

Center Research Situation on the Correlation Between SCFA and Ulcerative Colitis

Shangshu Li *

Huaer Zizhu Academy, Shanghai, 201619, China

* Corresponding Author Email: shangshuli41@gmail.com

Abstract. Ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract, characterized by mucosal damage, immune dysfunction and imbalance of the intestinal microbiota. In recent years, due to the improvement of diet and economic level, the incidence of UC has been on the rise worldwide. The human gut microbiota is a complex and dynamic microbial community that is indispensable for maintaining health and regulating the host's immune system. Among them, short-chain fatty acids refer to fatty acids with a carbon atom number less than 6, which can maintain intestinal homeostasis and exert anti-inflammatory effects. This article aims to systematically review the physiological and pathological mechanisms of SCFA in UC, as well as their application potential as therapeutic strategies. A comprehensive review is conducted on the current application status, clinical evidence and challenges of strategies such as probiotics, dietary intervention (such as high-fiber diet, Mediterranean diet) and microbiota transplantation. In order to provide theoretical basis and practical guidance for the nutrition and microecological therapy of UC.

Keywords: Ulcerative Colitis, SCFA, Probiotics, Dietary supplementation, Fecal microbiota transplantation.

1. Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory disease mainly involving the colonic mucosa and submucosa. The clinical manifestations are persistent or recurrent diarrhea, mucus, bloody stool and abdominal pain. Its incidence rate is on the rise worldwide, especially in industrialized countries, and has become an important public health issue. They may then extend upward along the colon. Generally, the small intestine is not affected. The fundamental mechanism of pathogenesis involves abnormalities in the immune tolerance function of the intestinal immune system toward microbial communities. This abnormality leads to a persistent state of inflammatory response.

The diversity and stability of the microbiota in the intestinal microbiome of UC patients will decrease with the duration of the disease. This phenomenon is related to the reduction of bacteria that produce short-chain fatty acid (SCFA), such as corresponding to the consumption of ruminococcus and *Helicobacter laminae*. The regulatory function of the gut microbiome on host health is mainly mediated by SCFA, which mainly include acetate, propionate and butyrate. In the intestinal microecology, acetate is the common fermentation product of most intestinal bacteria, while propionate and butyrate are mainly synthesized by specific bacterial communities. The decrease in SCFA content can affect the occurrence and development of UC through mechanisms such as disrupting the integrity of the intestinal barrier, inducing systemic low-grade inflammation, and causing energy metabolism disorders. The treatment protocols currently used in clinical practice still have certain limitations [1-4]. Therefore, supplementing SCFA or promoting their endogenous generation has become a highly promising new strategy in the treatment of UC. This thesis will delve deeply into the application of SCFA in UC, conducting a comprehensive review and discussion from its biological basis to clinical transformation.

2. Physiological Functions of SCFA

A healthy intestinal barrier structure consists of two important components: a mucus layer secreted and formed by goblet cells. It covers the surface of epithelial cells and acts as a barrier against bacteria. Tight junction structures formed between epithelial cells. They prevent various substances from leaking through intercellular spaces. Unlike other human cells that primarily utilize glucose, colonic cells preferentially use SCFA—particularly butyrate. They produce energy (ATP) through the β -oxidation pathway. Colonic epithelial cells derive 60-70% of their required energy from butyrate. This represents a unique energy metabolism method. If the metabolic function of epithelial cells is impaired, it will affect normal tissue repair functions. Four independent studies have found increased gene expression levels of tight junction proteins (including ZO-1, Occludin, etc.) and mucin (Muc-2). This phenomenon indicates enhanced intestinal barrier function. Butyrate can stimulate goblet cells to produce more MUC2 mucin. This effect makes the mucus layer thicker and more robust. Butyrate also increases the expression of tight junction proteins [5,6]. This ensures tighter connections between cells. It effectively reduces intestinal permeability. It prevents bacteria and antigenic substances from entering deep tissues.

SCFA (particularly butyrate) can effectively inhibit key inflammatory response pathways. NF- κ B is an important protein complex that regulates inflammatory responses. Under normal physiological conditions, it remains inactive. When activated, it initiates the inflammatory response process. Butyrate is a histone deacetylase (HDAC) inhibitor [7]. By inhibiting HDAC activity, it can increase histone acetylation levels. This change loosens chromatin structure, thereby activating anti-inflammatory gene expression. Butyrate simultaneously prevents NF- κ B from entering the cell nucleus. The deficiency of SCFA will lead to the inhibition and weakening of pro-inflammatory signaling pathways such as NF- κ B, and some immune cells will remain in an activated state continuously, releasing a large amount of cytokines such as TNF- α , IL-1 β , and IL-13, thus forming a pro-inflammatory microenvironment [8].

SCFA can affect metabolism and energy homeostasis. SCFA has different beneficial effects on the energy metabolism of several types of human tissues, including glucose, lipid and cholesterol metabolism. The mechanism by which SCFA regulates glucose homeostasis lies in its ability to bind to free fatty acid receptor-2 on the cell membrane, thereby directly stimulating colonic goblet cells (i.e., secretory cells) to secrete glucagon-like peptides. SCFA may promote the secretion of intestinal hormones YY peptide and glucagon-like peptide 1 by activating FFAR-2 and FFAR-3. These hormones can enhance the glucose absorption capacity of muscle and adipose tissue, etc [3].

3. Application Strategies of SCFA in the Treatment of UC

Increasing the level of SCFA in the colon has become a feasible strategy for the treatment of UC. The main methods include probiotics, dietary supplementation or fecal microbiota transplantation (FMT), etc.

3.1. Probiotics

Probiotics refer to live microorganisms that, when consumed in sufficient quantities, can exert beneficial effects on the health of the host. Some probiotics can produce SCFA by themselves or indirectly increase SCFA by regulating the overall microbiota structure.

A study compared the effects of live *Lactobacillus acidophilus* (La), heat-killed *acidophilus* (Hk La) and the culture supernatant of La (La Sup) on DSS-induced colitis through rat and mouse models. The results showed that live *Lactobacillus acidophilus* had the best effect, significantly improving weight loss, disease activity index (DAI), colonic shortening and intestinal barrier function, followed by heat-inactivated bacteria, and the supernatant was almost ineffective. Further mechanism research has found that La can significantly increase the production of SCFA, especially acetic acid, propionic acid and butyric acid, and enrich the bacterial community that produces SCFA [9].

3.2. Dietary Supplementation

A clinical study aimed to explore the preventive effect of apple peel dietary fiber on DSS-induced UC in mice and compare the efficacy of two extraction methods: high-pressure assisted water extraction (DFH) and enzymatic extraction (DFE). The study established a DSS-induced UC mouse model and set up different dose intervention groups to systematically evaluate the effects of apple peel dietary fiber on inflammatory response, oxidative stress, intestinal flora structure and SCFA content. The results show that the dietary fiber in apple peels can significantly alleviate the symptoms of colitis, specifically manifested as: improving the pathological damage of colon tissue, reducing the disease activity index (DAI), and decreasing splenomegaly and colonic shortening. Down-regulate the pro-inflammatory factors TNF- α and IL-6, and up-regulate the anti-inflammatory factor IL-10; Reducing oxidative stress is manifested as lowering the activities of MDA and MPO and increasing the level of SOD. In addition, dietary fiber intervention can significantly increase the content of SCFA (such as acetic acid, propionic acid, and butyric acid) in the intestinal tract, regulate the structure of the intestinal flora, increase the abundance of beneficial bacteria (such as Bacteroides phylum and Helicobacter genus), and reduce harmful bacteria (such as Proteobacteria phylum and Paraterreria genus) [10].

Another randomized controlled trial investigated the impact of the Mediterranean diet pattern (MDP) on intestinal inflammation, disease activity and gut microbiome in patients with ulcerative colitis (UC). The study randomly divided 28 UC patients into the MDP group (n=15) and the Canadian habitual diet group (CHD, n=13), and they underwent a 12-week dietary intervention. The results showed that the MDP group performed significantly better in multiple indicators. For instance, the MDP group exhibited higher levels of SCFA, acetic acid and butyric acid ($p < 0.05$), as these metabolites have anti-inflammatory and intestinal barrier function maintenance effects. Through 16S rRNA sequencing analysis, it was found that MDP significantly changed the structure of the intestinal microbiota, promoted the enrichment of protective bacteria, and simultaneously reduced the proportion of potential pathogenic bacteria. In addition, the level of fecal secretory IgA (sIgA) in the MDP group increased significantly, further strengthening the mucosal immune barrier. Studies have shown that the Mediterranean diet can effectively assist in maintaining clinical remission of UC by regulating the composition of gut microbiota, increasing beneficial metabolites and reducing inflammatory markers. It is recommended that MDP be adopted as a sustainable dietary strategy as an adjunctive treatment for UC patients to delay disease recurrence and improve their quality of life [11].

3.3. FMT

FMT aims to transplant the entire intestinal microbiota ecosystem of a healthy donor into the patient's body, fundamentally correcting the dysbiosis and thereby restoring the normal production of SCFA

Unigosside is a natural flavonoid component with extensive biological activity and high medicinal value. It can increase the number of intestinal flora closely related to the generation of SCFA. An animal study intends to use sodium dextran sulfate (DSS) to induce the construction of a UC mouse model, verify the improvement effect of AG on UC symptoms in mice, and explore the influence of this component on the intestinal flora and SCFA. The results showed that AG could significantly improve symptoms such as weight loss, colonic shortening, and splenomegaly in UC mice, and reduce the levels of disease activity index (DAI) and inflammatory factors (TNF- α , IL-1 β , IL-6). Histopathological observations indicated that AG could alleviate colonic mucosal injury, increase the proportion of goblet cells, upregulate the mRNA expression of tight junction proteins (occludin, ZO-1), and enhance intestinal barrier function. Further mechanism studies have shown that AG can regulate the structure of the intestinal microbiota, increase the diversity of the microbiota (with elevated Chao1 and Shannon indices), promote the proliferation of beneficial bacteria (such as Lactobacillaceae and Bifidobacterium), and inhibit pathogenic bacteria (such as Proteobacteria and Escherichia coli - Shigella). Meanwhile, AG significantly increased the content of SCFA in the

intestine, especially butyric acid and propionic acid. The FMT experiment further verified that the fecal microbiota liquid treated with AG could simulate the protective effect of AG itself, confirming that the anti-UC effect of AG is closely related to its regulation of the intestinal flora [12].

Regular exercise can also increase gut microbial diversity [13]. It promotes the growth and reproduction of SCFA-producing bacteria (such as butyrate-producing bacteria).

4. Conclusion

SCFA, as a core metabolite connecting diet, gut microbiota and host immunity, plays a crucial role in the pathogenesis and treatment of UC. The existing evidence-based evidence has shown encouraging therapeutic potential. However, to achieve its wide transformation into routine clinical practice, challenges such as individual differences, formulation delivery, and dosage standardization still need to be overcome. Development of new colon-targeted sustained-release formulations. For example, encapsulating butyrate or propionate in pH-sensitive or timed-release special capsules. This design ensures precise drug delivery to the colon area. It significantly improves treatment effectiveness and patient tolerance. Effectively solves the problem of SCFA being absorbed too early in the digestive tract. Development of specific small molecule agonists that can activate SCFA receptors. These drugs can simulate the SCFA signal transduction process. Avoid various problems associated with direct SCFA supplementation. Research on next-generation probiotics (NGPs) is currently underway. Examples include specific strains such as *Akkermansia* and butyrate-producing *Clostridium*. Using advanced synthetic biology techniques to design engineered bacteria. These modified strains can directly deliver SCFA or their precursor substances to inflammatory sites.

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