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Review Article

The interaction among gut microbes, the intestinal barrier and short chain fatty acids

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ABSTRACT

The mammalian gut is inhabited by a massive and complicated microbial community, in which the host achieves a stable symbiotic environment through the interdependence, coordination, reciprocal constraints and participation in an immune response. The interaction between the host gut and the microbiota is essential for maintaining and achieving the homeostasis of the organism. Consequently, gut homeostasis is pivotal in safeguarding the growth and development and potential productive performance of the host. As metabolites of microorganisms, short chain fatty acids are not only the preferred energy metabolic feedstock for host intestinal epithelial cells, but also exert vital effects on antioxidants and the regulation of intestinal community homeostasis. Herein, we summarize the effects of intestinal microorganisms on the host gut and the mechanisms of action of short chain fatty acids on the four intestinal barriers of the organism, which will shed light on the manipulation of the intestinal community to achieve precise nutrition for specific individuals and provide a novel perspective for the prevention and treatment of diseases.

1. Introduction

Undoubtedly, as with all multicellular organisms, humans and microorganisms coexist. The human body (skin, urinary system, reproductive system, gastrointestinal system) harbors plenty of bacteria, fungi, viruses, and archaea. Microorganisms living in the adult gut include bacteria, fungi, protozoa, archaea and some viruses, numbering over 10 trillion, more than 10 times the number of cells in the adult body (Felizardo et al., 2019). The total genome is approximately 150 times larger than the human genome, with bacteria (anaerobes bacteria) making up the majority, and colons contain 70% of the body's microorganisms (Qiao et al., 2014). With it being such a massive organ, the gut affords a place for microorganisms to colonize. Over a long period of co-evolution, gut microbes and hosts have equally selected each other, establishing a mutually beneficial relationship. On the one hand, the host provides a stable and nutrient-rich living environment for microbes and enables selective colonization for some microbes; on the other hand, these microbes and their metabolites not only affect the development of the host mucosal immune system, angiogenesis, repair, and renewal of the intestinal epithelium as well as maintenance of intestinal function, but also impact the expression of host genes and the regulation of host lipid metabolism (Tremaroli and Bäckhed 2012; Flint et al., 2012). Short chain fatty acids (SCFA), as a bacterial fermentation terminal product with multiple metabolic features, are crucial energy sources for the intestinal microbiota and host intestinal epithelium cells (IEC), which could maintain intestinal acid-base balance, inhibit the growth of harmful pathogens, modulate the host intestinal immunity, and thus reduce inflammatory responses. SCFA not only serve in the intestine where commensal bacteria reside, but also have a critical role in improving the barrier capacity of the organism's intestine and resisting invasion by foreign pathogens (Sadler et al., 2020).

This paper reviews the metabolic mechanism of SCFA as a microbial metabolite with multiple physiological functions and the

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mechanism of action on the four intestinal barriers (mechanical barrier, microbial barrier, chemical barrier and immune barrier), especially in shaping and improving the processes of intestinal microbiota and IEC through G-protein coupled receptors (GPCR) mediated immune pathways and histone deacetylase inhibitor (HDACI), which provides a theoretical basis for further exploration and development of precise nutrition for specific individuals and provide a novel perspective for the prevention and treatment of diseases (colitis, type II diabetes, obesity, etc).

2. Composition of intestinal microorganisms

The human intestine is a diverse ecosystem, accommodating trillions of microbial species. The human intestine contains about 10^{14} bacteria with more than 500 species (Sender et al., 2016), including about 10^5 microorganisms in the upper region of the small intestine, approximately 10^3 to 10^7 microorganisms in the ileum, and beyond 10^{12} microorganisms in the colon (Turnbaugh et al., 2007). These commensal bacteria form a complex trophic network that supports their survival and shapes the physiological environment and immune response of the intestinal system. In recent years, scholars have discovered that human intestinal microbes contain about 500 to 1,000 species of bacteria and about two million genes with 30 to 40 intestinal species accounting for more than 99% of the total bacterial population (Lynch and Pedersen, 2016).

The dominant phyla in the human intestine are Firmicutes and Bacteroidetes (more than 90%), but also contain the Proteobacteria, Actinobacteria, Verrucomicrobia, Fusobacteria and Cynobacteria with lower proportions (Adak and Khan, 2019). Healthy adult and infant intestinal microbes are relatively stable at the phyla level compared to the older, while specific microbiota at genus and species levels change depending on geography, environment, diet and age (Lynch and Pedersen, 2016; Adak and Khan, 2019) (Fig. 1). The composition of gut microbes varies widely among individuals, but similarities exist in the dominant bacteria. Arumugam et al. (2011) first proposed the definition of enterotype. Wu et al. (2011) found from a study of microbiota in healthy volunteers that enterotypes were closely linked to long-term diet and could be divided into 2 enterotypes, protein and animal fat (Bacteroides) and carbohydrates (Prevotella). Since the development of novel sequencing technologies that allow for more accurate analysis, the gut microbiome research community has generally questioned the traditional concept of gut phenotype and its study, emphasizing the necessity of redefining enterotypes as they may be continuous rather than discrete (Cheng and Ning, 2019). However, the supporters have suggested that the enterotypes are valid in describing the structure of the intestinal microbial community and have potential application in guiding clinical practice. Therefore, they have advocated the rational use of the enterotype concept to harmonize the different perspectives (Costea et al., 2017). Also, the microbial composition of the gut is extremely complex, which is influenced by numerous factors. According to recent studies, genotype, diet, age, disease, and lifestyle could affect the diversity of the microbiota (Conlon and Bird, 2015; Boulangé et al., 2016; Yatsunenko et al., 2012; Obón-Santacana et al., 2019). Among the above-mentioned factors affecting the microbiota, dietary factors play a decisive role, which is also verified by Ocvirk et al. (2020) and; O'Keefe et al. (2015). Besides, the article of Chewapreecha (2014) titled "Your gut microbiota are what you eat" detailed strong evidence of the close relationship between microbiota and diet. The intestinal microbes affect almost every organ system of the host and are interdependent and co-evolve with the host. The high adaptability of microorganisms to changes in host lifestyles illustrates that human behaviour impacts not only the exterior environment, but also the interior of our environment (Nagpal et al., 2016; Weinstock, 2012).

2.1. Major role of microbiota in the intestine

Intestinal microbes are interconnected with host metabolism and perform a central role in the intestine (Fig. 1). Numerous scholars have documented the central role of microbiota in participating in immune modulation (Chénard et al., 2020; Gao et al., 2018), modulating the metabolism of lipids (Dentin et al., 2004; Sheng et al., 2018; Schoeler and Caesar, 2019) and bile

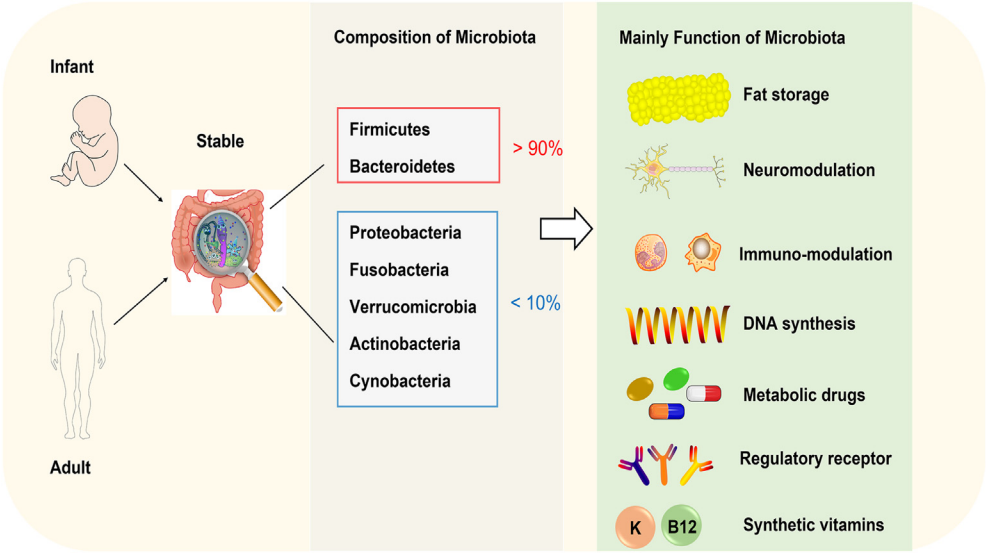

Fig. 1. Composition and functions of intestinal microorganisms. With the advanced study of gut microorganisms, scholars have observed diverse roles of gut microorganisms, including involvement in neuroimmunomodulation, organism metabolism (lipid and bile acids), the synthesis of DNA and vitamins. Moreover, the fermentation products of microorganisms could modulate receptors and make a substantial contribution to the development of clinical drugs. However, the colonization of gut microbes is primarily influenced by changes in diet, environment, and nutrient composition. Source: Chénard et al., (2020); Gao et al., (2018); Filosa et al., (2018); Schoeler and Caesar (2019); Molinaro et al., 2018; Zeng et al., (2019); Pan et al., (2018); Biesalski (2016); Huang et al., (2019); Mu et al., (2015); Li et al., (2015); Feng et al., (2020); Conlon et al., (2015); Strandwitz (2018).

acids (Rowland et al., 2017; Molinaro et al., 2018; Zeng et al., 2019) as well as neuromodulation (Filosa et al., 2018). In particular, the microbiota plays a pivotal role in affecting the intestinal barrier function of the organism.

2.2. Intestinal microorganisms and mucous layer

The surface of IEC is coated with a mucus layer, which is a physical barrier on the surface of epithelial cells and the first defence line of the mechanical barrier for the intestinal mucosa. The intestinal mucus layer is primarily composed of mucin (MUC) secreted by goblet cells, which is highly glycosylated and polymerized. Still, its structural patterns in the small intestine and colon are quite different. The mucus layer on the surface of the small intestine is single-layered and discontinuous and does not fully cover the surface of the epithelial cells of the small intestine. The mucus layer of the colon is classified into two layers; the outer layer is thinner and looser in structure, which is accessible to bacteria, and the inner layer is thicker and denser in construction, which is hardly penetrated by bacteria (Johansson et al., 2008). Scholars have shown that while colon bacteria are not commonly in direct contact with IEC, alterations in dietary structure (especially dietary fibre deficiency) can contribute to dysbiosis of intestinal microorganisms and intestinal inflammation (Colitis) (O'Keefe, 2019; Obón-Santacana et al., 2019), causing the mucus layer to thin or disappear, so then bacteria or their metabolites can cross the mucus layer on the surface of the intestinal mucosa and adhere to IEC, directly or indirectly inducing damage to IEC, resulting in a decreased mechanical barrier function of the intestinal mucosa and alternation in mucosal biomarkers of cancer risk (O'Keefe et al., 2015; Souza et al., 2005). Johansson et al. (2014) demonstrated that people with active ulcerative colitis have a penetrable inner mucus layer, which corresponds to a mouse model of *MUC2* deficiency, and have bacteria that is in contact with the epithelium directly, which then progresses to colitis. Therefore, people with active ulcerative colitis are probably linked with a deficiency of MUC2 protein. Interestingly, the study revealed that in the intestine of mice with a higher abundance of Erysipelotrichi, the bacteria were unable to penetrate the mucus and enter the mucosal layer, while in the intestine of mice with a higher abundance of Proteobacteria and TM7, bacterial translocation occurred frequently, indicating that intestinal bacteria may directly influence the production and quality of intestinal mucus (Jakobsson et al., 2014).

In addition, the diversity of bacteria and their metabolites also affect the formation of the mucus layer and undermine the mucus layer junction (Souza et al., 2005). A study revealed that sulfide produced by sulfate-reducing bacteria dissolved the MUC polymer network and thinned the mucus layer, which could be penetrated by the MUC-degrading bacterium *Akkermansia municiphila* and grew in it further to destroy the network structure of the mucus layer (Ijssennagger et al., 2015). The toxins released by *Bacteriodes fragilis* have a protein hydrolase-like effect, degrading MUC proteins and damaging the mucus layer structure (Rhee et al., 2009). Recently, Birchenough et al. (2016) identified a type of "sentinel" goblet cells located at the top of the colonic gland that can be perceived by Toll-like receptors on these cells when bacteria or their metabolites cross the mucus layer, triggering other goblet cells to discharge MUC2 to flush the invading bacteria and their metabolites back into the intestinal lumen and secrete abundant mucus to protect the IEC. The Paneth cells supply a niche for small intestinal stem cells in the intestinal crypts (Sato et al., 2010), which contain a multitude of endoplasmic reticulum and Golgi complexes with powerful protein secretion functions. The major proteins secreted by Paneth cells are bactericidal peptides such as α-defensins, lysozyme, secretory group IIA phospholipase A2, regenerating insulin-derived proteins regenerating islet-derived 3β (REG3β) and REG3γ, and angiogenin 4 (Bevins and Salzman, 2011). Bacterial metabolites like lipopolysaccharides, cytosolic acids, cytosolic acyl dipeptides, and lipid A are capable of stimulating the secretion of defensins from Paneth cells in the small intestine, which resist the invasion of intestinal microorganisms and exert a protective effect on IEC (Ayabe et al., 2000; Johansson and Hansson, 2011). The abnormal function of Paneth cells, like a mutation of the nucleotide-binding oligomerization domain 2 (*Nod2*) gene and abnormal function of the unfolded protein response (UPR) transcription factor X-box-binding protein 1 (XBP-1), causes the weakening of bacterial stimulation of Paneth cells, reduces the production of MUC and antibacterial substances, and a vast population of bacteria invades the epithelial cells and breaks the intestinal mucosal barrier (Kobayashi et al., 2005; Kaser et al., 2008).

2.3. Intestinal microorganisms and IEC

The IEC are the principal structural basis of the barrier of the intestinal mucosa. After the intestinal microorganisms and their toxic metabolites cross the mucus layer, they adhere directly to the IEC. The findings of an animal experiment demonstrated that *Escherichia coli CBL2* and *Shigella CBD8* showed extremely strong adhesion to IEC, mediating intestinal MUC secretion and tight junction damage, while *Bifidobacteriumbifidum IATA-ES2* promoted the production of chemokines and metalloproteinase inhibitors, contributing to the protection of the intestinal mucosa (Cinova et al., 2011). Moreover, the secretory immunoglobulin A (sIgA), which is co-assembled by IgA, synthesized by plasma cells and secreted by IEC, could recognize the intestinal microorganisms on the surface of the intestinal mucosa, especially gram-negative bacilli, wrap the bacteria and close the binding site specific for them to the IEC, inhibiting their adherence to the IEC. Meanwhile, it could also identify and bind the toxins in the intestinal tract, forming immune complexes, and eventually, being swallowed and removed by phagocytes (Corthésy, 2013). The colonic epithelial cells specifically express the Ly6/PLAUR domain containing 8 (Lypd8)protein, which in combination with the flagellum of Gram-negative bacteria inhibits bacterial motility, preventing the bacteria from entering the interior of the mucus layer, reducing their attachment to the epithelial cells and serving to protect the intestinal mucosal barrier. The impairments in sIgA and Lypd8 protein expression due to various factors will eventually increase the adhesion of bacteria to the intestinal epithelium (Okumura et al., 2016). The bacteria could be detected directly by the corresponding receptors on the IEC membrane and cytosolicized into endocytosis, or through their metabolites activating cellular signalling pathways that trigger cytoskeletal rearrangement to encapsulate the bacteria for endocytosis. For instance, *Yersinia* has a class of proteins that combine with integrins on the IEC membrane to cause cytoskeletal actin rearrangement by activating tyrosine kinase, and the bacteria are cytosed into the cell. Studies have revealed that toxin A produced by *Clostridium difficile* deacetylated tubulin proteins, disrupting the microtubular structure of IEC and affecting the integrity of the intestinal mucosal barrier. Simultaneously, potassium acetate intervention reduced the toxin A-mediated cytotoxic effect and improved the damaged intestinal mucosal barrier function (Lu et al., 2016).

Additionally, IEC are mainly differentiated from stem cells located in the intestinal mucosal crypts, and all IEC are renewed and shed once in approximately 2 to 5 d. The stem cells in the intestinal mucosal crypts continuously replenish the shed epithelial cells through proliferation and differentiation. Some bacteria and their virulent metabolites could stimulate the IEC to proliferate and shed rapidly, thereby destroying the integrity of the intestinal mucosal barrier (Sellin et al., 2009). It has been discovered that IEC infected by bacteria could accelerate the proliferation and shedding

of IEC regulated by the Wnt/β catena signalling pathway, which indicates that IEC may act as self-protectors by shedding. In contrast, several bacteria inhibit the proliferation and shedding of IEC, depriving them of shedding as a form of self-protection (Sellin et al., 2014), such as Shigella effector molecule lpaB, which induces the proliferation process of IEC to freeze in the G2/M phase (Iwai et al., 2007). Also, Non-LEE effector B (NleB) is a protein produced by *E. coli* that directly targets the death receptor signalling complex and associates with the "death domain" of various DD-containing proteins including tumor necrosis factor (TNF) receptor, Fas cell surface death receptor (FAS), receptor-interacting protein kinase (RIPKI), tumor necrosis factor receptor type 1-associated death domain (TRADD) and Fas-associated via death domain (FADD), ultimately arresting the IEC in the G1/2 cell cycle and retarding cell proliferation, and causing the disruption of the intestinal barrier when these bacteria are combined with the IEC to reduce the protective effect of their proliferation and shedding (Li et al., 2013a; Morikawa et al., 2010).

2.4. Intestinal microorganisms and tight junction

The tight junction is the major intercellular junction situated at the apical part of the epithelial cells and surrounds the cells in a hoop-like manner, tightly joining adjacent epithelial cells together, preventing the passage of toxic macromolecules and microorganisms, and protecting the intestinal mucosal barrier. Tight junction could be classified into structural and functional proteins, the main structural proteins are occludin, claudin and junctional adhesion molecule (JAM) and the primary functional proteins are zonula occludens-1 (ZO-1), ZO-2, ZO-3, Cingulin and Zonulin (Heinemann and Schuetz, 2019). The secretion system is a transport system that transfers toxic proteins synthesized by bacteria outside the bacteria or inside the host cells. In this way, enterobacteria transmit the virulent proteins generated by them to the IEC, affecting the expression and localization of the tight junction proteins. For example, *E. coli* transports NleA proteins into the cell by the type 3 secretion (T3SS) system leading to disruption of tight junction proteins (Thanabalasuriar et al., 2013). Similarly, *Shigella flexner* interferes with the expression of the tight junction proteins ZO-1, Clini, and occludin via T3SS. Studies have shown that *Helicobacter pylori* delivered effector proteins encoded by cytotoxicity-associated gene A to IEC through the type 4 secretion system, which inhibited ERK and protease-activated receptor-1 signalling pathways and interfered with the expression and localization of tight junction (Sakaguchi et al., 2002; Gerlach and Hensel, 2007). Also, some enzymes or toxic proteins, such as hemagglutinin/protease and ZO toxin, which activate intracellular signalling pathways and lead to mislocalization of tight junction proteins, are secreted directly into the extracellular gaps by enterobacteria, disrupting the intestinal mucosal barrier (Di Pierro et al., 2001; Schmidt et al., 2007).

Ethanol and acetaldehyde are important metabolites of intestinal bacteria. Dietary glycans are fermented by intestinal bacteria to produce ethanol, which is converted to acetaldehyde by bacteria-produced ethanol dehydrogenase (Ferreira et al., 2012). An in vitro study stimulated caco2 cells with low concentrations of 0.2% ethanol and observed that upregulation of CLOCK and period circadian regulator 2 (PER2) protein expression was accompanied by an increase in intestinal barrier permeability, while specific silencing of CLOCK and PER2 significantly inhibited ethanol-induced intestinal barrier hyper-permeability (Swanson et al., 2011). In contrast, acetaldehyde was shown to have an inhibitory effect on protein tyrosine phosphatase activity, while decreased tyrosine phosphorylation levels of ZO-1 and adhesion protein resulted in downregulation and redistribution of tight junction protein expression (Atkinson and Rao, 2001; Sheth et al., 2007) and detachment from the cytoskeleton (Suzuki et al., 2008). Additionally, pathogenic bacteria or bacterial metabolites like indole-3-acetic acid (Hendrikx et al., 2018) and indole-3-propionic acid (Venkatesh et al., 2014) stimulate inflammatory cells to produce numerous inflammatory factors, such as interferon-γ (IFN-γ) and TNF-α, which both detach tight junction proteins from the cytoskeleton of intestinal epithelial cells via MLCK and Rho associated coiled-coil containing protein kinase 1 (ROCK)-mediated pathways and downregulate the expression of tight junction proteins (Utech et al., 2005; Zeissig et al., 2007).

Certain tight junctions which are expressed by IEC possess the role of bacterial toxin receptors. Claudin3 and claudin4 are the first identified enterotoxin (CPE) receptors for *Clostridium perfringens* enterotoxin, and when bound to claudin3 and claudin4, CPE disengages from tightly linked protein chains, disrupting the integrity of the intestinal mucosal mechanical barrier (Katahira et al., 1997). The binding of CPE to claudin family proteins has also been shown to exert cytotoxic and perforin effects (Veshnyakova et al., 2012). *C. difficile transferase* (CDT) induces adhesion of *C. difficile* to cells and leads to cytoskeletal collapse and eventual cell death. The lipolytic-stimulated lipoprotein receptor LSR is thought to be a recognition receptor for CDT (Kuehne et al., 2014), and LSR was shown to be a tight junction-associated protein present at the junction of the three epithelial cells (Masuda et al., 2011; Papatheodorou et al., 2011). Of note, recent studies have identified that the side effects of some drugs on the intestine are also mediated through microbial modulation. As the long-term use of the gastroenteritis treatment drug colistin damaged the intestinal barrier, in the conventional mouse model, colistin caused significant impairment of the intestinal mucosa and tight junction proteins while decreasing *Enterobacter* spp. and increasing *Enterococcus* spp. but this phenomenon was not observed in germ-free (GF) mice (Wang et al., 2013). In summary, intestinal microbiota and their metabolites modulate intestinal mucus, tight junction proteins and IEC, which in turn affect the functional homeostasis of the intestinal barrier.

2.5. Microbiota imbalance and organism disease

Over recent decades, researchers have conducted extensive studies on the relationship between gut microbes and intestinal diseases of the organism (Johansson et al., 2014; O'Keefe et al., 2019; Ocvirk et al., 2020). Gut microbes as environmental factors impact host metabolism and are associated with the development of metabolic diseases such as obesity, fatty liver and type II diabetes (Yamashiro, 2017; Sommer and Bäckhed, 2013; Adak and Khan, 2019). Previous studies combined with GF animal models and colony transplantation techniques have revealed that gut microbes act as important regulators of host metabolism (Dalile et al., 2019; Velagapudi et al., 2010). Bäckhed et al. (2004) used a transgenic GF mouse model to find a direct link between gut microbes and host lipid metabolism. GF mice transplanted with gut microbes showed a 57% increase in total lipid content and a 61% increase in epididymal fat pad weight. Microbial colonization increased hepatic lipid deposition and upregulated the expression of key genes for hepatic lipid de novo synthesis in GF mice. Interestingly, GF mice colonized by obese individuals showed higher body fat deposition and energy uptake than GF mice colonized by normal individuals (Turnbaugh et al., 2006). GF mice have been reported to resist high-fat diet-induced obesity, possibly due to their higher fatty acid oxidation capacity in the liver and muscles (Bäckhed et al., 2007). Similarly, insulin sensitivity and glucose tolerance were enhanced in GF mice compared to conventionally fed mice (Rabot et al., 2010). Moreover, specific gut microbial deficiency (mainly *Streptococcaceae*, *lactobacilli*, Bacteroidetes, and *Clostridium-other*) increased glycogen

content and enhanced insulin sensitivity in the liver of mice (Ley et al., 2005; Turnbaugh et al., 2006; Chuang et al., 2012). The above studies suggest that the systemic and tissue-specific glucolipid metabolism of the host may be determined by its gut microbial structure. Recent in vivo studies have revealed that microbial metabolites and related signalling pathways play an important role in mediating the metabolism of gut microbes on their hosts (Krajmalnik-Brown et al., 2012).

With in-depth studies, the connection between microbiota species and host metabolism has been unveiled. This connection is illustrated by the enhancing abundance of Firmicutes, the decreased abundance of Bacteroidetes as well as the increased ratio of Firmicutes to Bacteroidetes which evidenced that alterations in intestinal microbiota composition were associated with body mass index (Sutoyo et al., 2020; Fadieienko et al., 2021). However, inconsistent reports exist (Schwiertz et al., 2010; Duncan et al., 2008), which is probably linked with the difference in test subjects and test environment samples. Studies have identified that Acfinobacteria and Tenericutes are positively associated with liver lipid content. The Coriobacteriaceae in the Acfinobacteria are extremely associated with liver fat, glucose and glycogen levels, and the metabolism of heterologous substances (Claus et al., 2011). Research also confirmed that the genera *Barnesiella* and *Roseburia* are correlated with hepatic fat content and lipid synthesis-related gene expression (Le Roy et al., 2013). Research in humans and rodents has shown that *Akkermansia muciniphila* abundance is negatively correlated with overweight, obesity and diabetes (Everard et al., 2013; Karlsson et al., 2012). This bacterium plays a vital role in fat deposition, inflammation and glucose metabolism (Lukovac et al., 2014; Derrien et al., 2004). *Faecalibacterium prausnitzii* is less abundant in the guts of obese individuals and type II diabetic patients (Karlsson et al., 2012; Remely et al., 2014), and *F. prausnitzii* was found to reduce intestinal permeability and enhance insulin sensitivity in obese mice (Martín et al., 2015). In addition, studies have indicated that the mechanisms of microbiota involved in the pathogenesis of type II diabetes may be associated with various factors, such as low chronic inflammation in the body (Donath et al., 2009), production of SCFA (Breton et al., 2016), and activation of nuclear receptor signalling pathways (Li et al., 2013b). Therefore, modifying the gut microbiological environment by intervening in the microbiota holds promise as a new tool in the prevention and treatment of type II diabetes and obesity.

3. SCFA overview

SCFA are fatty acids consisting of six carbon or less, such as acetate, propionate, isobutyrate, butyrate, isovalerate, valerate, isocaproate and caproate, which are mainly generated by anaerobic bacteria in the colon fermenting starch, starch-like, and non-starch polysaccharides (NSP, the main component of dietary fibre), even though SCFA can be generated naturally by the host metabolic pathway, particularly in the liver (Tan et al., 2014). Acetate, propionate and butyrate are the major SCFA, accounting for approximately 90% to 95% of SCFA in a molar ratio of 60:25:15, respectively (Alexander et al., 2019; Tazoe et al., 2008). Precisely as no unique bacteria hydrolyze all nutrient substrates, no unique bacterial fermentation of carbohydrates generates all three SCFA. Therefore, the type and distribution of SCFA in the gut reflect the metabolic collaboration of different microbial types. Studies in recent years have implicated the type and structure of the diet (Obón-Santacana et al., 2019; O'Keefe et al., 2015; O'Keefe et al., 2019), the diversity and number of host gut microorganisms (Ocvirk et al., 2020), and the timing of nutrients passage through the intestine, as factors affecting the production of SCFA and its related metabolic disease (Alexander et al., 2019).

3.1. The production of SCFA

The acetate is a product of fermentation by various bacteria and is manufactured from pyruvate by the acetyl-coenzyme A or Wood-Ljungdahl pathway (Ragsdale and Pierce, 2008). Propionate is the primary metabolite of *Bacteroidetes* fermentation and is generated from succinate conversion to methylmalonyl-CoA by the succinate pathway or produced from acrylate via the acrylate pathway using lactate as a precursor (Hetzel et al., 2003) (Fig. 2). Also, deoxyhexose like fucose and rhamnose can be used as a substrate for the synthesis of propionic acid via the propanediol pathway (Koh et al., 2016; Scott et al., 2006). Butyrate, the primary metabolite of the Firmicutes, was formed by the condensation of 2 acetyl-CoA molecules, then reduced to butyryl-CoA, which was converted to butyric acid by phosphotransferase and butyrate kinase (Ait-Belgnaoui et al., 2014; Ragsdale and Pierce, 2008). Butyryl-CoA was also convertible to butyrate via the acetyl-CoA transferase pathway, and some microorganisms in the intestine used both lactate and acetate to synthesize butyrate (Duncan et al., 2002), thus preventing lactate accumulation and stabilizing the intestinal environment. Butyrate could also be synthesized from proteins using the lysine pathway, which further indicates that microorganisms in the intestine could adapt to nutrient conversion and thus maintain the synthesis of SCFA (Louis et al., 2004; Vital et al., 2014).

3.2. The absorption and transportation of SCFA

The absorption of SCFA generated in the intestine is carried out by diffusion of lipid-soluble forms, SCFA/HCO_3^- ion exchange and active transport by a transporter carrier (Ritzhaupt et al., 1998). There are two modes of absorption by transport carriers: 1) via sodium-coupled monocarboxylate transport proteins (SMCT1, encoded by solute carrier family 5, member 8 [SLC5A8]), and 2) via a low-affinity monocarboxylate transporter protein-coupled to H^+ (MCT1, encoded by SLC16A1). Butyric acid is utilized primarily by colonic epithelial cells as an energy substance, while other absorbed SCFA flow into the portal vein (Goncalves et al., 2011). Propionic acid is metabolized in the liver and at low concentrations in the peripheral circulation, while acetic acid is at high concentrations in the peripheral circulation. A significant expression of *MCT1* and *SMCT1* was observed in the colons of humans, mice and rats, respectively, and the expression levels were higher than those in the ileum (Iwanaga et al., 2006). For ruminants, a result of quantitative Western-blot analysis revealed that the levels of MCT1 protein were superior in the proximal colon than in the small intestine (Kirat et al., 2006). SMCT1, on the other hand, was detected principally in the proximal and distal colon and the parietal membrane of the ileal intestinal epithelium. Moreover, GF mice could improve the reduced *SMCT1* expression in the colon and ileum through bacterial recolonization of the intestine (Cresci et al., 2010).

The expression of *MCT1*, a significant transporter protein for butyric acid uptake in IEC, was induced by butyric acid and carbohydrates. Studies have revealed that the expression levels of both the *MCT1* gene and its protein increased with increasing sodium butyrate concentration and culture time when different concentrations of sodium butyrate were incorporated into cultured human

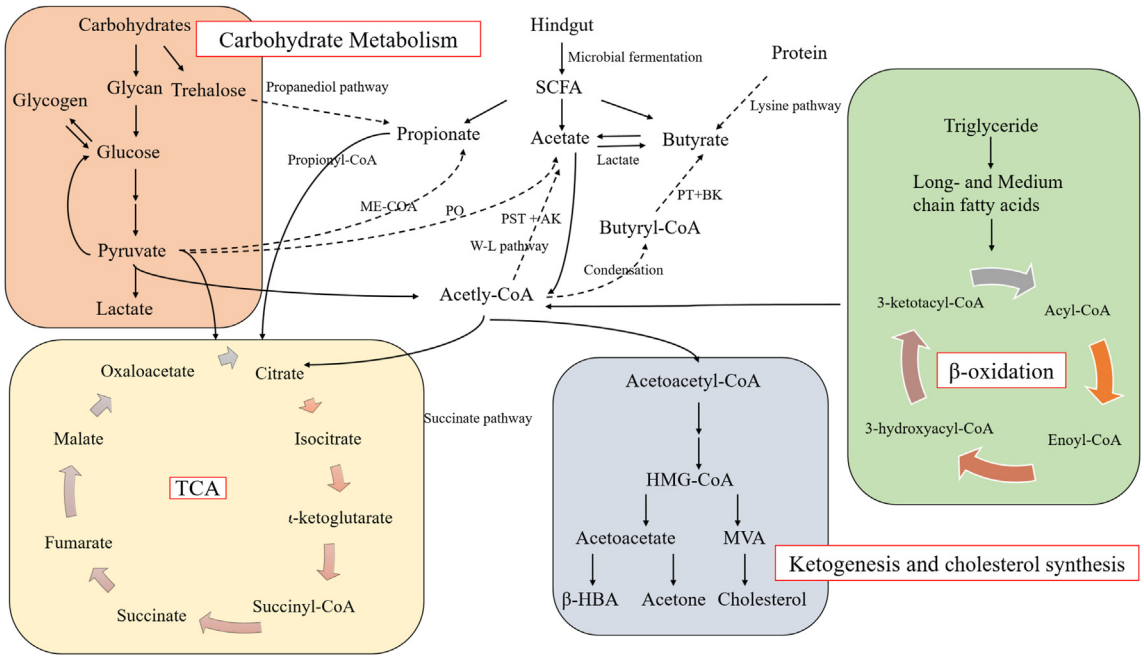

Fig. 2. The synthesis pathways of short-chain fatty acids (SCFA) and the primary role in carbohydrate and lipid metabolism. The microbial transformation of dietary fiber in the hindgut leads to the synthesis of the SCFA (mainly acetate, propionate and butyrate). The acetate is produced from pyruvate by the acetyl-coenzyme A (CoA) or W-L pathway. Propionate is formed from deoxyhexose via the propanediol pathway or from phosphoenolpyruvate via the succinate pathway or the acrylate pathway. Butyric acid is produced by synthesizing two molecules of acetyl-CoA to yield acetyl-CoA, then converted to butyryl-CoA by β-hydroxybutyryl-CoA and crotonyl-CoA. PST = phosphotransacetylase; AK = acetokinase; W-L = Wood-Ljungdahl; ME-COA = methylmalonyl-CoA; PO = pyruvic oxidase; PT = phosphotransferase; BK = butyrate kinase; TCA = tricarboxylic acid cycle; MVA = mevalonic acid; β-HBA = β-hydroxybutyric acid; HMG-CoA = β-hydroxy-β-methylglutaryl-coenzyme A. Source: Ragsdale and Pierce (2008); Hetzel et al. (2003); Scott et al. (2006); Louis et al. (2004); Duncan et al. (2002).

small IEC in vitro, and a notable increase in the maximum rate of sodium butyrate uptake was noticed, but there was no change in the Michaelis constant, indicating that the increased sodium butyrate uptake was achieved through increasing the expression of *MCT1* on the cell membrane (Cuff et al., 2002). Also, research in isolated porcine colonic mucosa culture revealed that the direct effects of butyrate resulted in upregulation of *MCT1* mRNA expression (Tudela et al., 2015).

4. SCFA and intestinal barriers

The intestinal barrier is a crucial barrier of the organism against invasion by foreign pathogens, including the mechanical, chemical, immune and microbial barriers. Disruption of the integrity of any of these barriers would lead to metabolic dysfunction of the body and affect the health of the intestine, which in turn results in a decrement in animal production performance (Camilleri et al., 2012).

4.1. Moderating effect of SCFA on mechanical barriers

It is an essential mission of intestinal microorganisms to maintain intestinal mucosal homeostasis, providing them with a suitable long-term habitat. Different microorganisms are involved in maintaining intestinal epithelial barrier integrity through cell-to-cell junctions and the ability to promote epithelial repair (Slifer and Blikslager, 2020). The intestinal mucosal mechanical barrier consists of IEC, the tight junction between epithelial cells and the mucus layer covering the surface of IEC. The abnormal intestinal mucosal mechanical barrier increases intestinal permeability and translocation of pathogenic microorganisms and their metabolites into the portal system, which eventually triggers chronic low-grade inflammation in the liver, resulting in the development of non-alcoholic fatty liver disease, liver fibrosis, cirrhosis and other liver diseases (Slifer and Blikslager, 2020). Currently, the mechanism of damage to the mechanical barrier of the intestinal mucosa is poorly known, but the evidence is mounting that enhancing the expression of tight junction-related proteins plays an imperative role in maintaining the intestinal mechanical barrier in animals and inhibiting pathogenic invasion into the organism (Fig. 3). A study demonstrated that 4 mmol/L butyrates promoted the relative expression of *occludin* and *ZO-1* mRNA in IPEC-J2 cells and promoted the relative expression of *claudin-1* mRNA in rat cdx2-IEC cells, decreased intestinal permeability and increased intestinal villus height in mice (Ma et al., 2012; Wang et al., 2012). Tong et al. (2016) revealed that propionic acid increased the expression of intestinal tight junction proteins ZO-1, occludin, and cadherin, which promoted intestinal function. Also, SCFA activated the AMPK pathway to upregulate the expression of *ZO-1* in intestinal epithelial cells, enhancing the transmembrane resistance (TER) of epithelial cells and protecting the integrity of the intestinal barrier (Voltolini et al., 2012), but excessive concentration resulted in cytotoxicity (Han et al., 2015). Wang et al. (2018) found that sodium butyrate improved intestinal morphology, increased jejunal *TER* expression, decreased fluorescein isothiocyanate-labeled dextran 4 kDa (*FD4*) expression (TER and FD4 are essential indicators of extracellular permeability and intestinal barrier), ameliorated intestinal damage caused by weaning stress, and enhanced intestinal barrier function in weaned piglets. Huang et al. (2015) discovered that sodium butyrate significantly increased the expression of occludin protein in the jejunum and colon of weaned piglets, and reduced diarrhea by decreasing intestinal permeability, which was in agreement with the study of Bai et al. (2010).

Therefore, SCFA regulate the mechanical barrier of the animal intestine mainly by promoting the expression of genes related to

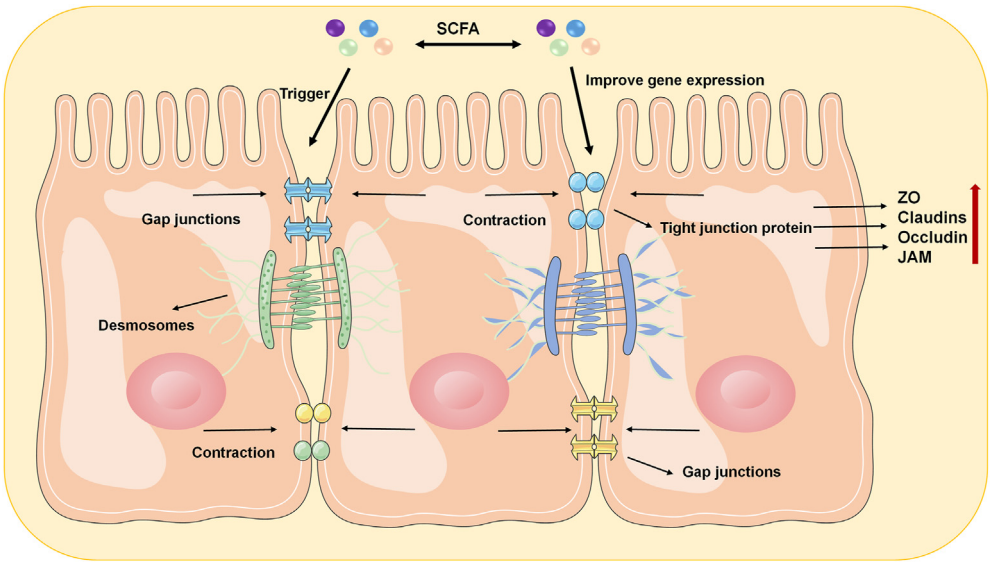

Fig. 3. Main effects of short-chain fatty acids (SCFA) on the mechanism barrier. SCFA protect the integrity of the mechanical barrier by enhancing the gene expression of intestinal tight junction proteins Occludin, zonula occludens (ZO), and claudins to promote contraction of tight junctions, desmosomes, and gap junctions, and reduce diarrhea by decreasing intestinal permeability. JAM = junctional adhesion molecule. Source: Ma et al. (2012); Tong et al. (2016); Slifer and Blikslager (2020); Huang et al. (2015).

the tight junction proteins claudin, occludin and ZO in the intestine and reducing the permeability of the intestine, thus improving the mechanical barrier function of the animal intestine.

4.2. Moderating effect of SCFA on the microbial barriers

The intestinal microorganisms of monogastric animals are generally classified into three categories regarding their abundance in the intestinal tract and their relationship with the host: the first is the beneficial microbiota (*Bifidobacterium*, *Lactobacillus*), which has nutritional and immunomodulatory roles in the intestine; the second is the opportunists (*E. coli*, *Enterococcus*), which may cause damage to the organism when the intestinal microecological balance is disrupted; and the third is the pathogenic microorganisms of variable species and population (*Clostridium Welchii*, *Pseudomonas aeruginosa*), which may cause disease in the organism when their population exceeds the standard level (Mitsuoka, 2000; Ma and Liu, 2016) (Fig. 4).

After SCFA enter the animal intestine, a part of them dissociates to produce H^+ for lowering pH, while another part enters the host and bacterial cells by free diffusion in the undissociated form (Hsiao and Siebert, 1999). The lipopolysaccharide of the bacterial outer membrane is a defensive barrier for bacteria, which effectively prevents large molecules or antibiotics from entering the bacterial cells. SCFA could enter the periplasmic space through the outer membrane pore proteins, and then protonate with the lipopolysaccharide carboxyl and phosphate groups of the bacterial outer membrane from the rear, thus weakening the defence of the bacterial outer membrane; with the gradual dissociation of the bacterial outer membrane lipopolysaccharide and protein (Alakomi et al., 2000). With the gradual dissociation of bacterial outer membrane lipopolysaccharide and protein components, the integrity of the bacterial outer membrane is destroyed, and the bacterial contents leak out, thus triggering bacterial death and achieving the purpose of bacterial inhibition (Brul and Coote, 1999).

The pKa value of SCFA is a dissociation constant that responds to the dynamic equilibrium of SCFA, when the pH of the external environment is larger than the pKa value of the SCFA, the SCFA dissociate H^+ to neutralize to maintain a dynamic equilibrium (Ricke, 2003). SCFA enter the interior of bacterial cells by free diffusion, but some studies have shown that the transmembrane transport of SCFA could also be achieved through channels in bacterial cell membrane proteins in the bacterial cell membrane. Since the bacterial cell interior is neutral or basic, the pKa value is larger than that of SCFA (Gadde et al., 2017). According to the dynamic equilibrium equation of organic acids: $RCOOH \rightleftharpoons H^+ + RCOO^-$, SCFA dissociate H^+ and acid ions $RCOO^-$, and the dissociated ions are unable to be discharged outside the cell by free diffusion (Maurer et al., 2005), so the H^+ accumulates in large quantities inside the bacterial cell, causing a decrease in the pH of the cell. As the bacteria urgently need to restore the original neutral or alkaline environment for the normal functioning of the cell, they consume a massive amount of ATP to excrete H^+ from the cell by active transport, affecting the energy required for normal growth and metabolism of the bacteria, forming a kind of energy competition (Gadde et al., 2017). As the $RCOO^-$ produced by intracellular dissociation of SCFA continues to increase, the intracellular osmotic pressure gradually rises, and to balance the elevated osmotic pressure, bacteria must exclude negatively charged ions from the cell, forcing them to expel precursors or cofactors necessary for their own growth, thus affecting normal bacterial growth (McLaggan et al., 1994). It was shown that when the concentration of $CH3COO^-$ produced by the dissociation of acetic acid in *E. coli* cells was gradually increased from 8 mmol/L at the beginning to 250 mmol/L, the negatively charged glutamate ion (Glu^-) in bacterial cells was reduced by nearly 80%, and the growth rate of *E. coli* was also significantly reduced, which indicates that *E. coli* releases the negatively charged Glu^- by maintaining intracellular osmotic pressure homeostasis, resulting in fewer nutrients for their own growth and slower growth rates (Roe et al., 1998). In addition, H^+ is pumped outside the cell via membrane transport proteins in bacterial cells and K^+ is pumped into the cell via ion channels, a process that further elevates the increase in intracellular osmotic pressure, ultimately causing overloading of the cell membrane, membrane structural cleavage, and leakage of contents, triggering bacterial death (Alakomi et al., 2000).

The continuous accumulation of $RCOO^-$ alters the homeostatic environment inside the bacterial cell, which in turn interferes with

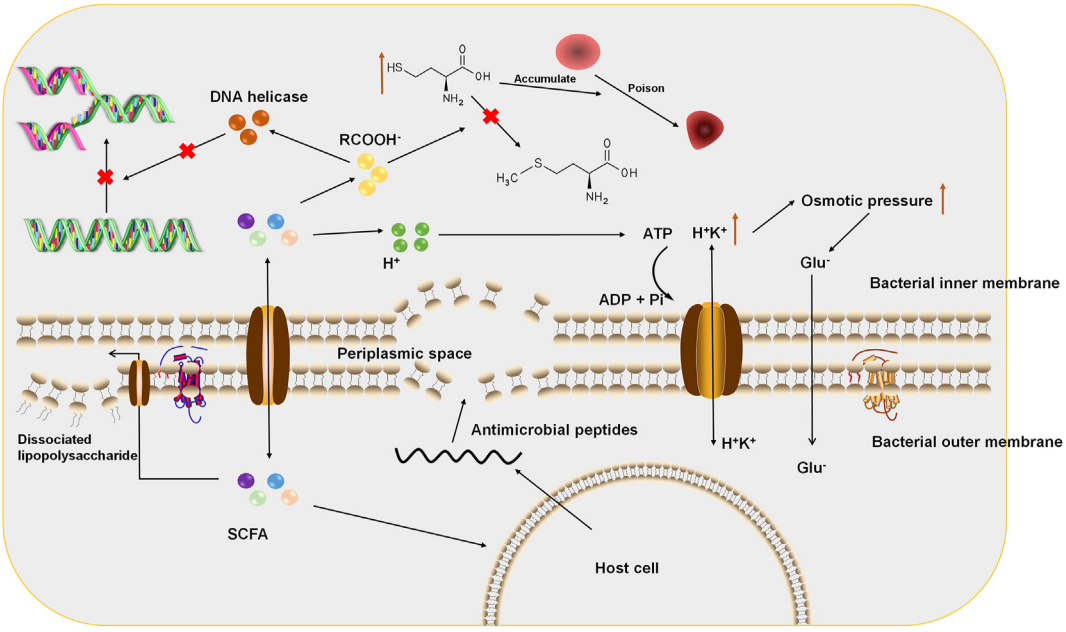

Fig. 4. Main effects of short-chain fatty acids (SCFA) on the microbial barrier. SCFA protonate with the lipopolysaccharide carboxyl and phosphate groups of the bacterial outer membrane from the posterior, which weakens the defence of the bacterial outer membrane and undergoes dissociation, leading to disruption of cellular integrity. The $COOH^-$ generated by SCFA dissociation also causes an imbalance of osmotic pressure inside the bacteria. Furthermore, SCFA could achieve bacterial inhibition by interfering with bacterial DNA and protein synthesis processes as well as triggering the host cell to produce the antimicrobial peptide. Source: Alakomi et al. (2000); Brul and Coote (1999); McLaggan et al. (1994); Roe et al. (1998); Alakomi et al. (2000); Rasch (2002); Roe et al. (2002); Jakubowski (2019).

a range of physiological and biochemical properties inside the bacteria. Studies have shown that SCFA interfere with DNA replication in *E. coli* by inhibiting ribonucleic acid reductase, which is required for DNA synthesis, thereby inhibiting bacterial growth (Rasch, 2002). SCFA not only affect DNA synthesis, but also reduce the efficiency of glucose utilization by bacteria by altering their metabolic pathways. In addition, SCFA inhibit bacterial growth by blocking or altering some key enzymes or synthetic pathways. It was shown that *E. coli K-12* treated with acetic acid showed a significant increase in homocysteine content and a decrease in methionine content in *E. coli K-12*, which is a precursor substance for the synthesis of methionine, indicating that the addition of acetic acid blocked the pathway of methionine synthesis from homocysteine, resulting in the inhibition of bacterial growth (Roe et al., 2002). In addition, the accumulation of homocysteine in the cells also has a toxic effect on bacteria, which stunts bacterial growth. It was shown that SCFA trigger the production of a certain antimicrobial peptide by the host cell itself through activation and modulation of the host immune system (Jakubowski, 2019).

The antimicrobial peptide achieves bacterial inhibition by lysing the bacterial cell membrane, causing leakage of the contents and bacterial death (Brogden, 2005). Since the antimicrobial peptide originates from the host itself, the pathogenic bacteria are also less likely to develop drug resistance, enhancing the safety of the host cells themselves (Schwab et al., 2007). It was shown that formic acid induced the expression of P2, a derivative peptide of human bactericidal/permeability-enhancing protein (Barker et al., 2000). Schwab et al. (2007) also showed that sodium butyrate significantly increased the expression of human beta-defensin-2 (*HBD-2*) during the translational phase. Additionally, 0.25 mmol/L and 0.5 mmol/L sodium butyrate significantly increased the relative expression of tracheal antimicrobial peptide (*TAP*) and β-defensin genes in cows, while the abundance of *Staphylococcus aureus* in host cells was reduced by nearly 50%. However, the exact mechanism of organic acid-induced antimicrobial peptide production in host cells to achieve bacterial inhibition is not clear, so further studies may be needed in the future.

In conclusion, SCFA mainly inhibit the growth of harmful bacteria by releasing H^+, lowering intestinal pH, competing for energy, forming antimicrobial peptides, and blocking the biosynthesis of harmful bacteria with the aim of achieving intestinal microecological balance.

4.3. Moderating effect of SCFA on chemical barriers

The intestinal chemical barrier mainly consists of the mucus layer covering the IEC. Intestinal microorganisms, a host inflammatory mediator and intestinal secretions (gastric acid, glycoproteins, digestive enzymes, etc.) could affect the intestinal chemical barrier (Fig. 5) (Johansson et al., 2008; Gaudier et al., 2009). MUC exists as the most dominant molecule in the mucus layer. It effectively prevents harmful macromolecules from entering the epithelial cell layer and serves an essential role in the intestinal chemical barriers. SCFA activate inflammatory vesicles in IEC, promote the production of anti-inflammatory factors, upregulate the gene expression of *MUC1*, *MUC2*, *MUC3* and *MUC4* in the intestine and the secretion of pancreatic enzymes in the pancreatic fluid, therefore, strengthening the intestinal chemical barrier function (Singh et al., 2014; Sun et al., 2017).

Gaudier et al. (2004) suggested that butyrate specifically regulates the expression of *MUC* genes in intestinal cupped cells at the transcriptional level, and upregulates the expression of *MUC2*, *MUC3* and *MUC5AC* genes. The regulation of different mucin genes by butyrate is additional, and the expression of the *MUC3* gene is regulated by butyrate, which is probably through the histone deacetylase (HDAC) pathway. In contrast, *MUC2* and *MUC5AC* gene regulation may involve butyrate metabolites. Diao et al. (2019) reported that administration of SCFA by gavage to weaned piglets lowered the expression of the pro-apoptotic genes *Bax* and *Caspase-3*, decreased the apoptotic index of cells, and stimulated

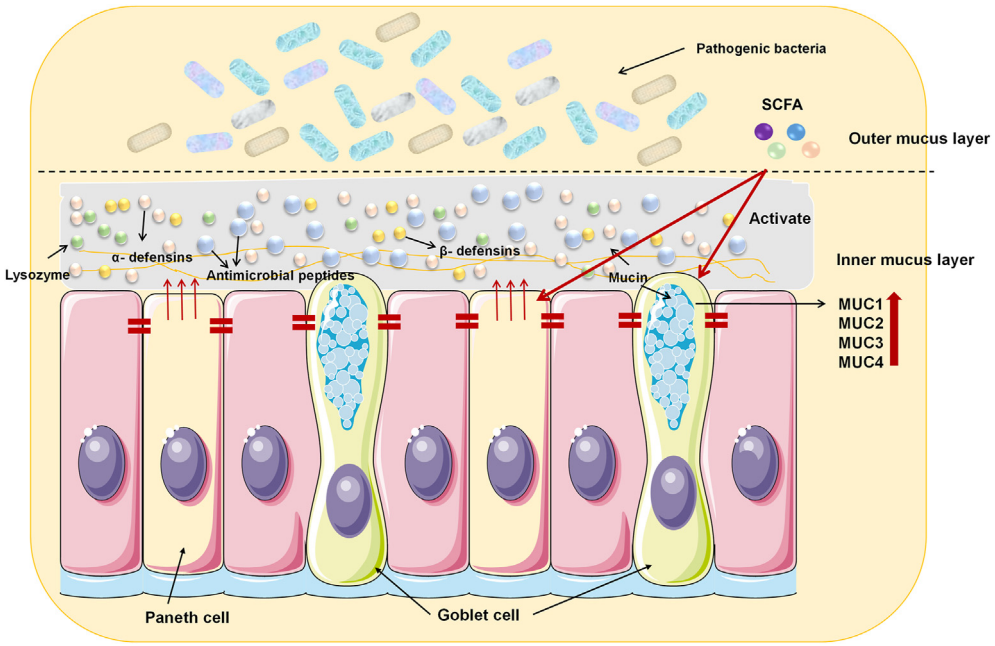

Fig. 5. Main effects of short-chain fatty acids (SCFA) on the chemical barrier. SCFA activate inflammatory vesicles in IEC, promote the production of anti-inflammatory factors, upregulate the gene expression of mucin-1 (*MUC1*), *MUC2*, *MUC3* and *MUC4* in the intestine. SCFA could trigger the secretion of α-defensins or certain antimicrobial peptides from small intestine Paneth cells to finish the inhibition of foreign pathogens. Source: Singh et al. (2014); Sun et al. (2017); Takakuwa et al., (2019).

the expression of the intestinal *MUC1* and *MUC2* genes via the MAPK signalling pathway to enhance the chemical barrier functions of the intestine. Bai et al. (2010) reported that SCFA increased the expression of the phosphatase gene (phosphatase and tensin homologue deleted on chromosome 10, PTEN) and enhanced the chemical barrier function of IEC by promoting the expression of *MUC2*, inducing the differentiation of cancer cells through the PTEN/phosphoinositide3-kinase (PI3K) signalling pathway. Also, a recent study revealed that butyric acid could trigger the Paneth cells from the small intestine to induce the α-defensin secretion (Takakuwa et al., 2019).

So, the regulation of the chemical barrier by SCFA was mainly achieved by promoting the expression of MUC-related genes, triggering the Paneth cells to secrete defensin, reducing the apoptotic index of intestinal cells and increasing the enzymatic activity of intestinal secretions. Additionally, SCFA regulate chemical barrier MUC-related genes through multiple signalling pathways to reinforce the chemical barrier function of the animal intestine.

4.4. Moderating effect of SCFA on immune barrier

The intestinal mucosa is responsible for recognizing various food and microbial antigens, which makes the intestine have the largest number of immune cells (Fig. 6). The intestinal mucosal epithelial cells not only recognize pathogens on the surface of pathogenic microorganisms but also identify some microbial metabolites. The SCFA produced by the metabolism of intestinal microorganisms are recognized and regulate the intestinal mucosal immune response process by regulating the functions of intestinal mucosal immune and non-immune cells and influencing the differentiation, recruitment and apoptosis of cells (Sadler et al., 2020; Vinolo et al., 2011a, 2011b; ; Li et al., 2018b). Wang et al. (2018) revealed that the supplementation of sodium butyrate lowered the levels of histamine, trypsin-like, TNF-α, IFN-γ and interleukin-6 (IL-6) in the jejunal mucosa of weaned piglets, which may be accomplished through the c-JUN NH_2-terminal kinase (JNK) signalling pathway. Also, Carretta et al. (2016) discovered that butyrate induces Ca^{2+} flow, phosphorylates p38 protein kinase (p38 MAPK) and extracellular regulated protein kinase (ERK1/2), promotes neutrophil degranulation and extracellular traps (a defence mechanism of innate immunity consisting of DNA and granule proteins) formation, modulates neutrophil function and affects the response of innate immunity.

SCFA also work on intestinal immunity through 2 different mechanisms. The most important of these is the activation of cellular receptors leading to cell proliferation or differentiation, and secondly, SCFA act as HDAC inhibitors.

4.4.1. GPCR pathway

The GPCR are expressed in a variety of cell types, including immune cells and IEC, and SCFA activate signal transduction pathways that regulate immune responses by binding to cell surface GPCR (such as GPR43, GPR41) and GPR109A, where GPR43 and GPR41 were activated by acetate, propionate and butyrate, and GPR109A is activated by butyrate (Russo et al., 2019). The GPCR serves as a receptor for SCFA; the ligand affinity of GPR43 is the same for acetate and propionate, both of which are superior to that of butyrate. Propionate ranked highest in the ligand affinity of GPR41, followed by butyrate and acetate was the lowest. The primary sites of *GPR43* expression were IEC, immune cells, and adipocytes; GPR41 was expressed in a variety of cells, including smooth muscle cells, IEC, enteroendocrine cells, and neuronal cells (Le Poul et al., 2003). GPRl09A is principally expressed in colonic epithelial cells, colonic cells, hepatocytes, adipocytes and immune cells. It is involved in adipocyte differentiation and lipid storage to adjust the energy homeostasis of the organism, as well as participating in SCFA in an intestinal-mediated inflammatory response and immune response activation (Singh et al., 2014; Kim, 2018; D'Souza et al., 2017).

SCFA exert anti-inflammatory roles in the intestinal mucosa by activating GPCR in IEC and immune cells. Among these cells, inflammatory responses could induce SCFA to activate the expression of *GPCR* (Singh et al., 2014). Monocytes and neutrophils, as innate

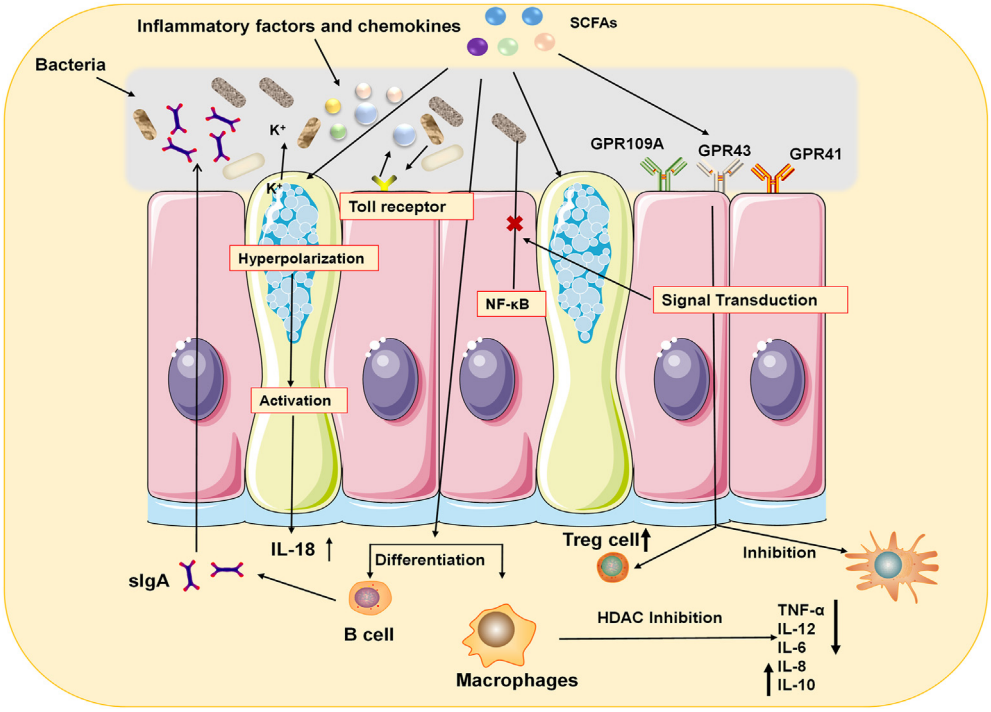

Fig. 6. Main effects of short-chain fatty acids (SCFA) on the immune barrier. SCFA protect the intestinal immune barrier by lowering the levels of tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ) and interleukin (IL)-6, activating the expression of G-protein coupled receptors (GPCR) to participate in the intestinal-mediated inflammatory and immune response, inhibiting the lipopolysaccharide-induced activation of nuclear factor kappa B (NF-κB), promoting potassium ion (K^+) efflux and hyperpolarization in intestinal epithelium cells (IEC) as well as IL-18 formation, suppressing histone deacetylase (HDAC) and downregulating the expression of pro-inflammatory cytokines. Moreover, SCFA could improve the intestinal integrity by inhibiting the Toll-like receptor 4 (TLR4) signalling pathway. Source: Wang et al. (2018); Kim (2018); D'Souza et al. (2017); Thangaraju et al. (2009); Macia et al. (2015); Li et al. (2018b); Rooks and Garrett (2016); Wen et al. (2012); Hayashi et al. (2013); Wu et al. (2017).

immune cells, could activate adaptive immune responses by crossing the epithelial barrier, recognizing and eliminating antigens secreted by cytokines/chemokines, preventing pathogens from invading. The SCFA induced neutrophil chemotaxis and proliferation of regulatory T cells (Treg cells) by binding to GPR43 (Smith et al., 2013). In both the dextran sulfate colitis model and the T-cell metastatic enteritis model, the GPR43-mediated SCFA reduced the inflammatory response by enhancing the frequency and function of forkhead box P3 (FOXP3) Treg cells (Smith et al., 2013; Maslowski et al., 2009). The elevated histological scores, neutrophil infiltration, and increased expression levels of pro-inflammatory cytokines in the intestinal mucosa of the knockout *GPR43* mice demonstrated the involvement of the SCFA/GPCR pathway in promoting inflammation. Activation of GPR41 and GPR43 could mediate the effect of acetate on IL-6 and IL-8, while butyric and propionate affect the content of IL-6 (Trompette et al., 2014).

The SCFA may also maintain the organism's health by modulating the inflammatory response at other sites through GPR41. Studies have reported that SCFA inhibited dendritic cells (DC) proliferation and ameliorated allergic respiratory inflammation in wild-type mice, but this phenomenon was not present in knockout GPR41 mice (Li et al., 2018a). Moreover, the SCFA induced Treg cell differentiation and production of the inflammatory cytokine IL-10 by mediating the activation of GPR109A, thereby reducing the prevalence of colitis and colon cancer in *Niacr1*$^{-/-}$ mice (Singh et al., 2014). In the IEC model, butyrate inhibits lipopolysaccharide-induced activation of nuclear transcription factor-κB (NF-κB) by triggering GPR109A in mouse colonocytes, which supresses the expression of intercellular cell adhesion molecule-1 (*ICAM-1*) and vascular cell adhesion protein 1 (*VCAM-1*) (Thangaraju et al., 2009). The secretion of inflammatory factors such as IL-2, IL-6 and TNF-α by inflammatory cells was blocked. SCFA could also interact with GPR109A and GPR43 on IEC to promote potassium ion (K^+) efflux and hyperpolarization in IEC and increase IL-18 formation, which maintains intestinal homeostasis (Macia et al., 2015).

Nevertheless, the SCFA not only have beneficial effects on host physiology, but also aggravate the disease. In an experimental renal disease model, excess SCFA have been proven to promote T cell-mediated inflammation of renal tissue with urethritis and hydronephrosis (Park et al., 2016; Sivaprakasam et al., 2016). Collectively, these studies demonstrated that GPCR are cell-specific and modulate host immunity in conjunction with SCFA, providing robust evidence for maintaining intestinal integrity by suppressing inflammation through the SCFA/GPCR pathway (especially GPR43 and GPR109A).

4.4.2. SCFA as HDACI

The enzyme-controlled histone post-translational modifications (HPTM) are fundamental to the modulation of gene expression, the foremost of which is the acetylation of histones controlled by acetyltransferases (HAT) and deacetylases (HDAC). Histone deacetylation is a prevalent mode of gene expression regulation. HDAC is a class of proteases that catalyzes such reactions and exerts an essential function in the structural modification of chromosomes and modulation of gene expression (Yuille et al., 2018).

Overexpression of *HDAC* leads to a decrease in histone acetylation, which inhibits gene expression (Fellows et al., 2018). In addition to its anti-inflammatory effects as a signalling molecule extracellularly, SCFA act as HDACI upon entering the cell via transporter proteins, which are involved in modulating the expression of genes that contribute to the pathogenesis of many diseases (Grabarska et al., 2013), among which butyrate was considered to represent the most effective HDACI amongst SCFA (Xiong et al., 2016; Chriett et al., 2019).

SCFA acts on monocytes and neutrophils by inhibiting HDAC, reducing the production of pro-inflammatory tumour necrosis factor by the cells and leading to inactivation of NF-κB and down-regulation of the expression of pro-inflammatory cytokines such as *IL-2*, *IL-6* and *IL-8* (Li et al., 2018b; Rooks and Garrett 2016; Glauben et al., 2006; Wen et al., 2012; Hayashi et al., 2013). An investigation into humans has revealed that butyrate differentiates monocyte-derived macrophages by inhibiting HDAC3 and augmenting anti-microbial function (Schulthess et al., 2019). Likewise, SCFA increased histone acetylation via HDAC inhibition, regulated mammalian target of rapamycin (mTOR), and induced *IL-10* expression in T cells and regulatory B cells (Bregs) by boosting the activity of the mTOR complex, enhancing glucose oxidation and creating acetyl coenzyme A. The mTOR-S6 kinase (S6K) pathway is crucial for the differentiation of T lymphocytes (Sun et al., 2018; Luu and Visekruna 2019). Therefore, unlike the GPR41 or GPR43 pathways, SCFA promote the differentiation of T lymphocytes into effector T cells and Treg by suppressing HDAC (Park et al., 2015). HDAC could prevent the degradation of FOXP3 by influencing the acetylation of FOXP3, and SCFA also increased *FOXP3* gene expression in Treg cells by suppressing HDAC, preventing proteasomal degradation and enhancing the stability and activity of FOXP3, which stopped the inflammatory response (Smith et al., 2013; Arpaia et al., 2013). On the other hand, in a murine model study, it was identified that acetylation of FOXP3 contributed to its binding to the IL-2 promoter region, resulting in the inhibition of endogenous IL-2 secretion, which can inhibit IFN-γ production by Treg cells. Meanwhile, SCFA cause a decrease in the expression of crucial DC regulators through the inhibitory effect of HDAC, which results in the attenuation of DC development (Merad et al., 2013; Chang et al., 2014).

For HPTM, except acetylation, there are other post-translational modifications such as methylation, propionylation, crotonylation, butyrylation and 2-hydroxyisobutyrylation (Kebede et al., 2017; Goudarzi et al., 2016). The latest research indicated that histone crotonylation directly stimulates transcription in a more substantial way than histone acetylation (Wei et al., 2017), and the SCFA are essential for the process of crotonylation, with the ability to link crotonyl-CoA to histone lysine residues (Sabari et al., 2015). Additionally, antibiotic treatment of mice resulted in decreased levels of intestinal luminal and serum SCFA with depletion of intestinal microbiota, causing increased expression of HDAC2 in the intestine and a significant decrease in histone crotonylation (Kelly et al., 2018). SCFA (main butyrate) promote histone crotonylation by inhibiting the decrotonylase activity of HDAC in colonic epithelial cells. The analysis of the levels of crotonylation in the murine colon, brain, liver, spleen and kidney tissues revealed that it was highest in the intestine, especially in the small intestine and the crypt portion of the colon and followed in the brain and serum, which indicated that crotonylation could occur not only in the intestine but also be expressed in distal tissues (brain and serum) (Fellows et al., 2018).

4.4.3. Toll-like receptor

IEC serve not only as a physical barrier to the intestinal mucosa but also as a signalling node in the internal and external environment, mediating interactions between the lamina propria microbiota and immune cells through intercellular communication, chemokine and cytokine signalling (Peterson and Artis, 2014). Activation of TLR by IEC in response to microbial antigen stimulation regulates immune function, maintaining the balance of the intestinal microorganisms and preventing microbial and toxin attacks on the intestine (Abreu, 2010). The TLR are abundantly expressed in a multitude of intestinal cells, and the most significant presence of TLR in the intestine are TLR2, which recognizes bacterial lipoproteins, lipoteichoic acid and TLR4, which recognizes the lipopolysaccharide component of the cell wall of Gram-negative bacteria, and TLR5, which identifies most motile bacterial flagellin in the colon. Upon activation, they produce inflammatory cytokines and chemokines triggering the immune response (Park et al., 2015). Yet, in response to bacterial stimulation, TLR could mediate the innate immune response and inflammatory response in IEC. It has been demonstrated that butyrate could reduce the expression of *TLR4* and the production of inflammatory cytokines in IEC (Liu et al., 2014). Xiao et al. (2018) discovered that butyrate could stabilize the intestinal environment by upregulating TLR4 expression by treating human colon cancer cells and mouse colon cancer cells with butyric acid. Besides, several studies indicated that the SCFA inhibited autoimmune hepatitis induced by Freund's complete adjuvant by sustaining the integrity of the small intestine. Wu et al. (2017) revealed that sodium butyrate reduced the production of IL-6 and TNF-α by inhibiting the TLR4 signalling pathway, which protected against liver and small intestine injury. Therefore, the role of SCFA in protecting the intestinal immune barrier, reducing the inflammatory response and preserving the immune homeostasis of the organism is substantial.

4.4.4. Others possible mechanism

Olfactory receptor 78 (OLFR78) is also one of the receptors for SCFA and was activated by acetate and propionate, but not by butyrate (Pluznick, 2014). The OLFR78 is expressed by vascular endothelial cells and the most abundant expression occurs in the renal vasculature. SCFA activate this receptor after being reabsorbed in the kidney (Natarajan and Pluznick, 2014). Currently, it has been determined that this receptor mainly triggers the release of epinephrine, which raises blood pressure. Still, other functions of this receptor have not been identified, and studies have speculated that it is probably also engaged in mediating the energy metabolism of the organism.

Thus, SCFA regulate the immune function of animals through multiple pathways, promoting the development of immune organs, the activity of immune substances, enhancing the expression of anti-inflammatory cytokines, reducing the expression of pro-inflammatory cytokines, as well as strengthening the antioxidant capacity, thus reinforcing the immune barrier function of animals. Additionally, since SCFA are volatile compounds with short half-lives and rapid metabolism in organisms, the concentration of SCFA affects their inhibitory effect on HDAC. Only high concentrations of SCFA could exert an impact on HDAC. Nevertheless, whether SCFA inhibit HDAC directly or indirectly through pathways such as GPCR is influenced by various factors such as concentration, receptors, transport carriers, and the type of cells or tissues being affected. It is expected that the results of these studies will support the theoretical search for disease treatment options and determine the importance of SCFA as HDAC inhibitors (Schilderink et al., 2013).

5. Conclusions

The interaction between the host and SCFA forms a stable intestinal environment. There are both direct and indirect interactions due to their complex mechanisms of action and the impact of environmental factors on the intestinal tract. SCFA contribute to regulating the immune response and play an anti-inflammatory role by activating GPCR receptors and inhibiting HDAC. As a microbial metabolite with multiple physiological functions, SCFA exert an influential regulatory role on the intestinal health and immune function of the organism. However, it is still obscure whether exogenous supplementation of SCFA could inhibit the proliferation of harmful bacteria in the intestinal tract of animals, and whether it could affect the development of IEC and strengthen the anti-inflammatory ability of the host. Therefore, it is

indispensable to understand whether the SCFA affect the host immune cells through interaction with microbiota and how the mechanism of activation in the process of disease development and transformation is essential to maintain the host intestinal health, growth and development of the organism, as well as to dig into new ideas for the prevention and treatment of diseases.

Author contributions

Jiayu Ma: Conceived and designed, Manuscript written, Literature collected. **Xiangshu Piao**: Supervision; Validation. **Xiangshu Piao**, **Jian Wang**, **Shenfei Long** and **Shad Mahfuz**: Writing-Reviewing and Editing. All authors contributed to the final manuscript, reading and endorsing it.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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