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Lysine acetylation in mitochondria: From inventory to function

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ABSTRACT

Cellular signaling pathways are regulated in a highly dynamic fashion in order to quickly adapt to distinct environmental conditions. Acetylation of lysine residues represents a central process that orchestrates cellular metabolism and signaling. In mitochondria, acetylation seems to be the most prevalent post-translational modification, presumably linked to the compartmentation and high turnover of acetyl-CoA in this organelle. Similarly, the elevated pH and the higher concentration of metabolites in mitochondria seem to favor non-enzymatic lysine modifications, as well as other acylations. Hence, elucidating the mechanisms for metabolic control of protein acetylation is crucial for our understanding of cellular processes. Recent advances in mass spectrometry-based proteomics have considerably increased our knowledge of the regulatory scope of acetylation. Here, we review the current knowledge and functional impact of mitochondrial protein acetylation across species. We first cover the experimental approaches to identify and analyze lysine acetylation on a global scale, we then explore both commonalities and specific differences of plant and animal acetylomes and the evolutionary conservation of protein acetylation, as well as its particular impact on metabolism and diseases. Important future directions and technical challenges are discussed, and it is pointed out that the transfer of knowledge between species and diseases, both in technology and biology, is of particular importance for further advancements in this field.
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1. Introduction

Mitochondria in plants and animals are cellular powerhouses that fuel metabolism with various molecular building blocks and ATP for movement and growth. Due to differences in the cellular requirements between tissues, organs, or even time of day, mitochondrial activities have to be tightly regulated in accordance with cellular metabolic demands. Furthermore, mitochondria have to work in concert with other subcellular metabolic pathways and organelles, which requires a high degree of regulation of the mitochondrial protein complement. The long-term regulation of protein identity and amount can be achieved by regulation of gene expression, translation, and protein turnover of both nucleus- and mitochondria-encoded gene products. The requirement for a change in the protein complement is generally transmitted via signaling networks that orchestrate most cellular physiology. Post-translational modifications (PTMs) of proteins are key mechanisms that play a role in all the aforementioned layers of gene expression regulation. Additionally, they have the ability to directly regulate protein function on shorter timescales via altering the activities of metabolic enzymes, as well as the localization of proteins. These aforementioned layers of PTM-based regulation mechanisms are well established as

Abbreviations: 3PG, 3-phosphoglycerate; Aβ, Abeta peptide; acetyl-CoA, acetyl-coenzyme A; ACYL, ATP-citrate lyase; AD, Alzheimer's disease; ATP, adenosine triphosphate; CR, caloric restriction; ETC, electron transfer chain; GDC, glycine decarboxylase; GO, gene ontology; GOT, glutamate oxaloacetate transaminase; HD, Huntington's disease; HF, heart failure; HOG, hierarchical orthologous group; HTT, huntingtin; IDH, isocitrate dehydrogenase; IPC, ischemic pre-conditioning; I/R, ischemia reperfusion; KAc, acetylated lysine; KDAC, lysine deacetylases; KATs, lysine acetylases; LCAD, long-chain acyl-CoA dehydrogenase; LDH, lactate dehydrogenase; mCK, mitochondrial creatinine kinase; mMDH, mitochondrial malate dehydrogenase; MS, mass spectrometer; NAD, nicotinamide adenine dinucleotide; NAM, nicotinamide; OXPHOS, oxidative phosphorylation; PD, Parkinson's disease; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatase; PEP, phosphoenolpyruvate; PGAM, phosphoglycerate mutase; PTMs, post-translational modifications; ROS, reactive oxygen species; RuBisCO, ribulose-1,5-bisphosphate carboxylase/oxygenase; SDH, succinate dehydrogenase; SILAC, stable isotope labelling with amino acids in cell culture; SHHF, spontaneously hypertensive heart failure; SIRT, sirtuin; SS, salt-sensitive; TCA cycle, tricarboxylic acid cycle.

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sophisticated cellular tools to define, alter or switch physiological states in all living organisms (Uy and Wold, 1977). For fifteen of the proteinogenic amino acids numerous and chemically diverse PTMs have so far been reported (Walsh et al., 2005). Lysine modifications, which compete for the modification of the ε-amino group of lysine, show a remarkable chemical diversity with at least twenty different PTMs reported on proteinogenic lysine residues under physiological conditions. These include mono-, di-, and trimethylation, ADP-ribosylation, formylation, hydroxylation, lipoylation, biotinylation, ubiquitination, neddylation and sumoylation. Significantly, there are also several acyl-CoA-dependent lysine modifications, such as acetylation, butyrylation, propionylation, glutarylation, crotonylation, malonylation, succinylation, as well as long-chain fatty acid acyl-CoA derivatives, which might be particularly important for mitochondrial physiology due to the occurrence of the corresponding metabolites within the mitochondrial matrix (Fig. 1). Unmodified lysine residues are usually positively charged under physiological conditions, and are thus important for ionic interactions within or between proteins for example. The PTMs of lysine may either retain this positive charge (e.g. methylation), neutralize this charge (e.g. lysine acetylation) or even add a negative charge (e.g. succinylation) (Montgomery et al., 2015) (Fig. 1). With the exception of lysine acetylation, not much is yet known about the other acyl-CoA dependent modifications in mitochondria of plants and animals with a few exceptions for some of these modifications in vertebrates (Park et al., 2013; Pougovkina et al., 2014b; Rardin et al., 2013; Tan et al., 2014; Weinert et al., 2013b).

1.1. General aspects of lysine acetylation

Acetyl-coenzyme A (acetyl-CoA) functions as a cofactor in lysine acetylation next to its role as metabolic intermediate. More than 50 years ago, lysine acetylation was first discovered on histones where it has an important role in the regulation of gene expression by modification of core histone tails through the activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Allfrey et al., 1964; Berger, 2007; Gershey et al., 1968). In comparison to phosphorylation, which has been extensively studied, technical challenges delayed the studies on lysine acetylation by 20 to 30 years (Gu and Roeder, 1997; Kouzarides, 2000; L'Hernault and Rosenbaum, 1985). Advances in mass spectrometry and affinity enrichment techniques propelled the detection of only a few acetylation sites to thousands of sites per study making it evident that most of the acetylation events occur in non-nuclear proteins (Choudhary et al., 2009; Norvell and McMahon, 2010; Wang et al., 2010b; Zhao et al., 2010). The number of acetylation sites identified in various organisms ranging from bacteria to humans and plants now rapidly approaches those of better studied PTMs, such as phosphorylation (Dittenhafer-Reed et al., 2015; Havelund et al., 2013; Henriksen et al., 2012; König et al., 2014a; Lundby et al., 2012; Svinkina et al., 2015; Weinert et al., 2013a; Weinert et al., 2015, 2011; Xiong et al., 2016). Studies show that calorie restriction or changes in nutrition affect the mitochondrial acetylome, but not that of the cytosol or nucleus (Pougovkina et al., 2014a), suggesting variable roles of lysine acetylation in the mitochondria, nucleus and cytoplasm. Since it was established that many non-histone proteins from central metabolic pathways like glycolysis, TCA cycle, β-oxidation, and additionally from photosynthesis in plants (Finkemeier et al., 2011; Wu et al., 2011), can undergo lysine acetylation the modifying enzymes were renamed lysine acetyltransferases (KATs) and lysine deacetylases (KDAC). Using acetyl-CoA as substrate, KATs transfer the acetyl moiety to the ε-amino group of lysine, which masks its positive charge. This change in charge state can have a strong impact on the function of proteins thereby regulating enzyme activity, protein interactions, and protein stability (Xiong and Guan, 2012; Yang and Seto, 2008). So far, little information is available on mitochondria-localized KATs in mammals, while none have yet been identified in plants. Two completely unrelated proteins have been implicated to act as mitochondrial KATs in mammals: GCN5L1 and ACAT1. GCN5L1 is weakly related to the classical nuclear-localized GCN5 acetyltransferase and was identified in an RNAi screen as a candidate KAT responsible for promoting mitochondrial protein acetylation, including the alpha subunit of the F-ATP synthase complex as well as of the complex I subunit NDUFA9 (Scott et al., 2012). ACAT1, however, is a mitochondrial metabolic enzyme usually acting as a thiolase responsible for condensation of two acetyl-CoAs to acetoacetyl-CoA. Next to its thiolase activity, a moonlighting activity as protein acetyltransferase was described for this enzyme, which controls the lysine acetylation level of the pyruvate dehydrogenase complex including the pyruvate dehydrogenase phosphatase (Fan et al., 2014). While both of these enzymes seem to have important functions in mitochondrial protein acetylation, non-enzymatic protein acetylation might also be of particular relevance, since auto-acetylation of mitochondrial proteins can occur efficiently at the pH of the matrix (pH ≥7.5) in actively respiring mitochondria (König et al., 2014a; Wagner and Payne, 2013). Yet, even if these sites are non-enzymatically acetylated, they might be particularly prone to auto-acetylation due to their specific sequence environment,

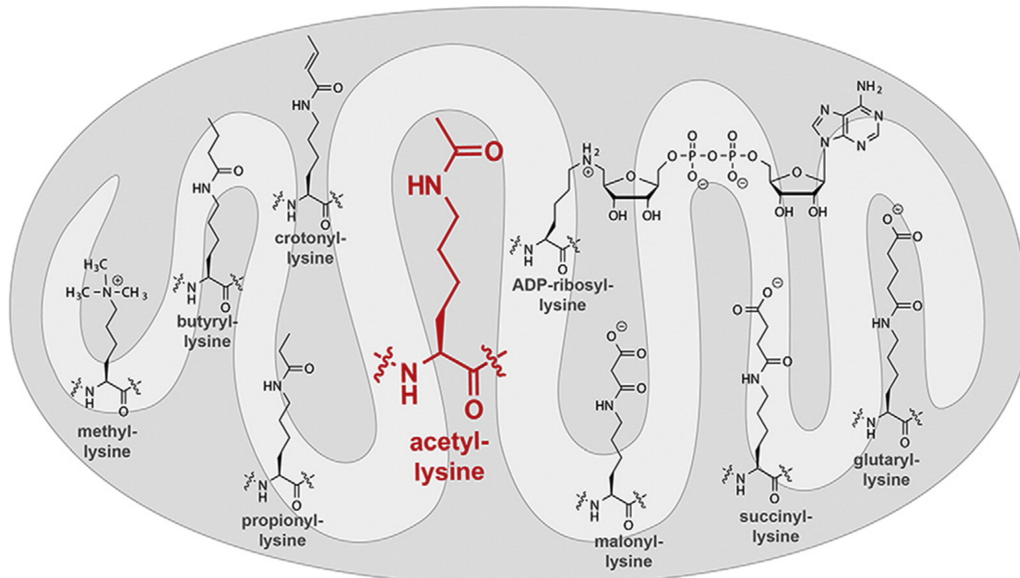

Fig. 1. Overview of important co-substrate-dependent lysine modifications of mitochondrial proteins.

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