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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 SCFAs[1] in the intestine. Once produced, SCFAs are mainly absorbed in the colon (90%–95%), reach circulation, and play roles for distal organs and tissues.[2]

The proposed mechanisms underlying SCFA-mediated modulation of the gut epithelium and whole-body system comprise at least three different modes of action.[1] First, SCFA-derived atoms serve as a carbon source for epithelial cells, thus directly fueling host metabolism and influencing lipid, glucose, and cholesterol metabolism.[3] Moreover, SCFAs act as diffusible signaling molecules that differentially activate G protein-coupled receptors such as GPR41, GPR43, and GPR109a.[2] 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.[4] Some authors suggest that epigenetic regulation represents a central mechanism by which the environment impacts mammalian gene expression in health and disease.[5] 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.[5] 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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T-cell production.[6] This phenomenon has been reported in various cells, including immune cells (peripheral blood mononuclear cells, macrophages, dendritic cells, and regulatory T cells), erythroid cells, epithelial cells, and glial C6 cells. How SCFAs promote acetylation, whether only by HDAC inhibition or by other mechanisms, remains elusive. In addition, how SCFAs regulate HDACs in detail is not clear.

SCFAs as Acyl-CoA precursors: There is a substantial body of evidence that supports the idea that SCFAs can not only inhibit HDAC to promote histone acetylation but also provide a pool of acyl groups for the generation of acetyl-CoA.[1] SCFAs can enhance the glycolytic rate and increase acetyl-CoA concentrations, thus connecting cellular metabolism and chromatin modifications.[7] Acetate, the principal SCFA in the colon, is readily absorbed and transported. Mammals express three isoforms of short-chain acyl-CoA synthetases (ACSSs) that convert acetate into acetyl-CoA by consuming ATP.[8] ACSS2 in the nucleus provides a rapid way to reconvert this acetate to acetyl-CoA for use in reacetylating histones and thereby maintaining the epigenetic code.[8] Previous studies found that acetate could activate oncogene expression by increasing H3K27 acetylation in promoter regions,[9] thus promoting lysosomal biogenesis, autophagy, cell survival, and tumorigenesis.

In addition to acetate, other SCFAs will also increase glucose-derived pyruvate and acetyl-CoA levels in eukaryotic cells, which leads to the accumulation of citrate.[1] Citrate can be transported to the cytosol and converted into cytosolic acetyl-CoA by ATP citrate lyase (ACLY). ACLY is the key cytosolic enzyme that converts citrate to acetyl-CoA, which is needed for histone acetyltransferase-dependent histone acetylation. Thus, the carbon atoms derived from SCFAs can be directly transferred to histones via a metabolic-epigenetic link leading to histone acetyltransferase-mediated histone acetylation as well as recently described histone propionylation and butyrylation.[1]

Remarkably, SCFAs seem to be unique molecules that regulate gene expression at the epigenetic level via histone acetyltransferases (HATs) and HDACs.[1] Interestingly, it has already been reported that pentanoate, although a potent HDAC inhibitor, might rather influence histone acetylation by serving as a metabolic input for the HAT substrate acetyl-CoA.[7] Further studies are still required to better understand the interactions between SCFAs, HDAC/acetyl-CoA, and histone acetylation.

SCFA-mediated histone acetylation in kidney diseases: Epigenetic alterations caused by the modification of gene expression, rather than changes in the genetic code, play an important roles in the etiology of kidney diseases. Epigenetic modifications due to SCFAs have already been implicated in the development of kidney diseases, leading to the dysregulation of reno-developmental processes.[10]

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 proteinuric 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 acetate metabolizing enzyme ACSS2, and upregulates histone H3K27 acetylation in renal cancer, thus mediating cell proliferation and invasion by regulating SNAI1 or monocarboxylate transporter 1.[11] 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.[12] In addition to carcinoma, ACLY was also highly induced in the kidneys of overweight or obese patients with CKD and leptin-deficient mice.[13] 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.[13] 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 indepth 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.

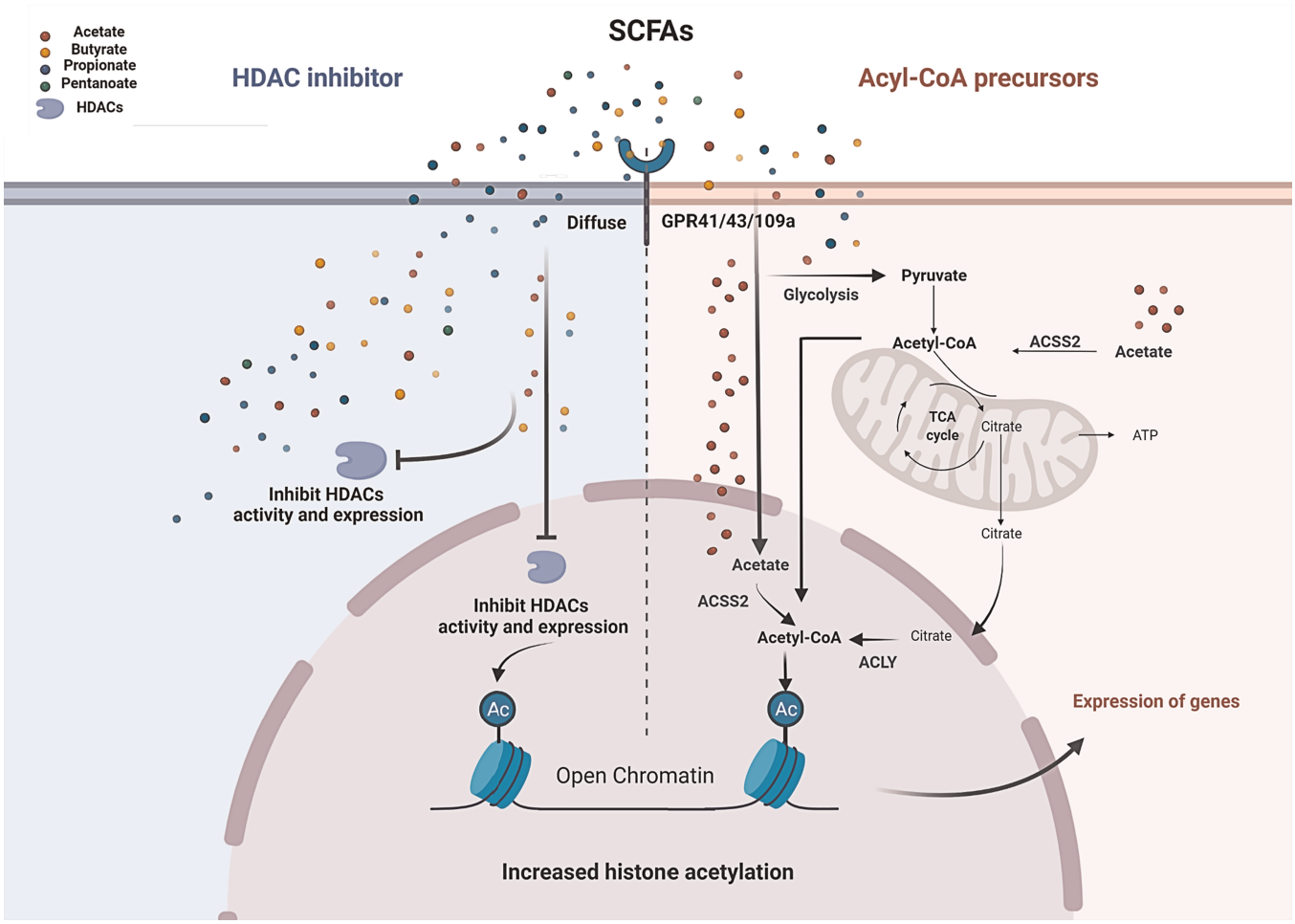

Figure 1: Epigenetic connection between SCFAs and histone modification. ACLY: ATP citrate lyase; ATP: Adenosine triphosphate; ACSS2: Short-chain acyl-CoA synthetase 2; HDAC: Histone deacetylase; GPR: G protein-coupled receptor; SCFAs: Short-chain fatty acids; TCA: Tricarboxylic acid.

References

1. Luu M, Monning H, Visekruna A. Exploring the molecular mechanisms underlying the protective effects of microbial SCFAs on intestinal tolerance and food allergy. Front Immunol 2020;11:1225. doi: 10.3389/fimmu.2020.01225.
2. Zaky A, Glastras S, Wong M, Pollock C, Saad S. The role of the gut microbiome in diabetes and obesity-related kidney disease. Int J Mol Sci 2021;22:9641. doi: 10.3390/ijms22179641.
3. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016;165:1332–1345. doi: 10.1016/j.cell.2016.05.041.
4. Janssen S, Lorincz M. Interplay between chromatin marks in development and disease. Nat Rev Genet 2022;23:137–153. doi: 10.1038/s41576-021-00416-x.
5. Chen B, Sun L, Zhang X. Integration of microbiome and epigenome to decipher the pathogenesis of autoimmune diseases. J Autoimmun 2017;83:31–42. doi: 10.1016/j.jaut.2017.03.009.
6. Waldecker M, Kautenburger T, Daumann H, Busch C, Schrenk D. Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. J Nutr Biochem 2008;19:587–593. doi: 10.1016/j.jnutbio.2007.08.002.
7. Luu M, Pautz S, Kohl V, Singh R, Romero R, Lucas S, *et al*. The short-chain fatty acid pentanoate suppresses autoimmunity by modulating the metabolic-epigenetic crosstalk in lymphocytes. Nat Commun 2019;10:760. doi: 10.1038/s41467-019-08711-2.
8. Lyssiotis C, Cantley L. Acetate fuels the cancer engine. Cell 2014;159:1492–1494. doi: 10.1016/j.cell.2014.12.009.
9. Gao X, Lin S, Ren F, Li J, Chen J, Yao C, *et al*. Acetate functions as an epigenetic metabolite to promote lipid synthesis under hypoxia. Nat Commun 2016;7:11960. doi: 10.1038/ncomms11960.
10. Yoshikawa M, Hishikawa K, Marumo T, Fujita T. Inhibition of histone deacetylase activity suppresses epithelial-to-mesenchymal transition induced by TGF-beta1 in human renal epithelial cells. JASN 2007;18:58–65. doi: 10.1681/asn.2005111187.
11. Li M, Long X, Wan H, Yin M, Yang B, Zhang F, *et al*. Monocarboxylate transporter 1 promotes proliferation and invasion of renal cancer cells by mediating acetate transport. Cell Biol Int 2021;45:1278–1287. doi: 10.1002/cbin.11571.
12. Teng L, Chen Y, Cao Y, Wang W, Xu Y, Wang Y, *et al*. Overexpression of ATP citrate lyase in renal cell carcinoma tissues and its effect on the human renal carcinoma cells in vitro. Oncol Lett 2018;15:6967–6974. doi: 10.3892/ol.2018.8211.
13. Chen Y, Deb D, Fu X, Yi B, Liang Y, Du J, *et al*. ATP-citrate lyase is an epigenetic regulator to promote obesity-related kidney injury. FASEB J 2019;33:9602–9615. doi: 10.1096/fj.201900213R.

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