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BIOCHEMISTRY. A Glucose-to-Gene Link

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A regulatory loop links glucose metabolism to chromatin alterations and the controlled expression of metabolic genes.

Eukaryotic cell growth demands an increase in glucose uptake and metabolism to support energetic and biosynthetic needs, accompanied by changes in gene expression that control cell lineage or fate. These gene expression patterns are determined by lineage-specific or differentiation stage–specific transcription factors, as well as by modifications of chromatin (the complex of nucleic acids and proteins that constitute chromosomes) that regulate access of transcription factors to specific DNA loci. On page 1076 of this issue, Wellen *et al*. propose a new mechanism to link glucose metabolism to chromatin modification and global transcriptional control via the enzyme ATP-citrate lyase and production of acetyl–coenzyme A (acetyl-CoA) (1).

Acetyl-CoA is a key intermediate in three major metabolic pathways (see the figure). As a product of pyruvate dehydrogenase in the mitochondria, it serves as an initiating metabolite of the tricarboxylic acid (TCA) cycle in fed or anabolic states. It is also the end product of the mitochondrial fatty acid β-oxidation pathway, again serving as an important TCA cycle initiator, particularly in fasted or catabolic states. And under glucose-replete conditions, citrate exits the mitochondria to be converted by ATP-citrate lyase to acetyl-CoA for lipid synthesis.

In addition to these roles, acetyl-CoA is the substrate of protein acetylases, including histone acetyltransferases that modify histone proteins and consequently chromatin structure. In yeast, deletion of the gene encoding acetyl-CoA synthetase (Acs2p), which produces acetyl-CoA from acetate, results in defective histone acetylation and altered transcription (2). Although mammals express a homolog of Acs2p (AceCS1), it has not been implicated in histone modification. The pool of acetyl-CoA used for histone acetylation and lipid synthesis must originate in the cytoplasm and/or nucleus rather than the mitochondria. Both ATP-citrate lyase and AceCS1 are expressed in the cytoplasm, but only expression of the former is essential to support the synthesis of lipids required for new membrane formation upon growth factor stimulation (3–5). Indeed, pharmacologic inhibition of ATP-citrate lyase has been proposed to prevent tumor growth (6).

Although ATP-citrate lyase deficiency decreases the amount of cellular acetyl-CoA (6), the effect of such metabolic limitation on protein acetylation had not been described. Wellen *et al*. show that suppressing ATP-citrate lyase expression (via small interfering RNA) decreased global histone acetylation in several different mammalian cell types. The authors also studied two conditions that induce histone acetylation—serum starvation and re-feeding, which synchronizes cells for entry into the cell division cycle, and differentiation of fibroblast cells into adipocytes. Reducing ATP-citrate lyase expression reduced histone acetylation in both

circumstances. Moreover, histone acetylation depended on glucose, with fatty acids unable to substitute, consistent with a requirement for a cytosolic or nuclear (not mitochondrial) pool of acetyl-CoA. The impairment of histone acetylation by reducing ATP-citrate lyase expression was not mimicked by a lack of the acetyl-CoA synthetase Acs2p, but could be rescued by acetate, indicating that Acs2p regulates histone acetylation only when acetate is present, and not when glucose is abundant.

These studies also uncovered an interesting connection between ATP-citrate lyase–mediated acetyl-CoA production and the expression of key genes involved in glucose metabolism (see the figure). Suppressing ATP-citrate lyase in differentiating adipocytes prevented the expression of a major adipocyte glucose transporter, Glut4, as well as glucose-metabolizing enzymes [hexokinase 2 (HK2), phosphofructokinase-1 (PFK-1), and lactate dehydrogenase–A (LDH-A)]. This effect was rescued by treating cells with acetate, thereby implicating acetyl-CoA in this regulatory loop. Moreover, acetylation of histones was reduced at the promoter of the Glut4-encoding gene in adipocytes that lack ATP-citrate lyase. However, these findings do not eliminate a possible role for transcription factors with global control effects on specific metabolic pathways. Indeed, one such factor, ChREBP, was suppressed by the absence of ATP-citrate lyase and restored by acetate, and others may have been similarly affected.

Surprisingly, reducing ATP-citrate lyase influenced acetylation of only a select set of substrates. The reason for this specificity is unclear, but several possibilities exist. Distinct histone acetyltransferases or histone deacetylases could interact with different substrates (7) and/or may have different affinities for acetyl-CoA, with those that regulate acetylation being most sensitive to acetyl-CoA limitation. In fact, Wellen *et al.* found that reducing the expression of either ATP-citrate lyase or a specific histone acetyltransferase (GCN5) suppressed global histone acetylation but not acetylation of tubulin, a cytoskeletal protein that is acetylated by the Elongator histone acetyltransferase complex (7). The site of acetyl-CoA generation may also play a role in specificity. Wellen *et al.* show that ATP-citrate lyase is found throughout the cell, including diffuse localization in the cytosol and nucleus. Specific roles of these discrete enzyme pools on histone acetylation remain to be determined.

Wellen *et al.* provide strong evidence in cultured cells that acetyl-CoA derived from glucose and ATP-citrate lyase generates a substrate for chromatin modification and a signal for activating a glycolytic metabolic program. However, its importance for normal physiologic adaptations (such as fasting and refeeding cycles in mammals) is unknown. Fasted mammals spare glucose and rely heavily on fatty acid and amino acid oxidation for energy needs, whereas glucose becomes the predominant fuel metabolite in the fed condition. Does this imply that chromatin remodeling is driven by acetyl-CoA derived from glucose in the fed state, and that this is a key mechanism for initiating glycolytic and lipogenic programs under such conditions? Such questions remain to be answered.

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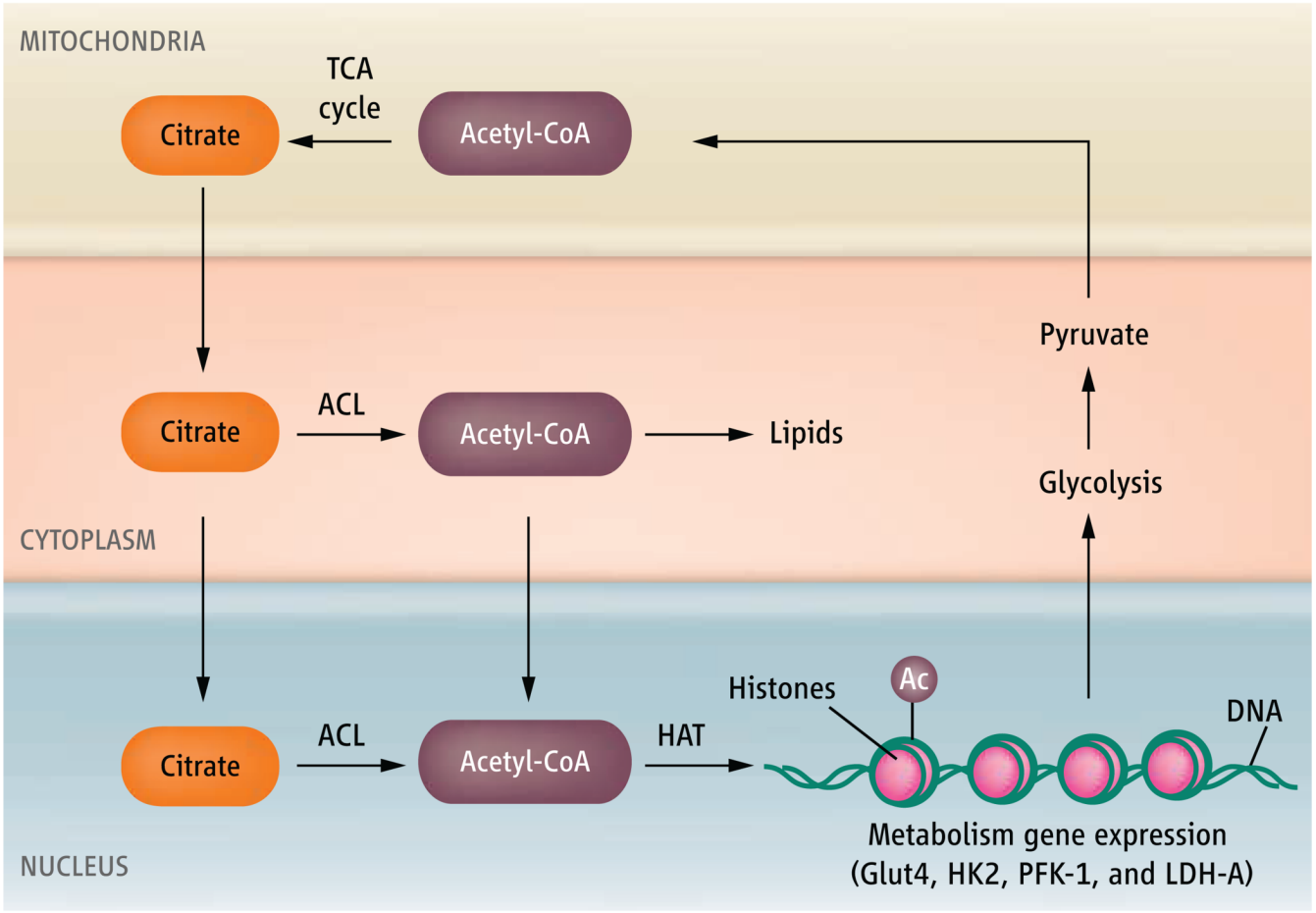

Figure 1. A mitochondria-nucleus circuit

Wellen *et al.* propose that in mammalian cells, adequate glucose leads to increased glycolysis and generation of mitochondrial citrate that is transported to the nucleus or the cytosol. ATP-citrate lyase (ACL) converts citrate to acetyl-CoA. In the nucleus, acetyl-CoA serves as a substrate for histone acetyltransferases (HATs) that modify histones with acetate (Ac) to affect the transcription of key metabolic genes. In the cytosol, acetyl-CoA supports lipid synthesis.