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# THE ROLE OF SHORT-CHAIN FATTY ACIDS IN IMMUNE REGULATION AND INTESTINAL HOMEOSTASIS IN INFLAMMATORY BOWEL DISEASE

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**ABSTRACT**

**Background:** Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is characterized by chronic relapsing intestinal inflammation driven by dysregulated immune responses and impaired epithelial barrier function. Increasing evidence highlights short-chain fatty acids (SCFAs)—particularly acetate, propionate, and butyrate—produced by gut microbiota as key mediators linking microbial composition to immune regulation and maintenance of intestinal homeostasis.

**Methodology:** This review was conducted through an extensive analysis of clinical, experimental, and translational studies indexed in PubMed, Google Scholar, and the Cochrane Library, focusing on gut microbiota composition, SCFA metabolism, epithelial barrier integrity, immune mechanisms, and SCFA-targeted therapeutic strategies in IBD.

**Results:** Patients with IBD consistently show reduced abundance of SCFA-producing bacteria, especially butyrate-generating taxa such as *Faecalibacterium* and *Roseburia*, accompanied by decreased fecal SCFA levels and impaired epithelial SCFA utilization. SCFAs exert potent anti-inflammatory effects via histone deacetylase inhibition and activation of SCFA-responsive G protein-coupled receptors, promoting regulatory immune phenotypes and suppressing pro-inflammatory signaling. Concurrently, they enhance intestinal barrier function by stimulating mucus production, reinforcing tight junctions, and supporting epithelial metabolic activity. Dietary fiber enrichment, prebiotics, probiotics, and microbiota-directed therapies demonstrate potential to restore SCFA availability and improve inflammatory and clinical outcomes, although responses remain heterogeneous.

**Conclusions:** SCFAs represent a crucial interface between gut microbiota, immune regulation, and epithelial barrier integrity, positioning SCFA-related mechanisms as promising therapeutic targets in IBD. Despite encouraging evidence, further well-designed, mechanistic, and personalized studies are needed to clarify causality, optimize SCFA-based interventions, and translate findings into effective clinical strategies.

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**KEYWORDS**

Inflammatory Bowel Disease, Short-Chain Fatty Acids, Gut Microbiota, Intestinal Barrier

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**1. Introduction**

Inflammatory bowel disease (IBD) is a chronic, recurrent inflammatory disorder of the gastrointestinal tract that primarily includes Crohn's disease (CD) and ulcerative colitis (UC). Intestinal mucosal inflammation in IBD is marked by recurrent episodes of abdominal pain, diarrhea, hematochezia, and weight loss, and is driven by the infiltration of neutrophils and macrophages (Guan, 2019). The precise etiology of IBD remains unclear, however, it is widely accepted that its pathogenesis is multifactorial, involving a complex interplay between genetic susceptibility, impaired intestinal barrier function, alterations in the gastrointestinal microbiota, dysregulated immune responses, as well as environmental and lifestyle factors (Cai et al., 2021). Genome-wide association studies have identified hundreds of IBD-associated loci involved in microbial recognition, autophagy, epithelial barrier function, and immune signaling, while environmental factors such as smoking, diet, and chemical exposures further modulate disease risk, partly through epigenetic mechanisms. These factors converge on the gut microbiome and mucosal immune system, leading to impaired host–microbe interactions, metabolic dysfunction, and chronic intestinal inflammation (Wan et al., 2025). According to Caron et al., the annual incidence of IBD varies considerably by region, with reported rates ranging from 10.5 to 46.14 per 100 000 individuals in Europe, compared with substantially lower estimates of 1.37 to 1.5 per 100 000 in Asia and the Middle East, 23.67 to 39.8 per 100 000 in Oceania, 0.21 to 3.67 per 100 000 in South America, and 7.3 to 30.2 per 100 000 in North America. The burden of IBD among children and adolescents and older people is rising globally (Caron et al., 2024). The human gut microbiota is a complex, dynamic and

highly heterogeneous ecosystem composed of bacteria, fungi, archaea, and viruses that collectively interact with the human host to maintain intestinal homeostasis (Chen et al., 2021). Dysregulation of gut microbiota composition and diversity has emerged as a critical factor in the initiation and progression of IBD. Dysbiosis in IBD is characterized by an early and sustained reduction in beneficial, short-chain fatty acid short-chain fatty acids (SCFA)-producing bacteria alongside the expansion of pro-inflammatory and pathogenic taxa. While microbial signatures differ between CD and UC, a shared feature is the depletion of SCFA producers, resulting in impaired barrier function and dysregulated immune responses. In contrast to pathogenic bacteria that promote inflammation through epithelial invasion and activation of NF- $\kappa$ B and IL-17-related pathways, SCFA-producing microbes exert protective effects by supporting epithelial integrity and suppressing intestinal inflammation (Qiu et al., 2022). Among microbial-derived metabolites, SCFAs have therefore emerged as key mediators linking gut microbiota composition to host immune regulation in IBD. The aim of this review is to provide an integrated overview of the mechanisms by which SCFAs regulate intestinal barrier integrity and mucosal immune homeostasis, to explore how disruptions in SCFA production and signaling contribute to the development of IBD, and to discuss the therapeutic potential of SCFA-based and SCFA-targeted interventions.

## 2. Materials and Methods

A comprehensive literature search was performed to identify studies investigating the role of short-chain fatty acids (SCFAs) in immune modulation within the context of inflammatory bowel disease. Electronic databases including PubMed, Google Scholar, and the Cochrane Library were systematically searched. The search strategy employed various combinations of keywords such as short-chain fatty acids, SCFAs, inflammatory bowel disease, ulcerative colitis, Crohn's disease, gut microbiota, immune response, intestinal inflammation, immune modulation, cytokines, and microbiota-derived metabolites. Relevant original research articles and review papers were screened based on their titles and abstracts, with full-text evaluation conducted for studies meeting the inclusion criteria.

## 3. Short-Chain Fatty Acids – General Characteristics

Saturated fatty acids with carbon chains ranging from 1 to 6 atoms are classified as SCFAs (D. Zhang et al., 2023). In the intestine, acetate, propionate, and butyrate represent the most abundant SCFAs (Deleu et al., 2021). Structurally, acetate, propionate, and butyrate are aliphatic carboxylic acids, each containing a single carbon in the carboxyl group and one, two, or three carbons in the aliphatic tail, respectively (Parada Venegas et al., 2019).

Acetate, propionate, and butyrate are generated by bacterial fermentation of non-digestible dietary fibers in the colon. Acetate, the most abundant SCFA, is produced from acetyl-CoA derived from glycolysis and can be converted into butyrate via butyryl-CoA:acetyl-CoA transferase (Miller & Wolin, 1996). Additional acetate production occurs through carbohydrate fermentation by *Bifidobacterium* spp. and mucin-degrading species such as *Akkermansia muciniphila*, which also generates propionate (Derrien et al., 2004). Propionate is formed mainly from carbohydrate metabolism, with minor contributions from amino acids and organic acids, and is predominantly produced by members of the Bacteroidetes phylum, whereas Firmicutes are the main butyrate producers (Louis & Flint, 2009, 2017). Key butyrate-producing taxa include *Faecalibacterium prausnitzii* and *Clostridium leptum* (Ruminococcaceae), as well as *Eubacterium rectale* and *Roseburia* spp. (Lachnospiraceae), with lactate- and acetate-utilizing species such as *Eubacterium hallii* and *Anaerostipes* spp. contributing additionally (Louis & Flint, 2017). Given their key roles in maintaining epithelial barrier integrity and modulating immune responses, depletion of these SCFA producers is a hallmark of dysbiosis in inflammatory bowel disease, highlighting the importance of SCFAs in disease pathogenesis.

Several environmental and host factors modulate SCFA production in the gut. Luminal pH, which is lower in the proximal colon (cecum ~5.5) than in the rectum (~6.5) due to SCFA absorption and bicarbonate exchange, influences microbial composition and fermentation outcomes. Mildly acidic conditions restrict growth of pH-sensitive bacteria such as *Bacteroides* while favoring Firmicutes and enhancing butyrate production, in part via the butyryl-CoA:acetate-CoA transferase pathway (Walker et al., 2005). Essential nutrients, particularly iron, strongly impact SCFA synthesis. A study in vitro on child gut microbiota indicated, that iron deficiency reduces butyrate and propionate production and decreases the abundance of key producers such as *Roseburia* and *Eubacterium rectale*, whereas iron supplementation restores SCFA levels and microbial composition, including increased butyrate production by *Ruminococcus intestinalis* (Dostal et al., 2015). Oxygen and hydrogen levels also shape microbial metabolism; obligate anaerobes like *Faecalibacterium prausnitzii* require low but non-zero oxygen to grow optimally, and hydrogen-consuming bacteria influence fermentation balance, further affecting SCFA production (Deleu et al., 2021; Khan et al., 2012).

#### 4. Effects of SCFAs on the Immune Response

Beyond their metabolic role, SCFAs have emerged as key regulators of immune responses, influencing immune cell development, differentiation and function. Their effects are largely mediated through two principal mechanisms: inhibition of histone deacetylases and activation of SCFA-sensing G protein-coupled receptors. These pathways underpin the HDAC-dependent and GPCR-dependent immunomodulatory effects of SCFAs described below.

##### 4.1 HDAC-dependent immunomodulatory effects of SCFAs

As major microbial-derived metabolites, SCFAs represent an important molecular link between the gut microbiota and the host immune system. One of the key immunomodulatory roles of SCFAs is the regulation of immune homeostasis through their effects on the number and function of regulatory T cells (Treg), primarily via histone deacetylase (HDAC) inhibition *in vivo* (O’Riordan et al., 2022). Inhibition of HDACs by SCFAs favours the development of an anti-inflammatory, tolerogenic immune phenotype, highlighting the role of the microbiota in the epigenetic control of host immune function (Vinolo et al., 2011). SCFA-mediated HDAC inhibition enhances the expression of the T cell transcription factor forkhead box P3 (Foxp3), which is essential for the suppressive activity of Treg cells and contributes to the attenuation of colitis in mouse models, in part through inhibition of HDAC9 (Tao et al., 2007). Consistent with these findings, multiple studies have demonstrated that SCFAs regulate the abundance of Foxp3<sup>+</sup> Treg cells in the colon under physiological conditions (Rooks & Garrett, 2016). In line with their epigenetic effects, exposure of peripheral blood mononuclear cells and neutrophils to SCFAs suppresses NF- $\kappa$ B signalling and diminishes tumour necrosis factor (TNF) production, similarly to the effects observed with global HDAC inhibitors (Vinolo et al., 2011). These findings identify SCFAs as crucial regulators of NF- $\kappa$ B activity and pro-inflammatory innate immune responses. Beyond local immune modulation, SCFAs also influence systemic immune cell development. Propionate treatment in mice was shown to modulate bone marrow haematopoiesis, leading to increased production of macrophage and dendritic cell precursors and enhanced recruitment of highly phagocytic dendritic cells to the lungs, which displayed a reduced capacity to drive T helper type 2 (TH2) effector responses (Trompette et al., 2014).

##### 4.2 GPCR-dependent signalling of SCFAs in immune regulation

In addition to HDAC inhibition, SCFAs exert their immunomodulatory effects through activation of G protein-coupled receptors (GPCRs), which are expressed on a broad range of cell types, including intestinal epithelial cells and immune cells. Through GPCR signalling, SCFAs influence the expansion and function of both haematopoietic and non-haematopoietic cell lineages (Rooks & Garrett, 2016). Activation of GPR109A by SCFAs, a receptor responsive to both niacin and butyrate, has been shown to protect against colitis and colon cancer by promoting anti-inflammatory effector molecule expression in monocytes and inducing the differentiation of regulatory T cells as well as IL-10-producing T cells (Singh et al., 2014). Supporting the importance of GPCR-mediated pathways, early studies demonstrated that GPCR-deficient mice develop severe and unresolved inflammation in experimental models of DSS-induced colitis, arthritis and asthma (Sun et al., 2017).

#### 5. SCFAs and the Intestinal Barrier

The intestinal barrier is organized into multiple interconnected layers, including an outer layer consisting of mucus, commensal microbiota, and defensive factors such as antimicrobial proteins and secretory immunoglobulin A (sIgA). Beneath this lies the epithelial layer formed by intestinal epithelial cells (IECs), while the innermost compartment comprises innate and adaptive immune cells (Di Tommaso et al., 2021). Recent advances in experimental and clinical research have shifted attention toward the intestinal epithelial barrier as a critical determinant of IBD pathophysiology. Accumulating data suggest that primary defects in barrier integrity may precede and facilitate the development of mucosal inflammation. This hypothesis is strongly supported by genetic studies demonstrating that risk-associated variants affecting genes involved in microbial sensing and autophagy, including NOD2 and ATG16L1, increase susceptibility to CD (Neurath et al., 2025). SCFAs have been shown to promote mucus layer formation through modulation of mucin gene transcription in intestinal goblet cells (Rooks & Garrett, 2016). SCFAs, with sodium butyrate as a prominent example, promote tight junction reassembly through AMPK activation and MLC2 phosphorylation, contributing to reinforcement of the intestinal epithelial barrier (Miao et al., 2016). With respect to gut barrier integrity, butyrate uptake by colonocytes has been shown to enhance barrier function by upregulating the expression of tight junction proteins, including claudin-1, claudin-7, ZO-1, ZO-2, occludin, and junctional adhesion molecule A (JAM-A) (Hays et al., 2024). Studies have demonstrated that butyrate enhances intestinal barrier integrity by activating genes encoding tight junction components and promoting their assembly via the

transcription factors STAT3 and SP1, resulting in maintenance or increased transepithelial electrical resistance (TEER) in human epithelial models, even under inflammatory conditions (Parada Venegas et al., 2019; Yan & Ajuwon, 2017). Moreover, as butyrate serves as a primary oxidative energy source for colonocytes, its uptake and metabolism increase epithelial oxygen consumption and help maintain an anaerobic environment, thereby promoting stabilization of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), whose transcriptional activity in the intestinal epithelium is protective for gut barrier integrity (Kelly et al., 2015). The transcription factor HIF-1 $\alpha$  has been shown to upregulate the expression of mucins (MUC), antimicrobial peptides (AMPs), and tight junction proteins, thereby supporting intestinal barrier function (Pral et al., 2021).

## 6. Disruption of SCFA Homeostasis in IBD

IBD is characterized by a substantial depletion of SCFA-producing microorganisms, primarily belonging to the Firmicutes, Bacteroidetes, and Verrucomicrobia phyla, with notable reductions in genera such as *Faecalibacterium*, *Roseburia*, and *Akkermansia*. This compositional shift is paralleled by lower faecal SCFA levels in UC and CD patients, together with diminished abundance of microbial pathways related to fatty acid fermentation and biosynthesis, an effect reported most prominently in UC (Lo Sasso et al., 2021). Consistent with these findings, reduced abundance of the key butyrate producer *Faecalibacterium prausnitzii* has been documented in IBD cohorts (Machiels et al., 2014). In line with the functional relevance of these alterations, clinical studies have demonstrated beneficial effects of sodium butyrate supplementation in IBD (Facchin et al., 2020). Importantly, evidence suggests that defects in intestinal SCFA absorption and metabolism may arise early in disease development, potentially preceding overt microbial dysbiosis. Supporting this concept, impaired epithelial oxidation of butyrate has been observed prior to the decline of butyrate-producing bacteria and is accompanied by concordant changes in host gene expression profiles (De Preter et al., 2012; Koleva et al., 2012; Z. Zhang et al., 2022)

## 7. Therapeutic implications

Increasing the intake of fermentable dietary fibre may serve as a therapeutic strategy to enhance endogenous SCFA production, thereby improving gut homeostasis, microbiota diversity, and host metabolic regulation (Cronin et al., 2021). Dietary interventions, particularly high-fibre dietary patterns such as Mediterranean, vegetarian, and vegan diets, have been shown to promote the expansion of SCFA-producing bacteria in patients with IBD. These interventions are associated with improvements in gut microbial diversity, reductions in inflammatory biomarkers including C-reactive protein and faecal calprotectin, favorable disease activity indices, and increased intestinal SCFA levels (Wagenaar et al., 2021).

Prebiotics are widely used as a strategy to enhance intestinal SCFA production, with compounds such as high-dose arabinoxylan oligosaccharides (AXOS) frequently employed for this purpose. However, the beneficial effects observed with prebiotic supplementation largely mirror those achieved through increased intake of prebiotic-rich foods, particularly with respect to gut health and intestinal barrier integrity (Damen et al., 2012; Rauch et al., 2022). In contrast, more pronounced and consistent effects on SCFA levels have been reported with probiotic interventions containing SCFA-producing bacterial strains, highlighting their greater therapeutic potential. Both in vitro and in vivo studies have demonstrated that probiotic supplementation can significantly increase intestinal SCFA levels. Probiotic formulations most frequently investigated include strains from the *Lactobacillus* genus, particularly *Lactobacillus plantarum* and *Lactobacillus rhamnosus*. Across experimental models and studies in healthy human volunteers, these interventions consistently promoted the expansion of *Bifidobacterium* species and other beneficial microbial populations, ultimately resulting in elevated total SCFA concentrations (Hou et al., 2022; Wang et al., 2014). Nevertheless, despite these promising findings, further well-designed, large-scale clinical studies are required to validate the efficacy of probiotic-based strategies for sustained modulation of SCFA production and their clinical relevance in disease-specific populations.

## 8. Conclusions

Short-chain fatty acids occupy a central position at the interface between the gut microbiota, the intestinal barrier, and the immune system, making them key contributors to the pathogenesis of inflammatory bowel disease. Acting through both epigenetic mechanisms, such as inhibition of histone deacetylases, and receptor-mediated signalling via SCFA-sensitive G protein-coupled receptors, these metabolites shape immune cell function and promote immunological tolerance within the gut. At the same time, SCFAs—most notably butyrate—support epithelial barrier integrity by enhancing tight junction organisation, stimulating mucus production, and sustaining epithelial metabolic activity.

In IBD, SCFA homeostasis is disrupted by a combination of microbial alterations, reduced metabolite availability, and impaired epithelial uptake and utilisation. Increasing evidence suggests that defects in SCFA metabolism may emerge early in disease development, potentially preceding pronounced microbial dysbiosis, underscoring the importance of host–microbiota metabolic interactions in disease onset and progression. Interventions aimed at restoring SCFA levels, including dietary fibre enrichment and the use of prebiotics or probiotics, have yielded encouraging results in terms of microbial composition, inflammatory markers, and clinical outcomes. Nevertheless, responses to these strategies remain heterogeneous, likely reflecting inter-individual differences in microbiota structure and metabolic capacity.

Taken together, these findings support SCFA-related pathways as attractive targets for therapeutic intervention in IBD. However, translating mechanistic insights into consistent clinical benefit will require further well-designed, large-scale studies, ideally incorporating integrative approaches to better capture the complexity of host–microbiota interactions and to enable the development of more personalised treatment strategies.

### Authors' contribution statement:

Conceptualization, M.C, R.S, N.C.; methodology, M.C.; E.S.C., D.C; check, M.C., R.S., N.C.,M.A.,J.B.,M.A., E.S.C. and K.M.; formal analysis, M.C., N.C., D.C. and R.S.; investigation, M.C.; resources, M.C., and J.B.; writing - rough preparation, M.C., R.S. and N.C.; writing - review and editing, D.C., J.B., M.A., A.Z., K.M., D.G., E.S.C.; visualization, N.C.; supervision, J.B., K.M., A.Z., D.G., and M.A.; project administration, M.C., R.S., and N.C.

All authors have read and agreed with the published version of the manuscript.

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