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Review article

The role of mitochondrial sirtuins in health and disease

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ABSTRACT

Mitochondria play a critical role in energy production, cell signalling and cell survival. Defects in mitochondrial function contribute to the ageing process and ageing-related disorders such as metabolic disease, cancer, and neurodegeneration. The sirtuin family of deacylase enzymes have a variety of subcellular localisations and have been found to remove a growing list of post-translational acyl modifications from target proteins. SIRT3, SIRT4, and SIRT5 are found primarily located in the mitochondria, and are involved in many of the key processes of this organelle. SIRT3 has been the subject of intense research and is primarily a deacetylase thought to function as a mitochondrial fidelity protein, with roles in mitochondrial substrate metabolism, protection against oxidative stress, and cell survival pathways. Less is known about the functional targets of SIRT4, which has deacetylase, ADP-ribosylase, and a newly-described lipoamidase function, although key roles in lipid and glutamine metabolism have been reported. SIRT5 modulates a host of newly-discovered acyl modifications including succinylation, malonylation, and glutarylation in both mitochondrial and extra-mitochondrial compartments, however the functional significance of SIRT5 in the regulation of many of its proposed target proteins remains to be discovered. Because of their influence on a broad range of pathways, SIRT3, SIRT4, and SIRT5 are implicated in a range of disease-states including metabolic disease such as diabetes, neurodegenerative diseases, cancer, and ageing-related disorders such as hearing-loss and cardiac dysfunction. We review the current knowledge on the function of the three mitochondrial sirtuins, their role in disease, and the current outstanding questions in the field.

1. Introduction

The sirtuin family of deacylase enzymes are highly conserved nicotinamide adenine dinucleotide $(NAD)^+$-dependant deacylases that remove a wide variety of acyl modifications from cellular proteins [1,2]. Three members of the sirtuin family, SIRT3, SIRT4 and SIRT5 are located in the mitochondrial matrix and are thought to play important roles in regulating post-translational modifications (PTMs) in this organelle.

Lysine acylation is one important form of post-translational modification, involving the addition of specific acyl groups to a lysine residue in proteins. These reversible acyl-modifications are known to alter the charge of the lysine residue and hence affect the function of proteins through a variety of mechanisms including altering enzyme activity, structure, substrate specificity, protein turnover and subcellular localisation of the target [3]. Due to their ability to deacylate a large variety of protein targets, sirtuins are associated with the regulation of numerous cellular processes, with well-described roles in metabolism, gene transcription, differentiation, apoptosis and the cell cycle, antioxidant defences, lifespan and circadian rhythm [4–9]. Accordingly sirtuins are implicated in a number of human diseases including cancers, metabolic disease such as diabetes and fatty liver, ageing and ageing deficits including age-related hearing loss, and neurological disease.

Abbreviations: AceCS2, acetyl-CoA synthetase 2; *ATP, adenosine triphosphate*; *AMPK*, AMP-activated protein kinase; ANT2/ANT3, adenine nucleotide translocase 2 and 3; *BMI, body mass index*; CtBP, C-terminal-binding protein; CPS1, carbamoyl phosphate synthetase 1; *CR, calorie restriction*; FOXO3a, forkhead box O3; GAPDH, glyceraldehyde phosphate dehydrogenase; GDH, glutamate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; *HI/HA, hyperinsulinism/hyperammonemia syndrome*; *HMGCS2*, 3-hydroxy-3-methylglutaryl CoA synthase 2; IDH2, isocitrate dehydrogenase 2; *KO, knockout*; *LCAD, long-chain acyl CoA dehydrogenase*; MCD, malonyl CoA decarboxylase; *MEF, mouse embryonic fibroblasts*; *mPTP, mitochondrial permeability transition pore*; mtHsp60, mitochondrial heat shock protein 60; *NAFLD, non-alcoholic fatty liver disease*; NDUFA9, NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9; NF-κβ, nuclear factor κβ; *NSCLC, non-small cell lung cancer*; OPA1, optic atrophy protein 1; OTC, ornithine transcarbamylase; PDH, pyruvate dehydrogenase; PGC1 α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; *PTM, post-translational modification*; ROS, reactive oxygen species; SDHa, succinate dehydrogenase subunit a; SOD1, superoxide dismutase 1; SOD2, Mn superoxide dismutase; STACs, sirtuin activating compounds; *T2D, type 2 diabetes*; TCA cycle, tricarboxylic acid cycle; UOX, urate oxidase; *WT, wildtype*

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2. The sirtuin family

The name sirtuin is derived from its founding member, yeast *Sir2* (silent information regulator 2), a protein linked with lifespan regulation in this species [10]. Sirtuins are highly conserved across species from bacteria to humans [11], with seven *Sir2* homologs (SIRT1-SIRT7) identified in mammals. The mammalian enzymes display diverse subcellular localisations within the cell as detailed in Fig. 1. SIRT1, SIRT6 and SIRT7 are chiefly nuclear in localisation, but all 3 enzymes have been reported outside the nucleus [12–14]. SIRT2 is located in the cytoplasm but has been reported to translocate to the nucleus under specific circumstances [15,16]. The predominantly mitochondrial-located sirtuins are SIRT3, SIRT4 and SIRT5, which are the main focus of this review. Although the literature generally agrees that the three mitochondrial sirtuins contain mitochondrial localisation sequences and primarily reside in either the mitochondrial matrix or intermembrane space in the case of SIRT5 [17–20], there are reports that these proteins are also found in the nucleus or cytosol and regulate the function of proteins in these compartments [21–24].

In addition to variations in subcellular location, it has also recently been revealed that members of the mammalian sirtuins catalyse a range of different enzymatic reactions beyond the deacetylase function originally described for these enzymes (see Fig. 1). These additional enzymatic roles include new roles for the mitochondrial sirtuin SIRT5 as a desuccinylase, demalonylase, and deglutarylase enzyme [25–27], and for SIRT4 in the regulation of lipoamidation [28]. Other deacyl functions described for sirtuins include depropionylation, demyristoylation, decrotonylation, and ADP-ribosylation, with this growing list of PTMs suggesting that additional functions of the sirtuin family may still be awaiting discovery [19,29–33]. Of the known acyl modifications, reversible lysine acetylation has been the most extensively studied to date, with a number of reports in the last decade demonstrating that acetylation is a highly prevalent and functionally relevant PTM in many pathways, particularly intermediary metabolism [4,34–37]. Indeed proteomic studies have shown that a very high proportion of mitochondrial proteins are subjected to lysine acetylation [4–6,8,35,36,38–41]. More recent proteomic screens utilising mass spectrometric methods have also shown that newer SIRT5-mediated PTMs such as succinylation and glutarylation are also highly enriched in the mitochondrial compartment [26,42], suggesting a complex interplay between different sirtuin-mediated processes and cellular energy metabolism.

While many critical functions have been shown to be regulated by sirtuins, this review will discuss the current knowledge on the mitochondrial sirtuins SIRT3, SIRT4 and SIRT5, their cellular targets, and their functional role on mitochondrial processes in both health and disease.

2.1. SIRT3

SIRT3 is the most well described of the mitochondrial sirtuins and is located primarily in the mitochondrial matrix [17]. SIRT3's primary function is as a deacetylase enzyme, and much of the lysine acetylation seen in the mitochondria has been shown by proteomic and biochemical methods to be regulated by SIRT3 activity [25,37,43]. Calorie restriction, fasting and exercise training have all been shown to increase SIRT3 levels in different tissues [44–47], in contrast a recent study reported a reduction in SIRT3 protein in skeletal muscle of fasted mice [48]. While somewhat contentious, these studies highlight that the levels of SIRT3 are responsive to the prevailing nutrient availability of the cell. More recently, there is some evidence in cells that SIRT3 may also be able to perform a decrotonylation reaction on histones, in addition to its function as a lysine deacetylase [30] (see Fig. 1).

2.2. SIRT3: function and targets

The first reported target of SIRT3 was a key mitochondrial enzyme Acetyl-CoA synthetase 2 (AceCS2) [49,50]. Acetyl-CoA synthetase catalyses the production of acetyl-CoA, an essential

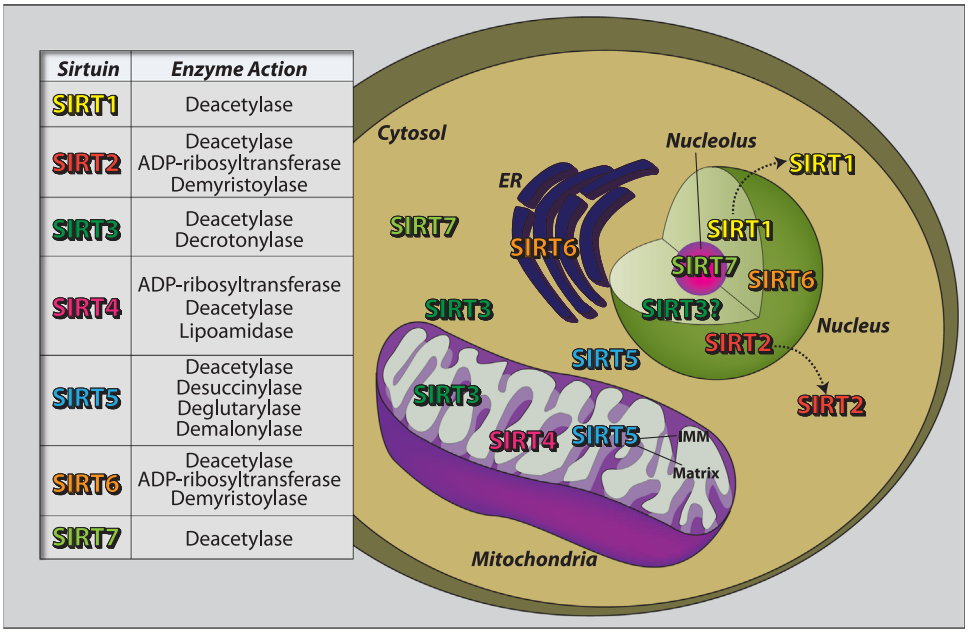

Fig. 1. The sirtuin family perform a variety of deacylase actions and localise in discrete compartments of the cell: cellular representation of the subcellular localisation of the sirtuin family as currently understood. Deacetylases SIRT1, SIRT2 and SIRT7 have been reported in both the nuclear and cytosolic compartments, with SIRT7 also having a nucleolar-specific location. The major mitochondrial sirtuins are SIRT3, SIRT4 and SIRT5. The deacetylase SIRT3 has also been reported to have cytocolic and nuclear targets, and a recently reported function as a decrotonylase. SIRT5 has several deacylase functions and is reported to be located in both the mitochondrial matrix, and the intramembrane space (IMM), in addition to having targets in the cytosol. SIRT6 has a newly emerging role as a deacetylase, ADP-ribosylase and demyristoylase and is reported to localise to both the nucleus and the endoplasmic reticulum (ER). Dotted lines represent reported translocation events.