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# Mitochondrial sirtuins and metabolic homeostasis

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The maintenance of metabolic homeostasis requires the well-orchestrated network of several pathways of glucose, lipid and amino acid metabolism. Mitochondria integrate these pathways and serve not only as the prime site of cellular energy harvesting but also as the producer of many key metabolic intermediates. The sirtuins are a family of $NAD^+$-dependent enzymes, which have a crucial role in the cellular adaptation to metabolic stress. The mitochondrial sirtuins SIRT3, SIRT4 and SIRT5 together with the nuclear SIRT1 regulate several aspects of mitochondrial physiology by controlling post-translational modifications of mitochondrial protein and transcription of mitochondrial genes. Here we discuss current knowledge how mitochondrial sirtuins and SIRT1 govern mitochondrial processes involved in different metabolic pathways.


## Introduction

Mitochondria are organelles composed of a matrix enclosed by a double (inner and outer) membrane.[1] Major cellular functions, such as nutrient oxidation, nitrogen metabolism, and especially adenosine triphosphate (ATP) production, take place in the mitochondria. ATP production occurs in a process referred to as oxidative phosphorylation (OXPHOS), which involves electron transport through a chain of protein complexes (I–IV), located in the inner mitochondrial membrane. These complexes carry electrons from electron donors (e.g. nicotinamide adenine dinucleotide (NADH)) to

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electron acceptors (e.g. oxygen), generating a chemiosmotic gradient between the mitochondrial intermembrane space and matrix. The energy stored in this gradient is then used by ATP synthase to produce ATP. One well-known side effect of the OXPHOS process is the production of reactive oxygen species (ROS) that can generate oxidative damage in biological macromolecules. However, to neutralize the harmful effects of ROS, cells have several antioxidant enzymes, including superoxide dismutase, catalase, and peroxidases.

The sirtuin silent information regulator 2 (Sir2), the founding member of the sirtuin protein family, was identified in 1984.[2] Sir2 was subsequently characterized as important in yeast replicative aging[3] and shown to possess $NAD^+$-dependent histone deacetylase activity,[4] suggesting it could play a role as an energy sensor. A family of conserved Sir2-related proteins was subsequently identified. Given their involvement in basic cellular processes and their potential contribution to the pathogenesis of several diseases,[5] the sirtuins became a widely studied protein family.

In mammals the sirtuin family consists of seven proteins (SIRT1–SIRT7), which show different functions, structure, and localization. SIRT1 is mostly localized in the nucleus but, under specific physiological conditions, it shuttles to the cytosol.[6] Similar to SIRT1, also SIRT6[7] and SIRT7[8] are localized in the nucleus. On the contrary, SIRT2 is mainly present in the cytosol and shuttles into the nucleus during G2/M cell cycle transition.[9] Finally, SIRT3, SIRT4, and SIRT5, are mitochondrial proteins.[10]

The main enzymatic activity catalyzed by the sirtuins is $NAD^+$-dependent deacetylation, as known for the progenitor Sir2.[4,11] Along with histones also many transcription factors and enzymes were identified as targets for deacetylation by the sirtuins. Remarkably, mammalian sirtuins show additional interesting enzymatic activities. SIRT4 has an important ADP-ribosyltransferase activity,[12] while SIRT6 can both deacetylate and ADP-ribosylate proteins.[13,14] Moreover, SIRT5 was recently shown to demalonylate and desuccinylate proteins,[15,16] in particular the urea cycle enzyme carbamoyl phosphate synthetase 1 (CPS1).[16] The (patho-)physiological context in which the seven mammalian sirtuins exert their functions, as well as their biochemical characteristics, are extensively discussed in the literature[17,18] and will not be addressed in this review; here we will focus on the emerging roles of the mitochondrial sirtuins, and their involvement in metabolism. Moreover, SIRT1 will be discussed as an important enzyme that indirectly affects mitochondrial physiology.

Sirtuins are regulated at different levels. Their subcellular localization, but also transcriptional regulation, post-translational modifications, and substrate availability, all impact on sirtuin activity. Moreover, nutrients and other molecules could affect directly or indirectly sirtuin activity. As sirtuins are $NAD^+$-dependent enzymes, the availability of $NAD^+$ is perhaps one of the most important mechanisms to regulate their activity. Changes in $NAD^+$ levels occur as the result of modification in both its synthesis and consumption.[19] Increase in $NAD^+$ amounts during metabolic stress, as prolonged fasting or caloric restriction (CR),[20–22] is well documented and tightly connected with sirtuin activation.[4,19] Furthermore, the depletion and or inhibition of poly-ADP-ribose polymerase (PARP) 1[23] or cADP-ribose synthase 38,[24] two $NAD^+$ consuming enzymes, increase SIRT1 action.

Analysis of the *SIRT1* promoter region identified several transcription factors involved in up- or down-regulation of *SIRT1* expression. FOXO1,[25] peroxisome proliferator-activated receptors (PPAR) $\alpha$/$\beta$,[26,27] and cAMP response element-binding[28] induce *SIRT1* transcription, while PPAR$\gamma$,[29] hypermethylated in cancer 1,[30] PARP2,[31] and carbohydrate response element-binding protein[28] repress *SIRT1* transcription. Of note, *SIRT1* is also under the negative control of miRNAs, like miR34a[32] and miR199a.[33] Furthermore, the *SIRT1* protein contains several phosphorylation sites that are targeted by several kinases,[34,35] which may tag the SIRT1 protein so that it only exerts activity toward specific targets.[36,37] The beneficial effects driven by the SIRT1 activation -discussed below- led the development of small molecules modulators of SIRT1. Of note, resveratrol, a natural plant polyphenol, was shown to increase SIRT1 activity,[38] most likely indirectly,[22,39,40] inducing lifespan in a range of species ranging from yeast[38] to high-fat diet fed mice.[41] The beneficial effect of SIRT1 activation by resveratrol on lifespan, may involve enhanced mitochondrial function and metabolic control documented both in mice[42] and humans.[43] Subsequently, several powerful synthetic SIRT1 agonists have been identified (e.g. SRT1720[44]), which, analogously to resveratrol, improve mitochondrial function and metabolic diseases.[45] The precise mechanism of action of these compounds is still under debate; in fact, it may well be that part of their action is mediated by AMP-activated protein kinase (AMPK) activation,[21,22,46] as resveratrol was shown to inhibit ATP synthesis by directly inhibiting ATP synthase in the mitochondrial respiratory chain,[47]