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Acetyl-CoA and the regulation of metabolism: mechanisms and consequences

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Acetyl-CoA represents a key node in metabolism due to its intersection with many metabolic pathways and transformations. Emerging evidence reveals that cells monitor the levels of acetyl-CoA as a key indicator of their metabolic state, through distinctive protein acetylation modifications dependent on this metabolite. We offer the following conceptual model for understanding the role of this sentinel metabolite in metabolic regulation. High nucleocytosolic acetyl-CoA amounts are a signature of a 'growth' or 'fed' state and promote its utilization for lipid synthesis and histone acetylation. In contrast, under 'survival' or 'fasted' states, acetyl-CoA is preferentially directed into the mitochondria to promote mitochondrial-dependent activities such as the synthesis of ATP and ketone bodies. Fluctuations in acetyl-CoA within these subcellular compartments enable the substrate-level regulation of acetylation modifications, but also necessitate the function of sirtuin deacetylases to catalyze removal of spontaneous modifications that might be unintended. Thus, understanding the sources, fates, and consequences of acetyl-CoA as a carrier of two-carbon units has started to reveal its underappreciated but profound influence on the regulation of numerous life processes.

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Introduction

In response to a dynamic nutrient environment, cells must assess their metabolic state to decide whether to grow, survive, or die. It has become evident that metabolites themselves must feed back to regulate gene expression, signal transduction, and various protein activities in cellular decision-making processes [1,2]. These small molecule metabolites play critical roles in relaying metabolic information to their protein and nucleic acid counterparts. However, despite increased recognition of such reciprocal interplay, many aspects of the mechanisms through which metabolites exert their influence on cellular regulatory mechanisms are still being unraveled.

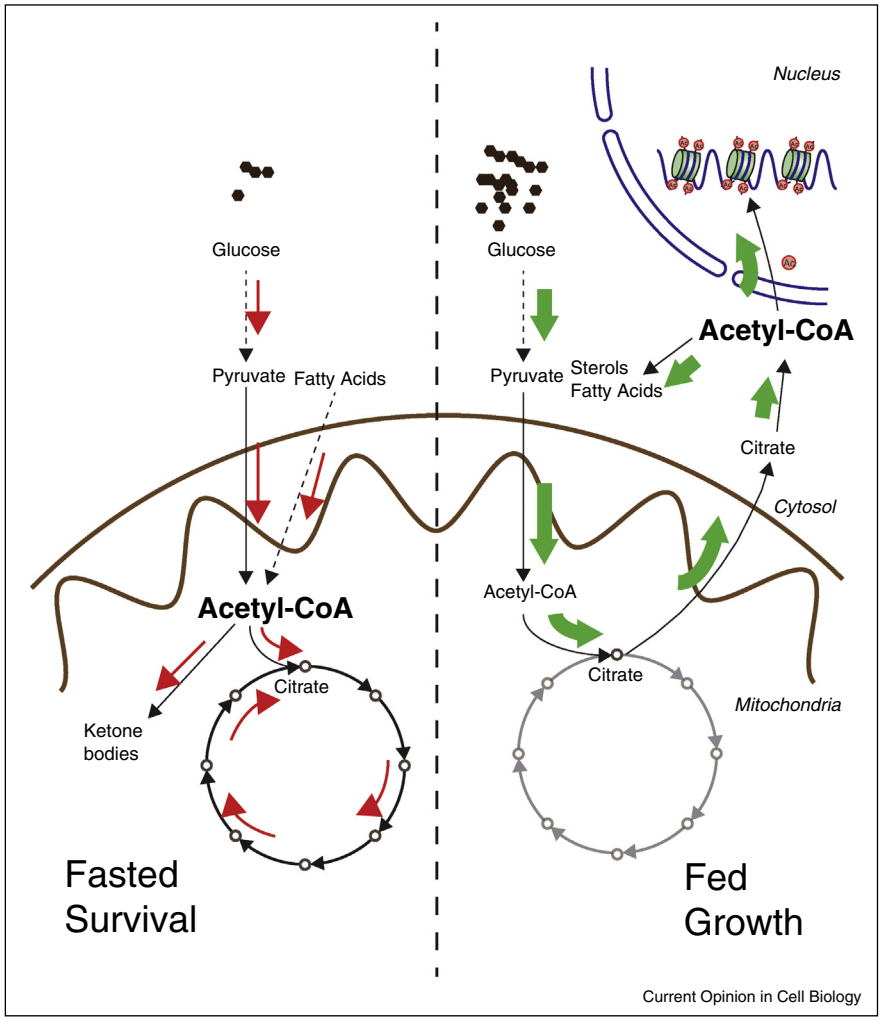
Amongst the thousands of metabolites present in the cellular milieu at any given time, which might represent the 'sentinel' metabolites that signify cellular metabolic state? One well-known signature of metabolic state is AMP, which indicates cellular energy charge and accumulates upon ATP insufficiency. AMP regulates the activity of the AMP-activated protein kinase (AMPK), which phosphorylates many proteins involved in cellular energy homeostasis [3]. Another example is NAD^+, which indicates the cellular redox status as a ratio of NAD^+ to NADH [4,5]. Herein, we discuss the hypothesis that acetyl-CoA represents an additional prominent gauge of the cell's metabolic state with substantial influence on numerous biological regulatory mechanisms.

Growth or fed state — high acetyl-CoA in cytosol/nucleus

Acetyl-CoA is a metabolite derived from glucose, fatty acid, and amino acid catabolism. During glycolysis, glucose is broken down into two three-carbon molecules of pyruvate. The mitochondrial pyruvate dehydrogenase complex then catalyzes the oxidative decarboxylation of pyruvate to produce acetyl-CoA, a two-carbon acetyl unit that is ligated to the acyl-group carrier, CoA [6]. In the mitochondria, citrate synthase then catalyzes the condensation of the acetyl moiety of acetyl-CoA with oxaloacetate to yield a six-carbon citrate molecule. Citrate can proceed to be oxidized via the TCA cycle, or alternatively it can be transported to the cytosol as a substrate for the enzyme ATP citrate lyase, which cleaves citrate to regenerate acetyl-CoA and oxaloacetate [7] (Figure 1). Under conditions of carbohydrate or glucose excess, the function of this pathway is to direct acetyl-CoA away from the mitochondria and back to the cytosol for the synthesis of fatty acids and sterols [8]. As such, cells can store excess carbohydrates as fat. Thus, the function of the ATP citrate lyase enzyme offers a clue to the logic and direction of carbon flow — acetyl-CoA units are shipped out of the mitochondria in the form of citrate when carbon sources are abundant, indicating a favorable nutrient state.

Nucleocytosolic pools of acetyl-CoA are also utilized for histone acetylation and the activation of gene expression.

Figure 1



Schematic model proposing a general logic of acetyl-CoA utilization under fed versus fasted or growth versus survival states. Under fed or growth states, acetyl-CoA is directed out of the mitochondria and to the cytosol and nucleus for use in lipid synthesis or histone acetylation. Nucleocytosolic amounts of acetyl-CoA increase relative to mitochondrial amounts. Under fasted or survival states, acetyl-CoA is channeled into the mitochondria for synthesis of ATP and ketone bodies. Mitochondrial amounts of acetyl-CoA increase relative to nucleocytosolic amounts. Fatty acid oxidation significantly increases mitochondrial acetyl-CoA.

ATP citrate lyase was shown to provide a source of acetyl-CoA for histone acetylation in mammalian cells [9]. The budding yeast *Saccharomyces cerevisiae*, which lacks ATP citrate lyase, relies on acetyl-CoA synthetase enzymes to supply acetyl-CoA for histone acetylation [10]. Moreover, a special cohort of yeast genes important for growth, such as those required for ribosome biogenesis and the G1 cyclin *CLN3*, are especially dependent on histone acetylation for their activation [11•,12]. As such, the expression of these growth genes is closely coupled to acetyl-CoA as an indicator of the cell's nutritional state. Thus, when carbon sources are abundant, nucleocytosolic amounts of acetyl-CoA accumulate and facilitate the processes of lipid synthesis and histone acetylation (Figure 1).

Survival or fasted state — high acetyl-CoA in mitochondria

During starvation, cells must typically shift from growth to survival mode and alter metabolism towards functions important for viability. Instead of shipping acetyl units out to the cytosol, there is now a greater requirement for acetyl-CoA to be oxidized in the mitochondria for ATP synthesis (Figure 1). Under such conditions, nucleocytosolic acetyl-CoA levels therefore decrease. Fatty acids are a significant source of this mitochondrial acetyl-CoA pool [13]. CoA synthesis is induced to activate fatty acids as fatty acyl-CoAs [14,15], which can then be transported into mitochondria via the carnitine shuttle for β-oxidation. As a result, acetyl-CoA is generated in the mitochondria for