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SIRT3: as simple as it seems?

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Abstract

Identification of conserved pathways regulating longevity holds out the eventual possibility of pharmacologic health- and lifespan extension in humans. Members of the sirtuin deacetylase/ADP-ribosyltransferase/deacylase family extend longevity in yeast and promote various aspects of mammalian healthspan. The mitochondrial sirtuin SIRT3 deacetylates numerous proteins in this organelle, regulating mitochondrial functions and suppressing diverse age-associated pathologies. However, recent findings raise the possibility that SIRT3 may regulate some mitochondrial functions indirectly, rather than by direct deacetylation of specific mitochondrial substrates. Specifically, it has been found that SIRT3 promotes activities of the upstream mitochondrial regulators AMPK and PGC1α. In addition, studies of tissue-specific SIRT3 knockouts suggest non-tissue-autonomous roles for SIRT3. Thus, mitochondrial regulation by SIRT3 is likely much more complex than initially appreciated, potentially involving both direct and indirect mechanisms. Unraveling these may reveal novel aspects of how the functional status of mitochondria is communicated to the rest of the cell, and to the organism overall.

Keywords

Sirtuin; mitochondria; deacetylase; acetylation; metabolism; reactive oxygen species; AMPK; PGC1α

Aging can be defined as a process leading to frailty, dysfunction, and increased mortality over time. Aging represents the major risk factor – indeed, in many cases the dominant risk factor – for chronic diseases that are the principal causes of disability and death in industrialized societies. Over the past decades, it has increasingly been recognized that the aging rate is subject to strong influence by dietary intake and by evolutionarily conserved nutrient signaling pathways. This raises the possibility that therapies directed at the aging process itself may eventually be used to treat or prevent degenerative diseases, promoting healthspan and perhaps even extending human lifespan. In this context, the sirtuin family of NAD^+-dependent deacetylases/ADP-ribosyltransferases/deacylases has received a great deal of attention in recent years. There is now a large body of evidence showing that mammalian sirtuins play major roles in promoting important aspects of healthspan and in suppressing specific age-associated pathologies [1]. Mammals possess seven sirtuins, SIRT1-SIRT7. Each is characterized by a catalytic domain that is fairly well conserved in all sirtuin proteins. Outside this domain, mammalian sirtuins possess divergent N- and C- termini, helping to confer upon these proteins distinct biological properties.

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SIRT3 promotes diverse aspects of mammalian healthspan

This Viewpoint focuses specifically on functions of the sirtuin SIRT3, and how this protein fulfills these roles mechanistically. SIRT3, like SIRT4 and SIRT5, is present in the mitochondrial matrix. Among these proteins, SIRT3 is the dominant mitochondrial deacetylase activity [2]. As with other sirtuins, the availability of mouse strains lacking SIRT3 has tremendously facilitated elucidation of functions of this protein. Under normal conditions, SIRT3-deficient mice appear essentially normal. However, studies of these animals under stress conditions or with advancing age have revealed major roles for this sirtuin in suppressing the onset of multiple pathologies (Fig. 1). We will briefly touch upon major roles of SIRT3 in promoting aspects of healthy aging in mammals. For a more comprehensive discussion of SIRT3 molecular functions, the reader is referred elsewhere [3].

SIRT3 as a tumor suppressor

Studies by three independent laboratories have revealed roles for SIRT3 in tumor suppression [4–6]. Female *SIRT3* knockout (KO) mice showed a 35% incidence of mammary tumors by two years of age, whereas this tumor was not observed at all in the control population [6]. At least one copy of the SIRT3 locus was deleted in 40% of human breast carcinomas, supporting a tumor suppressor role for SIRT3 in humans as well [5]. Mechanistically, SIRT3 suppresses cellular production of deleterious reactive oxygen species (ROS), via deacetylation and activation of SOD2 (mitochondrial superoxide dismutase) and IDH2 (isocitrate dehydrogenase 2) [7–9]. Through modification of these two targets, SIRT3 reduces cellular ROS levels, thereby protecting nuclear and mitochondrial DNA and other cellular macromolecules from ROS-related damage. In the absence of SIRT3, increased ROS promote genomic instability and activate hypoxia inducible factor 1α (HIF-1α) [4,5], a transcription factor that can promote metabolic reprogramming in cancer cells.

Importantly, the role of SIRT3 in neoplasia is cell type-specific, and potentially quite complex. For example, oral squamous cell carcinomas (OSCCs) – cancers that are notoriously treatment-resistant – express high SIRT3 levels [10]. *SIRT3* knockdown (KD) sensitizes OSCC cells to genotoxic therapy, suggesting an oncogenic role for SIRT3 in this cancer type. However, another group has found that SIRT3 enzymatic activity – as opposed to expression – is substantially *reduced* in OSCCs, relative to normal oral mucosa. Moreover, a single nucleotide polymorphism (SNP) in *SIRT3*, leading to an amino acid change in the SIRT3 protein coding sequence (V208I) and a reduction in SIRT3 enzymatic activity, is common in the germline of OSCC patients [11]. These data support a tumor suppressor role for SIRT3 in OSCC. However, in contrast a recent report linked the presence of an extra copy of *SIRT3* with tumor susceptibility in a family prone to glioma and hematopoietic malignancies [12].

SIRT3 promotes metabolic homeostasis

SIRT3 plays numerous roles that promote mitochondrial energy production and metabolic homeostasis, functions described in depth elsewhere [3]. One key role of SIRT3 is to regulate fatty acid metabolism. In response to a prolonged high fat diet (HFD), SIRT3-deficent mice develop worsened obesity, insulin resistance, dyslipidemia, fatty liver, and hepatic inflammation relative to controls [13]. One mediator of these effects is stearoyl-CoA desaturase 1 (SCD1), a protein that catalyzes conversion of saturated long-chain fatty acids into mono-unsaturated fatty acids. *SCD1* gene expression and enzymatic activity were elevated in SIRT3-deficient mice, and deletion of the *SCD1* gene ameliorated hepatic steatosis and insulin insensitivity in *SIRT3* knockouts on a HFD. A direct target of SIRT3

that is likely important in the susceptibility of SIRT3-deficient mice to metabolic syndrome is long-chain specific acyl-CoA dehydrogenase (LCAD), an enzyme involved in the β-oxidation of long-chain fatty acids. SIRT3 normally deacetylates this enzyme, activating it to promote lipid catabolism [14]. SIRT3 also deacetylates numerous components of the mitochondrial respiratory complexes to promote their activities, a role also likely relevant in the sensitivity of *SIRT3* KO mice to HFD [6,15–19]. SIRT3 also suppresses ROS levels in skeletal muscle to promote insulin signaling in this tissue and systemic glucose tolerance [20]. The hypomorphic *SIRT3* SNP mentioned above may confer an increased risk of metabolic syndrome in humans [13].

SIRT3 promotes cardiac stress resistance

Work in cell culture and animal models point to important roles for SIRT3 in maintaining cardiac fitness. Cardiac hypertrophy is a disease state characterized by enlargement and death of cardiomyocytes and cardiac fibrosis, often leading to arrhythmias, ischemia, or overt heart failure. This condition can be caused by chronic hypertension and usually occurs in older individuals. Deletion of *SIRT3* in mice leads to development of hypertrophy even under basal conditions, and marked susceptibility to hypertrophy-inducing drugs [21,22]. Conversely, SIRT3 overexpression is protective against induction of hypertrophy [21]. Multiple molecular target pathways have been proposed to account for the role of SIRT3 in cardioprotection [21–23]. One model focuses on the role of SIRT3 in deacetylating cyclophilin D to suppress activation of the mitochondrial permeability transition pore, thereby inhibiting induction of cell death in cardiomyocytes and other cell types [22,24].

SIRT3 promotes maintenance of hearing during dietary restriction

Sirtuins have been proposed to mediate some of the beneficial effects of dietary restriction (DR), a hypothesis that remains controversial [25]. However, recent work has connected SIRT3 directly to a specific protective effect of DR. Under *ad lib* feeding conditions, C57BL/6 mice show age-related hearing loss (AHL) as a consequence of gradual attrition of spiral ganglion neurons and sensory hairs cells in the cochlea. AHL in this strain is greatly diminished by DR. Crucially, this DR effect requires SIRT3; hearing function is normal in young *SIRT3* KO mice, but these animals show AHL even under DR feeding conditions [8]. This role of SIRT3 has been attributed to its function in suppressing cellular ROS levels. Specifically, SIRT3 deacetylates IDH2 to promote regeneration of reduced glutathione, a major mitochondrial anti-oxidant. SIRT3-deficient mice also show a variety of other biochemical anomalies in response to DR [8,26], suggesting that SIRT3 plays multiple functions in the organismal adaption to reduced caloric intake, and could be required for some of the other benefits of this intervention, such as enhanced tumor suppression or longevity itself. This hypothesis remains to be tested.

SIRT3 promotes hematopoietic stem cell maintenance in response to stress

Recent work has uncovered a role for SIRT3 in hematopoietic stem cell (HSC) function [27]. Although SIRT3 is dispensable for hematopoiesis in young animals, SIRT3-deficient HSCs show impaired self-renewal and reconstitution in serial transplantation experiments, or during normal aging. Strikingly, SIRT3 levels decline in wild-type HSCs with age, and reconstitution with ectopic SIRT3 can actually improve function in these cells. This function of SIRT3 has once again been attributed to the role of SIRT3 in suppressing ROS levels, in this case by deacetylating and activating SOD2.

Healthspan promotion by SIRT3: direct or indirect?

Mechanistically, how does SIRT3 promote such diverse aspects of mammalian healthspan? As noted above, SIRT3 deacetylates numerous mitochondrial proteins. Lysine acetylation is

a post-translational modification regulating many aspects of target protein biology: *e.g.*, enzymatic activity, protein-protein interactions, and stability, among others. This modification is particularly abundant on mitochondrial proteins [28]. Hence, most thinking in this field has focused on the notion that SIRT3 deacetylates a number of key targets to regulate them directly, thereby modulating mitochondrial functions. Indeed, as described above and elsewhere, there is ample evidence for this hypothesis [3].

However, a number of recent findings suggest that some of SIRT3's beneficial impacts may not occur simply through direct deacetylation of specific targets, but may instead result from broader, more indirect effects within the cell or even the whole organism. Notably, many phenotypes of SIRT3 deficiency are most evident in response to stress and/or with advancing age. This may indicate that some important effects of SIRT3 deficiency occur as a consequence of secondary events. Since SIRT3 has been proposed as a target for pharmacologic intervention, obtaining a complete mechanistic understanding of how this protein fulfills its functions is critical. For the remainder of this Viewpoint, we focus on this topic in two contexts: specifically, the role of SIRT3 in promoting AMPK and PGC1α activity, and potential non-tissue-autonomous effects of SIRT3 revealed by recent studies in tissue-specific *SIRT3* KO animals.

A primer on AMPK

Adenosine monophosphate-activated protein kinase (AMPK) is a highly conserved cellular energy sensor with key roles in health and longevity [29]. AMPK is a hetero-trimeric complex composed of a catalytic α subunit and regulatory β and γ subunits. AMPK is activated by reversible phosphorylation on the α subunit at T172. AMP serves as an allosteric activator of AMPK, and binding of either AMP or ADP to AMPK protects the enzyme from dephosphorylation and inactivation [30]. LKB1/STK11, a mammalian tumor suppressor, is one of the major kinases phosphorylating AMPK at T172; another is Ca^{2+}/calmodulin-activated protein kinase kinase-β (CaMKKβ). AMPK is also reversibly acetylated/deacetylated on lysines by the opposing activities of p300 and HDAC1, respectively [31]. Deacetylation of AMPK increases its interaction with LKB1 and consequently enhances its phosphorylation and activation [31]. ROS can also activate AMPK [29].

Once activated in response to reduced intracellular energy levels, AMPK has far-reaching effects in cells, particularly on metabolism. AMPK phosphorylates its downstream targets on serine and threonine residues, promoting catabolic functions and suppressing anabolic pathways to maintain cellular ATP levels [29]. Crucially, AMPK regulates mitochondrial functions. AMPK increases activity of PGC1α, a nuclear transcriptional coactivator that promotes mitochondrial biogenesis and expression of numerous nuclear-encoded mitochondrial genes [32]. At least two mechanisms account for this effect. First, AMPK directly phosphorylates and activates PGC1α, which can then coactivate at its own promoter to increase its expression [33,34]. Second, AMPK increases levels of cellular NAD^+, in turn activating the sirtuin SIRT1 to deacetylate and activate PGC1α [35,36]. Conversely, AMPK promotes degradation of dysfunctional mitochondria by activating mitophagy via the ULK1 kinase [37,38]. Hence, AMPK promotes mitochondrial gene expression, biogenesis, and turnover.

SIRT3 promotes activity of the AMPK-PGC1α axis

Studies from several laboratories have revealed that SIRT3 impacts AMPK phosphorylation and activity. The lower levels of ATP and increased ROS present in SIRT3-deficient cells would both lead to the prediction that SIRT3 deficiency should be associated with increased AMPK activity. However, in fact the opposite result has been obtained. Cells or muscle

tissue with decreased SIRT3 function show reduced AMPK phosphorylation and lower PGC1α levels [23,39,40]. This is also associated with reduced phosphorylation and activity of CREB (cAMP response element binding protein), a transcription factor that promotes PGC1α expression [41]. *SIRT3* KD impairs the ability of overexpressed PGC1α to promote mitochondrial biogenesis and expression of genes involved in ROS detoxification [42]. Interestingly, SIRT3 is a downstream target of PGC1α [42]; hence these two proteins appear to form a positive feedback loop to promote mitochondrial function.

Potential mechanisms of AMPK and PGC1α activation by SIRT3

Mechanistically, it is currently unclear how SIRT3 impacts AMPK and PGC1α (Fig. 2). One report suggests that SIRT3 can deacetylate and activate LKB1, a kinase upstream of AMPK [23]. SIRT3 has also been proposed to deacetylate the Forkhead transcription factor FoxO3A, thereby increasing its DNA-binding activity [43]; FoxO3A directly promotes PGC1α gene expression [44]. Both of these models likely require the presence of active extra-mitochondrial SIRT3 in the cell, the existence of which is still hotly contested [45]. Multiple independent studies have documented the mitochondrial matrix localization of human and mouse SIRT3 [2,46–52]. Prior to mitochondrial import, human SIRT3 retaining its mitochondrial targeting sequence has been shown to be enzymatically inactive [51]. In contrast, a few reports claim the presence of an active fraction of extra-mitochondrial SIRT3 in rat cardiomyocytes, neurons, and cultured human cells [53–56]. The existence of extra-mitochondrial SIRT3 has not been rigorously documented using SIRT3-deficient cells as negative controls, though in some cases *SIRT3* KD has been performed to this end. Many studies describing the existence of extra-mitochondrial SIRT3 have employed overexpression approaches, the use of which can induce artifactual extra-mitochondrial SIRT3 localization [46].

Conversely, it is also possible that mitochondrial SIRT3 acts directly on PGC1α or FoxO3A. Several reports suggest the existence of a mitochondrial fraction of PGC1α, associated with a complex containing mitochondrial DNA [57–59]. Analogous to the role of SIRT1 in deacetylating and activating nuclear PGC1α [60,61], it is possible that SIRT3 might deacetylate mitochondrial PGC1α to affect its activity. However, there is little functional information currently available regarding mitochondrial PGC1α. There are also reports that, in response to low glucose conditions, a fraction of FoxO3A localizes to the mitochondria, where it interacts with SIRT3 and promotes mitochondrial gene expression and respiration [43,62]. In this context, one group has been found that FoxO3A can serve as a substrate for SIRT3 [6]. However, neither of these models would explain in an obvious way how SIRT3 impacts signaling outside mitochondria.

Instead, or in addition, mitochondrial SIRT3 may regulate extra-mitochondrial AMPK and PGC1α indirectly, for example via effects on intracellular metabolite levels. Conceptually, this would represent an example of a retrograde response, whereby the functional status of mitochondria is communicated elsewhere in the cell, a phenomenon that is well characterized in yeast but incompletely understood in mammals [63]. For example, mitochondria play a key role in regulating intracellular calcium levels. Increased cytosolic Ca^{2+} activates calcium/calmodulin-dependent kinase IV (CaMKIV), which in turn promotes PGC1α expression through CREB [34]. Ca^{2+} also activates CaMKKβ, which phosphorylates AMPK at T172 [29]. Thus, hypothetical reduced cytosolic Ca^{2+} levels in SIRT3 deficiency could lead to impaired PGC1α activity. Here it should be stressed that SIRT3 has not actually been linked to Ca^{2+} homeostasis. However, mass spectrometry data indicate that the mitochondrial Ca^{2+} uniporter (MCU) is likely to be a target of SIRT3-mediated deacetylation [64].

Alternatively, respiratory chain dysfunction occurring in the absence of SIRT3 could lead to a decrease in the NAD^+/NADH ratio. In turn, this would reduce activity of all cellular sirtuins, including SIRT1, thus leading to hyperacetylation and decreased function of PGC1α. There is currently no evidence that AMPK is a target of SIRT1-mediated deacetylation, or indeed of any other sirtuin. However, if this were the case, AMPK would also be hyperacetylated and hypofunctional in response to SIRT3 deficiency. As NADH can compete with AMP to bind to the allosteric activation site of AMPK, it is possible that putative elevated cellular NADH levels occurring in the absence of SIRT3 could also inhibit AMPK activity directly [30]. Unfortunately, to our knowledge no direct measurements of NAD^+ or NADH levels have been performed in SIRT3-deficient cells.

Physiological consequences of defective nutrient signaling in SIRT3 deficiency

Whatever the mechanism, the observation that SIRT3 impacts key regulators of mitochondrial biology such as AMPK, PGC1α, and CREB has important implications for the study of this sirtuin. It is possible that some functions ascribed to roles for SIRT3 in directly targeting specific mitochondrial substrates actually stem, instead of or in addition, from roles for SIRT3 in modulating activities of upstream mitochondrial regulators. For example, AMPK lies upstream of PGC1α, mTOR, FoxO transcription factors, SIRT1, ULK1, p53, and other key regulators [65]. Through these and other targets, AMPK promotes mitochondrial biogenesis, stress resistance, lipid metabolism, and autophagy. AMPK is also required for aspects of the response to DR [66]. Thus, defective AMPK activation occurring in the absence of SIRT3 could impact any or all of these substrates and processes, with deleterious consequences for organismal fitness. Notably, there are phenotypic similarities between SIRT3-deficient mice and animals with perturbed AMPK or PGC1α levels. For example, mice with mutations in *PGC1α* show reduced cold resistance, susceptibility to hepatic steatosis and experimentally induced heart failure, impaired β-oxidation and ketogenesis, and increased ROS levels [32], similar to *SIRT3* mutants. Likewise, mice lacking hepatic AMPK activity show impaired β-oxidation and ketogenesis, and reduced cellular ATP levels, as seen in SIRT3 deficiency [67].

Dissecting the interplay between SIRT3, AMPK, and PGC1α

The potential roles of AMPK and/or PGC1α in SIRT3 function could be tested by rescuing the reduced activities of AMPK or PGC1α in *SIRT3* KOs, to determine whether this intervention ameliorates phenotypes of SIRT3 deficiency. For example, metformin, AICAR or other AMPK activators could be administered to SIRT3-deficent cells or mice, or PGC1α could simply be overexpressed in SIRT3-deficient cells or key tissues such as liver. ROS regulation, mitochondrial respiration, β-oxidation, and other major known SIRT3 target pathways could then be assessed. If the only role of SIRT3 were to modulate mitochondrial functions by deacetylating specific mitochondrial substrates, then such interventions would likely be ineffective at modifying the impacts of SIRT3 deficiency. Alternatively however, if a major role of SIRT3 were to promote activity of AMPK and PGC1α, then some of the phenotypes of SIRT3 deficiency would be rescued. Hence this approach might allow dissection of direct versus indirect roles for SIRT3 in regulating mitochondrial functions.

Tissue-non-autonomous effects of SIRT3

The idea that SIRT3 deacetylates mitochondrial substrates to exert its effects directly likely implies that SIRT3 functions in a cell- and tissue-autonomous manner. This view has been sharply challenged by recent analysis of mouse strains with targeted deletions of the *SIRT3* gene specifically in liver or skeletal muscle [68]. These strains display global mitochondrial protein hyperacetylation in tissues lacking SIRT3, similar to that observed in the germline *SIRT3* KO [45]. However, numerous other phenotypes previously observed in the context of

germline SIRT3 deficiency were not present in the tissue-specific KOs [68]. In particular, no decrease in *PGC1α* mRNA levels was observed in tissues lacking SIRT3. Moreover, in contrast to results obtained in the global *SIRT3* KO, there were no perturbations in blood amino acid, ketone, or acyl-carnitine levels. There were no mitochondrial energetic defects evident in *SIRT3*-ablated hepatocytes, and no defect in AMPK phosphorylation in SIRT3-deficient skeletal muscle or liver. Although SOD2 was hyperacetylated in tissues lacking SIRT3, SOD2 activity itself was not impaired, nor were levels of oxidative damage increased.

The absence of apparent phenotypes in *SIRT3* tissue-specific KOs is strikingly inconsistent with the strong effects reported in *SIRT3* germline KO animals. How might these differences be explained? The team that characterized the tissue-specific *SIRT3* KO mice did not analyze germline *SIRT3* KOs in parallel, to confirm that they could identify the phenotypes in this strain reported by others. Thus, it remains a formal possibility that technical differences in experimental protocols or husbandry conditions between laboratories may explain some of these discrepancies. In this regard, as noted above, many phenotypes of SIRT3 deficiency are most apparent upon stringent stress conditions: serial transplantation or aging in the case of HSC studies, and extended periods of high fat feeding or prolonged fasting in the case of metabolic studies. However, given the large number of phenotypic discrepancies noted between germline and conditional *SIRT3* knockouts, it is difficult to believe that technical approaches account for all of these differences. Conceivably, strain effects might offer one answer. Notably, most studies of globally SIRT3-deficent mice have been carried out in the 129 strain background, whereas the conditional *SIRT3* KO is in the C57BL/6 strain background, which is more typically used in metabolic studies.

The most exciting possibility is that the unexpected phenotypic discrepancies between the global and tissue-specific *SIRT3* KOs hint at novel aspects of mitochondrial regulation. For example, it is possible that SIRT3 deficiency early in development, as in the germline knockout, causes epigenetic reprogramming that predisposes SIRT3-deficient animals to diverse pathologies in adulthood. In this regard, gestational diabetes or an adverse early postnatal environment can lead to epigenetic alterations that confer susceptibility to cardiovascular disease and other metabolic sequelae later in life [69].

Alternatively, SIRT3 might function in specific tissues to impact mitochondrial metabolism and overall health more globally. For example, SIRT3 deficiency in the brain, adipose tissue, immune system, or other tissues might provoke neural signaling and/or elaboration of soluble factors that could alter mitochondrial function in distant organs. In *C. elegans*, the ability of mitochondrial defects to regulate mitochondrial stress responses tissue-non-autonomously, thereby affecting overall organismal longevity, is well documented [70]. In mammals, stimulation of the vagus nerve results in increased AMPK phosphorylation and decreased oxidative stress levels in the heart [71]. It has recently been reported that autophagy defects specifically in skeletal muscle induce mitochondrial dysfunction and secretion of the circulating hormone FGF21. FGF21 in turn causes “browning” of white adipose tissue, thereby conferring protection from diet-induced obesity and insulin resistance [72]. Such functions of SIRT3 could easily be tested by further studies using SIRT3 conditional KO animals.

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Summary

Sirtuins have been the subject of much excitement for their potential therapeutic utility. The mitochondrial sirtuin SIRT3 deacetylates many proteins in this organelle and promotes diverse aspects of mammalian healthspan. Recent work has revealed unexpected novel roles for SIRT3 in promoting activity of the upstream mitochondrial regulators AMPK and PGC1α, and potential epigenetic and/or tissue-non-autonomous roles for SIRT3 in regulating mitochondrial functions. Together, these data challenge the simple paradigm that SIRT3 functions only by deacetylating specific mitochondrial substrates. Elucidating the mechanistic basis for these effects will likely provide novel insights into mitochondrial signaling.

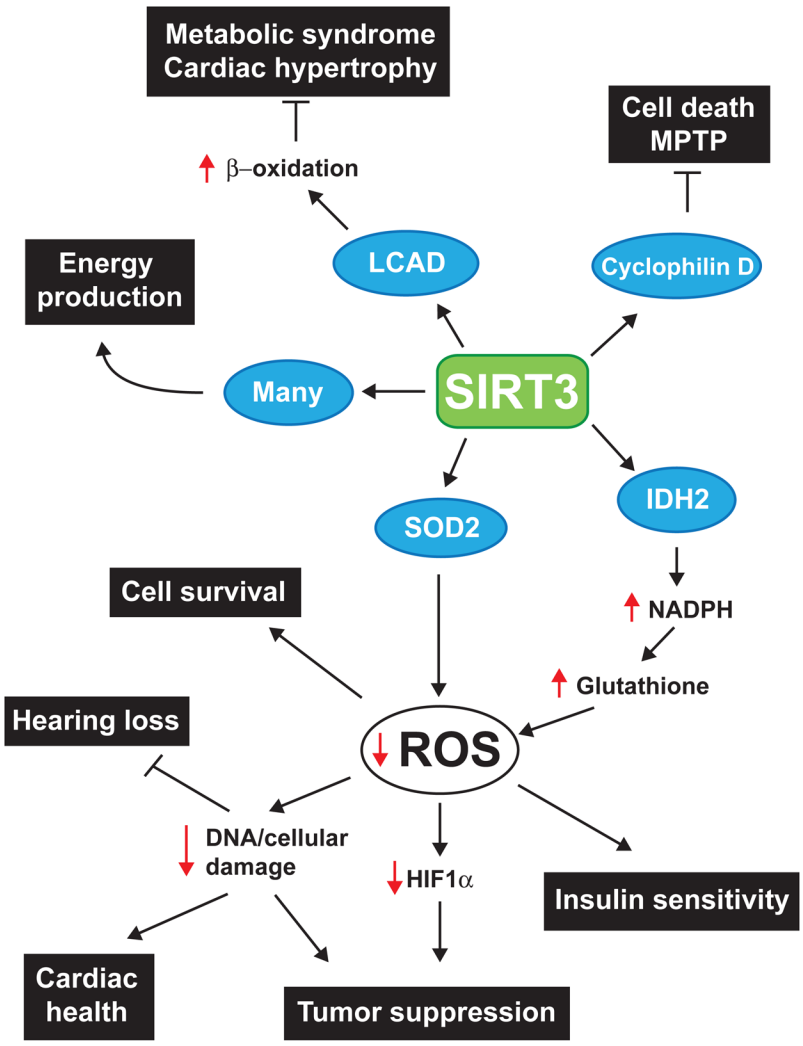

Figure 1. Schematic overview of SIRT3 targets and biological functions

Through its deacetylase activity, SIRT3 activates multiple protein targets (blue circles) modulating key cellular and physiological processes (black boxes) leading to improved healthspan. Many of these processes are mediated by decreased reactive oxygen species (ROS) production through deacetylated SOD2 and IDH2.

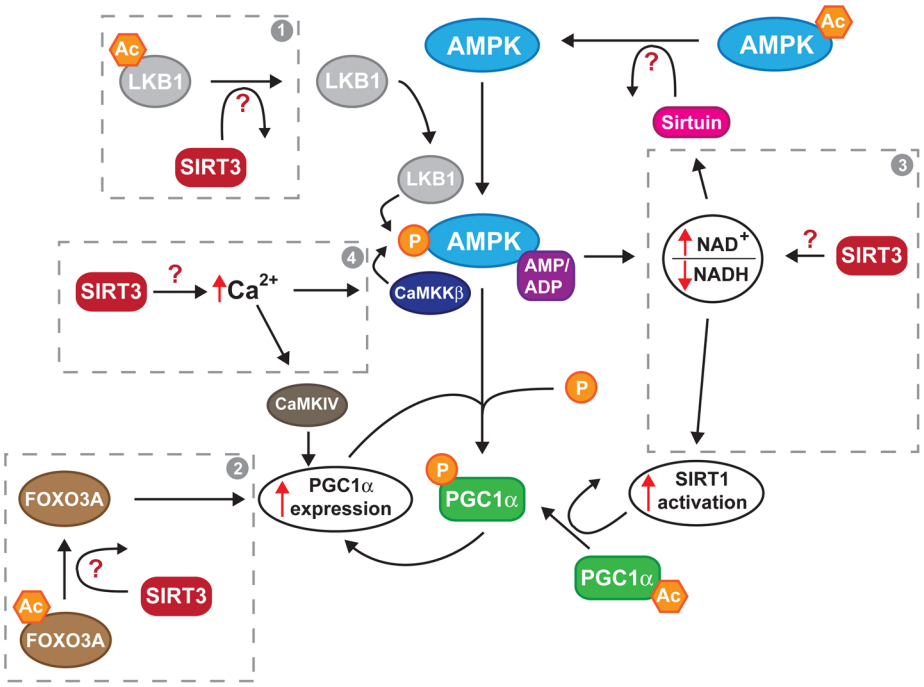

Figure 2. Promotion of AMPK-PGC1α signaling by SIRT3: hypothetical mechanisms

AMPK is phosphorylated by LKB1 and CaMKKβ, and in turn activates PGC1α. Four possible mechanisms through which SIRT3 might impact this pathway are depicted here: (1) by deacetylating and activating LKB1, (2) by deacetylating and activating FOXO3A, a transcriptional activator of PGC1α, (3) by increasing the NAD^+/NADH ratio, allowing for increased sirtuin activity which could function to activate AMPK and/or PGC1α through deacetylation, or (4) by promoting increased cytosolic calcium levels, thus promoting AMPK activity through CaMKKβ and PGC1α expression through CaMKIV.

Table 1

Abbreviations used in this Viewpoint.

AHL	Age-related hearing loss
AMPK	Adenosine monophosphate-activated protein kinase
CaMKIV	Calcium/calmodulin-dependent kinase type IV
CaMKKβ	Ca^{2+}/calmodulin-activated protein kinase kinase-β
CREB	cAMP response element binding protein
DR	Dietary restriction
HDAC	Histone deacetylase
HIF-1α	Hypoxia inducible factor 1α
HFD	High fat diet
HSC	Hematopoietic stem cell
IDH2	Isocitrate dehydrogenase 2
KO	Knockout
KD	Knockdown
LCAD	Long-chain specific acyl-CoA dehydrogenase
NAD^+	Nicotinamide adenine dinucleotide
OSCC	Oral squamous cell carcinoma
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1α
ROS	Reactive oxygen species
SCD1	Stearoyl-CoA desaturase 1
SIRT	Sirtuin; silent information regulator 2 (SIR2) homolog
SNP	Single nucleotide polymorphism
SOD2	Superoxide dismutase 2
ULK1	UNC51-like kinase