. pylori*. Patients infected with *H. pylori* have higher levels of Foxp3, a T-cell regulatory marker that may help to prevent the progression of inflammatory bowel disease. A long-term infection of colon via the *H. pylori* causes partial or complete loss of parietal cells, and *H. pylori* has been detected in colon mucosa and the colonic tissues (Jin et al. 2013; Thomson et al. 2011).
2. ***Mycobacterium avium* Complex**: MAP is indeed a pathogen discovered in the feces of animals. It infects and induces systemic infection in a broad range of animals, known as Johne's ("Yo-knees") disorder. Numerous systematic review and publication reviews had already indicated that the MAP species is consistently linked to Crohn's disease. A modest dosage of the MAP microorganism, or even many microorganisms infected a person at every given age, causes Crohn's

Table 12.1 Studies of microbiota in the pathophysiology of the ulcerative colitis

| Sr. No. | Nonessential microorganisms | Role in pathophysiology | Study observed on | References |
|---------|---|--|-------------------|---|
| 1. | <i>Helicobacter pylori</i> | Initiation of inflammation | Human | Jin et al. (2013), Bohr et al. (2004) |
| 2. | <i>Clostridium difficile</i> toxin/ <i>Clostridium difficile</i> | Causes disease exacerbation | Human | Rhodes (1996) |
| 3. | <i>Campylobacter concisus</i> | Initiate inflammation | Human | Jess et al. (2011), Gradel et al. (2009) |
| 4. | <i>Fusobacterium varium</i> | Acts as pro-inflammatory, produces high concentrations of butyric acid, causing intestinal lesions | Human | Ohkusa et al. (2003, 2005, 2010) |
| 5. | <i>Enterohepatic helicobacter</i> | Pro-inflammatory | Humans | Bohr et al. (2004) |
| 6. | <i>Campylobacter</i> spp. | Initiate inflammation, also acts as pro-inflammatory | Humans | Jess et al. (2011), Kalischuk et al. (2009) |
| 7. | <i>Campylobacter jejuni</i> | Initiates inflammation, also acts as pro-inflammatory | Humans | Jess et al. (2011) |
| 8. | <i>Mycobacterium avium</i> complex | Initiate inflammation | Human | Pierce (2010) |
| 9. | <i>Shigella</i> spp. | Initiate inflammation | Human | Gradel et al. (2009), Ternhag et al. (2008) |
| 10. | <i>Salmonella</i> spp. | Diminished protective activity of the mucus, initiate inflammation | Humans | Rhodes (1996), Ternhag et al. (2008) |
| 11. | <i>Yersinia</i> spp. | Initiate inflammation and produce toxic mediators | Human | de Oliveira et al. (2017) |

disease, whereas a large dose of MAP causes ulcerative colitis (Pierce 2010; Bibiloni et al. 2006; Ohkusa and Koido 2015).

3. ***Fusobacterium varium***: One of the findings has suggested that diagnostic accuracy and ELISA titer of antibody against *F. varium* was dramatically higher in individuals having active UC than other individuals or control in a cohort study which comprised patients had active UC, CD, ischemic colitis, colonic adenocarcinomas, and normal individuals. Furthermore, individuals with UC had considerably greater immunohistochemistry identification for *F. varium* throughout the intestinal mucosa than some other participants. Furthermore, in vivo investigations revealed that *F. varium* is responsible for generating extremely high levels of butyric acid that induces gastrointestinal ulcers in animals that are comparable to those seen in UC patients (Ohkusa et al. 2003).

12.3 Role of Microorganisms in the Management of Ulcerative Colitis

Human gut is the home for millions of bacteria. Some of these bacteria that live in the colon and rectum in the pH from 5 to 7 are *Bacteroides*, *Clostridium*, *Streptococcus*, *Enterococcus*, γ -*Proteobacteria*, *Lactobacillus*, *Fusobacteria*, *Eubacterium*, and *Peptostreptococcus*. The microbiota in the gut helps with the immuno-modulation of both innate and adaptive immunity. The cell types like effectors Treg cells (T regulatory), IgA-forming B cells, group 3 innate lymphoid cells, dendritic cells, and the lamina propria all help in the immune modulatory function. Pathogenic microbiome drives the development of pro-inflammatory mediators (e.g., TNF- α , IFN- γ) via upregulation of key genetic sequences; when nonpathogenic bacteria invade intestinal mucosal wall of normal individuals, cells of the immune system generate regulating mediators (e.g., transforming growth factor as well as IL-10). It should really be noted how certain bacterial species inhibit the generation of proinflammatory mediators as well as cause stimulated macrophages eventually die via apoptotic mechanism (Borrueal et al. 2002).

Their important function is to help with the synthesis of Vitamin- K as well as numerous vitamin-B substances that have key metabolic roles inside the intestinal flora, also they help to produce acetate, propionate, and butyrate. Butyrate emerges as a crucial power source for mammalian enterocytes, may trigger death in carcinoma cells, and can stimulate colonic glucose production, all of which shows the benefit on glucose and caloric expenditure. Because butyrate is needed by epithelium to utilize substantial O₂ via oxidative mechanism, ischemia occurs, which promotes oxygenation homeostasis inside the intestines and prevents gut microbial dysbiosis. It has been demonstrated that some microbial members of *Bacteroides* species conjugated linoleic acid (CLA) may be synthesized that helps with antidiabetic, antiatherogenic, antiobesogenic, hypocholesterolemic, and immune-modulating characteristics (Devillard et al. 2009; Sepehri et al. 2007).

Around 99% of intestinal microbiome comprises of four phyla—*Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* (Li et al. 2015). The anatomy of mucus layer has Muc2 as a polymeric sheet along with goblet cells that secretes bioactive molecules. The mucus layer of inner colonic is different from intestinal epithelial cells, and the bacteria in this reason do not trigger immune response. Although the inner mucus layer is not sterile and can come in contact of few bacteria, prolonged bacterial exposure has been associated with harmful immunological response, which could also misbalance MUC2 production as well as the features and function of the innermost mucous membrane (Bhinder et al. 2014). It has been seen that in case of ulcerative colitis, the thickness of mucus layer often decreases that makes it easy for the bacteria to reach epithelium and create an immune response.

An outermost layer is substantially highly elastic and has a greater amount than the internal lining due to proteolytic processing of Muc2 mucin. It produces large amount of mucin and mostly bacteria colonize around them. Thus, trails and studies have proven that Muc2 mucin helps build a mucous barrier/layer that prevent the

entry of bacteria into the colon epithelium, and any abnormalities in mucus wall can lead to the ulcerative colitis. Furthermore, numerous research studies focused on mouse ulcerative animals, including animals lacking Muc2 mucin as well as IL-10, which were immunostained to evaluate the Muc2 production throughout dextran sodium sulfate-treated animals. Microbial location in such mammal mucous was investigated, both bacterium and beads seemed to permeate the innermost mucous membrane. Any imbalance in the dysbiosis of gut and the bacterial clearance cause inflammatory response and can lead to ulcerative colitis (Swidsinski et al. 2005; Mayer 2000; Guarner and Malagelada 2003). Studies have shown that there is a decrease in Bacteroidetes and Firmicutes, while Proteobacteria and Actinobacteria increases in the mucosal inflammation (Li et al. 2015). Patients with ulcerative colitis have also shown reduction in *Butyricoccus* bacteria in the gut, and the oral administration of *B. pullicaecorum* improved the morphological as well as histopathological measures. The study also reported health benefits as well as lower rates of intestine myeloperoxidase (MPO) and inflammatory cytokines (IL-12, TNF- α) levels. Moreover, in a Caco-2 cell line, supernatant generated from *Butyricoccus pullicaecorum* cultures reduced the reduction of intestinal epithelial resistivity (TER) and enhanced IL-8 production generated with TNF- α as well as IFN γ (Eckhaut et al. 2013) (Table 12.2).

Table 12.2 Studies of microbiota in the management of the ulcerative colitis

| Sr. No. | Essential microorganisms | Effects | Study observed on | References |
|---------|-------------------------------------|---|-------------------------|--|
| 1. | <i>Lactobacillus acidophilus</i> | Anti-inflammatory, increases IL-10 levels | On mouse model | Bullock et al. (2004), Barroso et al. (2021) |
| 2. | <i>Bifidobacterium bifidum</i> | Interacts with TLR-2 and facilitates T-reg cell conversion | Human | De Kivit et al. (2014) |
| 3. | <i>Escherichia coli</i> | Pro-inflammatory | Randomized human trails | Kotlowski et al. (2007), Sepehri et al. (2011) |
| 4. | <i>Desulfovibrio desulfuricans</i> | Sulfate-reducing bacteria | Human | Roediger (1980) |
| 5. | <i>Faecalibacterium prausnitzii</i> | Anti-inflammatory | Human | Lepage et al. (2011) |
| 6. | <i>Pediococcus acidilactici</i> | Anti-inflammatory | Human | Nadal et al. (2009) |
| 7. | <i>Lactobacillus salivarius</i> | Anti-inflammatory | Human | Fyderek et al. (2009) |
| 8. | <i>Lactobacillus manihotivorans</i> | Anti-inflammatory and reduce thickness of mucus layer | Human | Fyderek et al. (2009) |
| 9. | <i>Lactobacillus rhamnosus</i> | Suppresses NF- κ B activation and prevents pro-inflammatory cytokine productions | Human | De Kivit et al. (2014) |

1. **Bifidobacterial species:** Among 30 species, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium lactis*, *Bifidobacterium breve*, as well as *Bifidobacterium adolescents* act as a good source of energy in the gut. These bacteria synthesize the short-chain fatty acid, e.g., propionate and acetate which is further utilized by the intestinal cells to produce energy. Also, the *Bifidobacterium* species helps with the metabolism of oxalate that prevents the formation of kidney stones (Macfarlane and Macfarlane 2003; Sidhu et al. 1998).
2. ***Escherichia coli*:** *Escherichia coli* is frequently located in the lower human as well as mammalian gut. Whenever *E. coli* colonizes at the larger intestinal of humans, this could improve digestion, nutritional processing, and uptake, as well as vitamin K synthesis. The mode of action and the nonpathogenic *E. coli* strain hypothesized throughout this research have been trying to block receptor sites to stop the establishment of adhesive microbes, antagonistic activity against pathogenic and nonpathogenic enterobacteria, most likely through the development of therapeutic drugs, and changes inside the pH as well as variable components of both the small intestinal lumen (Kotlowski et al. 2007; Sha et al. 2013). Studies also show that a random increase in the *E. coli* population might result in greater adherence scores than harmful *E. coli* colonies from normal subjects (Verma et al. 2010).
3. ***Lactobacillus* species:** *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus paracasei*, *Lactobacillus gasseri*, *Lactobacillus reuteri*, *Lactobacillus salivarius*, and *Lactobacillus helveticus* are the advantageous *Lactobacillus* genera. *Lactobacillus* is a Gram-positive, facultative anaerobic, rod-shaped bacterium. These lactic acid bacteria are involved in lactase synthesis, e.g., *Lactobacillus plantarum* (Mann and Li 2014). *Bifidobacterium* and *Lactobacillus* strains interact with TLR2 and/or TLR9 to both improve the functioning of the gastrointestinal epithelial layer and enable Treg cell conversions through CD103⁺ DCs (Mann and Li 2014).
4. ***Faecalibacterium prausnitzii*:** These bacteria are found to have the anti-inflammatory properties. These bacteria produce butyrate which is indeed a main energy source for them and can activate intestinal gluconeogenesis. In fecal microbiota of the ulcerative colitis patients, there is a reduced number of *F. prausnitzii*. It is essential to maintain the population of *F. prausnitzii* for a healthy gut (Machiels et al. 2014).

12.4 Conclusion

With all the above study and data, we can easily predict that the microbiota plays a very crucial role when it comes to the development and repair of the gut and the health of our immunity. Human immunity also has a significant impact on the activity of the intestinal wall. A wide range of bacteria in gut and their population are responsible for the normal functioning. We have studied different mechanisms

by which gut microbiota and its population difference can induce or heal the ulcerative colitis. Further research should focus to figure out the exact population difference or alteration of gut microbiota that can induce ulcerative colitis. Bacteria such as *Lactobacillus casei*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium breve*, *Streptococcus salivarius* subsp. *thermophiles*, and probiotic *Escherichia coli* have been demonstrated to lower inflammatory response as well as maintain recovery in ulcerative colitis patients. The microbiota in the gut helps with the immuno-modulation of both innate and adaptive immunity. Several cell types such as effector T regulatory cells, IgA forming B cells, group 3 innate lymphoid cells, dendritic cells, and the lamina propria help in the immuno-modulatory functions. Pro-inflammatory mediators are produced by invasive intestinal bacteria. Several clinical trials have been conducted and have revealed a positive effect on healing and treatment of ulcerative colitis. As our knowledge and understanding about different gut microbiota grow, it will help us better analyze our current medicine prescribed and how and what can be done to help keep the balance between the gut microbiota. These advancements will lead to an improved probiotic therapy that will restore the condition at the earliest.

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