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Multidimensional Mechanism and Clinical Prospect of Short-Chain Fatty Acids in Digestive Tract Diseases

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Abstract: *Short-chain fatty acids (SCFAs) are important metabolites produced by intestinal microorganisms through fermentation of dietary fiber, which play an important role in maintaining intestinal homeostasis, regulating immune function and metabolism. Studies have shown that SCFAs play an important role in inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), non-alcoholic fatty liver disease (NAFLD), severe acute pancreatitis (SAP), and colon cancer (CRC) by enhancing the intestinal barrier, inhibiting inflammation, regulating microbiota composition, and regulating energy metabolismand other digestive tract diseases. Clinical studies have preliminarily validated the therapeutic potential of SCFAs, and common supplementation methods include probiotics in combination with prebiotics, butyric acid enema, and fecal transplantation. Although its application faces challenges such as individual microbiota differences and insufficient persistence, SCFAs, as mediators of microbiome regulation, show broad prospects in the treatment of digestive tract diseases. Future research needs to optimize the delivery system of SCFAs, explore individualized treatment strategies based on multi-omics technology, and conduct large-scale randomized controlled trials to verify their long-term efficacy and safety.*

Keywords: *Short-Chain Fatty Acids (Scfas), Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS), Nonalcoholic Fatty Liver Disease (NAFLD), Severe Acute Pancreatitis (SAP), Colon Cancer (CRC), Iintestinal Microbiota*

1. Main Types, Generation and Absorption of SCFAs

Short-chain fatty acids (SCFAs) are important metabolites produced by intestinal microorganisms through fermentation of dietary fiber and undigested carbohydrates, mainly including acetic acid (C2), propionic acid (C3), and butyric acid (C4), as well as valeric acid (C5) and caproic acid (C6), which also have certain biological effects under specific conditions [1]. These metabolites play a key role in maintaining intestinal homeostasis, regulating the immune system, and regulating energy metabolism [2].Acetic acid is the most abundant of SCFAs, accounting for more than 60% of the total intestinal SCFAs, is metabolized by probiotics and can affect multiple organs, such as the liver and brain, through blood circulation[3]. Acetic acid regulates energy metabolism and plays an important role in fatty acid synthesis and immune regulation[4]. In addition, acetic acid also plays a role in maintaining intestinal pH balance and inhibiting the growth of pathogenic bacteria [5]. Propionic acid mainly acts on hepatic metabolism and can maintain glycemic homeostasis by inhibiting gluconeogenesis and regulating insulin sensitivity [6]. Propionic acid has also been shown to affect the inflammatory response and regulate the activation of host immune cells to reduce low-grade chronic inflammation [7]. In addition, propionic acid has also shown a positive effect in regulating cholesterol levels, possibly reducing serum cholesterol levels by affecting bile acid metabolism [8]. Butyric acid, as the main source of energy for colonic epithelial cells, plays a crucial role in maintaining intestinal barrier integrity and anti-inflammatory function [9][10][11]. Butyric acid has also been found to have a relieving effect on stress-induced gut-brain axis abnormalities and may have potential value in neurological disorders and mental health regulation [12].

Although valeric acid and caproic acid are found in low levels in the gut and are relatively poorly studied, there is growing evidence that they may also have important regulatory functions [13]. For example, valeric acid is mainly involved in branched-chain amino acid metabolism and regulates

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microbiota balance and fatty acid oxidation [14], while caproic acid may play a role in gut-brain axis signal transduction. However, the specific mechanism of action of these two SCFAs has not been fully elucidated, and future studies should focus on their potential value in gastrointestinal diseases and their interactions with major SCFAs.

The formation of SCFAs depends on the composition of the intestinal microbiota and the availability of substrates, among which Firmicutes and Bacteroidetes are the core microbiota of their generation [15]. The abundance of both and the balance of metabolites are critical for the metabolic health and immune regulation of the host [3]. Different flora synthesize SCFAs through specific metabolic pathways, for example, acetic acid is mainly produced by Bacteroides and Akkermansia muciniphila, and the production of propionic acid involves the succinic acid pathway, the acrylic acid pathway, or the 1,2-propanediol pathway, which is produced by Prevotella and Veillonella, while butyric acid is produced through the butyryl-CoA acetate transferase pathway, mainly by Faecalibacterium prausnitzii and Roseburia Responsible [16]. SCFAs are rapidly absorbed primarily in the colon and enter the host metabolic cycle through multiple pathways. Passive diffusion and specific transporter-mediated active transport are involved in the transmembrane transport of SCFAs, including monocarboxylate transporter 1 (MCT1) and sodium-coupled monocarboxylate transporter 1 monocarboxylate transporter 1 (SMCT1) plays a key role [17]. Acetic acid, due to its low lipophilicity, is able to enter the circulation directly through passive diffusion, while propionic acid and butyric acid rely primarily on MCT1-mediated transmembrane transport into colonic epithelial cells[18]. After absorption, acetic acid and propionic acid can enter the liver through the portal vein and serve as substrates for fatty acid synthesis and gluconeogenesis, respectively, while butyric acid is the main source of energy for colonic epithelial cells [3].

The absorption and metabolism of SCFAs not only affect local intestinal function, but also have a profound impact on whole-body health. Its formation and absorption are influenced by a variety of factors, including the composition of the gut microbiota, dietary fiber intake, and the acid-base environment of the gut [19]. In healthy states, SCFAs production and host metabolism maintain a dynamic equilibrium, while in certain pathological states, such as inflammatory bowel disease (IBD), nonalcoholic fatty liver disease (NAFLD), and irritable bowel syndrome (IBS), abnormal SCFAs metabolism may exacerbate the occurrence and progression of the disease. Therefore, regulating the production and absorption of SCFAs is not only critical for gut health, but may also have important implications for whole-body health through the gut-organ axis.

2. Basic Physiological Functions of SCFAs

2.1 Role of SCFAs in Immunomodulation

SCFAs are prominent in intestinal barrier protection and also play an important role in immune regulation. Studies have shown that SCFAs, especially butyric acid, regulate the function of host immune cells by inhibiting the activity of histone deacetylases (HDACs), including inhibiting the recruitment and migration of macrophages, neutrophils and dendritic cells, and reducing inflammatory responses. Butyric acid significantly reduces neutrophil chemoattractant expression, thereby reducing its migration to the intestine [11]. Studies have shown that butyric acid also activates signaling pathways through G protein-coupled receptors (GPR41, GPR43, etc.), regulates dendritic cell maturation and macrophage activity, promotes the differentiation of T cells and B cells, maintains intestinal local and systemic immune homeostasis, and exhibits obvious anti-inflammatory effects[7]. In addition, Wang et al. used single-cell RNA sequencing technology to find that butyric acid specifically induces the expression of synaptopodin (SYNPO), a protein associated with tight junctions in intestinal epithelial cells, to strengthen intestinal barrier function and promote repair after intestinal injury, thereby indirectly regulating immune function and alleviating intestinal inflammation [10]. At present, most of the research focuses on butyric acid, while the specific roles of acetic acid and propionic acid in immune regulation need to be further studied, and the unique mechanism of different SCFAs in the specific regulation of immune microenvironment should be further explored in the future.

2.2 Effect of SCFAs on Intestinal Barrier Function

SCFAs play an important regulatory role in intestinal barrier function, which is mainly achieved by increasing the expression of tight junction proteins (TJPs) and improving the integrity of intestinal epithelial cells.Saleri used porcine intestinal epithelial cell line (IPEC-J2) in vitro experiments to show

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that acetic acid and propionic acid could significantly increase the expression of intestinal tight junction protein claudin-4 at appropriate concentrations, and acetic acid was particularly prominent at 5 mM concentration. Butyric acid and lactic acid significantly increased gene expression of tight junction proteins ZO-1 and occludin at concentrations of 0.5 mM and 30 mM, respectively [20]. Song et al. found that acetic acid produced by intestinal microbiota can effectively increase the expression of ZO-1 and occludin, stabilize the intestinal barrier structure, and alleviate the intestinal damage caused by pathogenic bacterial infection in an animal model of sea cucumber infection with Vibrio splendidus [21]. It was further found that periodontal pathogen infection caused intestinal barrier function damage, and by inhibiting the expression of ATG5-LC3 in the autophagy pathway, the absorption of SCFAs by intestinal epithelial cells was reduced, resulting in a decrease in the expression of tight junction protein and a weakening of intestinal barrier function. Activation of the autophagy pathway can restore the expression of MCT1 and SMCT1 transporters, both of which are key transporters of SCFAs in cells, thereby increasing the absorption of SCFAs, re-enhancing the expression of ZO-1 and occludin, and repairing intestinal barrier function[22]. It can be seen that SCFAs not only directly regulate the gene expression of barrier proteins, but also further consolidate the structure and function of the intestinal barrier and reduce the risk of intestinal permeability and pathogen invasion through the optimization of metabolic absorption pathways.

Although the above in vitro and animal studies have preliminarily clarified the positive effects of SCFAs on the intestinal barrier, further exploration is still needed in actual clinical practice. Future studies should focus on verifying the appropriate dosage and intervention methods of different SCFAs in specific disease contexts, so as to guide clinical practice more accurately.

2.3 The Role of SCFAs in Gut Microbiota Homeostasis

While regulating immune homeostasis, SCFAs can also effectively stabilize the composition of intestinal microbiota. In a randomized double-blind controlled study of patients with inflammatory bowel disease (IBD), Facchin et al. found that the abundance of SCFAs-producing bacteria such as Lachnospiraceae in the intestinal tract of treated patients was significantly increased by oral microencapsulation of sodium butyrate [23] .Earley used real-time PCR to detect the composition of the colonic mucus layer microbiota in healthy individuals and patients with ulcerative colitis, and confirmed that the butyric acid-producing bacterium Roseburia hominis was highly enriched in the healthy state and significantly reduced in the inflammatory state, revealing that SCFAs maintain intestinal microbiota homeostasis by regulating the abundance of specific bacterial genera [24].

2.4 Role of SCFAs in Gut-brain Axis Regulation

In recent years, SCFAs have been shown to play an important role in regulating gut-brain axis function. Van de Wouw et al. used mice to construct a model of chronic psychosocial stress, and found that oral supplementation with a mixture of acetic acid, propionic acid, and butyric acid could significantly alleviate anhedonia, anxiety-like behavior, and increased stress response caused by chronic psychosocial stress, while SCFAs could also effectively reduce the increase in intestinal permeability caused by stress, suggesting that SCFAs could alleviate neuropsychological abnormalities by improving intestinal barrier function [12]..Some studies have shown the specific mechanism of SCFAs involved in the regulation of the gut-brain axis, and SCFAs not only regulate the release of neurotransmitters and hormones through G-protein coupled receptors (GPCRs, such as GPR41 and GPR43). Histone acetylation also affects gene expression, thereby exerting neuroprotective effects and improving host mood and cognitive function [18].. In addition, Wang et al. found that dietary supplementation of acetic acid, propionic acid and butyric acid could significantly delay the onset of puberty, and the mechanism of action involved SCFAs inhibiting the gene expression of the hypothalamic Kiss1–GPR54–PKC–ERK1/2 pathway through the gut-brain axis pathway, thereby inhibiting gonadotropin-releasing hormone (GnRH) secretion, which further supported the important position of SCFAs in endocrine regulation and gut-brain axis regulation [25].Together, the above results suggest that SCFAs not only play a role in maintaining intestinal homeostasis, but also affect the function of the central nervous system through complex neuro-endocrine pathways, and have a significant ameliorating effect on stress-related psychiatric and neuroendocrine disorders, which also provides a potential intervention strategy for the clinical treatment of related psychiatric and intestinal dysfunctions.

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2.5 The Role of SCFAs in Energy Metabolism and Host Metabolism

SCFAs not only maintain intestinal health, but are also widely involved in host metabolic regulation.Blaak et al. pointed out that SCFAs can improve host metabolic health by affecting energy uptake, lipid metabolism, and glucose metabolism. The team conducted human intervention studies using stable isotope tracing and other methods, and found that propionic acid and butyric acid are involved in gluconeogenesis regulation and energy supply to colon epithelial cells, respectively, which in turn affect systemic glucose homeostasis and insulin sensitivity [1]. Xu et al. confirmed that sodium butyrate supplementation can reduce HbA1c, reduce lipopolysaccharide (LPS)-induced endotoxemia, and significantly improve the integrity of the intestinal barrier, suggesting that butyric acid has obvious therapeutic potential for diabetes and its inflammatory complications [26]. In addition, Kimura et al. found that SCFAs are involved in lipidolysis, lipid synthesis, and gluconeogenesis through G protein-coupled receptors GPR41 and GPR43, emphasizing the importance of SCFAs as therapeutic targets for metabolic diseases [4]. Roessler et al. confirmed through human studies that oral propionic acid can significantly regulate the serum metabolome and significantly increase the level of secondary bile acids (such as glycocholic acid, deoxycholic acid, GUDCA, deoxycholic acid, DCA), and the increase of DCA is closely related to the decrease of serum cholesterol. This study suggests that propionic acid may reduce cholesterol and protect cardiovascular health by altering bile acid metabolism [8].

3. The Role of SCFAs in Digestive Tract Diseases

3.1 Role of SCFAs in Nonalcoholic Fatty Liver Disease (NAFLD)

Short-chain fatty acids play an important role in maintaining intestinal homeostasis, regulating energy metabolism, and immunomodulation [27]. In recent years, the role of SCFAs in the regulation of the gut-liver axis has attracted increasing attention, and studies have shown that they have an important impact on the occurrence and progression of nonalcoholic fatty liver disease (NAFLD) [28].. Yang et al. (2024) found that the gut microbiota composition of NAFLD patients was significantly altered, accompanied by abnormal SCFAs metabolism, by 16S rRNA sequencing and metabolomics analysis of the levels of gut microbiota and fecal short-chain fatty acids (SCFAs) in 104 subjects (including healthy controls and patients with NAFLD of varying severity). In particular, acetic acid and butyric acid levels were significantly reduced, which was significantly associated with fatty liver severity in patients with NAFLD. These changes correlate strongly with disease progression and help distinguish between subtypes of NAFLD of varying severity [29].

SCFAs reduce NAFLD-associated inflammatory response by enhancing intestinal barrier function. Zhou and Fan proposed that the reduction of SCFAs would disrupt the intestinal barrier and make it easier for bacterial endotoxins (LPS) to enter the liver, thereby activating intrahepatic Kupffer cells, inducing the expression of pro-inflammatory factors TNF-α and IL-6, and exacerbating liver inflammation [30]. Zhang et al. further confirmed that butyric acid can significantly upregulate the expression of intestinal tight junction proteins, significantly reduce intestinal permeability, and thereby reduce the risk of LPS crossing the intestine into the portal vein. In addition, butyric acid can further strengthen the integrity of the intestinal barrier by regulating intestinal mucus secretion and improving the composition of intestinal microbiota [31].

SCFAs also play a direct role in the regulation of liver inflammation. On the one hand, SCFAs significantly inhibit hepatocyte inflammatory damage by activating GPCRs and reducing the release of hepatic pro-inflammatory factors [7] [32]. On the other hand, Pant et al. further clarified the mechanism of butyric acid inhibition of liver inflammation, that is, by inducing the conversion of macrophages to M2 anti-inflammatory phenotype, reducing the proportion of M1 pro-inflammatory macrophages, thereby significantly reducing the chronic inflammatory response of the liver. At the same time, SCFAs can effectively reduce oxidative stress by regulating the NF-κB signaling pathway, thereby alleviating hepatocyte damage [33].

SCFAs regulate liver lipid metabolism through a variety of signaling pathways, which in turn affects liver fat deposition. Studies have shown that propionic acid can significantly reduce intrahepatic fat accumulation by activating the AMP-activated protein kinase (AMPK) pathway, inhibiting the expression of lipid synthesis-related genes such as SREBP-1c and FASN, and promoting the β oxidation of fatty acids [31]. In addition, SCFAs can further improve bile acid metabolism and hepatic lipid metabolism balance by activating farnesoid X receptor (FXR) and TGR5 receptor signaling

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pathways[30], and at the same time, affect glucose metabolism through GPR41 and improve NAFLD-related metabolic disorders.

Clinical studies suggest that dietary interventions that promote SCFAs production through SCFAs supplementation or SCFAs production may be a potential strategy for the treatment of NAFLD. In a randomized controlled trial (RCT), butyrate supplementation was shown to significantly reduce fatty liver index (FLI) and lipid levels, and significantly improve liver function and inflammatory markers in patients with NAFLD, demonstrating the positive effect of SCFAs on liver metabolism in patients with NAFLD [34].. A network meta-analysis of traditional and next-generation probiotics conducted by Zhu et al. found that by increasing the ability of the gut microbiota to produce SCFAs (e.g., using specific probiotic combinations), it can also effectively improve liver steatosis and inflammatory status, suggesting that restoring SCFAs levels through microecological interventions may be a promising research direction for the treatment of NAFLD [35].

SCFAs play a key role in the occurrence and progression of NAFLD through a variety of pathways, including intestinal barrier protection, lipid metabolism regulation, inflammation inhibition, and oxidative stress regulation. However, the current clinical research of SCFAs in the treatment of NAFLD is still in its infancy, and the long-term intervention effect and safety are not yet clear, so future studies need to design large-sample randomized controlled studies to verify the clinical efficacy and safety of SCFAs supplementation in the treatment of NAFLD, and explore individualized treatment strategies suitable for different patient subtypes.

3.2 Role of SCFAs in Irritable Bowel Syndrome (IBS)

Short-chain fatty acids are also associated with irritable bowel syndrome. Teige et al. analyzed the fecal microbiota and SCFAs of 60 IBS patients (including IBS-D, IBS-C, IBS-M subtypes) and 42 healthy control groups, and found that there was a significant imbalance in the intestinal microbiota of IBS patients, and the level of SCFAs was correlated with the symptom severity of different IBS subtypes, especially butyric acid and acetic acid showed a weak positive correlation with diarrhea symptoms, suggesting that SCFAs may be involved in the pathogenesis and symptomatic differences of IBS [36].

SCFAs levels vary among patients with different types of IBS. Studies have shown the effects of different interventions, including low-FODMAP diets, probiotics, and fecal transplantation, on SCFAs in the feces of IBS patients, and found that the level of propionic acid in the feces of IBS-D patients was significantly increased, while the level of acetic acid was decreased, suggesting that intestinal dysbiosis may be one of the main causes of abnormal SCFAs metabolism in patients with IBS-D [37]. Shaidullov et al. further noted in animal models of IBS that high concentrations of SCFAs, especially propionic acid, may exacerbate diarrheal symptoms of IBS-D by activating GPCRs to accelerate colonic motility [38]. In his study of the relationship between the gut microbiota and different subtypes of IBS, Nagamine pointed out that patients with IBS-C often exhibit low levels of SCFAs, which may be related to a decrease in beneficial bacteria such as butyric acid-producing bacteria, and that insufficient SCFAs can affect colonic motility, which in turn can worsen constipation symptoms [39].

SCFAs function through multiple mechanisms during the occurrence of IBS. SCFAs can regulate intestinal motility and visceral sensitivity by activating GPCRs, which in turn affects intestinal peristalsis and defecation frequency [40]. SCFAs may also affect signaling between the enteric nervous system and the central nervous system, especially butyric acid, which has an analgesic effect, which can significantly reduce visceral hyperalgesia and relieve abdominal pain in patients with IBS [41].

However, there are conflicting results for the role of butyric acid in IBS. On the one hand, Nozu found that butyric acid enema treatment could significantly reduce visceral hyperalgesia and increase intestinal permeability in IBS model animals. The mechanism is mainly related to the activation of AMP-dependent protein kinase (AMPK) and PPAR-γ signaling pathways by butyric acid, and the regulation of nitric oxide (NO), opioid receptors, and central dopamine D2 receptor pathways, suggesting that butyric acid has clear anti-inflammatory, analgesic, and intestinal barrier protection effects [42].. On the other hand, a growing number of studies are suggesting the opposite of this view. Long et al. used animal models to show that the release of nerve growth factor (NGF) from intestinal glial cells (EGCs) increased significantly after butyric acid treatment, which enhanced the sensitivity of intestinal sensory nerves, resulting in increased visceral hyperalgesia [43].. Li et al. further found in a rat model of diarrhea-type IBS that animals showed obvious visceral hypersensitivity after sodium butyrate enema. The mechanism was explored by immunofluorescence staining, Western blot,

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real-time quantitative PCR and patch-clamp technology, and it was found that butyric acid promoted the obvious degranulation of colonic mast cells, caused the up-regulation of lincRNA-01028 expression and the decrease of miR-143 expression in dorsal root ganglia (DRG) neurons, and then activated protein kinase C (PKC), which in turn led to the enhancement of transient receptor potential vanillin isoform 1 (TRPV1) channel activity. Promotes visceral pain transmission and increased sensitivity [44]. These results suggest that the effect of butyric acid on the sensitivity of IBS viscera has a clear duality. This difference may depend on the dose of butyric acid, the local intestinal microenvironment of action, and the specific subtype of IBS. In the future, further in-depth research is needed to clarify the specific mechanism of action of butyric acid under different conditions, so as to better guide its precise application in the clinical intervention of IBS.

Dietary intervention is regarded as an important strategy to regulate the metabolism of SCFAs. Ju et al. proposed that intestinal acidic stimulation can activate the central nervous system, leading to abnormal regulation of mood, neuroendocrine, and autonomic nervous systems, thereby exacerbating IBS symptoms. The low-FODMAP diet is a scientific dietary approach to help alleviate the symptoms of functional gastrointestinal diseases such as IBS by restricting hard-to-absorb carbohydrates, and it can significantly reduce the concentration of fecal propionate in IBS patients, thereby alleviating IBS-D-related diarrhea symptoms, but the effect of probiotics and fecal microbial transplantation (FMT) on the level of SCFAs is still controversial[33]. Nagamine noted that some probiotics may help improve intestinal barrier function and reduce inflammation and abdominal pain in IBS patients by increasing the production of butyric acid, but there are significant differences in efficacy and individual differences between different strains [39].

Although the role of SCFAs in IBS is not yet fully unified, a growing body of research has confirmed that they play an important role in regulating intestinal function, visceral sensitivity, and inflammatory response. At present, most of the studies focus on the mechanism of butyric acid, but there is still a lack of in-depth and systematic research on the specific roles of acetic acid and propionic acid in different isoforms of IBS. Therefore, the specific intervention effects of different combinations of SCFAs on patients with IBS subtypes should be further explored in the future, so as to provide a basis for the precise treatment of IBS.

3.3 Role of SCFAs in Inflammatory Bowel Disease (IBD)

The role of short-chain fatty acids (SCFAs) in inflammatory bowel disease (IBD) includes immune regulation, intestinal barrier repair, microbiota homeostasis maintenance, metabolic regulation, and hypoxia signaling pathway regulation. Franzosa found significant changes in the gut microbiota of IBD patients, with a decrease in the abundance of SCFAs-producing bacteria, leading to a decrease in the levels of SCFAs, especially butyric acid, which in turn affected intestinal immunity and barrier function, further supporting the critical role of SCFAs in the pathogenesis of IBD [45].

SCFAs play an important role in immune regulation through G protein-coupled receptors. These receptors are widely distributed in intestinal immune cells and epithelial cells, and regulate the release of inflammatory cytokines and the function of immune cells through downstream signaling pathways. Butyric acid regulates regulatory T cell proliferation through GPR109A and reduces the activation of Th17 cells, thereby decreasing the secretion of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β [46][47]. In addition, SCFAs also affect gene expression by inhibiting histone deacetylases (HDACs) and enhance anti-inflammatory effects [48]. Lührs et al. used in vitro culture of human intestinal lamina proprina macrophages and found that butyric acid inhibited the activation of the NF-κB signaling pathway, thereby reducing the release of pro-inflammatory factors, thereby alleviating the inflammatory response in IBD [49]. Notably, Jaworska et al. analyzed the levels of SCFAs and their receptors in the blood and feces of IBD patients and found that the expression levels of SCFAs receptors decreased in IBD patients, resulting in a reduced response to SCFAs-mediated immunomodulatory effects, thereby exacerbating the progression of inflammation. The importance of SCFAs receptors in the immune regulation of IBD has been further validated [50].

SCFAs enhance intestinal barrier function through a variety of mechanisms and improve intestinal integrity in patients with IBD. Facchin et al. showed that microencapsulated sodium butyrate, a sodium butyrate preparation processed by microencapsulation technology, can significantly increase the expression of tight junction proteins, thereby reducing intestinal permeability, reducing the penetration of pathogenic bacteria and inflammatory mediators, and improving intestinal barrier function [23].. Another study by Earley et al. showed that the colonic mucus layer of healthy individuals is rich in butyric acid-producing bacteria, while the colonic mucus layer of IBD patients lacks these key

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microflora, affecting the integrity and anti-inflammatory capacity of the mucus layer [24].

In addition, it has been found that HIF-1α is a key transcription factor for intestinal cells to maintain homeostasis in a hypoxic state, and SCFAs can stabilize HIF-1αThe HIF-1α signaling pathway regulates the expression of high-molecular-weight glycoprotein MUC2 and tight junction protein, and increases the thickness of the intestinal mucus layer, thereby improving intestinal barrier function. This suggests that SCFAs still have an important protective role in the hypoxic microenvironment of IBD [51]. However, HIF-1α may also exacerbate the IBD inflammatory response in some cases by inducing pro-inflammatory gene expression. Therefore, HIF-1α-mediated regulation of SCFAs may have different effects in different IBD isoforms, and further investigation of the specific mechanisms is needed.

SCFAs also promote fatty acid β-oxidation by activating the PPAR-γ pathway, reduce the production of inflammation-associated lipid mediators, and inhibit the inflammatory response. Yan et al. summarized the role of SCFAs in the regulation of IBD-related lipid metabolism and found that SCFAs can affect the immune inflammatory response by regulating arachidonic acid and its metabolites such as prostaglandins and leukotrienes [52]. In addition, SCFAs also play an important role in the maintenance of IBD-related microbiota homeostasis. Shin et al. have shown that SCFAs can promote the growth of beneficial microflora while inhibiting the expansion of pathogenic bacteria, thereby maintaining intestinal microbiota balance [53]. Therefore, probiotic strategies to supplement SCFAs or promote SCFAs production may provide a new direction for IBD treatment.

SCFAs have great potential for use in the treatment of IBD, especially in patients with ulcerative colitis (UC) with butyrate enema. Scheppach et al. found that 200 mL of butyric acid enema at a concentration of 100 mmol/L per day was used to treat UC patients with a significant improvement in clinical symptoms and a reduction in the degree of colonic mucosal inflammation on endoscopy [54].. However, some studies suggest that the efficacy of SCFAs may depend on the subtype of IBD, the stage of inflammation, and the characteristics of the individual microbiome. Trapecar et al. found that SCFAs may exacerbate T cell-mediated inflammation in specific immune contexts through an in vitro gut-liver mimicry system [55]. Therefore, the clinical application of SCFAs still needs to be further optimized.

The role of SCFAs in IBD involves a variety of intertwined regulatory pathways, including immune regulation, intestinal barrier protection, metabolic regulation, and hypoxia signaling pathway regulation.There are significant individual differences in the efficacy of SCFAs in the treatment of IBD,which may be related to the microbiota composition, genetic background, changes in the host intestinal microenvironment and dietary factors, so future studies need to further explore the individualized factors and related markers of the efficacy of SCFAs to improve the clinical treatment effect.

3.4 Role of SCFAs in Severe Pancreatitis

The role of short-chain fatty acids (SCFAs), especially butyric acid, in severe acute pancreatitis (SAP) is of increasing concern. SAP is often associated with impaired intestinal barrier function, leading to bacterial translocation and endotoxin release, exacerbating systemic inflammatory response (SIRS) and ultimately leading to multi-organ dysfunction (MODS) [56]. Studies have shown that butyric acid plays a key role in the occurrence and progression of SAP by strengthening the intestinal barrier, inhibiting inflammatory factors, regulating the immune system, and improving the imbalance of intestinal microecology. Pan et al. observed a significant decrease in the expression of ZO-1 and Occludin proteins in SAP mice, and the expression levels of these proteins were restored after butyric acid supplementation, suggesting that butyric acid can enhance intestinal barrier function and reduce gut leakage [57].

In the pathological process of SAP, systemic inflammatory response and excessive release of pro-inflammatory cytokines are important factors for disease exacerbation. Butyric acid is able to alleviate systemic inflammation by inhibiting the NLRP3 inflammasome and nuclear factor kappa B (NF-κB) signaling pathways and reducing the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β [56]. . In addition, Xiao et al. used a 4% sodium taurocholate-induced rat SAP model to study the changes of Treg cells in the SAP rat model, and found that the proportion of Treg cells increased significantly after butyric acid treatment, accompanied by an increase in the expression of Foxp3 and GPR109A, suggesting that butyric acid may activate Treg cells through the GPR109A receptor pathway, reduce inflammation and alleviate SAP progression[58]. These results suggest that

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butyric acid can not only directly inhibit the release of inflammatory factors, but also achieve immunomodulatory effects by promoting the activation of anti-inflammatory immune cells.

The occurrence of SAP is also closely related to the imbalance of the intestinal microbiota, and studies have shown that the composition of the intestinal microbiota in SAP patients is significantly altered, among which probiotics (such as Prevobacterium faecium) are significantly reduced, while potential pathogenic bacteria (such as E. coli).) proliferates in large numbers. van den Berg et al. found that the level of short-chain fatty acids decreased in SAP mice, while the diversity of the gut microbiota was significantly reduced, in a mouse model of necrotizing pancreatitis. It has been further shown that butyric acid supplementation can reverse this imbalance, increase the abundance of Prevobacterium faecium, and reduce colonization of E. coli, thereby reducing SAP-associated bacterial translocation and infectious complications [59]. In addition, Wang et al. studied the role of the microbiota-metabolic-immune axis in SAP-associated lung injury, and analyzed the changes of intestinal microbiota in SAP mice, and the results showed that the decrease in SCFAs level was closely related to the aggravation of SAP lung injury. Butyric acid supplementation can reduce the level of inflammatory factors in the lungs, thereby improving SAP-related distal organ damage [60].

Although animal experiments have shown that butyric acid has a significant effect on SAP, its clinical application still faces challenges. First, the optimal mode of administration has not yet been determined, and the development of precision delivery systems such as nanocarriers or butyric acid derivatives may be needed in the future. Second, the effective dose range is unclear and needs to be evaluated in further clinical trials. In addition, Chen et al. found that the oligosaccharide GV-971 extracted from seaweed could increase the production of SCFAs and improve SAP inflammation by regulating the intestinal microbiota [61], providing a new idea for future intervention strategies. Future studies should combine multi-omics techniques to further elucidate the mechanism of action of butyric acid, and optimize its application strategy through clinical trials to promote its clinical translation in SAP therapy.

3.5 Role of SCFAs in Colon Cancer (Colorectal Cancer)

Epidemiological studies have shown that changes in short-chain fatty acids (SCFAs) levels are strongly associated with colorectal cancer (CRC) risk. Alvandi et al. (2022) noted in a systematic review and meta-analysis of 23 observational studies that the fecal concentrations of acetic acid, propionic acid, and butyric acid were significantly reduced in patients with CRC, high-risk populations, and patients with adenoma, and that the decrease in total SCFAs was statistically significantly associated with an increased risk of CRC (SMD=2.02), suggesting that it may have a protective effect in the development of CRC [62].. However, some studies have failed to confirm this association. Sze et al. (2019) performed fecal SCFAs testing in 172 healthy individuals, 198 adenoma patients, and 120 CRC patients, and found no significant association between SCFAs concentration and tumor status, and SCFAs failed to significantly improve the predictive performance of CRC diagnostic models [63]. Lu et al. (2023) also found a causal relationship between genetic predictors and CRC risk by analyzing genetic loci related to SCFAs metabolism (e.g., PWY-5022 butyric acid synthesis pathway) in European populations [64]. Niccolai et al. found that although the total amount of SCFAs in CRC patients decreased, the proportions of butyric acid, isobutyric acid, and isovaleric acid increased, and the proportion of acetic acid decreased, and this imbalance may provide potential non-invasive diagnostic clues for CRC and adenoma [65]. Overall, although most studies support an association between decreased levels of SCFAs and an increased risk of CRC, their applicability as diagnostic biomarkers needs to be further validated.

The critical role of gut microbiota in the production of SCFAs has been widely recognized. Oral supplementation with Lactobacillus reuteri increased intestinal SCFAs levels, increased the abundance of butyric acid-producing bacteria such as Firmicutes and Bacteroidetes, and inhibited the pathogenic potential of Proteobacteria and Fusobacteriota [66].. Wu et al. (2024) found that Fusobacterium nucleatum colonization inhibited the growth of butyric acid-producing bacteria, significantly reduced butyric acid levels, and accelerated tumor progression in a mouse model of CRC [67]. However, some pathogenic bacteria can also produce butyric acid, but cause harmful effects. Okumura et al. (2021) pointed out that Porphyromonas gingivalis is the same as Porphyromonas asaccharolytica The butyric acid produced can induce epithelial cell senescence and inflammatory response, and promote tumorigenesis, suggesting that SCFAs have a "double-edged sword" effect in the context of a specific microecology [68]. Chen et al. (2025) found that bifidobacterial metabolites significantly inhibit CRC progression in mouse experiments, emphasizing the potential of probiotic fatty acid metabolism in regulating the intestinal tumor environment [69].

ISSN 2618-1584 Vol. 7, Issue 4: 1-14, DOI: 10.25236/FMSR.2025.070401

The biological effects of SCFAs, especially butyric acid, within colon cells depend on specific transporters and receptor signaling pathways. Wang et al. (2019) pointed out that butyric acid mainly exists in the form of anions at physiological pH and cannot enter cells through simple diffusion, and its transport mainly relies on MCT1 and SMCT1, the expression of which is essential for butyric acid to regulate the metabolism and proliferation of tumor cells [70]. In patients with CRC, SMCT1 expression is often downregulated by DNA methylation, which restricts the entry of butyric acid into tumor cells and reduces its antitumor effects [71]. In addition, MCT1 is not only involved in the uptake of SCFAs, especially butyric acid, but also plays a role in lactate emission from tumor cells, revealing its dual function in CRC [70]. The biological effects of SCFAs are also mediated by a variety of G protein-coupled receptors (GPCRs), especially GPR109A, FFAR2, and FFAR3. Li et al. (2024) found that butyric acid activates downstream signaling pathways through GPR109A receptors and promotes apoptosis of CRC cells by establishing an oral delivery system of Lactobacillus microgels [66]. Binienda and Fichna (2024) noted that in patients with CRC, the expression of FFAR2/3 is downregulated, and activation of these receptors through the specific agonist GW9508 effectively inhibits tumor cell proliferation and promotes apoptosis [71]. In addition, butyric acid also enhances the tumor cell killing ability of CD8+ T cells by activating TLR5 on the surface of CD8+ T cells, initiating the NF-κB signaling pathway, and thereby improving the efficacy of anti-PD-1 immunotherapy [72]. Recently, Binienda et al. (2025) found that butyric acid significantly inhibited the proliferation, migration, and invasion of CRC cells by upregulating the expression of FFAR2 and FFAR4 receptors in a mouse CRC model, revealing an important role of GPCRs in the anticancer effects of butyric acid [73]. Therefore, the intracellular role of SCFAs depends on the synergistic effect of transporters and GPCRs signaling pathways, which profoundly affects the metabolism and immune regulation of CRC.

The role of butyric acid in CRC cell death, especially in the regulation of apoptosis, ferroptosis, and cell cycle arrest, has been widely confirmed. He et al. (2023) found that butyric acid effectively reversed the inherent resistance of CRC cells to ferroptosis by inhibiting class I histone deacetylase (HDAC) activity, upregulating c-Fos gene expression, inhibiting glutathione transporter xCT activity, reducing intracellular glutathione synthesis, and promoting ferroptosis[74].. Mederle et al. (2025) found that sodium butyrate up-regulated the expression of pro-apoptotic factors such as Bax, Caspase-3, and PUMA, and inhibited anti-apoptotic proteins such as MCL-1, directly inducing mitochondria-dependent apoptosis in CRC cells [75]. At the same time, Kim and Yang (2024) found that sodium butyrate can down-regulate the expression of thymidylate synthase (TYMS), enhance the efficacy of 5-FU, and significantly improve the sensitivity of CRC cells to chemotherapy [76]. In addition, the anti-tumor effect of butyric acid in CRC cells showed a significant cell type dependence. Oncel et al. (2024) found that butyric acid significantly reduced the migration and invasion of tumor cells by inhibiting the activity of focal adhesion kinase (FAK) and Src signaling pathways and upregulating the expression of E-cadherin. Survival analysis further showed that high expression of E-cadherin was closely related to a 13% increase in the 5-year survival rate of CRC patients, suggesting that butyric acid regulates tumor metastasis through the FAK/Src/E-cadherin pathway, which has potential clinical intervention value [77]. In terms of metabolic regulation, Zhang et al. (2024) found that sodium butyrate can up-regulate the mitochondrial metabolism-related protein SIRT4, promote the autophagic degradation of HIF-1α protein, and then inhibit the expression of glucose transporter GLUT1 and lactate dehydrogenase LDHA, reduce glucose uptake and lactate production, and finally significantly inhibit aerobic glycolysis and tumor growth in CRC cells. This finding reveals the potential of butyric acid to inhibit CRC progression by regulating energy metabolism in the hypoxic tumor microenvironment [78]. These studies have shown that butyric acid induces CRC cell death through multiple pathways, highlighting its potential in anti-tumor therapy.

SCFAs, especially butyric acid, profoundly affect the fate of CRC cells through epigenetic modifications and transcriptional regulatory networks. Nshanian et al. (2025) revealed by chromatin immunoprecipitation sequencing (ChIP-seq) that butyric acid and propionic acid can inhibit histone deacetylase (HDAC) and enhance the butylation and propionylation of histones H3K18 and H4K12, thereby promoting the opening of chromatin structure, thereby enhancing the expression of anti-tumor genes and inhibiting cancer cell proliferation and invasion [79].. Xi et al. (2021) constructed a ceRNA network regulated by sodium butyrate, and found that genes such as HMGA2 and LOXL2 were significantly regulated in CRC cells, and the expression changes of these genes were closely related to the clinical prognosis of CRC patients, revealing the role of butyric acid in tumor suppression through the non-coding RNA network [80]. In addition, butyric acid inhibits nuclear translocation by enhancing the acetylation modification of STAT1 protein, reduces the expression of PD-L1 on the surface of CRC cells, and enhances CD8+ T cell-mediated immune clearance [81]. In addition, Pan et al. (2024) found that sodium butyrate can inhibit the expression of miR-183, and then up-regulate its target gene

ISSN 2618-1584 Vol. 7, Issue 4: 1-14, DOI: 10.25236/FMSR.2025.070401

DNAJB4, significantly inhibit the proliferation and migration of tumor cells, and induce apoptosis. The direct regulatory relationship between miR-183 and DNAJB4 was further verified by the dual luciferase reporter assay. This study revealed the molecular basis of butyric acid's anti-CRC effect through miRNA-mediated epigenetic mechanisms, and provided a new idea for the development of precision treatment strategies based on SCFAs [82].

There are significant differences in the response of different molecular subtypes of CRC to SCFAs, which is closely related to its intrinsic genetic characteristics and the integrity of signaling pathways. Mowat et al. (2023) found that butyric acid could significantly up-regulate the expression of MHC-I molecules and antigen presentation-related genes in the microsatellite instability (MSI-H) CRC subtype,and enhance the tumor killing ability of CD8+ T cells. In contrast, chromosomally unstable (CIN) CRC cells have a weaker response to butyric acid, suggesting that the strength of the immune response is closely related to the sensitivity of SCFAs [83]. This difference also relates to key signaling pathways on which SCFAs depend, such as FOXO3A and STAT1. Park et al. (2020) found that butyric acid significantly enhanced sensitivity to radiotherapy by activating FOXO3A expression in CRC organoid models, while the immunosensitizing effect of butyric acid on CRC isoforms with impaired FOXO3A function was attenuated [84]. This further proves that mechanistic studies for the prevention of CRC provide important evidence

In the tumor immune microenvironment, SCFAs, especially butyric acid, are involved in immune regulation through multiple mechanisms. First, butyric acid can activate TLR5 on the surface of $CD8^+$T cells, activate the NF-κB signaling pathway, and enhance its killing function, thereby increasing the response rate of anti-PD-1 immunotherapy [72]. Second, butyric acid can improve the immunosuppressive state of tumors as a whole by regulating Th1/Th2 balance, inhibiting Treg cell expansion, and decreasing the expression of inflammatory factors such as IL-6 and TNF-α [85]. In addition, SCFAs can also affect the polarization state of cells such as Treg and Th17, further enhancing antigen-specific immune responses [86].

It is worth noting that these immunomodulatory effects not only improve the tumor microenvironment, but also enhance the sensitivity of CRC to multiple treatment methods to a certain extent. Butyric acid has been shown to significantly enhance chemoradiotherapy-induced apoptosis by activating FOXO3A expression and downregulating thymidylate synthase (TYMS) [76] [84]. At the same time, the activation of immune pathways by butyric acid can also synergistically enhance the therapeutic efficacy of PD-1 inhibitors [72]. Therefore, the multiple mechanisms of SCFAs in tumor treatment are not only reflected in the direct anti-proliferative effect, but also in the synergistic sensitizer of chemoradiotherapy and immunotherapy, which provides theoretical support for the realization of multimodal precision therapy for CRC.

In summary, SCFAs, especially butyric acid, play a multi-dimensional and multi-layered role in the pathological mechanism of colorectal cancer (CRC). SCFAs not only effectively inhibit the proliferation, migration and survival of CRC cells, but also significantly enhance the efficacy of radiotherapy, chemotherapy and immunotherapy by regulating energy metabolism (e.g., SIRT4/HIF-1α axis inhibition of glycolysis), epigenetic networks (e.g., miR-183/DNAJB4 axis), and tumor immune microenvironment (e.g., GPR109A, FFAR2/FFAR4 and TLR5-mediated immune activation). Of particular note, butyric acid exhibits selective sensitivity to CRC of different molecular subtypes by regulating specific signaling pathways (e.g., FAK/Src/E-cadherin, SIRT4/HIF-1α), which provides a theoretical basis for individualized treatment. Future research should focus on the combination of high-throughput omics technology to screen sensitive populations in response to SCFAs, use CRC organoid models to verify the intervention effect, and explore potential synergistic therapeutic targets through bioinformatics. In view of the good safety profile and multi-target action characteristics of SCFAs, they have important clinical translation potential in many aspects such as CRC prevention, early screening, treatment sensitization and recurrence inhibition. In the future, it is necessary to verify the comprehensive application value of SCFAs in the precision prevention and treatment of CRC through a multi-center and prospective clinical trial system, so as to promote its progress towards clinical practice.

4. Conclusion and Outlook

Overall, short-chain fatty acids (SCFAs), as key metabolites in intestinal microbiota homeostasis, have been shown to play a central role in the regulation of the intestinal barrier, inflammatory immunity, energy metabolism and epigenetics, especially SCFAs represented by butyric acid have

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shown broad therapeutic potential in digestive tract diseases such as inflammatory bowel disease, colorectal cancer, irritable bowel syndrome, non-alcoholic fatty liver disease, and severe pancreatitis. Existing studies have shown that SCFAs are involved in tumorigenesis, immune tolerance and mucosal repair by affecting multiple pathways such as GPR receptor signaling, HDAC inhibition, T cell polarization, ferroptosis sensitivity, etc., and have a clear mechanistic basis and good biosafety. Despite this, SCFAs still face challenges such as low delivery efficiency, poor targeting, and large individual differences in clinical translation. Future research should seek breakthroughs in multi-omics collaborative analysis, synthetic biology-mediated construction of engineered strains, development of intestinal targeted delivery systems, and AI-assisted analysis of individual microbiota data. In addition, it is necessary to pay attention to the bridging role of SCFAs in systemic disease networks such as the "gut-liver axis", "gut-brain axis" and "gut-tumor axis". Large-scale, multi-center, long-term follow-up prospective clinical trials will also be a key link for SCFAs to realize the transformation from basic mechanism to precision medicine. As an important medium of microecological therapy, SCFAs are expected to become a new therapeutic strategy that connects intestinal microbiota and systemic disease regulation in the future, providing a multi-dimensional prevention and treatment path for digestive tract diseases and even other chronic diseases.

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