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ATP Citrate Lyase: a new player linking skeletal muscle metabolism and epigenetics

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Abstract

Intermediates generated in several metabolic processes are employed to regulate transcription through covalent histone and DNA modifications. In *Cell Reports*, Das et al. show that acetyl-CoA generated by ATP citrate lyase is utilized to acetylate histone H3 at MyoD regulatory regions resulting in increased MyoD expression and improved muscle regeneration after injury.

Increasing evidence shows that, in addition to providing essential energy, metabolic flux actively participates in numerous processes including development, stem cell homeostasis and regeneration [1]. Metabolic dysregulation is closely associated with disorders such as obesity and cancer [2]. Acetyl-coenzyme A (acetyl-CoA), a metabolic intermediate used in mitochondria energy production, is required for the *de novo* synthesis of cholesterol and fatty acid in the cytosol by providing a carbon source. It is also employed in histone and other protein acetylation by providing acetyl groups [3,4]. ATP citrate lyase (ACL) is the enzyme catalyzing the generation of acetyl-CoA and oxaloacetate from citrate in the presence of ATP and CoA. This reaction is responsible for the extra-mitochondrial acetyl-CoA production [3]. By linking glucose metabolism to macromolecular biosynthesis and epigenetics, ACL has been described to be involved in embryonic growth, liver homeostasis, cancer cell proliferation, as well as metabolic disorders including hyperlipidemia [5]. However, whether ACL functions in non-liver tissues, such as skeletal muscle, is still poorly understood.

Skeletal muscle strengthening and contraction are energy-consuming processes, and skeletal muscle mass is directly linked with muscle metabolism. Exercise is often helpful for improving muscle function by increasing metabolic capacity, indicating that metabolic changes somehow regulate muscle function. Interestingly, ACL activation induced through the IGF1/PI3K/AKT pathway increases cardiolipin synthesis and mitochondrial supercomplex activity, which ultimately enhances mitochondrial function in skeletal muscle [6]. However, whether muscle stem cells, also known as satellite cells (SCs), and muscle

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regeneration are affected by ACL remains to be determined. A recent paper by Das *et al.* shed light on ACL specific functions in skeletal muscle by revealing that ACL/acetyl-CoA modulates SC differentiation and muscle regeneration by affecting histone acetylation level at gene regulatory regions [7].

In both mouse and human myoblasts, Das *et al.* observed that reducing ACL selectively decreased fast myosin (fast MyHC, MYH1) expression and increased slow myosin (slow MyHC, MYH7) expression. In *ex vivo* experiments, overexpression of ACL did not alter SC proliferation, and rather promoted their differentiation resulting in increased fast myosin expression and myotube size. By contrast, ACL knockdown inhibited SC differentiation.

Suspecting that ACL might regulate the expression or activity of myogenic transcription factors, Das *et al.* knocked-down MyoD and found that such intervention abolished ACL's effect on fast myosin expression and that, conversely, MyoD overexpression partially rescued reduced fast myosin expression caused by ACL inhibition. ACL knockdown resulted in a generalized reduction of histone H3 acetylation and prompted the authors to evaluate H3 acetylation at the MyoD regulatory regions. Chromatin immunoprecipitation with antibodies directed against Acetyl-H3(K9/K14) revealed that reducing ACL decreased H3 acetylation at a MyoD enhancer (DRR, Distal Regulatory Region) and promoter, and prevented MyoD expression. Acetyl-H3(K9/K14/K27) at a more distal MyoD enhancer (Core Enhancer) was not affected, indicating a role of ACL on H3 acetylation of specific MyoD regulatory regions. Complementary experiments revealed that ACL overexpression increased H3 acetylation at the DRR and MyoD promoter, and upregulated MyoD expression. ACL-mediated increased H3 acetylation and MyoD expression were counteracted by treatment of differentiating myoblasts with an inhibitor of the p300 histone acetyltransferase confirming that the effects of ACL on myogenesis are indeed mediated by acetylation. Das *et al.* previously reported that ACL activity is regulated by the IGF1/PI3K/AKT pathway [6]. It was therefore satisfying to observe that ACL silencing blunted some of the well-known effects of IGF-1 on skeletal muscle, including IGF-1-induced histone acetylation enrichment at the *MyoD* promoter.

Skeletal muscle regeneration relies on SCs, and thus provides an excellent experimental perturbation in which to investigate SC activation, proliferation, and differentiation *in vivo* [8]. Das *et al.* tested ACL's role in injured tibialis muscle by overexpressing it before injury. Notably ACL overexpression increased muscle weight, average fiber cross-sectional area, and led to formation of large myofiber number during muscle regeneration. ACL overexpression significantly enhanced expressions of Pax7, MyoD and Myf5, as well as of Myh3, Myh8, Myh1, Myh2 and Myh4. The increased MyoD expression correlated with augmented H3 acetylation at the DRR and *MyoD* promoter. These findings indicate that ACL, by influencing histone acetylation, critically regulates both SC activation and differentiation and, in doing so, mediates muscle repair after injury.

ACL inhibition has been shown to dramatically reduce the net amount of cellular acetyl-CoA in cancer cells [9]. Whether this also occurs in normal mammalian cells has not been tested. However, since glucose acts as the major carbon source of acetyl-CoA, ACL knockdown or overexpression is likely to respectively reduce or increase the net abundance

of acetyl-CoA also in normal muscle cells. The concomitant upregulation of ACL expression and increased Acetyl-H3(K9/K14), but not Acetyl-H3(K27), during differentiation is of interest and suggests the possibility that different histone acetyltransferase may have distinct sensitivity for acetyl-CoA level alteration. Overall, these findings indicate that the ACL/acetyl-CoA/p300 pathway is a previously undescribed transduction arm for IGF-1 function.

Myogenesis is a precisely controlled process by gene networks. The work of Das *et al.* provides an additional mechanistic explanation to how growth factors regulate myogenesis by providing evidence that IGF-1 activates the ACL/acetyl-CoA/p300 pathway leading to SC differentiation through transcriptional regulation of master regulatory genes. Considering the important roles exerted by IGF-1 in muscle physiology [10], manipulating ACL activity might provide new ways to treat muscle diseases and aging. Moreover, since Acetyl-H3(K9/27) acetylation-mediated gene expression participates in the progress of hematological malignancies such as leukemia [11, 12], the ACL/acetyl-CoA/H3 acetylation pathway may play key roles in hematological malignancies, and its manipulation provide promising therapeutic targets for combatting these diseases.

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Figure 1. Model of the IGF1/AKT/ACL/Acetyl-CoA pathway regulating gene expression in skeletal muscle cells

Citrate is generated from glucose-derived pyruvate through tricarboxylic acid (TCA) cycle in the mitochondria, and transported into cytoplasm. After being phosphorylated by IGF1/AKT signaling, ACL converts citrate into acetyl-CoA, which is utilized for p300-mediated histone acetylation. This acetylation induces muscle-specific gene expression, resulting in SC differentiation.