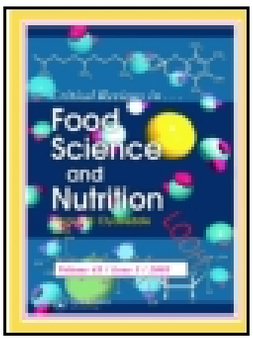

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REVIEW

The role of short-chain fatty acids in immunity, inflammation and metabolism

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ABSTRACT

Short-chain fatty acids (SCFAs) are carboxylic acids with carbon atom numbers less than 6, which are important metabolites of gut microbiome. Existing research shows that SCFAs play a vital role in the health and disease of the host. First, SCFAs are the key energy source for colon and ileum cells, and affect the intestinal epithelial barrier and defense functions by regulating related gene expression. Second, SCFAs regulate the function of innate immune cells to participate in the immune system, such as macrophages, neutrophils and dendritic cells. Third, SCFAs can also regulate the differentiation of T cells and B cells and the antigen-specific adaptive immunity mediated by them. Besides, SCFAs are raw materials for sugar and lipid synthesis, which provides a theoretical basis for studying the potential role of SCFAs in regulating energy homeostasis and metabolism. There are also studies showing that SCFAs inhibit tumor cell proliferation and promote apoptosis. In this article, we summarized in detail the role of SCFAs in immunity, inflammation and metabolism, and briefly introduced the role of SCFAs in tumor cell survival. It provides a systematic theoretical basis for the study of SCFAs as potential drugs to promote human health.

KEYWORDS

SCFAs; immunity; inflammation; metabolism; tumor cell

Key points

- SCFAs regulate the immune system and inflammation by reducing the recruitment and migration of immune cells (macrophages, neutrophils and dendritic cells) and the differentiation of T cells and B cells.
- The synthesis of SCFAs is related to dietary fiber in the diet, mainly through specific intestinal microbial fermentation.
- The identified receptors for SCFAs mainly include GPR41, GPR43, GPR109A, Olfr-78 (murine)/OR51E2 (human), PPARγ and AHR.
- SCFAs enter cells mainly through transporters (MCT1/4 and SMCT1/2) and passive diffusion.
- SCFAs inhibit tumor cell proliferation and promote apoptosis.
- SCFAs have the opposite effect of pro-inflammatory and anti-inflammatory, which may be related to the concentration of SCFAs and the activated receptors.
- SCFAs can be used to synthesize glucose and lipid, control obesity and maintain glucose homeostasis.
- Appropriate addition of dietary fiber to the diet may be a novel strategy for the treatment of diabetes.

Introduction

The human microbiome refers to the collection of microorganisms living on and in our bodies, of which the largest and most diverse microbiota inhabits the intestine (Yao et al. 2020). The microbiome and the host have co-evolved, in which the host provides a stable environment for the microbes and the microbiome provides the host with a wide range of functions, such as maintaining the immune system, resisting pathogens, producing nutrients and vitamins and digesting complex dietary cellulose (Koh et al. 2016). Emerging evidence suggests that gut microbiome is an important factor in intestinal homeostasis and host health and disease. The role of gut microbiome in host health is mainly mediated by the metabolites of short-chain fatty acids (SCFAs) which are the main metabolites produced by specific gut microbiome fermenting resistant starch and dietary fiber (Tan et al. 2014).

More and more studies showed that the gut microbiome plays a vital role in the host's immune system, and the host immune system will also protect specific gut microbiome from interference (Ratajczak et al. 2019). The result of this interaction between the microorganism and the host is to stabilize certain internal environments of the human body. When the microbial balance in the body is disturbed, it may lead to host metabolic dysfunction and chronic inflammation (Nagalingam and Lynch 2012). Environmental factors, high-fat diets and the use of antibiotics, as well as high sugar, sanitary conditions, and low fiber can cause the imbalance of the gut microbiome and interfere with host health (Logan, Jacka, and Prescott 2016). At present, the gut microbiome is recognized to have many beneficial functions, such as preventing diseases (inflammatory immune-related diseases and colon cancer), and regulating metabolism

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(Rescigno 2014; Schwarzer et al. 2016). The regulation function of gut microbiome on host health is mostly mediated by SCFAs which are mainly composed of acetic acid, propionic acid and butyric acid. SCFAs affect the host's blood lipids and blood glucose levels and are the energy source for certain cells of the host, and can also regulate the colonic environment, inflammation, metabolism, immune function, and tumor cell proliferation and apoptosis (Cho et al. 2013; Koh et al. 2016).

In this review, we mainly introduce in detail the role of SCFAs in the host immune system, inflammatory response, metabolism and tumor cell proliferation and apoptosis, and briefly summarize the production, transport and signal transduction of SCFAs. It provides a systematic theoretical basis for the study of SCFAs as potential drugs to promote human health.

The production, transport and signal transduction of SCFAs

The production of SCFAs

SCFAs are short-chain fatty acids composed of less than 6 carbon atoms (C1-C6). SCFAs can be naturally produced through the host's metabolic pathway especially in the liver, but the main part of the host to produce SCFAs is the colon (Hoverstad and Midtvedt 1986). Acetate (C2), propionate (C3) and butyrate (C4) are the most common SCFAs, which are released by specific gut microbiome fermenting cellulose and resistant starch. The concentration of SCFAs is higher in the proximal colon (70 ~ 140 mM) and lower in the distal colon (20 ~ 70 mM) and distal (20 ~ 40 mM) (Wong et al. 2006). The undigested protein, dietary fiber, and a small amount of peptides in the upper digestive tract and stomach will be metabolized by the microbiota to produce SCFAs after entering the cecum and colon (Macfarlane and Macfarlane 2012). The main products produced by gut microbiome fermentation of dietary fiber and protein are SCFAs, of which butyrate plays a key role and propionate and acetate are less reported (Cummings et al. 1987). However, the metabolites of microorganisms will turn into energy sources that are unfavorable to the host, such as excess amino acids when the supply of fermentable protein or cellulose exceeds supply (Cummings and Macfarlane 1991; Wall et al. 2009), which in turn will lead to reduced activity of the fermentation of the microbial community to produce SCFAs (Russell et al. 2011). At present, studies have revealed that adding dietary fiber to a diet rich in fat or protein can restore the level of beneficial microbial metabolites and reduce the level of harmful microbial metabolites such as increased production of short-chain fatty acids (Sanchez et al. 2009).

SCFAs transport

Most short-chain fatty acids are produced and function near the intestine, but some SCFAs (such as acetate and propionate) can reach the liver. In the liver, SCFAs can be used as substrates of the tricarboxylic acid cycle to generate energy and participate in the synthesis of glucose. Besides, a small amount of SCFAs in the intestine exist in a combined state, which can directly pass through the intestinal epithelial barrier.

Short-chain fatty acids enter cells through passive diffusion and transport proteins, including sodium-coupled monocarboxylate transporter 1/2 (SMCT1/2) and monocarboxylate transporter 1/4 (MCT1/4). MCT1 and MCT4 are called H^+ coupled transporters, which are mainly expressed in the apical membrane (MCT1) and basolateral membrane (MCT1 and MCT4) of the colonic epithelium, and mediate the outflow of short-chain fatty acids into the blood and inflow from the lumen (Goncalves, Araujo, and Martel 2011; Sivaprakasam et al. 2017). SMCT1 and SMCT2 refer to Na^+ coupled transporters, which are only expressed in the apical membrane of colonic epithelium, and mediate the influx of SCFAs from the lumen (Iwanaga et al. 2006; Sivaprakasam et al. 2017). Studies have also shown that the expression level of MCT1 protein is proximal colon > distal colon > small intestine in ruminants (Kirat et al. 2006). What's more, SMCT1 is mainly expressed in the apical membrane of intestinal epithelial cells in the ileum, distal colon and proximal. A study revealed that the expression of SMCT1 in the colon increased after germ-free mice were re-colonized with bacteria (Cresci et al. 2010). However, in macrophages, neutrophils and dendritic cells, whether SCFAs can also pass through the cell membrane through transporters still needs further study.

2.3. Scfas signal transduction

At present, short-chain fatty acids participate in the regulation of host health or disease mainly through two mechanisms. The first mechanism is to regulate the epigenetics of target cells after SCFAs enter the cell. For example, SCFAs can directly inhibit histone deacetylases (HDACs) to control the expression of related genes. One of the main characteristics of SCFAs (mainly referring to propionate and butyrate) is that they have endogenous HDACs inhibitor (HDACi) activity (Chriett et al. 2019; Grabarska et al. 2013). The other mechanism is that SCFAs conduct cell signal transduction through cell membrane receptors. The proven SCFAs receptors mainly include G protein-coupled receptors GPR109A (also called hydroxycarboxylic acid receptor 2, HCAR2), GPR43 (also called free fatty acid receptor 2, FFAR2) and GPR41 (also called Free fatty acid receptor 3, FFAR3) (Le Poul et al. 2003; Tolhurst et al. 2012; Wang et al. 2016), as well as other cell membrane receptors belonging to G protein-coupled receptors family: Olfr-87 in mice, and OR51E2 in humans (Ohira, Tsutsui, and Fujioka 2017). However, recently, it has been reported that SCFAs can also act on the aryl-hydrocarbon receptor (AHR) and play a systemic role (Rosser et al. 2020). Besides, studies indicated that SCFAs (mainly referring to butyrate and propionate) are involved in the activation of peroxisome proliferator-activated receptor γ (PPARγ), which stimulates the synthesis of angiopoietin-like protein 4 (ANGPTL4) [Table 1 (Alex et al., 2013; Bolognini et al. 2016; Brown et al., 2003; Kasubuchi et al. 2015; Kimura et al. 2013; Macia et al.

Table 1. Identified receptors for short-chain fatty acids.

Receptor	Ligand	Location	Function after activation	Ref.
GPR41(free fatty acid receptor 3, FFAR3)	acetate, propionate, butyrate (C3 > C4 > C2)	large intestine lamina propria cells, spleen cells, lymph nodes, bone marrow, adipocytes, polymorphonuclear leukocytes, and in peripheral nervous system cells, distal tubules and kidney collecting ducts	metabolism, inflammation and immunity	(Brown et al., 2003; Trompette et al. 2014)
GPR43(free fatty acid receptor 2, FFAR2)	acetate, propionate, butyrate	digestive tract epithelial cells, immune system cells, adipocytes in adipose tissue	metabolism, inflammation and immunity	(Brown et al., 2003; Kimura et al. 2013)
GPR109A (hydroxycarboxylic acid receptor 2, HCA2)	niacin, ketone bodies, β-hydroxybutyric acids, butyrate	large intestinal epithelium, macrophages, monocytes, dendritic cells, neutrophils, and adipocytes	metabolism, cancer and immunity	(Bolognini et al. 2016; Macia et al. 2015; Singh et al. 2014)
Olfr-78 (murine) OR51E2 (human)	acetate, propionate	neurons, enteroendocrine cells, the epithelium of the large intestine, renal arteries, smooth muscles of blood vessels	Regulating blood pressure	(Ohira, Tsutsui, and Fujioka 2017; Pluznick 2016; Pluznick et al., 2013)
PPARγ (Peroxisome proliferator-activated receptors γ)	propionate, butyrate	large intestine adenocarcinoma cells	Stimulate the synthesis of angiopoietin-like protein	(Alex et al., 2013)
Aryl-hydrocarbon receptor (AHR)	butyrate	Treg, dendritic cells, stem Cells, Breg	Immunity	(Rosser et al. 2020)

2015; Ohira, Tsutsui, and Fujioka 2017; Pluznick 2016; Pluznick et al., 2013; Rosser et al. 2020; Singh et al. 2014; Trompette et al. 2014)].

The role of SCFAs in immunity

Since ancient times, the human microbiome and the host's immune system have regulated each other and evolved together. Microorganisms (mainly refers to gut microbiome here) participate in regulating the host's immune system mainly by producing metabolites SCFAs. Previous studies have shown that specific metabolic-related receptors expressed by immune cells include: GPR109, GPR43, Purinoceptor P2X ligand-gated ion channel 7 (P2X7), GPR41, Farnesoid X receptor (FXR), G protein bile acid coupled receptor 5 (TGR5), aryl hydrocarbon receptor precursor (AHR), pregnane X receptor (PXR) and so on. Short-chain fatty acids, as the most abundant metabolites of gut microbiome in the intestinal lumen, play a vital and multi-angle role in regulating the host's immune system (Figure 1). First, SCFAs are the key energy source for colon and ileum cells, and affect the intestinal epithelial barrier and defense functions by regulating related gene expression. Second, SCFAs regulate the function of innate immune cells to participate in the immune system, such as macrophages, neutrophils and dendritic cells. Third, SCFAs can also regulate the differentiation of T cells and B cells and the antigen-specific adaptive immunity mediated by them.

Immunomodulatory effect of SCFAs on different immune cells

In vivo studies showed that short-chain fatty acids can inhibit hematopoietic activity, especially bone marrow production, and reduce mature myeloid cells (Thorburn et al. 2015; Trompette et al. 2014). Consistently, the presence of SCFAs (butyrate) can prevent monocytes from differentiating into macrophages and dendritic cells in vitro (Nascimento et al. 2011; Nencioni et al. 2007; Singh et al. 2010; Zimmerman et al. 2012). Besides, SCFAs (butyrate) inhibit the differentiation and maturation of dendritic cells by inhibiting histone deacetylation (Bosisio et al. 2008; Nencioni et al. 2007).

Importantly, extensive data indicate that SCFAs affect the recruitment of immune cells to the periphery. SCFAs (butyrate) can reduce the expression of monocyte chemoattractant protein-1 (MCP-1) and the release of vascular cell adhesion molecule-1 (VCAM1), thereby participating in regulating the recruitment and migration of macrophages to the intestine (Aguilar et al. 2014; Maa et al. 2010; Zapolska-Downar et al. 2004). Not only that, SCFAs (butyrate) can also regulate leukocyte trafficking by inhibiting the recruitment of macrophages and dendritic cells, which is achieved by reducing the expression of chemokines in dendritic cells derived from human monocytes (Such as CCL3, CCL4, CCL5, CXCL9, CXCL10 and CXCL11) (Blais, Seidman, and Asselin 2007; Kolaczkowska and Kubes 2013; Nastasi et al. 2015). In neutrophils, the presence of SCFAs (butyrate) reduces the expression of chemotactic receptors C5AR and CXCR2 on the cell model, and inhibits the chemotaxis of neutrophils in vivo through the G protein-coupled receptor GPR43 (Maslowski et al. 2009). Therefore, SCFAs (butyrate) reduce the recruitment of neutrophils to the intestine (Liu et al. 2014; Zhang et al. 2010). In addition, studies indicated that the treatment of SCFAs (mainly butyrate) reduces the number of neutrophils in the crypts and surface epithelium of patients with inflammatory bowel disease (IBD) (Luhrs et al. 2002).

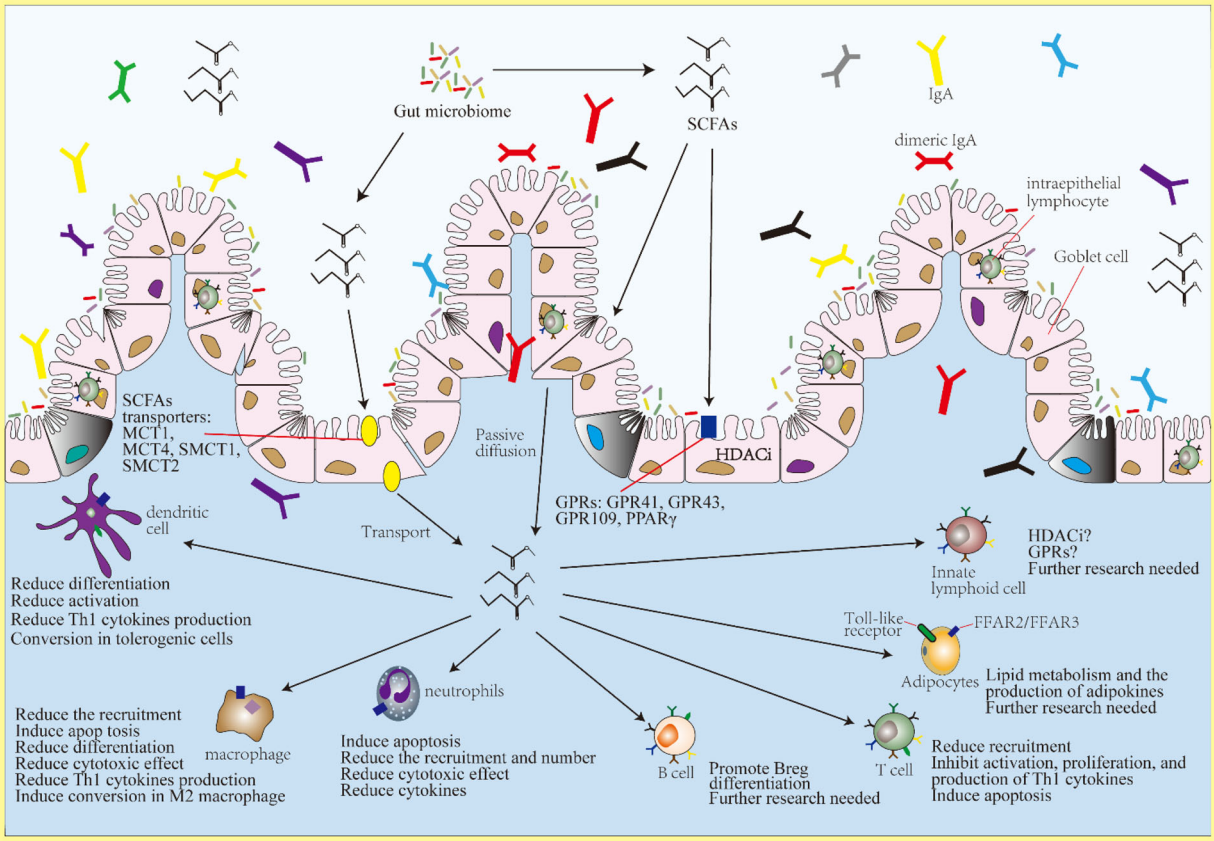

Figure 1. The role of SCFAs in immunity and inflammation.
In intestinal epithelial cells, intestinal microbial metabolites short-chain fatty acids (SCFAs) can enter intestinal tissue by passive diffusion and transporter. Transporters include MCT1, MCT4, SMCT1 and SMCT2. In addition, SCFAs can also activate G protein coupled receptors (GPRs) in intestinal epithelial cells, causing a series of downstream reactions. SCFAs can regulate the activities of many immune cells to participate in the regulation of host immune system.

In addition to regulating innate immune cells, SCFAs can also directly or indirectly regulate the differentiation of T cells to participate in specific cellular immunity (Kim, Park, and Kim 2014). For example, when T cells act as antigen-presenting cells to present antigens, the presence of SCFAs will directly regulate them. Interestingly, an earlier report showed that SCFAs (butyrate) cannot inhibit the proliferation of FoxP3^{+} T cells, but can inhibit the proliferation of CD4^{+} T cells (Fontenelle and Gilbert 2012). Besides, a certain concentration of SCFAs reduces the recruitment of T cells in the blood circulation to the active site of immune response (Maslowski et al. 2009; Vinolo et al. 2011a). After treatment with SCFAs (butyrate), the expression of chemokine receptor CXCR2 in lymphocytes decreased, which contributes to reducing the recruitment of T cells to the site of inflammation (Maslowski et al. 2009). On the other hand, SCFAs stimulate the thymus to secrete Treg, and the concentration of SCFAs is proportional to the number of Treg in the peripheral blood of normal mice (Tao et al. 2007). All in all, short-chain fatty acids play a vital role in effector T cells and regulatory T cells. This may be closely related to the internal immune environment, or it may be due to the ability of short-chain fatty acids to regulate the expression of related genes during the activation of lymphocytes. In addition, SCFAs are not selective in regulating T cells and effector T cells as histone deacetylase inhibitors. In contrast, short-chain fatty acids can enhance the tendency of the desired cytokine to polarize the environment during T cell differentiation or activation. However, T cells in the intestine may be the main target cells of short-chain fatty acids due to the higher concentration of short-chain fatty acids in colon/ileum tissues and intestinal-associated lymphoid tissues. Besides, in addition to the tissues surrounding the intestine, the role and mechanism of SCFAs in other tissues are still unclear, and further research is still needed.

Next, we talk about the role of SCFAs in B cells. At present, the research of SCFAs in B cells is much less than that of T cells. In vitro studies showed that SCFAs (butyrate) regulate B cells to produce more antibodies, which is related to histone deacetylation in B cells (Newman et al. 1989; Yamamoto et al. 1997). In detail, during the differentiation process of B cells into plasma cells, short-chain fatty acids regulate the epigenetics of B cells by inhibiting histone deacetylation. Not only that, short-chain fatty acids can also increase the metabolism of B cells, such as lipogenesis, oxidative phosphorylation and glycolysis. These important metabolic processes provide energy for the production of B cell structures and the differentiation of plasma cells (Kim 2018). In addition to the inhibitory effect of histone deacetylation, Rosser et al.'s study proved that SCFAs (butyrate)

support Breg function by increasing the level of 5-hydroxytryptamine-derived metabolite 5-hydroxyindole-3-acetic acid (5-HIAA), which is related to the aryl-hydrocarbon receptor (AHR) on the Breg cell membrane (Rosser et al. 2020).

Adipocytes involved in immune regulation of SCFAs

In addition to conventional immune regulation, studies showed that SCFAs can also regulate the immune system through fat cells. Previous studies indicated that adipocytes play a role in the immune system by affecting the production of adipokines and lipid metabolism, but they can also express Toll-like receptors (TLRs) which are the target receptors of fungal cell wall components and bacterial endotoxins (Desruisseaux et al. 2007). Several interesting phenomena are: free fatty acid receptor 3 (FFAR3) is highly expressed in pre-adipocytes; the role of pre-adipocytes and adipocytes in immune regulation has been proven; in specific pre-adipocytes, after receiving the treatment of short-chain fatty acids (especially butyrate) at a concentration of 2 mM, the expression of MCP-1 in the cells increased significantly. These phenomena all indicate that short-chain fatty acids can participate in the regulation of immune response through adipocytes (Garland 2011). In addition to the above evidence, fatty acids produced by the body's catabolism during infection stimulate an inflammatory response, leading to the activation of Toll-like receptors on the cell membrane of adipocytes (Song et al. 2006). Therefore, it is reasonable that short-chain fatty acids (SCFAs) participate in regulating the immune response through adipocytes.

The role of SCFAs in inflammation

As we all know, inflammation and immunity are inseparable. In recent years, the role of short-chain fatty acids (SCFAs) in the body's inflammatory response has also been widely demonstrated. Epidemiological evidence suggests that adding dietary fiber to the diet can improve cardiovascular function and reduce systemic inflammation (Anderson et al. 2009; Esposito and Giugliano 2006), while a low-fiber diet is positively related to inflammatory diseases (Morrison and Preston 2016). Specifically, two weeks after adding soluble fiber to the diet, the levels of circulating pro-inflammatory mediators such as interleukin 6 (IL-6), interleukin 8 (IL-8) and tumor necrosis factor (TNF) decreased (Macfarlane et al. 2013). In immunity and inflammation, when a certain part is invaded by pathogens, immune cells will recruit and secrete pro-inflammatory/anti-inflammatory cytokines to protect the body from harm. However, after this balance of immune-inflammation is broken, for example, excessive secretion of pro-inflammatory cytokines, it will lead to systemic inflammation and pathological diseases (Swirski and Nahrendorf 2013). Most importantly, short-chain fatty acids regulate inflammation by regulating the production of cytokines in immune cells (neutrophils, macrophages, dendritic cells, T cells and B cells). For example, SCFAs (butyrate and propionate) reduce the expression of tumor necrosis factor (TNF) and nitric oxide synthase (NOS) in monocytes induced by LPS (Vinolo et al. 2011a). These effects are mediated by activating target receptors (free fatty acid receptor 2/3 or G protein coupled receptor GPR109A) or inhibiting histone deacetylases.

SCFAs regulating inflammation via FFAR2, FFAR3, GPR109A and HDACs

Interestingly, short-chain fatty acids (SCFAs) exhibit conflicting results between pro-inflammatory and anti-inflammatory effects in the host's inflammatory response, which may be due to the different binding receptors of SCFAs and different local concentrations. A study indicated that during airway inflammation, SCFAs down-regulate the expression of IL-8 by targeting to activate free fatty acid receptors 2 and 3 on macrophages and neutrophils to improve the host's condition (Halnes et al. 2017). Short-chain fatty acids (acetate) also inhibit LPS-induced tumor necrosis factor (TNF) secretion by mouse and human monocytes by activating the free fatty acid receptor pathway (Masui et al. 2013). In macrophages, short-chain fatty acids (butyrate) exert anti-inflammatory effects by binding to and activating free fatty acid receptor 3 (FFAR3/GPR41) to down-regulate the levels of pro-inflammatory factors (inducible NOS, TNF, MCP-1, and IL-6) (Ohira et al. 2013). These results indicate that SCFAs exhibit strong anti-inflammatory capability, which is dependent on free fatty acids 2 and 3 (FFAR2/3). Therefore, SCFAs as FFAR2 and FFAR3 agonists may be potentially effective drugs for the treatment of inflammatory diseases. On the contrary, the pro-inflammatory effects of SCFAs have also been reported. Studies have shown that when FFAR2/3 is activated, it will further activate the downstream mTOR, PI3K or MAPK signaling pathways to exhibit pro-inflammatory effects (Seljeset and Siehler 2012; Thorburn, Macia, and Mackay 2014). In addition, SCFAs (acetate) up-regulate the production of pro-inflammatory cytokines and chemokines (IL-6, CXCL1 and CXCL2) by activating FFAR3 or FFAR2 and its downstream extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway and MAPK/p38 signaling pathway. These studies show that SCFAs can also activate FFAR2 and FFAR3 to participate in the pro-inflammatory effects. For the two completely opposite effects of SCFAs in inflammation, the possible mechanisms still need to be further explored. Based on current research reports, this may be related to the local concentration of SCFAs.

In addition to free fatty acid receptors, SCFAs have also been proven to participate in the regulation of inflammation by binding to GPR109A. The role of GPR109A plays an important role in inflammation and immunity. For example, stimulation of IFN-γ increases the expression of GPR109A in macrophages (Schaub, Futterer, and Pfeffer 2001). Besides, studies indicated that the activation of GPR109A can directly participate in anti-inflammatory immunity. Among short-chain fatty acids, propionate and acetate have a higher affinity for GPR109A, while butyrate has a lower affinity for GPR109A. However, there are also reports

showing that in colitis, butyrate participates in the regulation of inflammation by activating GPR109A (Chai, Digby, and Choudhury 2013; Singh et al. 2014). Therefore, it is of great significance to study the role of GPR109A-mediated SCFAs on immune cells in inflammatory diseases such as rheumatoid arthritis due to the anti-inflammatory and immunomodulatory effects of GPR109A. And it is expected to become a potential target for the treatment of inflammatory and immune-related diseases.

SCFAs not only exert anti-inflammatory effects through signal transduction, but also directly enter cells through passive diffusion or transporters (MCT1/4 and SMCT1/2). After entering the cell, SCFAs are used for energy synthesis on the one hand, and participate in inflammation regulation by inhibiting histone deacetylation on the other hand. In dendritic cells and macrophages, SCFAs (propionate and butyrate) exert their anti-inflammatory effects mainly by inhibiting histone deacetylation. In neutrophils and LPS-stimulated monocytes, SCFAs (propionate and butyrate) inhibit tumor necrosis factor (TNF) expression, NF-κB signaling pathway and histone deacetylase, and promote the production of anti-inflammatory cytokine IL-10 (Aoyama, Kotani, and Usami 2010; Chang et al. 2014; Usami et al. 2008; Vinolo et al. 2011b). However, it is not yet fully understood which specific HDACs mediate the regulation of the inflammatory response of SCFAs in immune cells due to their broad-spectrum inhibitory effect on HDACs, which may also be the reason for the pleiotropic effects of SCFAs. Therefore, in different immune cell types, gene knockout of specific histone deacetylase is necessary to clarify its specific role with short-chain fatty acids in inflammatory diseases.

SCFAs regulating inflammation via endothelial cells

In addition to immune cells, SCFAs can also regulate inflammation by endothelial cells. In endothelial cells, SCFAs activate anti-inflammatory signaling pathways by inhibiting HDACs, which suggests that SCFAs as HDACs inhibitors (HDACi) have therapeutic potential and hope in the treatment of inflammatory diseases. SCFAs, especially butyrate as HDACi, reduce the production of pro-inflammatory cytokines and oxidative stress to inhibit vascular inflammation and regulate endothelial function (Didonna and Opal 2015). SCFAs (butyrate) can reduce lung injury caused by sepsis and reduce the expression of IL-6 and cyclooxygenase-2 (COX-2) in endothelial cells (Ogawa et al. 2003). According to previous studies, the regulation of SCFAs in the inflammatory response mainly depends on free fatty acid receptors and inhibition of histone deacetylase. However, in endothelial cells, current studies only suggest that SCFAs participate in the regulation of inflammation by inhibiting histone deacetylase. Therefore, the regulation of SCFAs mediated by free fatty acid receptors in endothelial cell inflammatory response still need to be studied in depth.

The mechanism of SCFAs regulating inflammation

In short, there are two main mechanisms for SCFAs to regulate inflammation. (1) Through cell signal transduction: SCFAs bind to cell membrane surface G protein-coupled receptors (FFAR2, FFAR3, GPR109A), and regulate the downstream NF-κB pathway, MAPK pathway, Ca^{2+} concentration, and cAMP synthesis to participate in the regulation of inflammation. (2) After SCFAs enter cells through passive diffusion and transport proteins (MCT1/4 and SMCT1/2), they inhibit histone deacetylase and participate in the regulation of inflammation (Gill et al. 2018; Huang et al. 2017; Jeong et al. 2014; Roger et al. 2011) (Figure 2). However, whether immune cells express SCFAs transporters still needs to be explored.

The role of SCFAs in metabolism

Regulating immunity and participating in the control of inflammation are the two most important roles of SCFAs, but the role of SCFAs in host metabolism has also been proven. SCFAs can be used as raw materials to synthesize lipids and glucose, which may be the basis for SCFAs to participate in regulating host metabolism. Below we introduce several roles of SCFAs in metabolism.

Control of obesity

Epidemiological evidence indicated that gut microbiome are closely related to obesity, and adding dietary fiber to the diet can contribute to losing weight (Cho et al. 2013). This may be related to SCFAs, the metabolites of gut microbiome, if there is a causal relationship. There is evidence that in white adipose tissue, short-chain fatty acids reduce fatty acid intake by combining with GPR43 to inhibit fat accumulation (Kimura et al. 2013). In addition, in brown adipocytes, the activation of GPR43 promotes mitochondrial biogenesis and increases the cell's ability to use energy to generate heat (Hu et al. 2016). However, these phenomena are difficult to observe in vivo, but the fasting fat oxidation increases after an overweight man receives SCFAs (acetate) infusion in the distal colon. Furthermore, SCFAs can also mediate and regulate energy intake. For example, SCFAs (propionate) stimulate fat cells to produce the satiety hormone leptin by activating the cell surface FFAR3 (Xiong et al. 2004). There are some opposite voices suggesting that increased synthesis of short-chain fatty acids may be positively correlated with obesity. A comparative study of the fecal microbiota emphasized that compared with the normal population, the gut microbiome of overweight and obese individuals was significantly different, and the concentration of short-chain fatty acids (especially propionate) in the feces increased in the obese population (Schwiertz et al. 2010; Turnbaugh et al. 2006). Therefore, more evidence is needed to clarify the relationship between SCFAs and obesity due to the current contradictory conclusions.

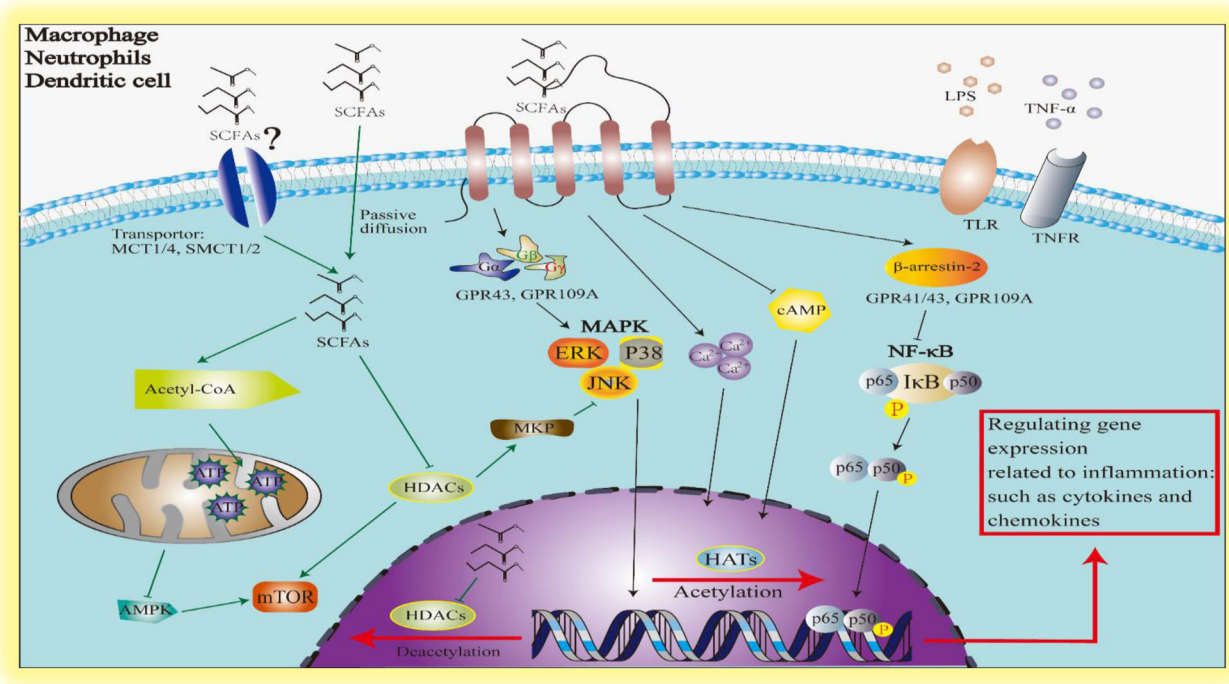

Figure 2. Mechanism of SCFAs regulating inflammation.
In macrophages, neutrophils and dendritic cells, short-chain fatty acids (SCFAs) can activate MAPK pathway through G protein coupled receptor, inhibit β-arrestin2/NF-κB pathway, inhibit the synthesis of cyclic adenosine monophosphate (cAMP), and promote calcium ion (Ca^{2+}) into nucleus, thus regulating the gene expression related to inflammation and immunity. In addition, SCFAs can enter cells through passive diffusion to inhibit mitochondrial/AMPK/mTOR pathway, inhibit histone deacetylation, and inhibit MAPK pathway via promoting MKP expression. However, in macrophages, neutrophils and dendritic cells, whether SCFAs can also pass through the cell membrane through transporters still needs further study.

Control of glucose homeostasis

The role of SCFAs in controlling glucose homeostasis may be due to their involvement in glucose synthesis. Studies indicated that adding arabinoxylan in the diet can improve the glucose tolerance of patients with type II diabetes by increasing the concentration of plasma SCFAs (Boll et al. 2016; Lu et al. 2004). In short, the mechanism by which SCFAs control glucose homeostasis is that SCFAs can directly stimulate colonic goblet cells (secretory cell) to secrete glucagon-like peptides (GLP-1) by binding to the FFAR2 receptor on the cell membrane (Tolhurst et al. 2012). There are also reports showing that SCFAs (propionate) activate GLP-1 mediated neural networks through free fatty acid receptors, thereby regulating ileal cells to participate in glucose homeostasis, which suggests that adding SCFAs to the diet may directly improve glucose tolerance (Zadeh-Tahmasebi et al. 2016). Studies on mice that knock out the FFAR2 gene ($GPR43^{-/-}$ mice) also revealed that SCFAs can directly promote pancreatic b-cell proliferation by binding to free fatty acid receptor FFAR2 (Villa et al. 2016). In mice, SCFAs (propionate) can increase intestinal gluconeogenesis through the intestinal-brain pathway mediated by FFAR3, which may be related to increased glucose homeostasis and weight loss (De Vadder et al. 2014; Perry et al. 2016). Therefore, it is of great significance to study the role of SCFAs in controlling glucose homeostasis. Adding specific SCFAs to the diet may be a novel method to treat diabetes.

Appetite regulation

One of the mechanisms by which SCFAs (propionates) regulate appetite may be the activation of free fatty acid receptor 3 on adipocytes to secrete the satiety hormone leptin (Xiong et al. 2004). There was a study indicating that inulin, a substance that increases propionate levels in the colon, can increase the appetite of healthy men and cause their energy intake to decrease (Byrne et al. 2016). What's more, some SCFAs can pass through the blood-brain barrier and reach the appetite regulation center in humans to control appetite (Deelchand et al. 2009; Freeland and Wolever 2010). Studies in mice clarified that this may be caused by inhibiting the neural circuits in the brain that control the release of PY in the intestine (Frost et al. 2014). In addition, GPR41 has been found to be expressed on human sympathetic ganglia (Kimura et al. 2011). In summary, these observations indicate that short-chain fatty acids (SCFAs) may regulate feeding behavior mainly through neural pathways.

Regulation of lipid metabolism

In addition to regulating glucose homeostasis, another important role of SCFAs in host metabolism is to affect lipid metabolism. In the liver, SCFAs (acetate) are involved in the synthesis of cholesterol and the production of new fat, but both of these processes can be inhibited by SCFAs (propionate) (Demigne et al. 1995; Nishina and Freedland 1990). Therefore, the ratio of acetate to propionate may be an

important determinant of SCFAs involved in regulating lipid metabolism. Besides, studies showed that propionate use alone can reduce visceral fat and liver fat (Chambers et al., 2015). The increase of short-chain fatty acids in the circulation is closely related to the decrease of lipogenesis and lipolysis of fat cells (Hong et al. 2005). In insulin-stimulated adipocytes, short-chain fatty acids inhibit lipid accumulation through GPR43 signaling, leading to smaller adipocytes and more sensitive responses, which may be related to fatty inflammatory infiltration (Kimura et al. 2013; Sun, Kusminski, and Scherer 2011).

SCFAs inhibit tumor cell proliferation and promote apoptosis

In addition to its important role in immunity, inflammation and metabolism, SCFAs also have an impact on tumor cell proliferation and apoptosis. In vitro culture in bovine kidney epithelial cells, the addition of 10 mM butyrate can cause cell cycle arrest and cell growth inhibition in a reversible manner. The mechanism is that butyrate affects the early stage of mitosis G1 (Gupta et al. 1994). The treatment of SCFAs (mainly butyrate and propionate) can inhibit the proliferation, migration and invasion of colon cancer cells (Kim et al. 2019).

Gut microbiome can metabolize complex carbohydrates into oligosaccharides and ferment them into SCFAs, which can be used to explain that adding dietary fiber to the diet in human and animal models reduces the risk of colon cancer (Perrin et al. 2001; Zeng, Lazarova, and Bordonaro 2014). In cells and tissues, the role of SCFAs (butyrate) depends mainly on their concentration. (1) Low concentration ($<$0.5 mM): at this time, butyrate is mainly used for cell energy supply and stimulates the proliferation of normal colon cells; (2) Physiologically relevant concentration (depending on cell type, generally 0.5 $\sim$ 5 mM): available to inhibit histone deacetylases (HDACs) (Perego et al. 2018). Studies showed that, at physiologically relevant intracellular concentrations (0.5 $\sim$ 5 mM), butyrate induces cell cycle arrest and apoptosis in a p53-dependent manner (Fung et al. 2012; Perego et al. 2018). Furthermore, in vitro studies suggested that butyrate regulates the transcription of many genes by inhibiting histone deacetylation, such as p21/Cip1 and cyclin D3 (Blottiere et al. 2003; Zeng et al. 2017). In addition, at a concentration of 0.5 mM or higher, butyrate inhibits the migration and invasion rate of cancer cells by increasing the expression of anti-metastatic genes (such as metalloproteinases) and inhibiting the activation of pre-metastatic genes (such as matrix metalloproteinases) (Emenaker et al. 2001; Zeng and Briske-Anderson 2005). In summary, SCFAs at an appropriate concentration may be a promising candidate for the future treatment of cancer, especially intestinal cancer.

Outlook

Gut microbiome play a vital role in maintaining the health of the host, which is mainly mediated by their metabolites SCFAs. SCFAs are produced by fermenting dietary fiber and protein by specific gut microbiome. Therefore, the concentration of SCFAs is higher in the colon and ileum and lower in the circulation. At present, SCFAs have been proved to be involved in regulating the host immune system, specifically regulating the differentiation and recruitment of immune cells, which is mainly mediated by G protein coupled receptors on the cell membrane of immune cells. In the inflammatory response, SCFAs exhibit two opposite effects, anti-inflammatory and pro-inflammatory. Based on existing evidence, it is speculated that this may be related to the local concentration of SCFAs, carbon chain length and activated receptors. In view of the prominent role of SCFAs in immunity and inflammation, supplementation of SCFAs may be an effective strategy for the future treatment of inflammatory and immune-related diseases, such as rheumatoid arthritis. However, the current research on SCFAs is too broad and in-depth and detailed research is still required.

In addition to regulating immunity and inflammation, studies have shown that SCFAs are also involved in controlling metabolism and tumor cell survival. SCFAs can be used for the synthesis of glucose and fat, which may be the theoretical basis for SCFAs to regulate metabolism. Controlling obesity, maintaining glucose homeostasis, regulating appetite and controlling lipid metabolism are all important manifestations of SCFAs involved in metabolism. In addition, in tumor cells (mainly colon cancer cells), the anti-tumor effect of SCFAs is related to its concentration. The appropriate concentration of SCFAs can regulate tumor cell cycle, inhibit proliferation and promote apoptosis. These data reveal the importance of SCFAs in human health. However, the fundamental difference between animal and human physiology determines the need to be cautious when inferring the effects of animals on human diseases, and clinical trials are needed to verify these effects in humans.

Disclosure statement

The authors declare that they have no competing interests.

Authors' contributions

YY and XYC drafted the manuscript. WDF assisted in reviewing literature. YQY modified the manuscript. YY and CHZ reviewed and edited the final manuscript. MDZ revised the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

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References

Aguilar, E. C., A. J. Leonel, L. G. Teixeira, A. R. Silva, J. F. Silva, J. M. Pelaez, L. S. Capettini, V. S. Lemos, R. A. Santos, and J. I. Alvarez-Leite. 2014. Butyrate impairs atherogenesis by reducing plaque inflammation and vulnerability and decreasing NFκB activation. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD* 24 (6): 606–13. doi: 10.1016/j.numecd.2014.01.002.

Alex, S., K. Lange, T. Amolo, J. S. Grinstead, A. K. Haakonsson, E. Szalowska, A. Koppen, K. Mudde, D. Haenen, S. Al-Lahham, et al. 2013. Short-chain fatty acids stimulate angiopoietin-like 4 synthesis in human colon adenocarcinoma cells by activating peroxisome proliferator-activated receptor γ. *Molecular and Cellular Biology* 33 (7): 1303–16. doi: 10.1128/MCB.00858-12.

Anderson, J. W., P. Baird, R. H. Davis, Jr., S. Ferreri, M. Knudtson, A. Koraym, V. Waters, and C. L. Williams. 2009. Health benefits of dietary fiber. *Nutrition Reviews* 67 (4):188–205. doi: 10.1111/j.1753-4887.2009.00189.x.

Aoyama, M., J. Kotani, and M. Usami. 2010. Butyrate and propionate induced activated or non-activated neutrophil apoptosis via HDAC inhibitor activity but without activating GPR-41/GPR-43 pathways. *Nutrition (Burbank, Los Angeles County, Calif.)* 26 (6):653–61. doi: 10.1016/j.nut.2009.07.006.

Blais, M., E. G. Seidman, and C. Asselin. 2007. Dual effect of butyrate on IL-1beta-mediated intestinal epithelial cell inflammatory response. *DNA and Cell Biology* 26 (3):133–47. doi: 10.1089/dna.2006.0532.

Blottiere, H. M., B. Buecher, J. P. Galmiche, and C. Cherbut. 2003. Molecular analysis of the effect of short-chain fatty acids on intestinal cell proliferation. *The Proceedings of the Nutrition Society* 62 (1):101–6. doi: 10.1079/PNS2002215.

Boll, E. V., L. M. Ekstrom, C. M. Courtin, J. A. Delcour, A. C. Nilsson, I. M. Bjorck, and E. M. Ostman. 2016. Effects of wheat bran extract rich in arabinoxylan oligosaccharides and resistant starch on overnight glucose tolerance and markers of gut fermentation in healthy young adults. *European Journal of Nutrition* 55 (4):1661–70. doi: 10.1007/s00394-015-0985-z.

Bolognini, D., A. B. Tobin, G. Milligan, and C. E. Moss. 2016. The pharmacology and function of receptors for short-chain fatty acids. *Molecular Pharmacology* 89 (3):388–98. doi: 10.1124/mol.115.102301.

Bosisio, D., M. Vulcano, A. Del Prete, M. Sironi, V. Salvi, L. Salogni, E. Riboldi, F. Leoni, C. A. Dinarello, G. Girolomoni, et al. 2008. Blocking TH17-polarizing cytokines by histone deacetylase inhibitors in vitro and in vivo. *Journal of Leukocyte Biology* 84 (6):1540–8. doi: 10.1189/jlb.0708401.

Brown, A. J., S. M. Goldsworthy, A. A. Barnes, M. M. Eilert, L. Tcheang, D. Daniels, A. I. Muir, M. J. Wigglesworth, I. Kinghorn, N. J. Fraser, et al. 2003. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *The Journal of Biological Chemistry* 278 (13): 11312–9. doi: 10.1074/jbc.M211609200.

Byrne, C. S., E. S. Chambers, H. Alhabeeb, N. Chhina, D. J. Morrison, T. Preston, C. Tedford, J. Fitzpatrick, C. Irani, A. Busza, et al. 2016. Increased colonic propionate reduces anticipatory reward responses in the human striatum to high-energy foods. *The American Journal of Clinical Nutrition* 104 (1):5–14. doi: 10.3945/ajcn.115.126706.

Chai, J. T., J. E. Digby, and R. P. Choudhury. 2013. GPR109A and vascular inflammation. *Current Atherosclerosis Reports* 15 (5):325 doi: 10.1007/s11883-013-0325-9.

Chambers, E. S., A. Viardot, A. Psichas, D. J. Morrison, K. G. Murphy, S. E. Zac-Varghese, K. MacDougall, T. Preston, C. Tedford, G. S. Finlayson, et al. 2015. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut* 64 (11):1744–54. doi: 10.1136/gutjnl-2014-307913.

Chang, P. V., L. Hao, S. Offermanns, and R. Medzhitov. 2014. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proceedings of the National Academy of Sciences of the United States of America* 111 (6): 2247–52. doi: 10.1073/pnas.1322269111.

Cho, S. S., L. Qi, G. C. Fahey, Jr., and D. M. Klurfeld. 2013. Consumption of cereal fiber, mixtures of whole grains and bran, and whole grains and risk reduction in type 2 diabetes, obesity, and cardiovascular disease. *Am J Clin Nutr* 98 (2):594–619. doi: 10.3945/ajcn.113.067629.

Chriett, S., A. Dąbek, M. Wojtala, H. Vidal, A. Balcerczyk, and L. Pirola. 2019. Prominent action of butyrate over β-hydroxybutyrate as histone deacetylase inhibitor, transcriptional modulator and anti-inflammatory molecule. *Scientific Reports* 9 (1):742 doi: 10.1038/s41598-018-36941-9.

Cresci, G. A., M. Thangaraju, J. D. Mellinger, K. Liu, and V. Ganapathy. 2010. Colonic gene expression in conventional and germ-free mice with a focus on the butyrate receptor GPR109A and the butyrate transporter SLC5A8. *J Gastrointest Surg* 14 (3):449–61. doi: 10.1007/s11605-009-1045-x.

Cummings, J. H., and G. T. Macfarlane. 1991. The control and consequences of bacterial fermentation in the human colon. *The Journal of Applied Bacteriology* 70 (6):443–59. doi: 10.1111/j.1365-2672.1991.tb02739.x.

Cummings, J. H., E. W. Pomare, W. J. Branch, C. P. Naylor, and G. T. Macfarlane. 1987. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* 28 (10):1221–7. doi: 10.1136/gut.28.10.1221.

De Vadder, F., P. Kovatcheva-Datchary, D. Goncalves, J. Vinera, C. Zitoun, A. Duchampt, F. Backhed, and G. Mithieux. 2014. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell* 156 (1-2):84–96. doi: 10.1016/j.cell.2013.12.016.

Deelchand, D. K., A. A. Shestov, D. M. Koski, K. Uğurbil, and P.-G. Henry. 2009. Acetate transport and utilization in the rat brain. *Journal of Neurochemistry* 109 Suppl 1 (Suppl 1):46–54. doi: 10.1111/j.1471-4159.2009.05895.x.

Demigne, C., C. Morand, M. A. Levrat, C. Besson, C. Moundras, and C. Remesy. 1995. Effect of propionate on fatty acid and cholesterol synthesis and on acetate metabolism in isolated rat hepatocytes. *The British Journal of Nutrition* 74 (2):209–19. doi: 10.1079/bjn19950124.

Desruisseaux, M. S., M. E. Nagajyothi, Trujillo, H. B. Tanowitz, and P. E. Scherer. 2007. Adipocyte, adipose tissue, and infectious disease. *Infect Immun* 75 (3):1066–78. doi: 10.1128/IAI.01455-06.

Didonna, A., and P. Opal. 2015. The promise and perils of HDAC inhibitors in neurodegeneration. *Annals of Clinical and Translational Neurology* 2 (1):79–101. doi: 10.1002/acn3.147.

Emenaker, N. J., G. M. Calaf, D. Cox, M. D. Basson, and N. Qureshi. 2001. Short-chain fatty acids inhibit invasive human colon cancer by modulating uPA, TIMP-1, TIMP-2, mutant p53, Bcl-2, Bax, p21 and PCNA protein expression in an in vitro cell culture model. *The Journal of Nutrition* 131 (11):3041S–6S. doi: 10.1093/jn/131.11.3041S.

Esposito, K., and D. Giugliano. 2006. Diet and inflammation: A link to metabolic and cardiovascular diseases. *European Heart Journal* 27 (1):15–20. doi: 10.1093/eurheartj/ehi605.

Fontenelle, B., and K. M. Gilbert. 2012. n-Butyrate anergized effector CD4+ T cells independent of regulatory T cell generation or activity. *Scandinavian Journal of Immunology* 76 (5):457–63. doi: 10.1111/j.1365-3083.2012.02740.x.

Freeland, K. R., and T. M. Wolever. 2010. Acute effects of intravenous and rectal acetate on glucagon-like peptide-1, peptide YY, ghrelin, adiponectin and tumour necrosis factor-alpha. *British Journal of Nutrition* 103 (3):460–6. doi: 10.1017/S0007114509991863.

Frost, G., M. L. Sleeth, M. Sahuri-Arisoylu, B. Lizarbe, S. Cerdan, L. Brody, J. Anastasovska, S. Ghourab, M. Hankir, S. Zhang, et al. 2014. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nature Communications* 5(:3611 doi: 10.1038/ncomms4611.

Fung, K. Y., L. Cosgrove, T. Lockett, R. Head, and D. L. Topping. 2012. A review of the potential mechanisms for the lowering of colorectal oncogenesis by butyrate. *Br J Nutr* 108 (5):820–31. doi: 10.1017/S0007114512001948.

Garland, S. H. 2011. Short chain fatty acids may elicit an innate immune response from preadipocytes: A potential link between

bacterial infection and inflammatory diseases. *Medical Hypotheses* 76 (6):881–3. doi: 10.1016/j.mehy.2011.02.041.

Gill, P. A., M. C. van Zelm, J. G. Muir, and P. R. Gibson. 2018. Review article: Short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. *Alimentary Pharmacology & Therapeutics* 48 (1):15–34. doi: 10.1111/apt.14689.

Goncalves, P., J. R. Araujo, and F. Martel. 2011. Characterization of butyrate uptake by nontransformed intestinal epithelial cell lines. *The Journal of Membrane Biology* 240 (1):35–46. doi: 10.1007/s00232-011-9340-3.

Grabarska, A., M. Dmoszyńska-Graniczka, E. Nowosadzka, and A. Stepulak. 2013. [Histone deacetylase inhibitors - molecular mechanisms of actions and clinical applications]. *Postepy Higieny i Medycyny Doswiadczalnej (Online)* 67(:722–35. doi: 10.5604/17322693.1061381.

Gupta, S., G. Alpini, R. P. Vemuru, E. Hurston, and D. A. Shafritz. 1994. Butyrate synchronization of hepatocytes: Modulation of cycling and cell cycle regulated gene expression. *Growth Factors (Chur, Switzerland)* 10 (3):171–80. doi: 10.3109/08977199409000235.

Halnes, I., K. J. Baines, B. S. Berthon, L. K. MacDonald-Wicks, P. G. Gibson, and L. G. Wood. 2017. Soluble fibre meal challenge reduces airway inflammation and expression of GPR43 and GPR41 in asthma. *Nutrients* 9 (1). doi: 10.3390/nu90100:57.

Hong, Y. H., Y. Nishimura, D. Hishikawa, H. Tsuzuki, H. Miyahara, C. Gotoh, K. C. Choi, D. D. Feng, C. Chen, H. G. Lee, et al. 2005. Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. *Endocrinology* 146 (12):5092–9. doi: 10.1210/en.2005-0545.

Hoverstad, T., and T. Midtvedt. 1986. Short-chain fatty acids in germfree mice and rats. *The Journal of Nutrition* 116 (9):1772–6. doi: 10.1093/jn/116.9.1772.

Hu, J., I. Kyrou, B. K. Tan, G. K. Dimitriadis, M. Ramanjaneya, G. Tripathi, V. Patel, S. James, M. Kawan, J. Chen, et al. 2016. Short-chain fatty acid acetate stimulates adipogenesis and mitochondrial biogenesis via GPR43 in brown adipocytes. *Endocrinology* 157 (5):1881–94. doi: 10.1210/en.2015-1944.

Huang, W., L. Zhou, H. Guo, Y. Xu, and Y. Xu. 2017. The role of short-chain fatty acids in kidney injury induced by gut-derived inflammatory response. *Metabolism: clinical and Experimental* 68(:20–30. doi: 10.1016/j.metabol.2016.11.006.

Iwanaga, T., K. Takebe, I. Kato, S. Karaki, and A. Kuwahara. 2006. Cellular expression of monocarboxylate transporters (MCT) in the digestive tract of the mouse, rat, and humans, with special reference to slc5a8. *Biomedical Research (Tokyo, Japan)* 27 (5):243–54. doi: 10.2220/biomedres.27.243.

Jeong, Y., R. Du, X. Zhu, S. Yin, J. Wang, H. Cui, W. Cao, and C. J. Lowenstein. 2014. Histone deacetylase isoforms regulate innate immune responses by deacetylating mitogen-activated protein kinase phosphatase-1. *Journal of Leukocyte Biology* 95 (4):651–9. doi: 10.1189/jlb.1013565.

Kasubuchi, M., S. Hasegawa, T. Hiramatsu, A. Ichimura, and I. Kimura. 2015. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. *Nutrients* 7 (4):2839–49. doi: 10.3390/nu7042839.

Kim, C. H. 2018. Immune regulation by microbiome metabolites. *Immunology* 154 (2):220–9. doi: 10.1111/imm.12930.

Kim, C. H., J. Park, and M. Kim. 2014. Gut microbiota-derived short-chain Fatty acids, T cells, and inflammation. *Immune Network* 14 (6):277–88. doi: 10.4110/in.2014.14.6.277.

Kim, K., O. Kwon, T. Y. Ryu, C. R. Jung, J. Kim, J. K. Min, D. S. Kim, M. Y. Son, and H. S. Cho. 2019. Propionate of a microbiota metabolite induces cell apoptosis and cell cycle arrest in lung cancer. *Molecular Medicine Reports* 20 (2):1569–74. doi: 10.3892/mmr.2019.10431.

Kimura, I., D. Inoue, T. Maeda, T. Hara, A. Ichimura, S. Miyauchi, M. Kobayashi, A. Hirasawa, and G. Tsujimoto. 2011. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proceedings of the National Academy of Sciences of the United States of America* 108 (19):8030–5. doi: 10.1073/pnas.1016088108.

Kimura, I., K. Ozawa, D. Inoue, T. Imamura, K. Kimura, T. Maeda, K. Terasawa, D. Kashihara, K. Hirano, T. Tani, et al. 2013. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. *Nature Communications* 4:1829. doi: 10.1038/ncomms2852.

Kirat, D., J. Masuoka, H. Hayashi, H. Iwano, H. Yokota, H. Taniyama, and S. Kato. 2006. Monocarboxylate transporter 1 (MCT1) plays a direct role in short-chain fatty acids absorption in caprine rumen. *The Journal of physiology* 576 (Pt 2):635–47. doi: 10.1113/jphysiol.2006.115931.

Koh, A., F. De Vadder, P. Kovatcheva-Datchary, and F. Backhed. 2016. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. *Cell* 165 (6):1332–45. doi: 10.1016/j.cell.2016.05.041.

Kolaczkowska, E., and P. Kubes. 2013. Neutrophil recruitment and function in health and inflammation. *Nature Reviews. Immunology* 13 (3):159–75. doi: 10.1038/nri3399.

Le Poul, E., C. Loison, S. Struyf, J. Y. Springael, V. Lannoy, M. E. Decobecq, S. Brezillon, V. Dupriez, G. Vassart, J. Van Damme, et al. 2003. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *The Journal of Biological Chemistry* 278 (28):25481–9. doi: 10.1074/jbc.M301403200.

Liu, B., J. Qian, Q. Wang, F. Wang, Z. Ma, and Y. Qiao. 2014. Butyrate protects rat liver against total hepatic ischemia reperfusion injury with bowel congestion. *PloS One* 9 (8):e106184. doi: 10.1371/journal.pone.0106184.

Logan, A. C., F. N. Jacka, and S. L. Prescott. 2016. Immune-microbiota interactions: Dysbiosis as a global health issue. *Current allergy and Asthma Reports* 16 (2):13. doi: 10.1007/s11882-015-0590-5.

Lu, Z. X., K. Z. Walker, J. G. Muir, and K. O'Dea. 2004. Arabinoxylan fibre improves metabolic control in people with Type II diabetes. *European Journal of Clinical Nutrition* 58 (4):621–8. doi: 10.1038/sj.ejcn.1601857.

Luhrs, H., T. Gerke, J. G. Muller, R. Melcher, J. Schauber, F. Boxberge, W. Scheppach, and T. Menzel. 2002. Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. *Scandinavian Journal of Gastroenterology* 37 (4):458–66. doi: 10.1080/003655202317316105.

Maa, M. C., M. Y. Chang, M. Y. Hsieh, Y. J. Chen, C. J. Yang, Z. C. Chen, Y. K. Li, C. K. Yen, R. R. Wu, and T. H. Leu. 2010. Butyrate reduced lipopolysaccharide-mediated macrophage migration by suppression of Src enhancement and focal adhesion kinase activity. *The Journal of Nutritional Biochemistry* 21 (12):1186–92. doi: 10.1016/j.jnutbio.2009.10.004.

Macfarlane, G. T., and S. Macfarlane. 2012. Bacteria, colonic fermentation, and gastrointestinal health. *Journal of AOAC International* 95 (1):50–60. doi: 10.5740/jaoacint.sge_macfarlane.

Macfarlane, S., S. Cleary, B. Bahrami, N. Reynolds, and G. T. Macfarlane. 2013. Synbiotic consumption changes the metabolism and composition of the gut microbiota in older people and modifies inflammatory processes: A randomised, double-blind, placebo-controlled crossover study. *Alimentary Pharmacology & Therapeutics* 38 (7):804–16. doi: 10.1111/apt.12453.

Macia, L., J. Tan, A. T. Vieira, K. Leach, D. Stanley, S. Luong, M. Maruya, C. Ian McKenzie, A. Hijikata, C. Wong, et al. 2015. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. *Nature Communications* 6:6734. doi: 10.1038/ncomms7734.

Maslowski, K. M., A. T. Vieira, A. Ng, J. Kranich, F. Sierro, D. Yu, H. C. Schilter, M. S. Rolph, F. Mackay, D. Artis, et al. 2009. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 461 (7268):1282–6. doi: 10.1038/nature08530.

Masui, R., M. Sasaki, Y. Funaki, N. Ogasawara, M. Mizuno, A. Iida, S. Izawa, Y. Kondo, Y. Ito, Y. Tamura, et al. 2013. G protein-coupled receptor 43 moderates gut inflammation through cytokine regulation from mononuclear cells. *Inflammatory Bowel Diseases* 19 (13):2848–56. doi: 10.1097/01.MIB.0000435444.14860.ea.

Morrison, D. J., and T. Preston. 2016. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* 7 (3):189–200. doi: 10.1080/19490976.2015.1134082.

Nagalingam, N. A., and S. V. Lynch. 2012. Role of the microbiota in inflammatory bowel diseases. *Inflammatory Bowel Diseases* 18 (5): 968–84. doi: 10.1002/ibd.21866.

Nascimento, C. R., C. G. Freire-de-Lima, A. da Silva de Oliveira, F. D. Rumjanek, and V. M. Rumjanek. 2011. The short chain fatty acid sodium butyrate regulates the induction of CD1a in developing dendritic cells. *Immunobiology* 216 (3):275–84. doi: 10.1016/j.imbio.2010.07.004.

Nastasi, C., M. Candela, C. M. Bonefeld, C. Geisler, M. Hansen, T. Krejsgaard, E. Biagi, M. H. Andersen, P. Brigidi, N. Odum, et al. 2015. The effect of short-chain fatty acids on human monocyte-derived dendritic cells. *Scientific Reports* 5(:16148. doi: 10.1038/srep16148.

Nencioni, A., J. Beck, D. Werth, F. Grunebach, F. Patrone, A. Ballestrero, and P. Brossart. 2007. Histone deacetylase inhibitors affect dendritic cell differentiation and immunogenicity. *Clinical Cancer Research : An official journal of the American Association for Cancer Research* 13 (13):3933–41. doi: 10.1158/1078-0432.CCR-06-2903.

Newman, J. D., G. S. Eckardt, A. Boyd, and L. C. Harrison. 1989. Induction of the insulin receptor and other differentiation markers by sodium butyrate in the Burkitt lymphoma cell, Raji. *Biochemical and Biophysical Research Communications* 161 (1):101–6. doi: 10.1016/0006-291X(89)91566-0.

Nishina, P. M., and R. A. Freedland. 1990. Effects of propionate on lipid biosynthesis in isolated rat hepatocytes. *The Journal of Nutrition* 120 (7):668–73. doi: 10.1093/jn/120.7.668.

Ogawa, H., P. Rafiee, P. J. Fisher, N. A. Johnson, M. F. Otterson, and D. G. Binion. 2003. Butyrate modulates gene and protein expression in human intestinal endothelial cells. *Biochemical and Biophysical Research Communications* 309 (3):512–9. doi: 10.1016/j.bbrc.2003.08.026.

Ohira, H., Y. Fujioka, C. Katagiri, R. Mamoto, M. Aoyama-Ishikawa, K. Amako, Y. Izumi, S. Nishiumi, M. Yoshida, M. Usami, et al. 2013. Butyrate attenuates inflammation and lipolysis generated by the interaction of adipocytes and macrophages. *Journal of Atherosclerosis and Thrombosis* 20 (5):425–42. doi: 10.5551/jat.15065.

Ohira, H., W. Tsutsui, and Y. Fujioka. 2017. Are short chain fatty acids in gut microbiota defensive players for inflammation and atherosclerosis? *Journal of Atherosclerosis and Thrombosis* 24 (7):660–72. doi: 10.5551/jat.RV17006.

Perego, S., V. Sansoni, G. Banfi, and G. Lombardi. 2018. Sodium butyrate has anti-proliferative, pro-differentiating, and immunomodulatory effects in osteosarcoma cells and counteracts the TNFα-induced low-grade inflammation . *International Journal of Immunopathology and Pharmacology* 32(:394632017752240. doi: 10.1177/0394632017752240.

Perrin, P., F. Pierre, Y. Patry, M. Champ, M. Berreur, G. Pradal, F. Bornet, K. Meflah, and J. Menanteau. 2001. Only fibres promoting a stable butyrate producing colonic ecosystem decrease the rate of aberrant crypt foci in rats. *Gut* 48 (1):53–61. doi: 10.1136/gut.48.1.53.

Perry, R. J., L. Peng, N. A. Barry, G. W. Cline, D. Zhang, R. L. Cardone, K. F. Petersen, R. G. Kibbey, A. L. Goodman, and G. I. Shulman. 2016. Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. *Nature* 534 (7606):213–7. doi: 10.1038/nature18309.

Pluznick, J. L. 2016. Gut microbiota in renal physiology: Focus on short-chain fatty acids and their receptors. *Kidney International* 90 (6):1191–8. doi: 10.1016/j.kint.2016.06.033.

Pluznick, J. L., R. J. Protzko, H. Gevorgyan, Z. Peterlin, A. Sipos, J. Han, I. Brunet, L. X. Wan, F. Rey, T. Wang, et al. 2013. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. *Proceedings of the National Academy of Sciences of the United States of America* 110 (11):4410–5. doi: 10.1073/pnas.1215927110.

Ratajczak, W., A. Rył, A. Mizerski, K. Walczakiewicz, O. Sipak, and M. Laszczyńska. 2019. Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). *Acta Biochimica Polonica* 66 (1):1–12. doi: 10.18388/abp.2018_2648.

Rescigno, M. 2014. Intestinal microbiota and its effects on the immune system. *Cellular Microbiology* 16 (7):1004–13. doi: 10.1111/cmi.12301.

Roger, T., J. Lugrin, D. Le Roy, G. Goy, M. Mombelli, T. Koessler, X. C. Ding, A. L. Chanson, M. K. Reymond, I. Miconnet, et al. 2011. Histone deacetylase inhibitors impair innate immune responses to Toll-like receptor agonists and to infection. *Blood* 117 (4):1205–17. doi: 10.1182/blood-2010-05-284711.

Rosser, E. C., C. J. M. Piper, D. E. Matei, P. A. Blair, A. F. Rendeiro, M. Orford, D. G. Alber, T. Krausgruber, D. Catalan, N. Klein, et al. 2020. Microbiota-Derived Metabolites Suppress Arthritis by Amplifying Aryl-Hydrocarbon Receptor Activation in Regulatory B Cells. *Cell Metabolism* 31 (4):837–51. e810. doi: 10.1016/j.cmet.2020.03.003.

Russell, W. R., S. W. Gratz, S. H. Duncan, G. Holtrop, J. Ince, L. Scobbie, G. Duncan, A. M. Johnstone, G. E. Lobley, R. J. Wallace, et al. 2011. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *The American Journal of Clinical Nutrition* 93 (5):1062–72. doi: 10.3945/ajcn.110.002188.

Sanchez, J. I., M. Marzorati, C. Grootaert, M. Baran, V. Van Craeyveld, C. M. Courtin, W. F. Broekaert, J. A. Delcour, W. Verstraete, and T. Van de Wiele. 2009. Arabinoxylan-oligosaccharides (AXOS) affect the protein/carbohydrate fermentation balance and microbial population dynamics of the Simulator of Human Intestinal Microbial Ecosystem. *Microbial Biotechnology* 2 (1):101–13. doi: 10.1111/j.1751-7915.2008.00064.x.

Schaub, A., A. Futterer, and K. Pfeffer. 2001. PUMA-G, an IFN-gamma-inducible gene in macrophages is a novel member of the seven transmembrane spanning receptor superfamily. *European Journal of Immunology* 31 (12):3714–25. doi: 10.1002/1521-4141(200112)31:12<3714::aid-immu3714>3.0.co;2-1.

Schwarzer, M., K. Makki, G. Storelli, I. Machuca-Gayet, D. Srutkova, P. Hermanova, M. E. Martino, S. Balmand, T. Hudcovic, A. Heddi, et al. 2016. Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition. *Science (New York, N.Y.)* 351 (6275):854–7. doi: 10.1126/science.aad8588.

Schwiertz, A., D. Taras, K. Schafer, S. Beijer, N. A. Bos, C. Donus, and P. D. Hardt. 2010. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring, Md.)* 18 (1):190–5. doi: 10.1038/oby.2009.167.

Seljeset, S., and S. Siehler. 2012. Receptor-specific regulation of ERK1/2 activation by members of the "free fatty acid receptor" family. *Journal of Receptor and Signal Transduction Research* 32 (4): 196–201. doi: 10.3109/10799893.2012.692118.

Singh, N., A. Gurav, S. Sivaprakasam, E. Brady, R. Padia, H. Shi, M. Thangaraju, P. D. Prasad, S. Manicassamy, D. H. Munn, et al. 2014. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 40 (1):128–39. doi: 10.1016/j.immuni.2013.12.007.

Singh, N., M. Thangaraju, P. D. Prasad, P. M. Martin, N. A. Lambert, T. Boettger, S. Offermanns, and V. Ganapathy. 2010. Blockade of dendritic cell development by bacterial fermentation products butyrate and propionate through a transporter (Slc5a8)-dependent inhibition of histone deacetylases. *The Journal of Biological Chemistry* 285 (36):27601–8. doi: 10.1074/jbc.M110.102947.

Sivaprakasam, S., Y. D. Bhutia, S. Yang, and V. Ganapathy. 2017. Short-Chain Fatty Acid Transporters: Role in Colonic Homeostasis. *Comprehensive Physiology* 8 (1):299–314. doi: 10.1002/cphy.c170014.

Song, M. J., K. H. Kim, J. M. Yoon, and J. B. Kim. 2006. Activation of Toll-like receptor 4 is associated with insulin resistance in adipocytes. *Biochemical and Biophysical Research Communications* 346 (3):739–45. doi: 10.1016/j.bbrc.2006.05.170.

Sun, K., C. M. Kusminski, and P. E. Scherer. 2011. Adipose tissue remodeling and obesity. *The Journal of Clinical Investigation* 121 (6):2094–101. doi: 10.1172/JCI45887.

Swirski, F. K., and M. Nahrendorf. 2013. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. *Science (New York, N.Y.)* 339 (6116):161–6. doi: 10.1126/science.1230719.

Tan, J., C. McKenzie, M. Potamitis, A. N. Thorburn, C. R. Mackay, and L. Macia. 2014. The role of short-chain fatty acids in health and disease. *Advances in Immunology* 121(:91–119. doi: 10.1016/B978-0-12-800100-4.00003-9.

Tao, R., E. F. de Zoeten, E. Ozkaynak, C. Chen, L. Wang, P. M. Porrett, B. Li, L. A. Turka, E. N. Olson, M. I. Greene, et al. 2007. Deacetylase inhibition promotes the generation and function of regulatory T cells. *Nature Medicine* 13 (11):1299–307. doi: 10.1038/nm1652.

Thorburn, A. N., L. Macia, and C. R. Mackay. 2014. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* 40 (6): 833–42. doi: 10.1016/j.immuni.2014.05.014.

Thorburn, A. N., C. I. McKenzie, S. Shen, D. Stanley, L. Macia, L. J. Mason, L. K. Roberts, C. H. Wong, R. Shim, R. Robert, et al. 2015. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nature Communications* 6(:7320 doi: 10.1038/ncomms8320.

Tolhurst, G., H. Heffron, Y. S. Lam, H. E. Parker, A. M. Habib, E. Diakogiannaki, J. Cameron, J. Grosse, F. Reimann, and F. M. Gribble. 2012. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 61 (2):364–71. doi: 10.2337/db11-1019.

Trompette, A., E. S. Gollwitzer, K. Yadava, A. K. Sichelstiel, N. Sprenger, C. Ngom-Bru, C. Blanchard, T. Junt, L. P. Nicod, N. L. Harris, et al. 2014. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med* 20 (2): 159–66. doi: 10.1038/nm.3444.

Turnbaugh, P. J., R. E. Ley, M. A. Mahowald, V. Magrini, E. R. Mardis, and J. I. Gordon. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444 (7122):1027–31. doi: 10.1038/nature05414.

Usami, M., K. Kishimoto, A. Ohata, M. Miyoshi, M. Aoyama, Y. Fueda, and J. Kotani. 2008. Butyrate and trichostatin A attenuate nuclear factor kappaB activation and tumor necrosis factor alpha secretion and increase prostaglandin E2 secretion in human peripheral blood mononuclear cells. *Nutrition Research (New York, N.Y.)* 28 (5):321–8. doi: 10.1016/j.nutres.2008.02.012.

Villa, S. R., M. Priyadarshini, M. H. Fuller, T. Bhardwaj, M. R. Brodsky, A. R. Angueira, R. E. Mosser, B. A. Carboneau, S. A. Tersey, H. Mancebo, et al. 2016. Loss of Free Fatty Acid Receptor 2 leads to impaired islet mass and beta cell survival. *Scientific Reports* 6:28159. doi: 10.1038/srep28159.

Vinolo, M. A., H. G. Rodrigues, E. Hatanaka, F. T. Sato, S. C. Sampaio, and R. Curi. 2011a. Suppressive effect of short-chain fatty acids on production of proinflammatory mediators by neutrophils. *The Journal of Nutritional Biochemistry* 22 (9):849–55. doi: 10.1016/j.jnutbio.2010.07.009.

Vinolo, M. A., H. G. Rodrigues, R. T. Nachbar, and R. Curi. 2011b. Regulation of inflammation by short chain fatty acids. *Nutrients* 3 (10):858–76. doi: 10.3390/nu3100858.

Wall, R., R. P. Ross, F. Shanahan, L. O'Mahony, C. O'Mahony, M. Coakley, O. Hart, P. Lawlor, E. M. Quigley, B. Kiely, et al. 2009. Metabolic activity of the enteric microbiota influences the fatty acid composition of murine and porcine liver and adipose tissues. *The American Journal of Clinical Nutrition* 89 (5):1393–401. doi: 10.3945/ajcn.2008.27023.

Wang, N., D. Y. Guo, X. Tian, H. P. Lin, Y. P. Li, S. J. Chen, Y. C. Fu, W. C. Xu, and C. J. Wei. 2016. Niacin receptor GPR109A inhibits insulin secretion and is down-regulated in type 2 diabetic islet beta-cells. *General and Comparative Endocrinology* 237:98–108. doi: 10.1016/j.ygcen.2016.08.011.

Wong, J. M., R. de Souza, C. W. Kendall, A. Emam, and D. J. Jenkins. 2006. Colonic health: Fermentation and short chain fatty acids. *Journal of Clinical Gastroenterology* 40 (3):235–43. doi: 10.1097/00004836-200603000-00015.

Xiong, Y., N. Miyamoto, K. Shibata, M. A. Valasek, T. Motoike, R. M. Kedzierski, and M. Yanagisawa. 2004. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *Proceedings of the National Academy of Sciences of the United States of America* 101 (4):1045–50. doi: 10.1073/pnas.2637002100.

Yamamoto, I., T. Adachi, Y. Kishiro, M. Fujiwara, and E. Gohda. 1997. Interleukin-2-dependent augmentation of the anti-TNP antibody production by sodium butyrate in cultured murine splenic B cells. International *Journal of Immunopharmacology.* 19 (6):347–54. doi: 10.1016/S0192-0561(97)00036-2.

Yao, Y., X. Cai, C. Chen, H. Fang, Y. Zhao, W. Fei, F. Chen, and C. Zheng. 2020. The role of microbiomes in pregnant women and offspring: research progress of recent years. *Frontiers in Pharmacology* 11:643 doi: 10.3389/fphar.2020.00643.

Zadeh-Tahmasebi, M., F. A. Duca, B. A. Rasmussen, P. V. Bauer, C. D. Cote, B. M. Filippi, and T. K. Lam. 2016. Activation of Short and Long Chain Fatty Acid Sensing Machinery in the Ileum Lowers Glucose Production in Vivo. *J Biol Chem* 291 (16):8816–24. doi: 10.1074/jbc.M116.718460.

Zapolska-Downar, D., A. Siennicka, M. Kaczmarczyk, B. Kołodziej, and M. Naruszewicz. 2004. Butyrate inhibits cytokine-induced VCAM-1 and ICAM-1 expression in cultured endothelial cells: The role of NF-kappaB and PPARalpha. *The Journal of Nutritional Biochemistry* 15 (4):220–8. doi: 10.1016/j.jnutbio.2003.11.008.

Zeng, H., and M. Briske-Anderson. 2005. Prolonged butyrate treatment inhibits the migration and invasion potential of HT1080 tumor cells. *The Journal of Nutrition* 135 (2):291–5. doi: 10.1093/jn/135.2.291.

Zeng, H., D. L. Lazarova, and M. Bordonaro. 2014. Mechanisms linking dietary fiber, gut microbiota and colon cancer prevention. *World Journal of Gastrointestinal Oncology* 6 (2):41–51. doi: 10.4251/wjgo.v6.i2.41.

Zeng, H., D. P. Taussig, W. H. Cheng, L. K. Johnson, and R. Hakkak. 2017. Butyrate inhibits cancerous HCT116 colon cell proliferation but to a lesser extent in noncancerous NCM460 Colon Cells. *Nutrients* 9 (1). doi: 10.3390/nu90100:25.

Zhang, L., S. Jin, C. Wang, R. Jiang, and J. Wan. 2010. Histone deacetylase inhibitors attenuate acute lung injury during cecal ligation and puncture-induced polymicrobial sepsis. *World Journal of Surgery* 34 (7):1676–83. doi: 10.1007/s00268-010-0493-5.

Zimmerman, M. A., N. Singh, P. M. Martin, M. Thangaraju, V. Ganapathy, J. L. Waller, H. Shi, K. D. Robertson, D. H. Munn, and K. Liu. 2012. Butyrate suppresses colonic inflammation through HDAC1-dependent Fas upregulation and Fas-mediated apoptosis of T cells. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 302 (12):G1405–1415. doi: 10.1152/ajpgi.00543.2011.