Epigenetic connection between gut microbiota-derived short-chain fatty acids and chromatin histone modification in kidney diseases

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Gut microbiota-derived metabolites influence host physiology and pathology, where short-chain fatty acids (SCFAs) are the main class of gut microbiota-derived metabolites.¹ SCFAs are fatty acids containing 1 to 6 carbon atoms, including acetate, propionate, butyrate, and pentanoate, which provide 6% to 10% of the body’s total daily energy and 60% to 70% of the colonic epithelial energy needed.² Anaerobic bacteria principally generate the SCFAs³ in the intestine. Once produced, SCFAs are mainly absorbed in the colon (90%–95%), reach circulation, and play roles for distal organs and tissues.⁴

The proposed mechanisms underlying SCFA-mediated modulation of the gut epithelium and whole-body system comprise at least three different modes of action.⁵ First, SCFA-derived atoms serve as a carbon source for epithelial cells, thus directly fueling host metabolism and influencing lipid, glucose, and cholesterol metabolism.⁶ Moreover, SCFAs act as diffusible signaling molecules that differentially activate G protein-coupled receptors such as GPR41, GPR43, and GPR109a.⁷ Finally, SCFAs, especially butyrate and propionate, could be potent histone deacetylase (HDAC) and lysine deacetylase inhibitors and thus modulate the expression of various genes involved in biological processes.

Although it is well-known that SCFAs influence the host philosophy, less special attention has been given to the mechanisms between SCFAs and histone epigenetic regulation, especially for kidney diseases. Currently, a considerable number of studies have focused on the roles of histone modifications in diseases.⁸ Some authors suggest that epigenetic regulation represents a central mechanism by which the environment impacts mammalian gene expression in health and disease.⁹ Since HDACs are targets of microbiota-derived SCFAs that can regulate their activity and affect histone modification and transcriptional regulation, their investigation is of interest.

From this article, the roles of intestinal microbiota-derived SCFAs, as well as crosstalk between SCFAs and histone modification, are discussed in kidney diseases.

SCFAs in kidney diseases: Growing evidence highlighted that SCFAs exhibited positive effects on kidney diseases in both patients and experimental animals [Supplementary Table 1, http://links.lww.com/CM9/B142].

Epigenetic connection between SCFAs and histone modification: The microbial population regulates histone modification in the host’s organs and tissues. As the production of SCFAs is based on the gut microbiota, it is reasonable to question whether SCFAs could regulate histone modification directly. According to the published papers, SCFAs are crucial in mediating the regulation of epigenetic modifications, especially histone acetylation. The potential mechanisms are mainly from two aspects: HDAC inhibitors and acyl-CoA precursors.

SCFAs as HDAC inhibitors: In light of the fact that SCFAs are known to inhibit both the expression and activity of HDACs, several studies have suggested that host–SCFA interactions are mediated through histone modification.¹⁰ The inhibition of HDACs by SCFAs, which in turn, increased histone acetylation, decreased histone compactness, and thus influenced gene expression and biological processes, such as myogenic antigen differentiation, colonocyte P53 expression, and nuclear factor of activated

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As we discussed, SCFAs interacted with histone acetylation from two aspects, HDAC inhibitors and acyl-CoA precursors. For AKI, SCFAs inhibited histone deacetylase activity and modulated the levels of enzymes involved in chromatin modification to alleviate kidney injury in ischemia–reperfusion. For CKD, both prevention supplementation and post-treatment with butyrate could significantly decrease HDAC activity in gentamicin-induced nephrotoxicity, diabetic kidney, and proteasome kidney disease, and thus suppress plasma glucose, creatinine, urea, and histological alterations. These results showed that inhibition of HDAC by SCFAs improved renal function and ameliorated kidney damage both in AKI and CKD [Supplementary Table 1, http://links.lww.com/CM9/B142].

Unlike HDAC inhibition-mediated effects, which have been extensively studied in kidneys, SCFAs as acyl-CoA precursors are rarely explored. Acetate influences histone acetylation mainly as an acyl-CoA precursor by influencing ACSS2, where acetate increases the protein content of the acetyl metabolizing enzyme ACSS2, and upregulates histone H3K27 acetylation in renal cancer, thus mediating cell proliferation and invasion by regulating SNAI1 or monocarboxylate transporter 1. In addition to ACSS2, another key acetyl-CoA enzyme ACLY has also been involved in kidney diseases. ACLY inhibition using siRNA technology inhibited cell proliferation and migration but promoted cell apoptosis in human renal carcinoma cells. In addition to carcinoma, ACLY was also highly induced in the kidneys of overweight or obese patients with CKD and leptin-deficient mice. Raising the ACLY concentration promoted H3K9/14 and H3K27 hyperacetylation, leading to the upregulation of several rate-limiting lipogenic enzymes and fibrogenic factors. In mesangial cells, ACLY is synergistically induced by high glucose, palmitate, and TNF-α. Under these conditions, H3K9/14 and H3K27 hyperacetylation, as well as the induction of the lipogenic and fibrogenic proteins, are completely blocked in the presence of the ACLY inhibitor SB-204990.

**Conclusion:** In recent decades, SCFAs, such low-cost and potent small molecules, have been fully studied not only in the intestinal system but also in the kidneys. They have been implicated in various kidney diseases, although controversies remain. While SCFAs seem to be of great importance in modulating the host’s epigenome through histone modifications, there is still a lack of understanding concerning the mechanism, especially in kidneys [Figure 1]. More in-depth studies are needed to investigate the relationship between SCFAs and histone modifications and their roles in kidney diseases in the future.

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**Conflicts of interest**

None.
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