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Short-chain fatty acids as modulators of redox signaling in health and disease

Carmen González-Bosch [a,b,*], Emily Boorman [a,c], Patricia A. Zunszain [c], Giovanni E. Mann [a]

[a] King's British Heart Foundation Centre of Research Excellence, School of Cardiovascular Medicine & Sciences, Faculty of Life Sciences & Medicine, King's College London, 150 Stamford Street, London SE1 9NH, UK
[b] Departamento de Bioquímica y Biología Molecular, Universitat de València, Instituto de Agroquímica y Tecnología de Alimentos (IATA/CSIC), Avenida Agustín Escardino 7, 46980 Paterna, Valencia, Spain
[c] Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

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ABSTRACT

Short-chain fatty acids (SCFAs), produced by colonic bacteria and obtained from the diet, have been linked to beneficial effects on human health associated with their metabolic and signaling properties. Their physiological functions are related to their aliphatic tail length and dependent on the activation of specific membrane receptors. In this review, we focus on the mechanisms underlying SCFAs mediated protection against oxidative and mitochondrial stress and their role in regulating metabolic pathways in specific tissues. We critically evaluate the evidence for their cytoprotective roles in suppressing inflammation and carcinogenesis and the consequences of aging. The ability of these natural compounds to induce signaling pathways, involving nuclear erythroid 2-related factor 2 (Nrf2), contributes to the maintenance of redox homeostasis under physiological conditions. SCFAs may thus serve as nutritional and therapeutic agents in healthy aging and in vascular and other diseases such as diabetes, neuropathologies and cancer.

1. Introduction

The key roles played by the major short-chain fatty acids (SCFAs) acetate, propionate and butyrate (commonly named as their anions) as mediators of the beneficial effects of dietary fibre and gut microbiota in human health has led to renewed interest in their mechanisms of action [1]. Here, we review in detail the *in vitro* and *in vivo* evidence supporting a role of SCFAs in regulating redox homeostasis, crosstalk between the redox sensitive Kelch-like ECH-associated protein 1 (Keap1)-Nrf2 signaling pathway and metabolism of free fatty acids (FFAs), and the novel roles that specific SCFAs play in activating Nrf2-regulated gene transcription (see **Section 4** and Tables 3 and 4). We also address the beneficial effects of specific SCFAs on redox homeostasis under physiological and pathological conditions, and critically evaluate the potential of these biomolecules as nutritional and therapeutic targets in diseases such as diabetes, neuropathology and cancer.

1.1. SCFAs signaling functions

Short-chain fatty acids, mainly produced by colonic bacteria, have been linked with benefits for human health due to their metabolic and signaling properties [2]. The specific physiological functions of this type of fatty acid are related to their aliphatic tail length. FFAs are classified based on their carbon chain length, with SCFAs having <6 carbon atoms, MCFAs 6–12 carbons atoms and long-chain fatty acids (LCFAs) more than 12 carbon atoms (see Table 1).

FFAs are versatile molecules involved in many physiological functions in mammals. In addition to their well characterized structural and metabolic roles, recent evidence highlights their involvement in cell signaling in a wide range of physiological and pathological conditions [3,4]. Evidence for a role of SCFAs in organs outside the digestive system stems from the fact that numerous transmembrane proteins, receptors and transporters, that specifically bind SCFAs and other monocarboxylic acids, are expressed in a large variety of cell types, including neurons [5,6]. For example, butyrate and other fermentation or diet derived SCFAs

* Corresponding author. Departamento de Bioquímica y Biología Molecular, Universitat de València, (IATA/CSIC), Avenida Agustin Escardino 7, 46980 Paterna, valencia, Spain.
E-mail addresses: carmen.gonzalez@uv.es, carmen.gonzalez@uv.es (C. González-Bosch), emily.boorman@kcl.ac.uk (E. Boorman), patricia.zunszain@kcl.ac.uk (P.A. Zunszain), giovanni.mann@kcl.ac.uk (G.E. Mann).

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List of abbreviations

Aβ	amyloid β peptide
AMPK	AMP-activated protein kinase
BBB	blood-brain barrier
BMECs	brain microvascular endothelial cells
ARE	antioxidant response element
cAMP	cyclic adenosine monophosphate
CNS	central nervous system
COX	cyclo-oxygenase
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
ERK1/2	extracellular-signal-regulated kinase 1/2
FFA	free fatty acid
FFAR	free fatty acid receptor
GPR	G protein-coupled receptor
GPx	glutathione peroxidase
GSH	glutathione
GSK-3β	glycogen synthase kinase-3β
GST	glutathione S-transferase
HAT	histone acetyltransferase
HBMEC	human brain microvascular endothelial cells
HDAC	histone deacetylase
HO-1	heme oxygenase 1
H3K9/14	histone H3 acetylated in lysine 9/14
ICAM-1	intercellular adhesion molecule 1
IEC-6	rat primary epithelial cells
IL:	interleukin
iNOS	inducible nitric oxide synthase
JNK	Jun N-terminal kinase
Keap1	Kelch-like ECH-associated protein 1
LCFA	long-chain fatty acid
LOX	lipoxygenase
LPS	lipopolysaccharide
LRP-1	LDL Receptor Related Protein 1
MDA	malondialdehyde
MAP kinase	Mitogen-activated kinase
MCFA	medium-chain fatty acid
MCP-1	monocyte chemotactic protein 1
Mn-SOD	Mn-superoxide dismutase
NaAc	sodium acetate
NaB	sodium butyrate
NaP	sodium propionate
NF-κB	Nuclear factor kappa B
Nlrp3	NOD-like receptor family pyrin domain containing 3
NO	nitric oxide
NOS	nitric oxide synthase
NOX	NADPH oxidase
NQ1	NAD(P)H:quinone oxidoreductase-1
Nrf2	Nuclear erythroid 2-related factor 2
n-3 PUFAs	omega-3 polyunsaturated fatty acids
Olfr78	olfactory receptor 78
P53	tumor suppressor p53
PGC1-α	peroxisome proliferator-activated receptor γ co-activator 1 α
PPARγ	peroxisome proliferator-activated receptor gamma
ROS	reactive oxygen species
SCFA	short-chain fatty acid
SFN	sulforaphane
SMCT1	sodium-coupled monocarboxylate transporter 1
Sp1	specificity protein 1
SOD	superoxide dismutase
TCA	tricarboxylic acid cycle

like acetate and propionate have shown promising effects in various diseases including obesity, diabetes, inflammatory (bowel) diseases, and colorectal cancer as well as neurological disorders [7].

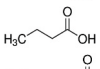
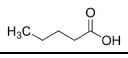
The health benefits of FFAs have been associated in part with their capacity to regulate metabolic, inflammatory, and neural pathways by maintaining energy homeostasis [8]. Interestingly, as discussed in this review, microbiota metabolites and epigenetic regulation may form the basis of future research (see **Section 6**).

2. Role of SCFAs in energy and anabolic metabolism

SCFAs are important substrates for energy metabolism and anabolic processes in mammals, and there is evidence that diet-driven changes in microbiota diversity lead to variations in SCFAs [9]. Acetate, propionate, and butyrate are the main SCFAs formed in the human colon at an estimated ratio of about 3:1:1 [10], reaching the highest concentrations (70–140 mM) in the proximal colon [11], with a concentration gradient falling from the lumen to the periphery [12] (see Fig. 1). These SCFAs are absorbed from the gut into the hepatic portal circulation and/or lacteal lymphatic system, with total concentrations ranging from 375 μM to 148 μM in portal and hepatic blood, respectively, to 79 μM in peripheral blood [11,13]. Butyrate and propionate, mostly metabolized by hepatocytes, appear at 1–15 μM in the systemic circulation, with acetate ranging between 100 and 200 μM [14,15]. Of relevance to aging (see **Section 8**), only acetate has been detected in cerebrospinal fluid at around 35 μM [16]. While the significance of these biological gradients is poorly understood, they may be critical in defining physiologically relevant roles of specific SCFAS during immune and inflammatory responses [17]. This is particularly important for clinical translation of findings in animal models, which often utilize oral SCFAs supplementation or high dietary fibre supplementation to induce changes in SCFAs production [18].

Notably, mother's milk constitutes an important source of SCFAs for new-born mammals in the form of triglycerides and phospholipids, while animal milk and milk products constitute the main dietary source of SCFAs, mainly butyrate, in adult humans [19]. SCFAs can also be

Table 1
Nomenclature and structure of SCFAs.

Number of carbon atoms	Systematic name	Common name	Common anion name	Structure	Simplified formula
2	Ethanoic	Acetic	Acetate		(C2:0)
3	Propanoic	Propionic	Propionate		(C3:0)
4	Butanoic	Butyric	Butyrate		(C4:0)
5	Pentanoic	Valeric	Valerate		(C5:0)

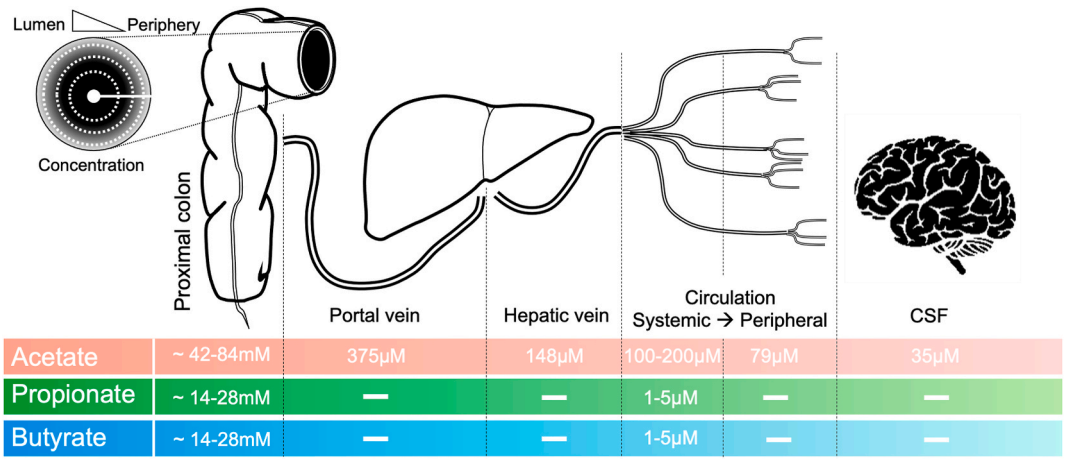


Fig. 1. Schematic illustrating the origin of SCFAs and their target tissues. Gradient concentration of SCFAs between gut lumen and periphery is illustrated.

formed in the mammalian liver through the peroxisomal β-oxidation of long-chain fatty acids (LCFAs) [20].

A feature of SCFAs that distinguishes them from LCFAs is that they are rapidly absorbed in the intestine due to their water solubility and transported via the hepatic portal bloodstream to the liver, where they are readily metabolized instead of being stored as fat [9,19]. SCFAs modulate tissue metabolism of carbohydrates and lipids by inhibiting glycolysis and stimulating lipogenesis and gluconeogenesis [21]. However, the traditional view that FFAs serve as metabolic substrates only during carbohydrate restriction has been revised based on observations that ketone bodies play pivotal roles as signaling mediators, drivers of protein post-translational modification and modulators of inflammation and oxidative stress when carbohydrates are abundant [22]. The antioxidant and oxidative stress-mitigating roles of ketone bodies have been widely described in the context of neuroprotection, cardio-protection and cancer [23] and will not be reviewed further.

3. Molecular mechanisms underlying SCFAs signaling: free fatty acid receptors

The regulatory functions of SCFAs depend on specific receptors expressed in different cell types, as well as their developmental stage and differentiation process [5,6]. In *vitro* and *in vivo* studies have shown that the physiological functions of free fatty acid receptors (FFARs) contribute not only to the regulation of metabolic energy but also affect the immune system [24]. These transmembrane receptors are members of G protein-coupled receptors (GPR) that detect extracellular molecules and then activate intracellular signal transduction pathways to promote cellular responses [25].

FFARs are activated by free fatty acids with different carbon chain lengths and, under physiological conditions, several FFAs can activate the same receptor, whereas one FFA can activate several FFARs. In fact, SCFAs are ligands of FFAR2/GPR43 and FFAR3/GPR41, but the former is preferentially activated by C3:0-C6:0 and the latter by C2:0-C4:0. Notably, long-chain fatty acids activate both FFAR1/GPR40 and FFAR4 (GPR120), whereas medium chain fatty acids (C6:0-C12:0) can also activate FFAR1/GPR40 [5]. In addition, several FFAs are able to activate specific receptors, such as propionic (C3:0) (Olfr78), butyric (C4:0) (GPR109A), and capric (C10:0) and lauric (C12:0) acids (GPR84) (see Table 2 and Fig. 2). Kimura et al. (2020) have recently described FFARs in detail, and we refer readers to their comprehensive and elegant review [5].

Depending on the type of α subunit of the heterotrimeric proteins associated with the FFARs, the reported physiological function of FFARs mainly involves activation of intracellular calcium (Ca^{2+}), cyclic adenosine monophosphate (cAMP) or extracellular-signal-regulated kinase 1/2 (ERK1/2) signaling, via G protein (Gq or Gi/o)-dependent or G protein-independent pathways [25,26]. Furthermore, there is evidence supporting functional redundancy of FFARs that might contribute to maintenance of fatty acid homeostasis under different physiological conditions [5].

Table 2
SCFA receptors and ligand specificity.

	Acetic (C2:00)	Propionic (C3:0)	Butyric (C4:0)	Pentanoic (C5:0)
FFAR3 (GPR41)	++	+	++	++
FFAR2 (GPR43)	++	++	++	+
GPR109A			++	
Olfr78	++	+		

Abbreviations: FFAR1: free fatty acid receptor 1; FFAR2: free fatty acid receptor 2; FFAR3: free fatty acid receptor 3; GPR40: G protein-coupled receptor 40; GPR41: G protein-coupled receptor 41; GPR43: G protein-coupled receptor 43; GPR109A: G protein-coupled receptor 109 A; olfr78: olfactory receptor 78. Note + and ++ denote low and high affinity, respectively [5,6].

4. Protective role of SCFAs against oxidative and mitochondrial stress involving Keap1-Nrf2 signaling

The health benefits of redox signaling have been defined as "oxidative eustress", whereas the deleterious outcomes in pathophysiology and disease due to higher levels of reactive oxygen species (ROS) is referred to as "oxidative distress" [27]. Under physiological conditions, different ROS play key roles in redox signaling via different post-translational modifications, therefore controlling specific ROS-mediated signaling pathways offers a strategy for refining future redox medicine [28,29].

The evidence that living organisms have developed mechanisms for the advantageous use of free radicals revealed the biological relevance of redox regulation in health and disease [30]. One of the main sources of cellular ROS are mitochondria which constitute a metabolic hub facilitating crosstalk between the metabolic state of the cell with relevant signaling pathways, including those regulating immune responses [31]. Notably, mitochondrial ROS serve as an alarm of extracellular environment changes that in small amounts can promote adaptation to the stressor but in larger quantities produce cell damage and subsequent cell death [32]. Therefore, the original concept of oxidative stress is linked to cellular energy balance, has led to characterization of compartmentation of redox processes and the spatiotemporal organization of hydrogen peroxide metabolism and its relationship to bioenergetics [33]. Discovery of the role of Keap1-Nrf2 system as the major

Table 3
SCFAs mediated activation of the Keap1-Nrf2 defense pathway protects against oxidative stress *in vitro*.

Cell type		Species	SCFA	Treatment	key findings	References
Endothelial	HBMEC	Human	Propionic	Propionate 1 μM 12–24h	↓LRP-1 Protected BBB via Nrf2 signaling	[49]
Fibroblast	BMECs mammary	Bovine	Butyric	NaB 2 mM, 1–12h	↑ nuclear Nrf2 ↑H3K9/14ac ↓H_2O_2↓apoptosis through GPR109A/AMPK/Nrf2	[50]
Epithelial	IEC-6	Rat	Butyric	NaB 2 mM, 24–48h	↑ nuclear Nrf2 ↑GST, NQO1 ↓p53	[64]
Hepatocyte	HepG2	Human	Butyric	NaB 0.3 mM 96h +800 μM H_2O_2, 4h	↑ nuclear Nrf2 ↑HO1, NQ1 ↑MnSOD, GPx ↓ ROS ↓apoptosis ↓ GSK-3β ↓ glycolysis ↑β-oxidation ↑TCA	[65]

Abbreviations: AMPK: AMP-activated protein kinase; BBB: blood-brain barrier; BMECs: brain microvascular endothelial cells; FFAR2: Free fatty acids receptor 2; GPx: glutathione peroxidase; GSK-3β: glycogen synthase kinase-3β; GR109A: G-protein-coupled receptor; HO1: heme oxygenase-1; H3K9/14; histone H3 acetylated in lysine 9/14; HBMEC: human brain microvascular endothelial cells; ICAM-1: intercellular adhesion molecule 1; IEC-6: rat primary epithelial cells; IL-1β: interleukin 1 beta; LRP-1: LDL Receptor Related Protein 1; MCP-1: monocyte chemotactic protein 1; Mn-SOD: Mn-superoxide dismutase; NaB: sodium butyrate; NQ1: NAD(P)H: quinone oxidoreductase-1; Nrf2: nuclear erythroid 2-related factor 2; ROS: reactive oxygen species; TCA: tricarboxylic acid cycle.
Upward arrow (↑) indicates an increase and downward arrow (↓) a decrease in respective measured outcomes.

Table 4
SCFAs afford protection against oxidative stress via activation of Keap1-Nrf2 pathway in animal models.

Species	Strain/diet	SCFA	Treatment	Key findings	References
Rat	High-fat diet, 9 weeks	Butyric	NaB (300 mg/kg), every 2d, 7 weeks	↓HDAC1 ↑H3K9ac Nrf2 promoter ↑Nrf2, SOD, GSH ↑Insulin signaling	[91]
	Obesity-prone rats	Butyric	4% NaB, 12 weeks	Reversion of bone loss and body weight gain ↑nuclear Nrf2 ↑HO1, NQO1 ↑ Nrf2/GSK-3β signaling ↑ PGC-1α, TFAM	[92]
Mouse	C57BL/6 ($Nrf2^{-/-}$)	Butyric	NaB (5 g/kg/day), 20 weeks	↓ Renal oxidative damage ↓HDAC ↑Nrf2, HO1, NQ1 No Nrf2 nuclear translocation	[93]
	C57BL/6 with experimental autoimmune uveitis	Butyric	NaB orally (1 g/kg/day) 14d	↓ Ocular inflammatory response ↓Th17 cells ↑Treg cells Nrf2/HO1 dependent	[94]
	C57BL/6 ($Nrf2^{-/-}$) diabetes-induced	Butyric	NaB (5 g/kg/day) 20 weeks	↓ Aortic endothelial dysfunction Nrf2-dependent ↓HDAC ↑Nrf2 transcript and protein No significant Nrf2 nuclear translocation	[66]

Abbreviations: ERK: extracellular-signal-regulated kinase; FFAR2: free fatty acids receptor 2; GSH: glutathion; GPX2: glutathione peroxidase 2; GSK-3β: glycogen synthase kinase-3β; GR109A: G-protein-coupled receptor; HDAC1: histone deacetylase 1; HO1: heme oxygenase 1; H3K9ac; histone H3 acetylated in lysine 9/14; ICAM-1: intercellular adhesion molecule 1; IL-1β: interleukin 1 beta; JNK: Jun N-terminal kinase; LRP-1: LDL Receptor Related Protein 1; MCP-1: monocyte chemotactic protein 1; MDA: malondialdehyde; SOD1-3: superoxide dismutase 1–3; NaB: sodium butyrate; NQ1: NAD(P)H: quinone oxidoreductase-1; Nrf2: nuclear erythroid 2-related factor 2; PGC1-α: peroxisome proliferator-activated receptor γ co-activator 1 α; p38: mitogen activated (MAP) kinase p38.
Upward arrow (↑) indicates an increase and downward arrow (↓) a decrease in respective measured outcomes.

regulator of redox homeostasis has informed new approaches to improve human health and combat diseases [34].

4.1. Natural compounds acting as regulators of cellular redox homeostasis via Nrf2 signaling

Several health benefits of SCFAs and other food derived non-nutrient molecules are related to their ability to modulate gene expression and thereby influence intracellular signaling pathways [35]. Plant-derived compounds can activate signaling pathways involved in the maintenance of cellular redox homeostasis [36,37]. One of the best characterized targets of pharmacological and/or dietary interventions is nuclear erythroid 2-related factor 2 (Nrf2), a master regulator of cellular antioxidant defenses controlling more than 200 genes [34,38–43]. Under quiescent conditions, Nrf2 is sequestered by its cytosolic repressor Keap1 (Kelch-like ECH-associated protein 1), promoting rapid proteasomal degradation via ubiquitination, whereas oxidative and electrophilic stress promote nuclear accumulation of *de novo* synthesized Nrf2, which together with small Maf proteins binds to the antioxidant response element (ARE) in the promoter of target genes to upregulate phase II and antioxidant enzymes to counteract oxidative stress [38,40–42,44]. Thus, current research in this field is focused on identifying biomolecules with significant nutrigenomic potential and efficacy as activators of Nrf2 [45,46]. Among them, broccoli-derived sulforaphane (SFN) is the most potent inducer of Nrf2-targeted cytoprotective genes [39,47,48]. As discussed in this section, specific SCFAs such as butyrate and propionate are activators of the Keap1-Nrf2 defence pathway [49,50] and lipid metabolism is regulated by Nrf2

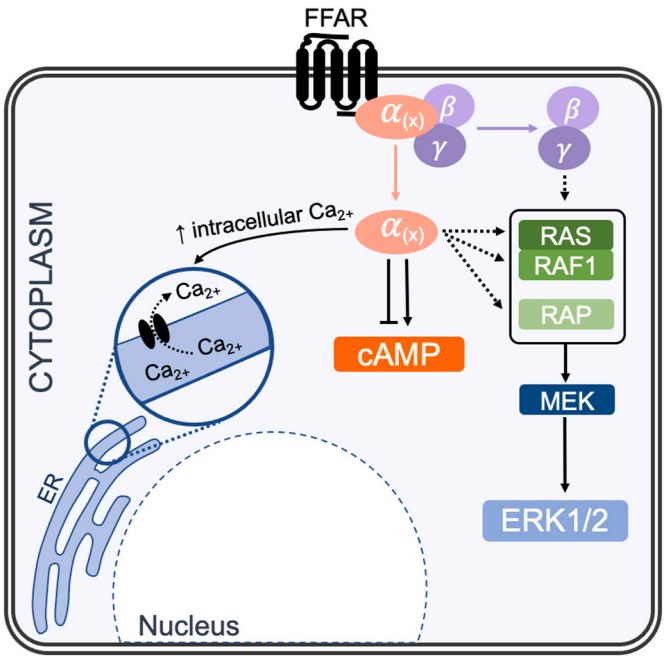


Fig. 2. Main signaling pathways of the free fatty acid receptors (FFARs). cAMP: cyclic adenosine monophosphate; ER: endoplasmic reticulum; ERK1/2: extracellular-signal-regulated kinase 1/2; FFAR: free fatty acid receptor; RAS: GTPase rat sarcoma virus; RAF1: Raf kinase 1; RAP: Ras related protein; MEK: mitogen-activated protein kinase kinase.

[51,52].

4.2. Crosstalk between Nrf2 and lipid metabolism

Despite the regulatory functions reported for the main gut microbiome fermentation products acetate, propionate and butyrate, their role in influencing cellular redox homeostasis is currently not well understood [53]. Nrf2 is a major regulator of cellular metabolism in normal, stressed and cancer cells directing the transcription of the metabolic processes [52]. There is increasing evidence that Nrf2 participates in hepatic fatty acid metabolism, suppressing fatty acid synthesis and desaturation [54,55]. Notably, Notch signaling, which enables regulation and control of development, differentiation, and homeostasis through cell-cell communication has been identified as a novel regulator of fatty acid transport across the endothelium [56], and the ROS-Nrf2-Notch pathway seems key for cellular homeostasis [57].

4.3. Specific SCFAs protect against oxidative damage via the Keap1-Nrf2 pathway

SCFAs have been screened for protection against oxidative damage, and the molecular mechanisms underlying this effect and the physiological significance are beginning to be elucidated [58]. In this section, we focus on their role in regulating the Keap1-Nrf2 pathway. Of relevance, targeting the Keap1-Nrf2 signaling pathway using pharmacological and/or dietary interventions has been shown to protect against oxidative stress induced vascular damage in ischemic stroke, gestational diabetes and atherosclerosis as well as other chronic diseases [38,59–63].

In Tables 3 and 4, we summarize selected cell culture and animal studies *in vivo* supporting an antioxidant role for specific SCFAs as modulators of Nrf2 redox signaling, with the majority of studies focused on butyrate. In both type of studies, epigenetic regulation involving histone deacetylases (HDACs) and/or Nrf2 nuclear translocation induced by butyrate are the main reported mechanisms of action.

Notably, studies in Nrf2 knockout mice with induced diabetes showed that butyrate mediates protection against endothelial dysfunction by P300 mediated activation of *Nrf2* via inhibition of HDAC while, under the same conditions, SFN facilitates Nrf2 nuclear translocation [64]. Recent evidence in bovine epithelial cells implicated GPR109A inactivation of AMPK signaling by butyrate to promote Nrf2 nuclear accumulation [50]. In this case, butyrate also induced epigenetic modification on the Nrf2 promoter associated with synergistic antioxidant effects. Interestingly, in rat intestinal epithelial cells butyrate, in addition to enhancing antioxidant activities via Nrf2, decreased mRNA and protein levels of the tumor suppressor p53 [65], supporting crosstalk between p53 and Nrf2 in the regulation of cellular redox homeostasis [66–68].

Relatively few studies investigating the antioxidant roles of SCFAs have focused on propionate, despite its similar plasma concentration and receptor affinity [69]. Hoyles et al. (2018) demonstrated the expression of the receptor FFAR3 in human brain endothelium and determined that a physiologically relevant propionate concentration (1 μM) protected the blood-brain barrier (BBB) against oxidative stress via Nrf2 signaling [49]. Notably, acetate, propionate and butyrate can cross BBB, affecting BBB integrity and transport rates by reducing permeability and regulating the expression of tight junction proteins [70]. A study using a germ-free mouse model suggested that the microbiota and its metabolites (especially butyrate) can upregulate tight junctional protein expression in the BBB, thereby regulating the interaction between the periphery and the central nervous system (CNS) [71]. This beneficial effect of specific SCFAs on the BBB may affect the transport of molecules such as docosahexaenoic acid (DHA), an omega-3 fatty acid highly enriched in brain, that is essential for normal brain growth and cognitive function and inhibits inflammation in endothelial cells to reduce cardiovascular risk [72,73]. DHA cannot be synthesized *de novo* in the brain and must be supplied from the blood via specific transporters like the major facilitator super family domain containing 2a (Mfsd2a) and/or through passive diffusion across the endothelial membrane [74,75].

DHA in the plasma is found esterified with phospholipids and other lipids and its uptake into the brain seems to involve endothelial lipase [76]. The significant enrichment of DHA within the brain must be regulated by a number of additional pathways associated with the activation and metabolism of DHA. Once in the brain, DHA is esterified into membrane phospholipids, being released and converted to bioactive mediators during neurotransmission and following brain injury [77]. The antioxidant properties of DHA and its metabolites, resolvins, neuroprotectins and 4-hydroxy-2E-hexenal, are mediated by Nrf2 activation and involve upregulation of heme oxygenase 1 (HO-1) to protect the brain against ischemic damage [78–80]. Post-stroke administration of DHA is effective in reducing brain injury [81–83] and improving sensorimotor function [84,85]. Notably, stroke lowers blood SCFA concentrations, and SCFA supplementation has been reported to reduce damage following post-stroke reperfusion [86–89]. As SCFAs improve functional outcomes after stroke, further research focused on their link with neuroprotective functions of Nrf2 and DHA is warranted.

The experimental data summarized in Tables 3 and 4 provide convincing evidence that SCFAs, in particular butyrate but also propionate, by direct or indirect mechanisms, activate the Keap1-Nrf2 signaling pathway to maintain redox homeostasis under physiological conditions (see Fig. 3).

Considering that butyrate is a fatty acid oxidized in mitochondria and acts as a signal transduction molecule via FFAR2, FFAR3 and GPR109A, it is reasonable to postulate its involvement in energy and redox homeostasis via the Nrf2 pathway.

Thus, specific SCFAs produced by microbial fermentation or provided in the diet, contribute to host redox homeostasis via epigenetic regulation and/or promoting Nrf2 nuclear translocation, highlighting an interesting link between the microbiota, redox signaling and host metabolism.

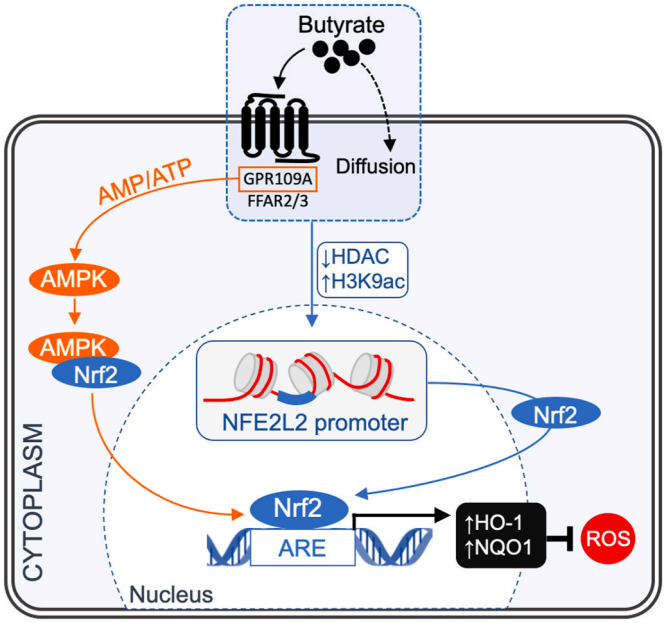


Fig. 3. Schematic illustrating the mechanisms underlying modulation of the Keap1-Nrf2 defense pathway by butyrate: HDAC inhibition, Nrf2 nuclear translocation. AMPK: AMP-activated protein kinase; ARE: antioxidant response element; GPR109A: G-protein-coupled receptor; FFAR2/3: free fatty acids receptor 2/3; H3K9ac histone H3 acetylated in lysine 9: HDAC: histone deacetylase; HO-1: heme oxygenase 1; Nrf2: nuclear erythroid 2-related factor 2; NQO1: NAD(P)H: quinone oxidoreductase-1; ROS: reactive oxygen species.

5. Anti-inflammatory properties of SCFAs related to antioxidant signaling

SCFAs play an important role in beneficial effects of dietary fibre and gut microbiota, through regulation of inflammation in the gut and other organs [90]. In fact, SCFAs may suppress inflammation by reducing migration and proliferation of immune cells, reducing cytokine levels and inducing apoptosis, but marked changes in SCFAs concentrations in blood or tissues can also cause immunological and metabolic imbalances [17]. Therefore, appropriate concentrations of SCFAs are needed to maintain normal metabolism and in the prevention and treatment of disease [24]. Table 5 includes selected experiments showing that treatment with SCFAs can activate cellular antioxidant mechanisms and downregulate pro-inflammatory mediators.

SCFAs are generally considered to have beneficial effects in cardiovascular disease, and studies in different animal models report inhibitory effects of butyrate on NLRP3 inflammasome formation associated with activation of antioxidant signaling pathways [91,92]. Notably, treatment of endothelial cells with low concentrations of SCFAs does not disrupt barrier integrity under inflammatory conditions and moreover increases mitochondrial respiratory capacity [93,94]. In addition, butyrate plays an important role in the assembly of tight junctions in intestinal and vascular endothelial cells by inducing cyclo-oxygenase (COX), lipoxygenase (LOX) and reducing inducible NO synthase (iNOS) [95,96]. These findings suggest that supplementation of SCFAs, especially butyrate, may serve as therapeutic nutrients for inflammatory diseases due to their contribution to redox homeostasis.

The anti-inflammatory effects of butyrate and other SCFAs are partly achieved through HDAC inhibition [97,98]. Notably, butyrate modulates immune responses in intestinal macrophages via the reduction of NO due to inhibition of iNOS and decreased activation of nuclear NF-kB [99]. In rats, butyrate inhibition of HDAC leads to downregulation of secondary response genes like Nos2 and Il6 [100]. Thus, butyrate may behave as a microbial signal to maintain host immunity [101]. It is important to note that the beneficial effects of SCFAs-mediated HDAC inhibition may depend not only on the concentration of SCFAs but also on the target tissue or cell type [102].

The demonstrated redox signaling roles of specific lipids underpins the importance of emerging metabolomics and redox lipidomics for diagnosis and therapeutics [103,104]. In addition, systems-level models that permit interpretation of big data, particularly those that account for multiple interactions between metabolic intermediates, are necessary to understand the scope, scale, and complexity of effectors and targets of redox metabolism [29,105].

6. Protective effects of SCFAs on redox dysregulation in disease

In recent years, both human and animal experiments have revealed that gut microflora dysbiosis can accelerate the progression of cardiovascular diseases [106], diabetes [107], and neurodegenerative diseases [108], with SCFAs playing a key role. Gut dysbiosis and increased gut permeability are associated with heightened levels of oxidative stress [109]. Although our understanding of gut microbiota-host interactions has advanced significantly, many questions remain concerning the mechanistic links between the gut microbiome and host diseases, in particular those related with redox dysregulation [58].

In Table 6, we have selected reports that illustrate the effect of specific SCFAs on redox homeostasis in different pathological conditions. For example, mice receiving dietary butyrate supplementation exhibit reduced oxidative stress, attenuated endothelial dysfunction, and decreased aortic atherosclerotic lesions [18]. In rat aortic cells, butyrate and acetate, at pharmacological concentrations (5–10 mM), also improve endothelial dysfunction induced by angiotensin II by stimulating NO production and decreasing NADPH oxidase and mitochondrial ROS generation [110].

Butyrate and its synthetic derivative, N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA), protect mice against insulin resistance and liver steatosis by acting on hepatic mitochondria, reducing lipid accumulation and oxidative stress [111]. In a recent study in mice with type 2 diabetes mellitus, dysbiosis was associated with a reduction in butyrate-forming bacteria coupled to a decrease in cecal and fecal butyrate content leading to increased activity of the colon HDAC3 [112]. Butyrate treatment also reduced inflammatory markers and ROS

Table 5
Anti-inflammatory effects of SCFAs under cell culture conditions.

Cell type		Species	SCFA	Treatment	Key findings	References
Endothelial	EOMA	Mouse	Butyric	1 mM NaB, 2h	↓O_2^{-}·↓Nlrp3	[96]
Immune system	Macrophage	Rat	Butyric	3 mM NaB, 24h	↓HDAC↓*Il-6*↓NO	[97]
	BMDM	Mouse	Butyric	1 mM NaB, 24h	↓HDAC↓*Nos2*↓NO↓IL-6	[98]
Myoblast	L6	Human	Butyric	5 mM NaB, 24h	↓HDAC↑*SOD2*↑*Catalase*↑*FOXO3a*↑*PGC1α*	[99]
Glomerular mesangial	SV-40 MES 13	Mouse	AceticButyric	25 mM NaAc, 5 mM NaB, 24h	↓ROS↓MDA↑SOD↓IL-1β	[100]

Abbreviations: BMDM. Bone-marrow-derived macrophage; CCL2: chemokine (C–C motif) ligand 2; EOMA: Hemangioendothelioma; GSH: glutathione; HDAC: histone deacetylases; IL-6: interleukin 6; IL-8: interleukin 8; IL-1β: interleukin 1 beta; iNOS: inducible nitric oxide synthase; LPS: lipopolysaccharide; MDA: malondialdeyde; NaAc: sodium acetate; NaB: sodium butyrate; Nlrp3: NOD-like receptor family pyrin domain containing 3; NO: nitric oxide; *Nos2*: nitric oxide synthase 2; O_2^{-}: superoxide ion; SCFA: short chain fatty acid; ROS: reactive oxygen species; SOD: superoxide dismutase.
Upward arrow (↑) indicates an increase and downward arrow (↓) a decrease in respective measured outcomes.

Table 6
Protective effects of SCFAs in animal models of cardiovascular diseases and diabetes.

Species	Animal model	SCFA/MCFA	Treatment	Key findings	References
Mouse	(ApoE^{-}/) mice	Butyric	1% NaB, orally10 weeks	↓ Lesion area in aorta↓SOD↓Protein nitrosylation	[18]
	HFD-induced obese	Butyric	100 mg/kg NaB,6 weeks	↑GSH↑GST↑NQO1↓H_2O_2	[109]
	Non-obese type 2 diabetic MKR	Butyric	20 mg/kg NaB,8 weeks	↓HDAC3↓NOX4↓IL-1β	[110]
	HFD-induced obese SK-N-MC cells	Butyric	0.5 mM NaB,30 min	↑Sp1-p21/Nrf2↓NOX2↑SOD1↓ROS↓NF-kB↓Aβ accumulation	[111]

Abbreviations: Aβ: amyloid β peptide; GSH: glutathione; GST: glutathione S-transferase; HDAC3: histone deacetylase 3; HFD: high fat diet; H_2O_2: hydrogen peroxide; IL-1β: interleukin 1 beta; NF-kB: nuclear factor kappa B; NOX2: NADPH oxidase 2; NOX4: NADPH oxidase 4; NQO1: NAD(P)H: quinone oxidoreductase-1; Nrf2: nuclear erythroid 2-related factor 2; p21: transcription factor p21; ROS: reactive oxygen species; SK-N-MC cells: human neuroblastoma cells; SOD: superoxide dismutase; Sp1: specificity protein 1.
Upward arrow (↑) indicates an increase and downward arrow (↓) a decrease in respective measured outcomes.

production, a mechanism of action previously discussed in **Section 5**.

Acetate has been reported to improve the viability of islets and the mouse insulinoma cell line MIN6 subjected to oxidative stress by enhancing metabolism of ROS, whilst butyrate promotes "oxidative eustress" by inhibiting FFAR2 and NO generation [113]. These findings suggest that SCFAs play an essential role in supporting β-cell metabolism and promoting survival under stressful conditions contributing to reduce diseases such as diabetes. Interestingly, acetate, propionate and butyrate recapitulate chromatin modification states and transcriptional responses associated with gut microbiota in multiple murine tissues [114]. Notably, accumulating evidence indicates that the beneficial effect of these SCFAs in obesity and diabetes are related to their influences on host epigenetics [115]. In fact, butyrate and propionate protect against diet-induced obesity in mice by regulating gut hormones via FFAR3-independent mechanisms [116].

Oxidative stress is also linked to the etiology of many neurodegenerative diseases such as Alzheimer's disease (AD), Amyotrophic lateral sclerosis, Friedreich's ataxia, Huntington's disease, Multiple sclerosis, and Parkinson's disease [117]. Interestingly, there are data linking regulation of redox homeostasis by specific SCFAs with the development of neurodegenerative diseases, constituting an interesting target for pharmacological interventions in psychiatric disorders [118]. In fact, while many studies have shown that saturated long chain fatty acids (C:20-C:26) increase the risk of AD by promoting amyloid-β peptide (Aβ) generated oxidative stress [119], SFCAs can activate Nrf2 and thereby prevent Aβ accumulation [120]. Recent studies have reported a link between butyrate and Nrf2 in protection against high cholesterol-induced neuronal amyloidogenesis in mice [121]. Obesity increases Aβ accumulation in the brain and reduces butyrate-producing bacteria, and notably butyrate treatment has been reported to decrease expression levels of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) and Aβ accumulation. In this study, butyrate taken up by cells via a sodium-coupled monocarboxylate transporter 1 (SMCT1), prevented excessive ROS generation by inhibiting NOX2 and upregulating SOD1, following activation of the cyclin-dependent kinase inhibitor 1 (p21)/Nrf2 pathway through acetylation of Sp1. Notably, in mouse microglia, DHA suppresses Aβ-induced ROS production by upregulating the Nrf2/HO-1 pathway [122]. These results highlight that SCFAs link the microbiota with the maintenance of host redox homeostasis through Nrf2 signaling via mechanisms that may involve omega-3 fatty acids, as discussed in **Section 4**. The experimental data reviewed in this and other sections highlight redox signaling roles of butyrate and other SCFAs and their potential as therapeutic nutrients alone or in combination with other treatments.

Human trials suggest that many biological effects may be mediated by SCFAs (see Table 7), and, as shown, promising *in vitro* and animal studies have been published, albeit they cannot easily be extrapolated to humans [123]. Although the interplay of SCFAs with the gut microbiome and the associated immune system as well as the role of SCFAs in the gut-brain connection has been established [24,124], a better understanding of the mechanism of action of FFAs will facilitate translation for control and prevention of metabolic diseases.

7. Lessons from the plant immune system

The health benefits of specific FFAs discussed in this review implicate plant-derived compounds in the maintenance of mammalian cellular redox homeostasis [125]. The fact that specific FFAs act as Nrf2 regulators suggests that plant-derived compounds may serve as natural redox regulators [126]. The FFA hexanoic acid (C6:0) is particularly interesting, because it is a natural priming agent that protects plants against a wide range of pathogens inducing defense mechanisms and controlling plant redox homeostasis [127]. This FFA was considered a SCFA in previous classifications, and in fact acts as ligand of the SCFA receptor FFAR3 and the MCFA receptor FFAR1 in mammalian cells [5]. There are reports demonstrating that treatment of endothelial cells with hexanoic acid improves energy production and attenuates pro-inflammatory cytokine generation [94], with no effects on endothelial barrier integrity [93]. Moreover, hexanoic acid has anti-proliferative and anti-inflammatory properties in mammalian cells [128,129].

Of relevance, hexanoic acid protects tomato plants against infection by the necrotrophic pathogen *Botrytis cinerea* by regulating GSH levels and potentiating redox-sensitive genes encoding GSTs, peroxiredoxins and glutathione reductase amongst others [130]. Notably, the activation of redox-related genes by this priming agent closely resembles that induced by sulforaphane (SFN) in the preconditioning of mammalian cells [131,132]. In plants, SFN is a secondary metabolite, contributing to the hypersensitive response as well as priming defense genes to protect against biotic stresses [133]. In Arabidopsis plants, treatment with SFN protects against *Hyaloperonospora arabidopsidis* inducing histone epigenetic modifications in the promoter of defense genes [134]. Therefore, the mechanisms of action of the FFA hexanoic acid and SFN in priming

Table 7
Clinical trials assessing the impact of supplementation with SCFAs.

Patients	SCFA	Treatment/Time	Major results	References
10 patients with distal ulcerative colitis	Butyrate	100 mM NaB, 2 weeks + placebo 2 weeks	NaB irrigation ameliorated distal ulcerative colitis	[121]
30 patients with diverticulitis/22 controls	Butyrate	300 mg/day NaB, 12 months	Microencapsulated NaB reduced clinical diverticulitis incidence	[122]
13 overweighted and obese men	Acetate Propionate Butyrate	40–120 mM NaAc, NaP, NaB, 12h	Acute rectal administration of SCFAs modulates whole-body substrate and energy metabolism, with an increase in fasting fat oxidation and resting energy expenditure	[123]

Abbreviations: NaAc: sodium acetate; NaB: sodium butyrate; NaP: sodium propionate; SCFAs: short chain fatty acids.

plants resemble those reported for butyrate and SFN in the pre-conditioning of mammalian cells, supporting conservation of redox-activated pathways.

8. Conclusions and future perspectives

In this review, we discussed the role of SCFAs in regulating redox homeostasis mainly via targeting Keap1-Nrf2 signaling, as illustrated in Fig. 4. These compounds, especially butyrate, exhibit anti-inflammatory and anti-proliferative properties related to their redox signaling activity. SCFAs can inhibit HDAC activities, contributing to the epigenetic regulation of genes, including Nrf2. Among the natural compounds that can modulate the Keap1-Nrf2 pathway, SCFAs offer an advantage as their activity depends on specific receptors and transporters [5], potentially avoiding widespread activation of Nrf2 with undesirable effects on the redox status of healthy versus cancerous tissues [135].

Accelerated biological aging is a feature of age-related morbidities, which share common features, including low-grade persistent inflammation, diminished Nrf2 activity, a depleted metabolic capability and a low diversity gut microbiome [136]. In support of the beneficial effect of the microbiome metabolites in aging, recent multi-omics approaches in mice revealed a pattern of shared pathways of improved health and lifespan that included SCFAs and essential polyunsaturated fatty acid (PUFA) metabolism [137]. Notably, SCFA concentrations are likely less than optimal in older adults, possibly due to insufficient daily dietary fibre intake and to a lower capacity to produce butyrate in the elderly gut microbiome [138]. High fibre supplementation increases butyrate levels that attenuate pro-inflammatory cytokine expression in microglia in aged mice [139]. Long-term treatment with butyrate reduced muscle atrophy in mice during aging, leading to reduced fat mass, improved glucose metabolism, and increased enzymes involved in oxidative metabolism, mainly catalase, in old mice [140]. Interestingly, the beneficial effects exerted by butyrate on muscle mass during aging are consistent with inhibition of HDAC3, supporting that inhibitors of specific HDACs could be used to treat age-related metabolic disease and sarcopenia [141]. In fact, an optimal status of relevant nutrients to effectively reduce inflammation and oxidative stress, strengthens the immune system, is important for human health, and particularly relevant at this time when the world is facing the coronavirus-disease 2019 (COVID-19) crisis [142].

The majority of studies *in vitro* have screened 'modulators' of redox homeostasis in cells cultured under hyperoxic conditions in incubators gassed with 5% CO_2 and room air (21%, 20.9 kPa O_2). Under these conditions, cells are exposed to elevated O_2 levels never encountered *in vivo*, and as consequence Nrf2-regulated antioxidant defences are upregulated to reduce oxidative stress [143–145]. To our knowledge, there are no reported studies of the effects of SCFAs under physiologically relevant O_2 levels and thus such studies are necessary to recapitulate SCFAs mediated redox signaling *in vivo*. Based on emerging data, the use of specific SCFAs as nutritional and therapeutic agents in inflammation, cancer and aging warrants further investigation. The design of improved experimental approaches to explore the mechanisms of production and action of SCFAs in cellular redox signaling under physiological conditions will underpin strategies for developing personalized nutrition and therapeutics for redox medicine.

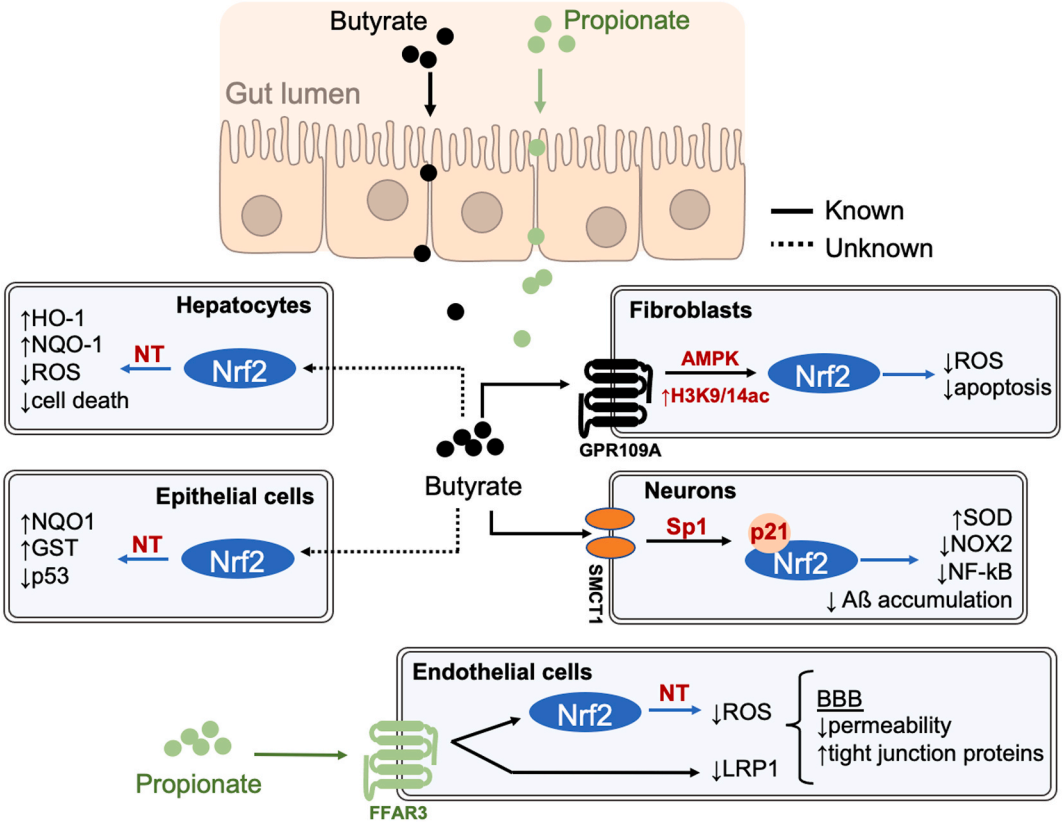


Fig. 4. Schematic highlighting redox regulation by SCFAs in different cell types. Aβ: amyloid β peptide; AMPK: AMP-activated protein kinase; BBB: blood-brain barrier; FFAR2: free fatty acid receptor 2; FFAR3: free fatty acid receptor 3; GR109A: G-protein-coupled receptor; GST: glutathione S-transferase; HDAC: histone deacetylase 1; HO1: heme oxygenase 1; H3K9/14 ac: histone H3 acetylated in lysine 9/14; iNOS: inducible nitric oxide synthase; LRP-1: LDL Receptor Related Protein 1; NF-kB: Nuclear factor kappa B; NO: nitric oxide; NOX2: NADPH oxidase 2; NQ1: NAD(P)H: quinone oxidoreductase-1; Nrf2: nuclear erythroid 2-related factor 2; NT: nuclear translocation; p21: p53: tumor suppressor p53; ROS: reactive oxygen species; SMCT1: sodium-coupled monocarboxylate transporter 1; SOD: superoxide dismutase; Sp1: specificity protein 1.

Declaration of competing interest

Authors declare no conflicts of interest.

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