Microbiota Short-Chain Fatty Acids Modulate Antioxidant Defences

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Food nutrients play a key role in human metabolism and health via the modulation of multiple mechanisms, including energy metabolism, intestinal homeostasis, antioxidant homeostasis, and immune responses. The intestine is an essential organ involved in human nutrition, the metabolic activity of gut microbes is essential for maintaining host health, and alterations in its composition induce metabolic shifts that may have adverse effects. The consensus on microbiota-mediated healthy effects on the host is based on the microbe-induced biotransformation of food components into bioactive metabolites. Bioactive molecules exhibit, in combination with food components, the ability to modulate the metabolic pathways of the host or to modify the composition and metabolism of the microbiota. Studies indicated the efficacy of the carbohydrates accessible to the microbiota (MACs), polyphenols, and polyunsaturated fatty acids (PUFAs) in increasing the microbial population with the ability to yield biologically active metabolites (e.g., polyphenol metabolites, short-chain fatty acids (SCFAs)) capable of modulating redox homeostasis of the host.

MACs polyphenols PUFAs gut microbiota active metabolites

1. Introduction

The beneficial effects associated with the diversity of the microbial population arise from the metabolic activities of specific microbial populations. Under eubiotic conditions, the commensal relationship between the microbiota and the host mainly consists of the capacity of bacteria to generate bioactive metabolites, starting from the ingested food, which exhibits the ability to modulate different metabolic pathways of the host [1]. For example, the production of carboxylic acids with aliphatic tails with fewer than six carbon atoms such as acetate (C2), propionate (C3), and butyrate (C4), resulting from the anaerobic fermentation of dietary plant polysaccharides, is the most relevant metabolic activity of enteric microbiota. These molecules are collectively referred to as Short-chain Fatty Acids (SCFAs) [2].

The growth of anaerobic SCFA-producing bacteria is favored by the low oxygen concentrations in the intestine where the two most abundant populations, namely, Bacteroidetes and Firmicutes, mainly produce acetate/propionate and butyrate, respectively [3]. Interestingly, due to butyrate generation during acetate metabolism, their coexistence can be consequential to mutual metabolic gain, thus resulting from the utilization of acetate produced by Bacteroidetes and Firmicutes to produce butyrate and propionate [4]. This example strongly supports the concept that the production of SCFAs is finely tuned by the balance of the bacterial species present in the gut.

The homeostatic condition of the intestinal microbiota can be restored by the level of SCFAs, and many studies in vivo describe the link between gut dysbiosis and the production of SCFAs (**Table 1**).

Table 1. Studies reporting the link between gut dysbiosis/production of SCFAs in several human diseases. An increase or decrease in the levels considered is indicated by upward (↑) or downward arrow (↓), respectively.

Disease	Model	Microbiota Alteration Production of SCFAs	Ref.
Diabetes	Randomized clinical trial High-fiber diet	Type 2 diabetes ↓ SCFAs High fiber intake ↑ SCFAs ↑ SCFA-producing bacteria	[5]
	Meta analysis Dietary fiber	↑ Butyrate, propionate ↑ *Bifidobacterium*	[6]
	313 patients	↓ Acetate-to-butyrate converter *Firmicutes* (*Roseburia*) ↓ Propionate ↑ Pathogens (*Enterobacteriaceae*, *Proteobacteria*)	[7]
Inflammatory Bowel Disease (IBD)	127 patients 87 healthy controls	↓ Butyrate-producing bacteria (*Firmicutes*) ↓ SCFAs (acetate, propionate, butyrate)	[8]
	10 inactive Crohn patients 10 healthy controls	↓ SCFA-producing bacteria ↓ *Roseburia inulinivorans*, ↓ *Ruminococcus torques*, ↓ *Clostridium lavalense*, ↓ *Bacteroides uniformis* ↓ *Faecalibacterium prausnitzii*	[9]
Nonalcoholic Fatty Liver Disease	14 nonalcoholic fatty liver, 18 nonalcoholic steatohepatitis 27 healthy controls	↑ SCFA levels ↑ SCFA-producing bacteria (*Fusobacteriaceae*, *Prevotellaceae*)	[10]
	25 nonalcoholic fatty liver 25 nonalcoholic steatohepatitis 25 healthy donors	↓ *Ruminococcaceae* ↓ *Clostridiales* ↑ *Bacteroidetes* ↓ *Firmicutes*	[11]
	30 patients F0/1 fibrosis stage	↑ *Bacteroidetes* (F ≥ 2) ↑ *Ruminococcus* (F ≥ 2)	[12]

Disease		Model	Microbiota Alteration Production of SCFAs	Ref.
		27 patients F ≥ 2 fibrosis	↓ *Prevotella*	
Neurodegeneration	Parkinson's Disease	Nonparametric meta-analysis	↑ *Akkermansia* ↓ Fecal SCFAs (acetate, propionate, butyrate)	[13]
		96 patients 85 controls	↓ Fecal SCFAs ↑ Plasma SCFAs ↑ Pro-inflammatory bacteria	[14]
		95 patients 33 controls	↓ Fecal SCFAs (propionic acetic, butyric) ↑ Plasma SCFA (propionic acetic)	[15]
		25 patients	↓ *Firmicutes*, *Bifidobacterium* ↑ *Bacteroidetes*	[16]
	Alzheimer's Disease	33 dementia 22 mild cognitive impairment 120 subjective cognitive decline	↓ SCFA-producing bacteria (*Ruminococcus*, *Eubacterium*) ↑ AD biomarkers (Amyloid-β1-42 and p-tau concentrations)	[17]
		Mouse model Sodium butyrate supplementation	↓ Amyloid-β1-42 protein (40%)	[18]

[19] [20]

mands of erving the local O_2 -inducible on of an bacteria) [21], indirectly regulating the functionality of the intestinal barrier [22]. In addition, SCFAs have been shown to display an inhibitory effect on the growth of potentially pathogenic bacteria such as Salmonella typhimurium [23] or Clostridium difficile [24].

2. Effect of SCFAs on Gut Homeostasis

Acetate, propionate, and butyrate in the colon are present in the molar ratio 60:25:15, although proportions can vary depending on factors such as diet, microbiota composition, the site of fermentation, and the genotype of the host [25]. These are the predominant SCFAs present in the proximal regions of the large intestine in humans and rodents, and they are present at mM levels [26][27][28].

Acetate, propionate, and butyrate reach the highest concentrations (70–140 mM) in the proximal colon [25] where they enhance mucin secretion by increasing the expression of the MUC2 gene [29], with a concentration gradient decreasing from the lumen to the periphery [30]. When these SCFAs are absorbed into the hepatic portal circulation and the lacteal lymphatic system, they reach total concentrations ranging from 375 µM to 148 µM in the portal and hepatic blood respectively, or 79 µM in peripheral blood [25][31]. Butyrate and propionate, mostly metabolized by hepatocytes, were reported in a range of 1–15 µM in the systemic circulation, while acetate ranged between 100

and 200 μM [32][33]. However, the small amounts of SCFAs present in the bloodstream are sufficient to elicit a wide range of biological functions in different tissues.

A study on a mouse model of induced colitis demonstrated that SCFAs preserve gut homeostasis by acting on the inflammasome pathway through the upregulation of interleukin-18 [34]. Accordingly, low levels of butyrate and propionate-producing bacteria were found in patients suffering from inflammatory bowel diseases (IBD) such as ulcerative colitis or Crohn's disease [8][9]. Several in vivo analyses have indicated that SCFAs regulate gut motility by stimulating mucosal receptors [35] or by increasing the release of the Peptide YY from gut endocrine cells, thus favoring intestine motility [36]. Other studies demonstrated that SCFAs act in preventing colonic diseases, by enhancing the absorption of minerals and decreasing the cholesterol concentration [37][38]. Experiments using germ-free animals reported that their reduced gut motility can be restored by the infusion of SCFAs [39].

Convincing evidence supports the idea that the beneficial effect of SCFAs extends beyond the colon. In fact, SCFAs participate in different physiological processes in the human body, being able to improve gut physiology, modulate the host's glucose and lipid metabolism, and affect immune function [40][41]. In particular, upon their transport from the intestinal lumen into the blood compartment of the host, SCFAs are absorbed by the liver for gluconeogenesis or by muscle to generate energy [42]. Among SCFAs, acetate is the primary substrate for cholesterol synthesis [43], while propionate inhibits cholesterol synthesis by reducing serum lipids and has a protective effect against colon cancer [44][45]. Notably, SCFAs modulate brain functions by acting on the production of neuroactive metabolites [46]. For example, butyrate and propionate can be transferred from the gut to the brain where they act as signalling molecules through the monocarboxylate transporters that are highly expressed in the blood–brain barrier [47]. Finally, butyrate has been reported to play a protective role against carcinogenesis in colon cancer cells by enhancing the expression of cell cycle inhibitory genes [48].

3. Signaling Mechanisms Induced by SCFAs

Besides the relevant role in intestinal health, SCFAs may play their signalling role via the activation of several biochemical pathways: G-protein-coupled receptors (GPCRs), histone deacetylases (HDACs), and Nrf2 [49][50][51] (**Figure 1**).

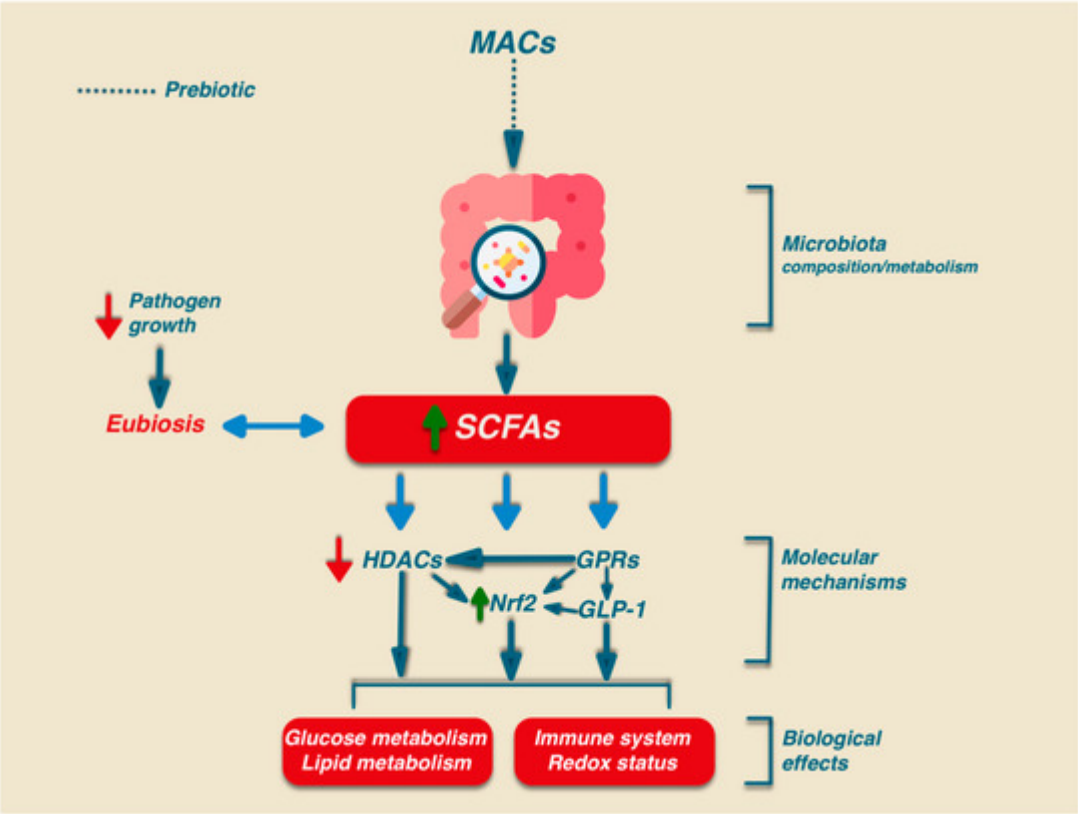

Figure 1. Biological effects of MACs. The intake of MACs can modulate the composition and metabolism of the microbiota, leading to increased production of SCFAs. SCFAs exert biological effects by modulating specific signaling pathways. HDACs: histone deacetylases; GPCRs: G-protein-coupled receptors; GLP-1: glucagon like peptide 1; Nrf2: Nuclear factor 2-related erythroid 2.

In humans, there are at least six GPRs that are sensitive to SCFAs, but among them, only GPR41, GPR43, and GPR109A are involved in SCFA-mediated signaling. GPR41 and GPR43 are the best-studied SCFA receptors [52] and are activated by acetate, propionate, and, to a lesser extent, also by butyrate. GPR41 is expressed in colon cells, in the blood vessels, and in the sympathetic nervous system, while GPR43 is mainly expressed in enteroendocrine L cells, lymphocytes, neutrophils, and monocytes [53]. GPR109A has a high affinity for niacin which can be activated by butyrate, and it is expressed only in human immune cells and colonocytes. In addition, GPR109A is highly expressed in adipocytes. The activation of this receptor in adipocytes has been linked to lipolysis and a decrease in plasma free fatty acids [54]. Activated GPCR receptors can regulate different signaling via the activation of many cellular functions such as the mitogen-activated protein kinase (MAPK) family of serine-threonine kinases, including extracellular signal-regulated kinase (ERK), c-jun N-terminal kinase (JNK), p38, and ERK5, through an intricate network of signaling. The activation of GPR43 also stimulates the phospholipase-C determining intracellular Ca2+ release and the activation of protein kinase C [55].

HDACs are a group of enzymes that affect gene transcription or alter protein activity by removing the acetyl group on the lysine ϵ-amino group of the target protein. The inhibition of HDACs is relevant for immune and inflammatory regulation by modulating either innate immunity through regulation of the Toll-Like Receptor (TLR) and Interferon

(IFN) signaling pathways or by regulating antigen presentation and B and T lymphocytes to achieve adaptive immunity [56][57]. In particular, the inhibitory effect of HDACs on SCFAs, mainly due to propionate and butyrate, results in an anti-inflammatory effect through the promotion of regulatory T cell (Treg) development as well as CD4+ T cell IL-10 production [57][58].

The shared molecular pathways activated by polyphenols, PUFAs, and SCFAs support the role of Nrf2, HDACs, and GPRs in the beneficial effects elicited by dietary MACs, polyphenols, and PUFAs. Since the activation of these pathways triggers a downstream signaling cascade, this can explain why dietary bioactive molecules can exert antioxidant/beneficial effects even when present in a low plasma concentration.

Interestingly, the functional link existing between antioxidant activity and gut microbiota homeostasis has been indicated by (a) the modulatory ability of SCFAs in the Nrf2 pathway [49], (b) the age-dependent decline in the concentration of SCFAs in the gut [59], and (c) the positive association between microbiota diversity and Nrf2 efficacy [60]. In addition, the link between the production of SCFAs and the Nrf2 pathway was indicated in a recent study showing the ability of Clostridium butyricum pretreatment to increase the SCFA contents in the cecum of Enterotoxigenic Escherichia coli K88 (ETEC K88)-infected mice. In particular, the data indicated that such improvement was associated with the amelioration of the oxidative damage induced by ETEC K88 infection through the activation of the Nrf2 pathway [61]. A summary of the differential ability of microbial SCFAs in activating different receptors involved in the Nrf2 pathway is shown in **Table 2**.

Table 2. A brief summary of SCFAs produced by the gut microbial population and of their response to different receptors; adapted from [3][49]. Low or high affinity is denoted by + or ++, respectively.

Phylum	Family	Genus		FFAR3 (GPR41)	FFAR2 (GPR43)	GPR109A
Firmicutes	*Lachnospiraceae*	*Coprococcus*				
		Barnesiella				
	Ruminococcaceae					
		Akkermansia	**ACETATE**	+ +	+ +	+ +
		Prevotella				
		Bifidobacterium				
Bacteroidetes	*Bacteroidaceae*	*Bacteroides*	**PROPIONATE**	+	+ +	+
	Prevotellaceae	*Prevotella*				
	Rikenellaceae	*Alistipes*				
Firmicutes		*Eubacterium*				

Phylum	Family	Genus		FFAR3 (GPR41)	FFAR2 (GPR43)	GPR109A
		Blautia				
		Coprococcus				
	Veillonellaceae	*Dialister*				
	Acidaminococcaceae	*Phascolarctobacterium*				
Verrucomicrobia	*Verrucomicrobiaceae*	*Akkermansia*				
Firmicutes	*Lachnospiraceae*	*Eubacterium*				
		Roseburia				
		Clostridium				
		Eubacterium				
		Anaerostipes	**BUTYRATE**	+ +	+ +	+ +
		Coprococcus				
	Ruminococcaceae	*Faecalibacterium*				
		Subdoligranulum				
	Erysipelotrichaceae	*Holdemanella*				

Finally, the interplay existing between different SCFAs further strengthens the complexity of their mechanism of action [62][63] (**Figure 1**).

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