Renal sensing of bacterial metabolites in the gut-kidney axis

Orestes Foresto-Neto 1,2, Bruno Ghirotto 1, Niels Olsen Saraiva Câmara 1,2*

1 Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, Brazil,

2 Nephrology Division, Department of Medicine, Federal University of São Paulo, Brazil

*Correspondence and reprint request author:
Niels Olsen Saraiva Camara
Department of Immunology
Institute of Biomedical Sciences
University of São Paulo,
Av. Prof. Lineu Prestes 1730, ICB IV, Sala 238
Zip 05508000, Cidade Universitária, São Paulo, Brazil
Email: niels@icb.usp.br
Abstract

Seminal works have now revealed the microbiota is connected with several diseases, including renal disorders. The balance between optimal and dysregulated host-microbiota interactions has changed completely our understanding of immunity and inflammation. Kidney injury is associated with accumulation of uremic toxins in the intestine, augmented intestinal permeability and systemic inflammation. Intestinal bacteria can signal through innate receptors and induce immune cell activation in lamina propria and release of inflammatory mediators into bloodstream. But gut microbiota can also modulate immune functions through soluble products as short chain fatty acids (SCFAs). The three most common SCFAs are propionate, butyrate and acetate which can signal through specific G-protein coupled receptors (GPCRs) such as GPR43, GPR41 and GPR109a, expressed on the surface of epithelial, myeloid, endothelial and immune cells, among others. The triggered signaling can change cell metabolism, immune cell activation and cell death. Here, we reviewed gut-kidney axis, how kidney cells can sense SCFAs and its implication in renal diseases.
**Introduction**

The microbes that inhabit the gut, which include fungi, bacteria, viruses, archaea and protozoans, outnumber the human cells and play a significant role in the regulation of the host immune responses \(^1\). The gut microbiota displays symbiotic relationships with humans and depending on host genetics and environmental factors they can be beneficial, such as mutualism and commensalism, or harmful in the case of parasitism. The balance between optimal and dysregulated host-microbiota interactions has changed completely our understanding of immunity and inflammation, and has shed light in the physiopathology of several disorders, including renal diseases. Increased amounts of pathobionts in the gut may lead to systemic inflammation and affect distant organs, as the impact of the microbiota in immune system extends far beyond the gastrointestinal tract \(^1\), \(^2\).

The most abundant bacteria phyla found in the human intestine include the gram-positive Firmicutes and Actinobacteria, both associated with the in-situ promotion of homeostasis, and the gram-negative Bacteroidetes and Proteobacteria, which display LPS molecules on their surfaces and therefore can trigger immune cell activation. The immune system has developed a series of evolutionary strategies to restrain the microbiota, limiting bacterial translocation and tissue inflammation in a steady-state condition, including mucus, high production of immunoglobulin A (IgA), induction of regulatory responses and synthesis of antimicrobial peptides \(^1\)–\(^3\).

In this sense, disruption of gut homeostasis has been associated with the development of several inflammatory diseases such as inflammatory bowel \(^4\), autoimmune \(^5\), cancer \(^6\) and kidney diseases \(^7\).
The human intestine has epithelial and biochemical barriers that keep the microbiota apart from the host's immune cells, however some commensals can be associated with the intestinal epithelium and modulate innate and adaptive immune responses. Innate immunity participates in the pathogenesis and progression of kidney diseases. Accordingly, it has already been demonstrated that the microbiota regulates the production of pro-IL-1β in intestinal resident macrophages through myeloid differentiation primary response 88 (Myd-88) signaling. Additionally, the segmented filamentous bacteria drive the small intestinal accumulation of Th1 and Th17 cells, both involved in renal inflammation.

Products from the bacteria metabolism can affect the kidneys by several mechanisms. Some species of gut bacteria produce uremic toxins, whereas protective gut microbiota produce short-chain fatty acids (SCFAs). They can modulate the inflammatory response by several mechanisms in the intestine and other organs, including kidneys. In particular, they participate in renal physiology through the regulation of the renin-angiotensin system and cell death. In this perspective article, we explore how the microbiota-derived metabolites affect the gut-kidney axis, highlighting the role of renal SCFAs sensing in this process and in the context of kidney diseases.

Exploring the gut-kidney axis

An intimate connection between gut and kidney, which is called the gut–kidney axis, has been proposed in the last few years, emphasizing a bidirectional talk (Figure 1). Kidney injury is associated with accumulation of uremic toxins in the
intestine and increased intestinal permeability. When high levels of urea end up at
the gut, urease-containing bacteria convert it into ammonia and ammonia
hydroxide, which elevate the intestinal lumen pH and causes mucosal damage and
inflammation 7, 15. In addition, abnormal kidney function and deficiency in renal
excretion leads to the augmented secretion of uric acid and oxalate in the colon 16,
17, favoring the proliferation of microbes capable of metabolizing these substrates.
Both gut secretion and bacterial metabolism reduce the circulatory levels of these
organic acids and can prevent crystal formation in kidneys 18, 19. Besides its
beneficial effects, metabolic changes in the intestinal microbiota can result in
dysbiosis. Gut bacteria harboring p-cresol- and indole-forming enzymes are
overgrown in patients with kidney diseases and promote fermentation of tyrosine
and tryptophan with a consequent increase in circulatory levels of indoxyl sulfate,
p-cresol and p-cresyl sulfate 20. Healthy renal tubules drain these uremic toxins via
organic anion transporters (OATs) localized at the basolateral and apical cell
membranes 21. In addition, proximal tubules can sense uremic toxins through
epidermal growth factor (EGF) receptors and promote their secretion by up-
regulating the OAT1 activity 22. However, once uremic toxins such as indoxyl
sulfate and p-cresol enter the renal tubular cells via OATs, they can stimulate the
production of transforming growth factor beta 1 (TGF-β1), chemokines and free
radicals, which are involved in physiological cell processes, but can also induce
oxidative stress and inflammation in both tubular and glomerular compartments,
leading to interstitial fibrosis and sclerosis, when in higher concentration 21.

Dysbiosis and lesions on the intestinal epithelium result in loss of intestinal cell
tight junction proteins and reduced mucus production, both associated with
intestinal barrier dysfunction 23. These facilitate the translocation of bacteria and
their toxins into the circulation, which can result in systemic inflammation or reach the kidneys. LPS from bacteria can be recognized by toll-like receptor-4 and trigger the signaling through MyD88, activating the nuclear factor kappa B (NF-κB) and the mitogen-activated protein kinase (MAPK), promoting kidney inflammation. Our group has recently shown that the deleterious effects of gut microbiota dysbiosis in kidney disease is at least in part dependent of the MyD88 signaling activation in intestinal epithelial cells and the consequent release of proinflammatory cytokines and chemokines by the intestinal epithelium. Taking into account that deficient excretion of renal function-associated metabolites can influence the gut microbiota composition and that the products derived from the altered microbiome exert effects on kidneys, we can assume that dysbiosis and kidney damage constitute a vicious cycle in renal diseases.

In the last decade, it has been proposed that intestinal dysbiosis-related liver damage also contribute to the progression of kidney disease, making rational the existence of a gut-liver-kidney axis (Figure 1). Intestinal barrier dysfunction allows bacterial translocation to the liver and activation of hepatocytes and immune cells such as Kupffer cells by bacterial components, favoring secretion of TNF-α, IL-1β, and IL-6. In addition, gut microbiota metabolizes dietary choline, L-carnitine and betaine (found in animal products like meat and eggs or plants like spinach and beets), and produce trimethylamine, which is absorbed into portal circulation and oxidized by hepatic flavin-containing monooxygenases to generate trimethylamine N-oxide (TMAO). Increased TMAO levels in blood due to variation in diet and microbiota composition or loss of renal function (impaired excretion capacity) have been associated with reduced cholesterol clearance, increasing cholesterol-laden foam cells and development of atherosclerotic plaques, which can affect the
kidneys. Although it remains unclear whether TMAO directly participates of the pathogenesis of human kidney disease or is simply a biomarker of underlying pathologies, experimental studies support the notion that TMAO plays a role in kidney and liver damage. Proinflammatory, pro-oxidant, and profibrogenic factors released in the circulation by the damaged liver affect the intestinal barrier integrity and the gut microbiota, promoting vascular and kidney tissue injury and contributing to the progression of kidney disease. On the other hand, kidney dysfunction leads to accumulation of urea and uric acid, which enhance intestinal dysbiosis while impairing the liver homeostasis.

Unlike uremic toxins, SCFAs are associated with protection against the progression of liver and kidney diseases. While high-fat diet is correlated with increased levels of LPS in the blood and inflammation, appropriate intake of dietary fibers is associated with higher production of SCFAs and improvement in damaged kidney by regulating the immune response or directly interacting with kidney cells.

**Microbiota-derived SCFAs in the control of immune cell metabolism: a link to renal inflammation**

Immune cells participate in the development of inflammatory kidney diseases through recognition of danger signals, activation of proinflammatory cascades and release of cytokines and chemokines. In this context, it has been described that SCFAs produced by the gut microbiota can modulate the immune cell activation in the kidneys (Figure 2).
SCFAs are metabolites produced mainly by the gut microbiota belonging to the Clostridia class \(^1\) through anaerobic fermentation of dietary fibers or through metabolism of amino acids such as leucine, arginine, glycine and lysine \(^34\), that play a significant role in the regulation of the in situ and systemic immune responses \(^2\). The three most common SCFAs are propionate (C\(_3\)H\(_6\)O\(_2\)), butyrate (C\(_4\)H\(_8\)O\(_2\)) and acetate (C\(_2\)H\(_4\)O\(_2\)) which can signal through specific G-protein coupled receptors (GPCR) such as GPR43 and GPR41, with an EC\(_{50}\) of approximately 0.5mM \(^35,36\), and GPR109a, with an EC\(_{50}\) of 1.6mM for butyrate \(^37\). These relative low potencies favor their selective activation in the gut, where the levels of SCFAs are higher, around 20-60mM \(^38\). These receptors are expressed on the surface of epithelial, myeloid, endothelial and immune cells, among others \(^39\). GPR41 can be found in adipose tissue, spleen, lymph nodes, peripheral blood mononuclear cells, kidneys, and pancreatic tissue whereas GPR43 is located in the colonic-ileal region, adipose tissue, kidneys and on the surface of monocytes \(^38,40\). GPR109a is located mainly in the adipose tissue, but can also be found in the colon, spleen, kidneys and on the surface of macrophages \(^37,40\). Signaling pathways downstream of these receptors are mediated by the cyclic adenosine monophosphate (cAMP), inositol trisphosphate (IP3) or ERK1/2 proteins \(^41\). SCFA transport can also be mediated by the H\(^+\)/monocarboxylate transporters (MCT) or the Na\(^+\)/monocarboxylate transporters (SMCT). Several MCT have been characterized in the human intestine by the presence of either mRNA or protein, including MCT1 (apical membranes), MCT4 and MCT5 (basolateral membranes, mainly in the distal colon), also referred to as SLC16A1, SLC16A3, and SLC16A4, respectively \(^42\). SMCT are mainly located in the apical portion of the colon, where they regulate the transport of SCFAs from the luminal site of the colon to the intestinal epithelial cells \(^43\). Interestingly, human
SMCT1 (also known as SLC5A8) has already been associated with tumor suppression, since its inactivation correlates with the development of human colorectal cancer\textsuperscript{44}.

Other less abundant SCFAs include formate (CH$_2$O$_2$), isobutyrate (C$_4$H$_{10}$O$_2$), valerate (C$_5$H$_{10}$O$_2$), isovalerate (C$_5$H$_{10}$O$_2$) and 2-methylbutanoate (C$_5$H$_{10}$O$_2$), whose roles have been less explored in the literature, and deserve future investigations. GPR41 and GPR43 bind to acetate, propionate, butyrate and formate\textsuperscript{45}, whereas GPR109a is mainly sensitive to butyrate\textsuperscript{46}. Formate can be transported through the Cl$^-$/formate exchanger, SLC26A6\textsuperscript{47}; isobutyrate and valerate can be transported by the SMCT1 (SLC5A8)\textsuperscript{48}; acetoacetate and beta-d-hydroxybutyrate can be transported mainly through SLC5A8\textsuperscript{49} and SLC5A12, although the latter with a lower affinity\textsuperscript{50}.

Immune cells display transporters and receptors for SCFAs, helping to maintain homeostasis through hampering the inflammatory response in the context of several diseases. It has already been demonstrated that SCFAs induce IL-10 and expansion of Foxp3$^+$ regulatory T cells in the gut of patients with inflammatory bowel diseases\textsuperscript{51}. Patients with type 2 diabetes have a decreased level of SCFA-producing bacteria\textsuperscript{52}, indicating that, in some diseases, complex interactions between the host immune system and the microbiota may contribute to inbuilt chronic inflammation.

In innate immunity, butyrate shifts macrophage metabolism towards oxidative phosphorylation (OXPHOS) and lipid metabolism inducing their polarization to the anti-inflammatory M2 profile\textsuperscript{53}. Recent studies have focused on the molecular mechanisms through which the microbiota derived SCFAs can regulate the
metabolism of several immune cell types. During adaptive immune responses, SCFAs act on CD8+ T cells, increasing OXPHOS, mitochondrial mass and glycolysis through GPR41 activation and boosting β-oxidation, which is important to their differentiation into memory cells. SCFAs also modulate CD4+ T cell responses, inducing IL-10 production by inhibiting histone deacetylases (HDACs) and activating the mammalian target of rapamycin (mTOR) pathway. Finally, these metabolites contribute to enhance antibody production in B cells as they increase ATP production, glycolysis, fatty-acid synthesis, and β-oxidation. Interestingly, SCFAs can be transported into the cytoplasm and lead to the production of acetyl-CoA through β-oxidation, fueling the tricarboxylic acid cycle and stimulating OXPHOS, which usually induces an anti-inflammatory or memory profile in immune cells. In this context, disruptions in the gut microbiome and decreased SCFAs production may affect the regulation of the immune response at different sites of the human body.

Although most of the studies focus on SCFAs, there are several other microbiota-derived metabolites that play a key role in regulating signaling pathways in the host such as bile and amino acids. Therefore, future studies should shift their focus from SCFAs to this broader range of gut metabolites, many of which we still do not know nor understand their signaling mechanisms in steady-state and disease.

**Sensing SCFAs by kidney cells**

Once produced by gut microbiota and distributed into the bloodstream, SCFAs can reach different tissues. In kidney cells, the expression of GPR41, GPR43,
Olfr78/OR51E2, and GPR109a has already been reported (Figure 2). GPR41 and GPR43 were identified in human distal and collecting tubules and treatment with propionate, acetate or butyrate was shown to reduce the TNFα-stimulated MCP-1 production by human renal cortical epithelial cells in a GPR41/43-dependent manner. Renal expression of GPR41 and GPR43 was reduced after ischemia and reperfusion injury (IRI), and treatment with acetate restored GPR43 expression and improved renal inflammation and dysfunction. Similar renoprotection was observed by treatment with propionate, butyrate or acetate-producing bacteria in ischemic animals.

Olfr78 (the murine ortholog of OR51E2) has been localized in the renal afferent arteriole, part of the juxtaglomerular apparatus of the kidney, and can mediate the secretion of renin and regulate blood pressure in response to SCFAs. However, the mechanisms by which Olfr78 induces the expression of renin remain to be clarified. Later, Natarajan et al. observed that GPR41 present in the vascular endothelium also responds to SCFAs and participates in blood pressure regulation by mechanisms independent of the plasma renin levels. By binding to their receptors on enteroendocrine cells, SCFAs can also stimulate the release of serotonin (5-hydroxytryptamine), which regulates the vascular tone, and therefore affects kidney perfusion.

High expression of GPR109a was detected in murine podocytes, and treatment with sodium butyrate or high butyrate-releasing high-amylose maize starch diet ameliorated the adriamycin-induced glomerular damage and renal inflammation and fibrosis in mice. In addition, this protective effect of butyrate was not abolished in Gpr109a−/− mice. Snelson et al. did not observe a GPR109a-
dependent beneficial effect of high-fiber diet in experimental type 1 diabetic kidney disease \(^{60}\), whereas other study showed that high-fiber diets or supplementation with acetate, butyrate, or propionate was protective against development of type 1 or type 2 diabetic kidney disease in mice. Conversely, GPR43- or GPR109a-deficient mice were not protected by the SCFAs, suggesting that renoprotection was dependent on these receptors \(^{61}\). These disparate results could be due to the different fiber concentration present in the two diets. In addition, microbiota composition can vary according to several factors as age, diet and environmental factors \(^{62}\).

Islam et al. proposed that propionate can also cross the membranes of mouse kidney cells through the transporter OAT2 and modulates the cellular metabolism, particularly gluconeogenesis \(^{63}\). Members of the membrane transport proteins MCTs and SMCTs are also expressed in kidney cells \(^{48,64-66}\) and are speculated to play a role in the entry of SCFAs (Figure 2). MCT1 and MCT2 (SLC16A1 and SLC16A7) promote H\(^+\)-coupled transport of lactate, pyruvate, and SCFAs (acetate, propionate, and butyrate) \(^{64,67}\). MCT1, detected on the basolateral side of the proximal tubule, may also be involved in taking up lactate or pyruvate for gluconeogenesis and \(\beta\)-oxidation \(^{65}\). Two members of the SMCT family, SLC5A8 and SLC5A12, are Na\(^+\)-coupled transporters for lactate, pyruvate, and SCFAs, expressed by tubular epithelial cells \(^{50}\). The proton/amino acid transporters (PATs) 1 and 2 (SLC36A1 and SLC36A2) have been shown experimentally to mediate the uptake of acetate, butyrate, and propionate by *Xenopus laevis* oocytes, and were are also detected in kidney tissue \(^{68}\).
SCFAs can directly induce renal cell cytoprotection by inhibiting apoptosis, pyroptosis and histone acetylation (Figure 2)\textsuperscript{13, 69}. When administrated in two intraperitoneal dosages (200 mg/kg), 30 minutes before ischemia and at the moment of reperfusion, acetate reversed the increase in renal HDACs activity and prevented the reduction in DNA methylation in mice undergoing kidney IRI \textsuperscript{32}. Administration of sodium butyrate (500 mg/kg/day, i.p.) for 21 days inhibited renal HDACs activity, fibrogenesis-related genes expression and DNA damage, as well as prevented the loss of renal function in diabetic rats \textsuperscript{70}. Accordingly, treatment with sodium butyrate (1 g/kg/day, 5 days/week for 12 weeks, oral administration) attenuated high glucose-induced HDAC2 upregulation and suppressed apoptosis of rat kidney tubular epithelial cells \textsuperscript{13}. Even though acetate and butyrate have been largely explored in HDACs inhibition in kidney diseases, other SCFAs may also have inhibitory effect in a less extent. Using a reporter gene designed to measure HDACs inhibition, Waldecker \textit{et al.} demonstrated that butyrate is effective in inhibiting HDACs in transfected HeLa cells at concentrations of $\geq 1$ mM, whereas superior concentrations are necessary for other SCFAs ($\geq 2$ mM for valerate and $\geq 10$ mM for propionate) \textsuperscript{71}. In MCF7 breast tumor cells, butyrate was the most potent HDAC inhibitor tested, followed by pyruvate (a substrate for acetate production) and propionate \textsuperscript{72}.

SCFAs in human kidney diseases

Although still scarce, studies evaluating the effect of SCFA in the clinics have increased in recent years. The available data support the existence of a link between alterations in gut microbiome and inflammation in human kidney
diseases, especially regarding the contraction of SCFA-producing bacteria. Wong et al. showed that patients with chronic kidney disease (CKD) exhibited significant expansion of bacterial families possessing urease and uricase, with concomitant reduction of families possessing butyrate-forming enzymes. Similarly, a significant reduction of butyrate-producing bacteria Roseburia spp. and Faecalibacterium prausnitzii was observed in patients with end-stage renal disease (ESRD) compared to healthy controls or patients with early stages of CKD. Wang et al. observed lower serum levels of SCFAs in CKD patients and an inverse correlation between butyrate level and renal function.

Metagenomic analyses are useful to better understand the gut microbiota changes in patients with cardiovascular and renal diseases. Individuals with first-grade hypertension presented lower abundance of Faecalibacterium prausnitzii, Roseburia hominis, Ruminococcaceae NK4A214, Ruminococcaceae_UCG-010, Christensenellaceae R-7, which are SCFAs-producing bacteria, prior to drug treatment. They also showed for the first time that higher fecal excretion of acetate, propionate, butyrate and valerate, together with lower plasmatic levels are associated with hypertension in humans.

A case-control study performed at the West China Hospital demonstrated that patients with occasional or recurrent renal calcium oxalate stones had lower SCFAs-producing gut bacteria as well as metabolic pathways associated with SCFAs production than the non-kidney stone controls. Gut dysbiosis at the species level can be observed in different stages of CKD. Metagenomics analyses showed that the top-discriminatory species between non-CKD controls and early stage CKD patients are Bacteroides eggerthii, Candidatus Stoquefichus sp. KLE1796.
(decreased in mild CKD) and *Cetobacterium somerae* (elevated in mild CKD). In advanced CKD, the SCFAs-producing bacteria *Prevotella sp.* 885 and *Roseburia faecis* were decreased, whereas *Merdibacter massiliensis* and *Clostridium glycyrrhizinilyticum* were increased in association with elevated levels of serum uremic toxin and bile acid compared to non-CKD controls. These results raise the possibility that specific gut microorganisms can become biomarkers for early diagnosis and prognosis monitoring of CKD. Notably, lower levels of propionic acid were highly discriminatory between non-CKD controls and patients with advanced CKD. Although these changes in gut microbiota as well as in SCFAs levels have been demonstrated in kidney diseases, it is still unclear whether the expression of SCFAs receptors/transporters is altered in immune cells or renal parenchymal cells of these patients.

To avoid phosphate intake and hyperkalemia, patients with kidney diseases have dietary restrictions of fiber-rich foods, which contribute to the decrease in the production of SCFAs by gut microbiota. It was already shown that high total fiber intake is associated with lower risk of inflammation and mortality and reduced serum urea and creatinine in patients with CKD or on hemodialysis. Therefore, nutritional strategies aiming to increase SCFAs synthesis may benefit CKD or hemodialysis patients, although this warrants further investigations. A single-center non-randomized pilot study demonstrated that supplementation with sodium propionate reduced C-reactive protein, IL-2 and IL-17, oxidative stress and gut-derived indoxyl sulfate and p-cresyl sulfate in patients on maintenance hemodialysis. Four weeks after ceasing the treatment, all improved parameters deteriorated again, evidencing the renoprotective effect of the ongoing SCFA supplementation. Finally, Meyer et al. showed that propionate supplementation...
(participants ingested 2 × 500 mg propionic acid per day) reduces the systemic inflammation in dialysis patients with ESRD and this effect was associated with the expansion of circulating regulatory T cells \(^8^6\). Together, these data suggest that SCFAs-related treatments can become therapeutic strategies for human kidney diseases.

**Concluding remarks**

Kidneys and gut are deeply interconnected, and intestinal dysbiosis can affect renal function as well as the increase in uremic toxins can change the gut microbiota composition (Figure 1). SCFAs are produced by commensal gut microbiota and affect the kidneys by a large range of mechanisms, including modulation of immune system and interactions with their cognate receptors and transporters present in kidney cells (Figure 2). The identification of these and other putative SCFAs receptors and transporters in renal cells will facilitate any pharmacological and non-pharmacological strategies to halt the progression of kidney diseases.

**Disclosures**

B. Ghirotto reports the following: Research Funding: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP). N. Camara reports the following: Scientific Advisor or Membership: Editorial Board of PlosOne Journal, Frontiers in Immunology and Immunity, Inflammation and Diseases. The remaining author has nothing to disclose.
**Funding**

This work was supported by the São Paulo Research Foundation (FAPESP- grants n° 2017/05264-7 and 2019/02893-9), the National Council for Scientific and Technological Development (CNPq) and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brasil (CAPES) – Financial Code 001.

**Acknowledgments**

The figures were created with BioRender.com.

**Author Contributions**

O Foresto-Neto: Conceptualization; Data curation; Formal analysis; Investigation; Writing - original draft

B Ghirotto: Conceptualization; Investigation; Project administration; Writing - original draft

N Olsen Saraiva Câmara: Conceptualization; Funding acquisition; Project administration; Supervision; Writing - review and editing
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**Figure legends**

**Figure 1. Gut microbiota dysbiosis and bacterial metabolites in the gut-liver-kidney axis.** Gut dysbiosis induces bacterial translocation to the liver, where it promotes the release of proinflammatory cytokines, oxidative species and profibrogenic factors. These molecules can enhance the gut dysbiosis and also induce kidney damage. Renal dysfunction results in accumulation of uremic toxins, which increase the gut dysbiosis and the liver damage. On the other hand, gut dysbiosis promotes an increased release of indoxyl sulfate, p-cresol, LPS and proinflammatory cytokines (due to the activation of the TLR4/Myd88/NF-κB pathway by LPS), which promote kidney damage. Also, gut dysbiosis increases the production of TMAO which can promote further liver damage and trigger kidney dysfunction. TLR4: toll-like receptor 4; Myd88: myeloid differentiation factor 88; NF-κB: nuclear factor kappa B; TMAO: trimethylamine-N-oxide.

**Figure 2. SCFAs at the control of immunometabolism and kidney function.** (A) The uptake of dietary fibers induces the production of SCFAs by the commensal gut microbiota, which signal through the G-protein coupled receptors GPR41, GPR43 and GPR109a or via the MCT and SMCT and regulate several metabolic processes. (B) Regarding immune cells, SCFAs activate the mTOR signaling pathway and inhibit HDACs activity, leading to increased IL-10 synthesis in CD4 T cells. They also directly influence the mitochondrial bioenergetics, by enhancing oxidative phosphorylation and β-oxidation. Finally, SCFAs can be converted into Acetyl-CoA and boost the activity of the tricarboxylic acid cycle. These alterations induce macrophage M2 polarization, increased memory responses in CD8 T cells and
higher antibody production in B cells. (C) Acetate, butyrate or propionate from dietary fibers/gut microbiota production or supplementation have several direct effects in kidney tissue. Signaling through the specific G-protein coupled receptors GPR41, GPR43 and GPR109a results in less inflammation and improves renal function in kidney diseases. Upon SCFAs-activation, Olfr78 (the murine ortholog of OR51E2) induces the secretion of renin and regulates blood pressure. SCFAs can also be transported by OATs, MCTs and SMCTs in kidney tissue, where they can modulate the cellular metabolism by increasing gluconeogenesis and interfere in kidney integrity by inhibiting apoptosis, pyroptosis and HDACs activity. (D) Finally, gut dysbiosis can inhibit the production of SCFAs by the microbiota and consequently, their modulatory effects on immune cells and kidneys. SCFAs: short-chain fatty acids; MCT: H+/monocarboxylate transporters; SMCT: Na+/monocarboxylate transporters; mTOR: mammalian target of rapamycin; HDAC: histone deacetylases; Acetyl-CoA: acetyl coenzyme A; Olfr78: olfactory receptor 78; OAT: organic anion transporters.
Figure 2