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# Acylations in cardiovascular diseases: advances and perspectives

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Cardiovascular diseases (CVD) have become the leading cause of morbidity and mortality worldwide.[1,2] During the past two decades, many experimental and preclinical studies have highlighted the critical roles of histone modifications (eg, acetylations and methylations) in regulating cardiovascular development, homeostasis, and disease progression by regulating gene transcription.[3] The well-studied histone acetylations such as H3K9ac and H3K27ac activate gene transcription and have shown critical functions in cardiovascular homeostasis and remodeling.[4] For instance, while class I and II histone deacetylases (HDACs) generally promote the development of cardiac hypertrophy and diabetic cardiomyopathy, most class III HDACs (Sirtuins) exhibit cardioprotective capacity.[5] The inhibitors of class I HDACs have been proven to repress cardiac remodeling and heart failure.

For a long time, the roles of other types of acylations in cardiac homeostasis remain largely unknown. Short-chain fatty acids (SCFAs) (eg, succinate, propionate, malonate, butyrate, 2-hydroxyisobutyrate, β-hydroxybutyrate, crotonate, and glutarate) from the gut microbiota and cellular metabolites, have been identified to participate in CVD, such as hypertension, ischemic injury, and diabetic CVD.[6] In 2011, Zhao *et al* identified eight types of short-chain lysine acylations on histones in mammalian cells, many of which have been demonstrated to be physiologically and pathologically important in CVD and associated risk factors such as obesity and diabetes [Figure 1].[7] However, the roles of short-chain lysine acylations such as crotonylation in cardiovascular homeostasis remain largely unknown.

## Histone crotonylation and cardiac hypertrophy

Crotonylation is a short-chain lysine acylation identified on histones. P300 and GCN5 are the typical writers of histone crotonylation, while class I HDACs and SIRT1-3 act as erasers. Chromodomain-Y-like and Short-chain enoyl-CoA hydratase (SCEH, also known as ECHS1) act as crotonyl-CoA hydratases to control intracellular crotonyl-CoA and histone crotonylation.[6] Histone crotonylation has been reported to trigger gene transcription and participate in biological processes, including mesoendodermal commitment of human embryonic stem cells, spermatogenesis, and neurobiology.[6,8] However, the roles of this newly identified histone crotonylation in the pathophysiological processes of CVD, such as cardiac hypertrophy, remain unknown.

In clinical patients, mutation of ECHS1 causes hypertrophic and dilated cardiomyopathy.[9] ECHS1 deficiency results in cardiac hypertrophy by elevating histone crotonylation and transcription of hypertrophic fetal genes.[10] Histone crotonylation (H3K18cr and H2BK12cr) is significantly upregulated and participates in human and mouse hypertrophic hearts. Histone crotonylation promotes the recruitment of the transcription factor nuclear factor of activated T-cell C3 on the promoters of hypertrophic genes such as the B-type natriuretic peptide. Therefore, histone crotonylation critically contributes to cardiac development and hypertrophic remodeling. Thus, enhanced histone crotonylation potentially is a mechanism underlying cardiac defects mediated by *ECHS1* mutations in humans and mice.

Histone acylations are critically regulated by metabolic enzymes that modulate the intracellular levels of metabolites (eg, acyl-CoA), supporting post-translational modification of histones.[5] The expression of fatty acid

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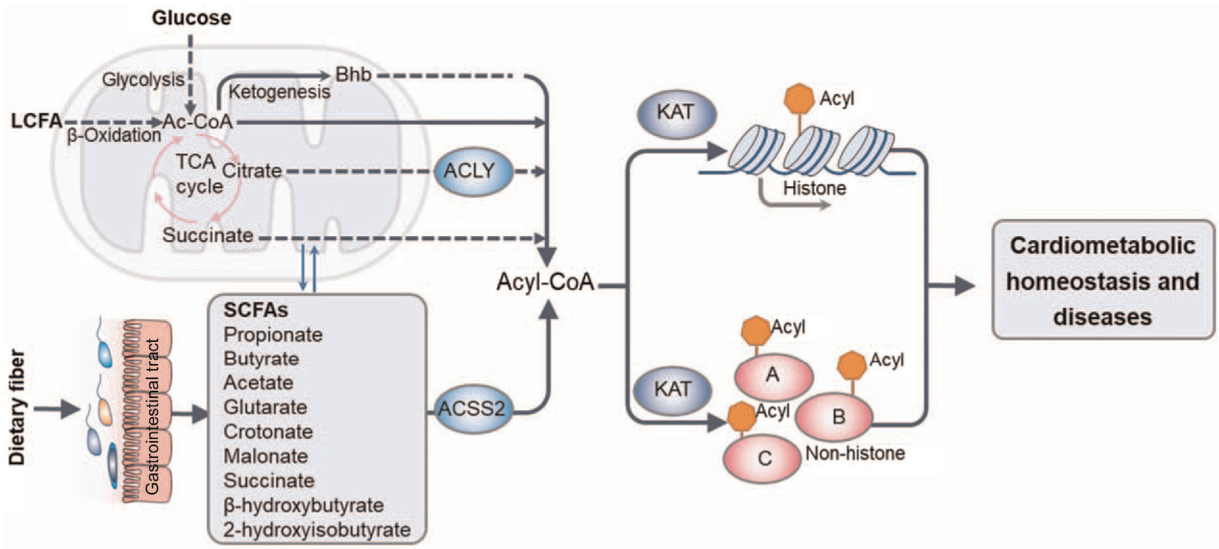


**Figure 1:** Lysine acylation is related to CVD. Energetic metabolism can generate acyl-CoA, which contributes to the acylation of histone and non-histone proteins. Acylation of histone regulates gene transcription while acylation of non-histone proteins regulates intracellular signaling to participate in cardiovascular homeostasis and diseases. ACSS2: Acetyl-CoA synthetase 2; ACLY: ATP citrate lyase; CVD: Cardiovascular diseases; KAT: Lysine acyltransferase; SCFAs: Short-chain fatty acids; TCA: Tricarboxylic acid. LCFA: Long-chain fatty acids; Bhb: β-hydroxybutyrate; Ac-CoA: Acetyl-coenzyme A; Acyl: ATP citrate lyase.

β-oxidation genes coincides with the β-oxidation byproduct crotonyl-CoA, determining the degree of histone crotonylation and gene transcription.[6] These findings highlight the regulatory effect of mitochondrial metabolism (by ECHS1) on histone crotonylation and gene transcription in cardiac remodeling Notably, unlike that of histone acetylation,[5] inhibition of histone crotonylation may serve as a therapeutic option for children with ECHS1 mutations and provide an alternative therapeutic strategy for patients with cardiac hypertrophy.

## Propionylation, succinylation, and malonylation in cardiovascular homeostasis

In addition to histone crotonylation, propionylation of histones (H3K14pr and H3K23pr) was recently identified Cardiac anomalies are present in a subset of patients with deficient H3K23pr catalyzed by BRPF1–KAT6 complexes.[11] Further studies are required to investigate how histone propionylation (H3K14pr and H3K23pr) participates in CVD. Interestingly, recent studies have highlighted that tropomodulin-3 propionylation in platelets promotes thrombosis risk in rodents,[12] and that propionate induces oxidative stress by manganese superoxide dismutase 2 propionylation, indicating that propionylation of non-histone proteins is also functional important in CVD.

In mitochondria, SIRT5-mediated desuccinylation of mitochondrial enzymes is crucial for cardiac function and mouse survival.[13] Besides, malonylation impairs mammalian target of rapamycin (mTORC1) kinase activity, eventually leading to angiogenic defects,[14] an event involved in myocardial infarction. Thus, the role of crotonylation of non-histone proteins may also be important for cardiac homeostasis. Furthermore, although the roles of SCFAs were reported in vascular biology, such as blood pressure,[6] it remains undetermined whether short-chain lysine acylations contribute to vascular biology.

In conclusion, the critical roles of SCFAs and related shortchain lysine acylations in the development of CVD have been identified.[6,10] Short-chain lysine acylations (eg, crotonylation and succinylation) of histones and nonhistone proteins have been reported to play critical roles in the development of cardiac diseases such as hypertrophy and ischemic injury [Supplementary Table 1, http://links.lww.com/CM9/A954]. These findings opened a new window informing the cardiovascular community that "acylations relevant to cardiac homeostasis are broader than simply acetylation," which requires further systemic investigation.[21-25] Some apparent questions appear.

(1) Further detailed studies are needed to test the roles of histone crotonylation and propionylation in cardiovascular development and diseases (eg, myocardial infarction, hypertension, and diabetic complications) and to elucidate the underlying mechanisms using approaches such as chromatin immunoprecipitation-seq and assay of transposase-accessible chromatin-seq The key regulators and activators that participate in this biological process were also elusive.
(2) Moreover, further studies are needed to determine the individual mechanisms underlying different types of histone acylations in cardiovascular homeostasis. A previous study implicated the spatial and temporal interactions between histone acetylation and crotonylation in regulating metabolic processes such as glycolysis.[15] Knowledge of how different types of histone acylations differentially regulate cardiac and vascular homeostasis and diseases is also critical for understanding histone acylations in cardiology.
(3) Finally, SCFAs are generally derived from gut microbiota and intracellular metabolites and contribute to blood glucose homeostasis.[6,16-18] It would also be interesting to test whether gut microbiota affects CVD such as atherosclerosis and hypertension by regulating short-chain lysine acylations of histones and such

pivotal intracellular signaling regulators as insulin-like growth factor signaling, mTOR, adenosine monophosphate (AMP) activated protein kinase, and Forkhead box O (FOXO) transcription factors.[19,20] These answers would help to illuminate the function and underlying mechanisms of different acylation types in cardiovascular development and diseases and to elucidate how different organs (eg, gut, liver, muscle, heart, and blood vessels) communicate with each other.

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## Conflicts of interest

None.

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