Trends in Biochemical Sciences

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Review

Mechanisms and Dynamics of Protein Acetylation in Mitochondria

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Reversible protein acetylation is a major regulatory mechanism for controlling protein function. Through genetic manipulations, dietary perturbations, and new proteomic technologies, the diverse functions of protein acetylation are coming into focus. Protein acetylation in mitochondria has taken center stage, revealing that 63% of mitochondrially localized proteins contain lysine acetylation sites. We summarize the field and discuss salient topics that cover spurious versus targeted acetylation, the role of SIRT3 deacetylation, nonenzymatic acetylation, and molecular models for regulatory acetylations that display high and low stoichiometry.

From Histone Regulation to Mitochondrial Acetylation

Mitochondria function as central mediators of metabolism and energy production [1]. Through the ability to oxidize sugars, fatty acids, and amino acids by reducing molecular oxygen and creating a H^+ gradient across the inner mitochondrial membrane, mitochondria couple this chemiosmotic gradient to the production of ATP. While it is general knowledge that the majority of cellular ATP is generated by these organelles, mitochondria play central roles in many fundamental cellular processes that include providing precursors for anabolic processes, acting as sentinels of cellular health, and coordinating nucleus–mitochondrion communication. Therefore, revealing previous unknown regulatory networks that operate within mitochondria has broad implications for our understanding of cellular homeostasis and pathology. Recent research on mitochondria has implicated protein lysine *N*-ε-acetylation as a major regulatory mechanism for modulating protein function.

The acetylation of histone proteins became the first well-established example of biologically functional protein acetylation. Allfrey *et al.* observed that histones in isolated calf thymus nuclei can be rapidly labeled with radiolabeled acetate, and that these acetylated histones were less inhibitory for RNA polymerase [2]. In the late 1990s the first histone acetyltransferases (HATs) and deacetylases (HDACs) were cloned and linked to the regulation of gene expression on chromatinized templates [3,4]. In this case, acetylation generally correlates with gene expression, acting in part to 'open up' chromatin for appropriate transcriptional machinery to access the DNA template. We now know that there are many acetyl-CoA dependent histone acetyltransferases and histone deacetylases that function to regulate all DNA-templated processes, and they are primarily thought to act through the direct reversible acetylation of histone lysine residues [5–7]. Current evidence supports the idea that site-specific acetylation is sufficient to alter nucleosome dynamics and chromatin folding [8,9]. In addition, acetylated lysines on histones can function as 'epitopes' for the recruitment of acetyl-lysine binding domains (e.g., bromodomains) that are contained within large

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Improvements in mass-spectrometry-based proteomics have uncovered protein acetylation as a prominent post-translational modification, and the latest methods report fold-change and stoichiometry.

Mitochondria appear to harbor a disproportionately high number of acetylated proteins.

Mitochondrial acetylation is thought to be largely non-enzymatic, mediated by reactive lysine residues and acetyl-CoA.

The NAD^+-dependent deacetylase SIRT3 removes mitochondrial acetylation, and loss of SIRT3 function is linked to increased ROS and altered oxidative metabolism.

Protein acetylation in mitochondria typically leads to loss of function in pathways associated with organelle integrity and oxidative metabolism.

Additional endogenous lysine acylations (e.g., succinylation, glutarylation) occur and can be catalytically removed by members of the sirtuin family.

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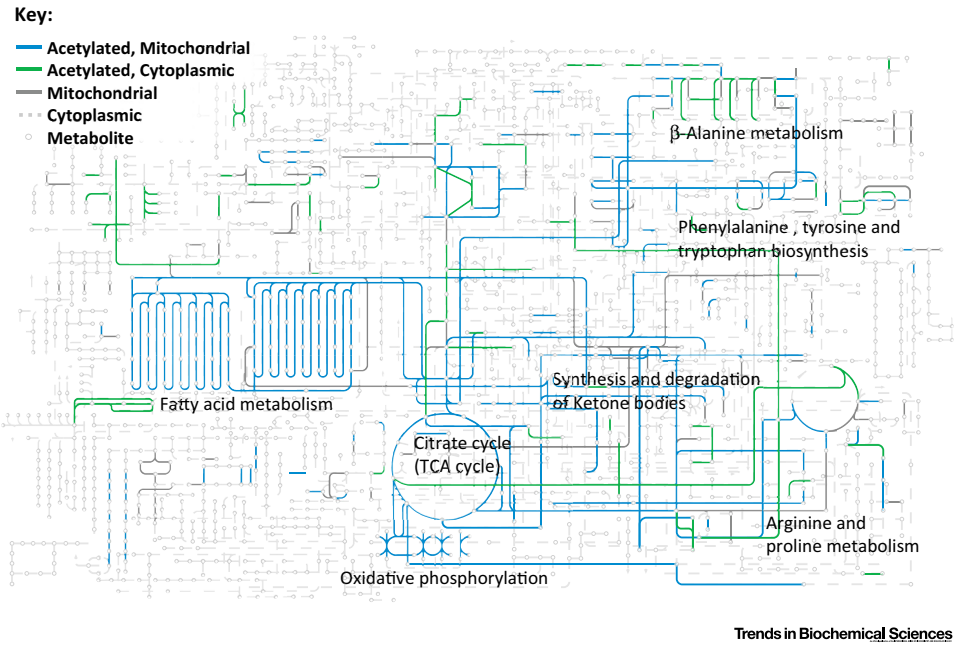

Figure 1. Acetylated Proteins in the Context of Global Metabolism. A large proportion of metabolic enzymes are acetylated. Mitochondrial proteins (in blue) and cytoplasmic proteins (in green) that have been found to be acetylated in *M. musculus* are overlaid on the Kyoto Encyclopedia of Genes and Genomes (KEGG) Metabolic Pathways reference pathway. The labeled pathways have had between 8% and 30% of their total lysines acetylated [18,58].

protein complexes such as histone acetyltransferases, methyltransferases, transcriptional coactivators, and ATP-dependent chromatin-remodelers [10].

The acetylation of p53 and α-tubulin were early examples that protein acetylation extends beyond histone proteins [11]. The observation that several deacetylases were localized outside the nucleus spurred further interest in exploring protein acetylation as a broader phenomenon [12]. Shortly thereafter, the metabolic enzyme acetyl-CoA synthetase was found to be regulated by reversible acetylation in both bacterial and mammalian systems, suggesting that non-histone protein acetylation may be an evolutionarily conserved, general mechanism of metabolic regulation. In this case, acetyl-CoA synthetase activity is controlled by acetylation of a single conserved lysine residue in the active site. Acetylation renders the enzyme inactive, while deacetylation restores full activity [13–15]. Collectively, these results demonstrated the existence of functionally-relevant non-histone targets, which inspired the use of unbiased discovery methods to identify and characterize other acetylation events. Immunoprecipitation with an antibody against acetyl-lysine followed by liquid chromatography coupled mass spectrometry (LC-MS) was the method of choice, and early acetyl-proteomic studies provided lists of acetylated peptides and the corresponding proteins. These catalogs were often dominated by metabolic proteins and particularly enriched with mitochondrial proteins. Such observations suggested that either the method was biased toward highly-abundant proteins, or there was something unique to metabolic proteins, especially those resident in the mitochondria. Subsequent proteomic studies have confirmed that the modification is widespread, particularly among metabolic and mitochondrial proteins (Figure 1).

Probing the Extent of the Mitochondrial Acetylome

Growing interest in the protein acetylation field has fueled concerted efforts to characterize the protein acetylome (or acetyl-proteome). By using various nutritional, genetic, and pharmacological model systems, the roster of acetylated lysine sites has expanded rapidly in the past

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