Therapeutics

FORUM REVIEW ARTICLE

The Role of Sirtuins in Antioxidant and Redox Signaling

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Abstract

Significance: Antioxidant and redox signaling (ARS) events are regulated by critical molecules that modulate antioxidants, reactive oxygen species (ROS) or reactive nitrogen species (RNS), and/or oxidative stress within the cell. Imbalances in these molecules can disturb cellular functions to become pathogenic. Sirtuins serve as important regulators of ARS in cells.

Recent Advances: Sirtuins (SIRTs 1–7) are a family of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases with the ability to deacetylate histone and nonhistone targets. Recent studies show that sirtuins modulate the regulation of a variety of cellular processes associated with ARS. SIRT1, SIRT3, and SIRT5 protect the cell from ROS, and SIRT2, SIRT6, and SIRT7 modulate key oxidative stress genes and mechanisms. Interestingly, SIRT4 has been shown to induce ROS production and has antioxidative roles as well.

Critical Issues: A complete understanding of the roles of sirtuins in redox homeostasis of the cell is very important to understand the normal functioning as well as pathological manifestations. In this review, we have provided a critical discussion on the role of sirtuins in the regulation of ARS. We have also discussed mechanistic interactions among different sirtuins. Indeed, a complete understanding of sirtuin biology could be critical at multiple fronts.

Future Directions: Sirtuins are emerging to be important in normal mammalian physiology and in a variety of oxidative stress-mediated pathological situations. Studies are needed to dissect the mechanisms of sirtuins in maintaining redox homeostasis. Efforts are also required to assess the targetability of sirtuins in the management of redox-regulated diseases. *Antioxid. Redox Signal.* 28, 643–661.

Keywords: sirtuins, redox signaling, oxidative stress, antioxidants

Introduction

THE SIRTUINS (SIRTs) are a family of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases (HDACs) that have been identified and explored in mammals during the last two decades. Over the years, sirtuins have been shown to play key roles in many cellular functions, including histone deacetylation, protein acylation, and deacetylation (25). The sirtuin family of seven enzymes has also been linked to several antioxidant and oxidative stress-related processes and functions, including longevity, mitochondrial function, DNA damage repair, and metabolism (105). In addition, the fact that their deacetylase activity is dependent on NAD⁺, a key redox signaling molecule, lends credence to the idea that sirtuins may be integral players in regulating cellular antioxidant and redox signaling (ARS) pathways. The coenzyme NAD⁺ mediates redox reactions by carrying electrons from one reaction to another (*i.e.,* NAD⁺, as an oxidizing agent, accepts an electron and converts into its reduced form, NADH, and vice versa). During metabolic activity, reduced compounds (glucose and fatty acids) are oxidized, resulting in a release of energy. As part of *β*-oxidation, glycolysis, and the Krebs cycle, this energy is transmitted *via* NAD⁺ by reduction to NADH. The NAD⁺/NADH ratio is a key component of the redox state of a cell, which can indicate the status of the metabolism and health of cells (142). Although cells have many defensive mechanisms to maintain a fine balance between antioxidant and oxidant

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systems, improper biochemical reactions within the cell as well as certain external factors can throw the cell into a state of oxidative stress. As defined by Sies and Jones, oxidative stress is ''an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control, and/or molecular damage'' (66, 150). Some of the key players in oxidative stress are reactive species (RS), which most commonly include reactive oxygen species (ROS) and reactive nitrogen species (RNS). Many diseases and disorders have been linked with oxidant/antioxidant imbalance within the cells. Indeed, studies have suggested the role of sirtuins in regulating antioxidants and redox signaling pathways. The available literature seems to suggest that sirtuins are important in the homeostasis of redox systems, which may be critical in the regulation of important biological processes and, therefore, pathogenesis of several diseases. Thus, sirtuins may serve as targets in the management of redox-regulated disease conditions. This review is focused on critically analyzing the potential roles of sirtuins in redox regulation, oxidative stress, and ROS-induced conditions.

Sirtuins: History and Discovery

Mammalian SIRTs were discovered following extensive research conducted on the silent information regulator (*SIR 1–4*) genes, which were shown to be involved in transcriptional silencing in *Saccharomyces cerevisiae* (134). In 1999, Kaeberlein and McVey showed that overexpression of Sir2 extended life span in yeast (67). In 2000, a study by Imai *et al.* identified Sir2 as an NAD-dependent HDAC that deacetylates lysines 9 and 14 of histone 3 (H3) and 16 of histone 4 (H4), suggesting that this histone modification ability may be a key to unlocking the connections between Sir2 and longevity, as well as metabolism, in yeast (61). The HDAC activity of sirtuins is important because histone acetylation and deacetylation are the key methods of gene regulation, and act *via* acetylating and deacetylating lysine residues of histone core of the nucleosome, thereby allowing or stopping the transcription of those genes in that area of the histone. Research conducted later showed sequence similarities in other organisms, from prokaryotes to eukaryotes, suggesting that sirtuins are highly conserved throughout evolution (49). Because of their HDAC activity, sirtuins have been categorized as HDACs, and their dependence on NAD^+ as a cofactor gave them a category of their own, Class III HDACs (44, 151). Seven members of this family have been identified so far in mammals, SIRTs 1–7, and each has a conserved NAD-binding and catalytic domain (although they differ in their N- and C-terminal regions), termed as the sirtuin core domain (44). Interestingly, each sirtuin is primarily located in a distinct subcellular compartment, which is closely associated with the divergent biological functions within the cell [discussed below and reviewed in Ref. (94)].

Since their identification in mammals, sirtuins have been implicated in many important cellular processes, including facilitating heterochromatin formation, transcription silencing, regulation of ion channels, and modulation of cellular redox state (15). The initial insight into the roles of Sir2 in yeast led many researchers to study the role of mammalian sirtuins in metabolism and, to date, studies have suggested that these enzymes play crucial roles in insulin secretion, glycolysis, urea cycle, mitochondrial biogenesis, glucogenesis, and

fat oxidation (15, 21, 53, 57, 165). These roles, together with their NAD dependence, suggest that mammalian sirtuins could be important in maintaining cellular homeostasis *via* affecting cellular energetics and redox balance. The dependence on NAD^+ for their deacetylase activity allows sirtuins an ideal opportunity to regulate redox reactions *via* modulating transcription factors that control antioxidant enzyme expression and cellular $NAD^+/NADH$ ratios (131). Several target proteins of mammalian sirtuins have been identified as effectors of key oxidative stress pathways [reviewed in Refs. (93, 158, 173, 178)]. However, the specific mechanisms underlying the effects of each sirtuin on these effectors and on antioxidant-driven and redox signaling are an intense and interesting area of research.

Reactive Oxygen and Nitrogen Species and Antioxidant Defense

Molecular oxygen and its derivatives are absolutely vital to the living system. In the body, a variety of chemically reactive molecules that contain oxygen, as well as nitrogen and other elements, are essential for cellular signaling and biochemical processes. The primary forms of these RS in the cell include ROS such as hydrogen peroxide (H_2O_2) and the superoxide anion radical ($O^{\bullet-}_2$), the RNS nitric oxide (NO), as well as many peroxides of lipids, proteins, and nucleic acids (87, 175). These free radicals show very different reactivity, for example, superoxide is a reducing radical; reactivity of NO remains low unless it reacts with another free radical; H_2O_2, which is used extensively in ROS research, is less reactive than other ROS, but retains the ability to cause oxidative stress through the subsequent transformation to destructive moieties. On the contrary, secondary RS such as the hydroxyl radical ($HO^{\bullet}$) and peroxynitrite ($ONOO^-$) are more toxic to the cell and generally form when an abundance of more than one primary RS is present (175).

RS are generated endogenously *via* numerous normal metabolic and biosynthetic pathways, including the respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P450 system (5, 6 and references therein). In addition, nonenzymatic cellular reactions can generate free radicals and ROS, for example, reactions between oxygen and organic compounds, as well as reactions initiated by ionizing radiation (14, 126). Normal biological levels of RS are necessary for spurring many critical reactions and signaling cascades [reviewed in Refs. (6, 127)]. However, when generated in excess or combined with other RS, they can have serious deleterious effects on cellular constituents [reviewed in Refs. (54, 175)]. Therefore, to ensure the tight regulation of ROS and other RS levels, the cell has a myriad of antioxidant defenses available. Antioxidants generally function by one of two pathways: by either breaking the radical continuation chain or by preventing it from occurring completely (127). The major antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) prevent generation of the oxidation chain by scavenging the molecules responsible for generating free radicals (127, 185). Another important set of antioxidant enzymes, known as peroxiredoxins (PRDX) (which are regulated/activated by sulfiredoxin), controls cytokine-induced peroxide levels [reviewed in Ref. (24)]. Many studies have shown that dietary/calorie restriction may have positive impacts on oxidative stress

by decreasing the levels of ROS and increasing the activity of antioxidant enzymes [reviewed in Ref. (167)]. Interestingly, sirtuins gained their popularity, in part, due to their connections with calorie restriction-mediated beneficial health effects, including longevity [reviewed in Refs. (53, 93)], suggesting that sirtuins may play an important role in regulating redox homeostasis.

The idea that sirtuins are involved in ARS also comes from their strong connections to several of the molecules of the antioxidant response element (ARE), which mediates signaling events involved in transcriptional regulation of gene expression in cells exposed to oxidative stress (Fig. 1). The ARE possesses biological and structural features that uniquely sense alteration of the cellular redox status and accordingly trigger transcriptional responses, mediated primarily by nuclear factor E2-related factor 2 (NRF2). NRF2 regulates the expression of several antioxidant and detoxification genes. NRF2 normally resides in the cytoplasm near Kelch like-ECH-associated protein 1 (KEAP1) and cullin 3 (CUL3), which degrade it by ubiquitination (76). Under oxidative stress, the KEAP1-CUL3 ubiquitination system is disrupted due to an interruption in critical cysteine residues of KEAP1. This allows NRF2 to translocate into the nucleus where it forms a heterodimer with one of the Maf proteins (MAFK, MAFG, MAFF) and binds to the ARE in the promoter region of antioxidative response genes resulting in initiation of their transcription (62, 114). Activation of NRF2 has also been shown to protect cells against cellular insults from electrophilic compounds. Once NRF2 is activated by electrophilic compounds, it translocates to the nucleus and binds to the electrophilic response element (ERE), which further modulates the expression of genes involved in the detoxication and elimination of electrophilic agents leading to enhancement in cellular

antioxidant capacity (190). These ARE/ERE-controlled antioxidant enzymes and other antioxidants are important because, if left uncontrolled, oxidative stress can lead to various types of chronic conditions such as autoimmune, cardiovascular, and neurodegenerative diseases, cancer, aging, and acute ailments such as trauma and stroke (141).

In a very recent study on the regulation of cellular iron homeostasis, SIRT2 has been shown to deacetylate NRF2, resulting in a reduction in total and nuclear NRF2 levels (184). Moreover, SIRT2 has also exhibited the ability to regulate nuclear levels of NRF2 by modulating AKT phosphorylation, resulting modulation in the levels of total glutathione (GSH) and glutamate cysteine ligase (GCL), indicating SIRT2 may be a key modulator of this aspect of the ARE (23). SIRT1 also appears to be involved, as knockdown of SIRT1 has been shown to inhibit the expression of NRF2, heme oxygenase 1 (HO-1), and SOD1, eliminating the neuroprotective effects of SIRT1 induced by hyperbaric oxygen preconditioning against transient focal cerebral ischemia (182). Moreover, grape antioxidant resveratrol, which is considered to be an activator of SIRT1, has also been shown to modulate NRF2-dependent antioxidant protein expression to promote neuroprotection against cerebral ischemic injuries (109). SIRT6 has also been demonstrated to coactivate NRF2 to protect human mesenchymal stem cells (hMSCs) from oxidative stress (122). Interestingly, oxidative stress-related pathways appear to involve in the modulation of sirtuins as well affecting its activity, expression, posttranslational modifications, NAD$^+$ levels, and protein/protein interactions [reviewed in Ref. (140)]. Below, we have discussed the potential links between the sirtuins and ARS molecules, as well as how this knowledge may be used in the management of relevant diseases.
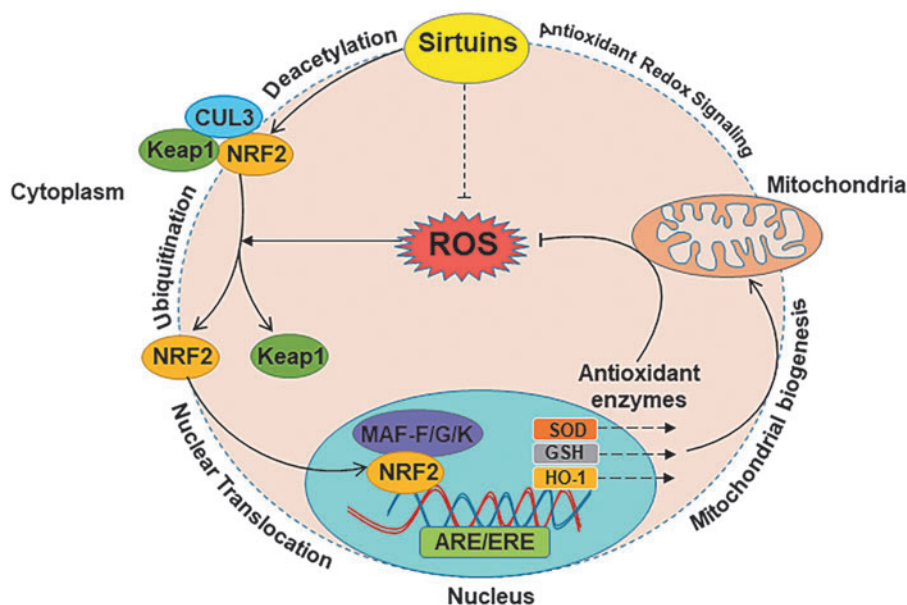

FIG. 1. **Schematic representation showing interaction of sirtuins with NRF2 that regulates the expression of several antioxidant and detoxification genes.** Under oxidative stress, the KEAP1-CUL3 ubiquitination system is disrupted, which allows NRF2 to translocate into the nucleus where it forms a heterodimer with one of the Maf proteins and binds to the ARE or ERE in the promoter region of antioxidative stress response genes resulting in mitochondrial biogenesis and antioxidant redox signaling. ARE, antioxidant response element; CUL3, cullin 3; ERE, electrophilic response element; GSH, glutathione; HO-1, heme oxygenase 1; KEAP1, kelch-like ECH-associated protein 1; NRF2, nuclear factor E2-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase.

Sirtuins in Oxidative Stress Signaling

From the available literature, it appears that all of the known mammalian sirtuins may be associated with oxidative stress signaling and antioxidant defense in the cell. A detailed account of individual sirtuins and their connection with redox regulation is provided below.

SIRT1

SIRT1 is the founding and most well-studied member of the mammalian sirtuin family. Although it has classically been thought to be of nuclear origin, multiple recent studies have shown SIRT1 to be localized to the cytoplasm as well (8, 176). SIRT1 has been shown to play important roles in development, cellular senescence, and cell death pathways [reviewed in Ref. (186)]. SIRT1 has also been shown to preferentially deacetylate lysine residue 9 of histone 3 (H3K9) and lysine 16 of histone 4 (H4K16) (61). SIRT1 initially gained its popularity because of studies suggesting its link with longevity and in calorie restriction (21, 53). However, its role in longevity has been widely debated due to lack of experimental repeatability, as well as inconsistencies between model systems (7, 18, 30, 48). Although the connection between SIRT1 and longevity is currently being widely investigated, its role in oxidative stress and redox signaling is much more clear and noncontroversial.

In two recent studies, synthetic small-molecule activators of SIRT1, SRT2104 and SRT1720, have been shown to extend life span, preserve bone and muscle mass, and improve the overall health of mice fed a standard diet (92, 98). One study found that SRT2104 treatment leads to reduced levels of protein carbonylation and formation of 4-hydroxynonenal (4-HNE) adduct, a marker of lipid peroxidation, in the liver and muscle, as well as increased SOD2 in muscles (92). This suggests that SIRT1 activation increases the antioxidant responses against age-dependent and ROS-mediated mitochondrial dysfunction in mice. It appears that this action of SIRT1 may be mediated by key redox-related transcription factors, including FOXO3a and p53. The FOXO (class O of forkhead box) family of transcription factors has been implicated in the regulation of a wide variety of genes related to antioxidant defenses [reviewed in Ref. (75)]. SIRT1 is known to deacetylate FOXO3a, which has been found to induce antioxidant responses *via* modulation in SOD2 and CAT (19, 55). FOXO3a has further been shown to regulate mitochondrial gene expression, resulting in modulated ROS levels (39). Although traditionally viewed as a tumor regulating protein, the key SIRT1 substrate, p53, has been found to have a fairly intricate regulative role in modulation of redox signaling [reviewed in Ref. (89)]. In nonstressed conditions, the transcription factor p53 is able to decrease intracellular ROS and increase certain antioxidant proteins, including SOD2 and GPX1, and downregulation of p53 has been shown to increase intracellular ROS levels and DNA oxidation levels (59, 138, 155). Moreover, Nemoto *et al.* demonstrated that SIRT1 regulates acetylation of PGC-1α, a master regulator of mitochondrial biogenesis (111). These regulatory pathway interactions suggest that SIRT1 is able to affect numerous cellular antioxidant defense mechanisms indirectly through the regulation of certain key effectors.

It appears that cellular oxidative stress may cause a dysregulation in normal SIRT1 functioning. It has been shown that in response to oxidative stress, SIRT1 is redistributed at the chromatin level causing deregulation at the transcription level (116). This study showed that H_2O_2 resulted in a significant modulation in a number of SIRT1-associated genes, including those involved in metabolism, apoptosis, ion transport, cell motility, and G protein signaling (116). Furthermore, SIRT1 was found to be required for DNA repair following H_2O_2-induced damage. This fits with another study showing that oxidative stress can trigger the dissociation of SIRT1 and the RNA-binding protein, HuR, which regulates the stability of several target messenger RNAs (mRNAs) (1). Under conditions of oxidative stress and DNA damage, HuR interacts with checkpoint kinase 2 (CHK2), leading to its dissociation from SIRT1 mRNA, activation of CHK2, and a shift by the cell toward apoptosis [(1) and reviewed in Ref. (17)]. Another enzyme required in the error-prone DNA repair pathway, poly (ADP-Ribose) polymerase 1 (PARP1), has been found to be activated in cells undergoing oxidative or genotoxic-induced senescence. This, in turn, leads to the reduction of NAD^+ availability and lower SIRT1 activity (45). The reduction in NAD^+ likely also has effects on other sirtuins, as well as cellular respiration, which can further contribute to oxidative stress. These complex interactions suggest that SIRT1 may be a key player in the mechanism responsible for maintaining homeostasis between DNA damage, senescence, and apoptosis under oxidative stress conditions.

In low oxygen conditions, the production of $O_2^{\bullet-}$ is increased by the respiratory chain (104). The elevated superoxide anions are converted to H_2O_2 *via* reaction of SOD with $O_2^{\bullet-}$ in the mitochondrial matrix, which eventually leads to gene transcription that allows the cell to respond to the low oxygen levels (143). In a 2009 study, H_2O_2-induced oxidative stress was shown to downregulate SIRT1 dose and time dependently in keratinocytes (22). Moreover, treatment with the SIRT1 activator resveratrol was shown to prevent H_2O_2-induced cell death, decrease cell proliferation, and suppress senescence. Alternatively, the SIRT1 inhibitors sirtinol and nicotinamide were found to enhance H_2O_2-induced cell death (22, 60). Collectively, these data suggest that SIRT1 is a crucial player in the prevention of oxidative damage *via* a variety of mechanisms (Fig. 2).

SIRT2

Similar to other members of the sirtuin family, SIRT2 is found ubiquitously throughout the body. However, it appears to be expressed especially in organ systems relevant to metabolism, including the brain, kidneys, pancreas, testes, liver, and fat tissue in mice (47). SIRT2 mainly localizes in the cytoplasm, where it deacetylates α-tubulin. However, SIRT2 is also found in the nucleus where it deacetylates H4K16 and takes part in regulating the cell cycle (48). Furthermore, SIRT2 has been shown to play a role in the development of the nuclear envelope, likely *via* deacetylation of ANKLE2, which is known to regulate reassembly of the nuclear envelope (68). Like other sirtuins, SIRT2 detects fuel in the cell, and it has been shown that its activity and expression are changed depending on the energy state of the cell: activated in low-energy status and repressed in high-energy status (47). This suggests an overlap in roles for SIRT2 in metabolism and cellular homeostasis.

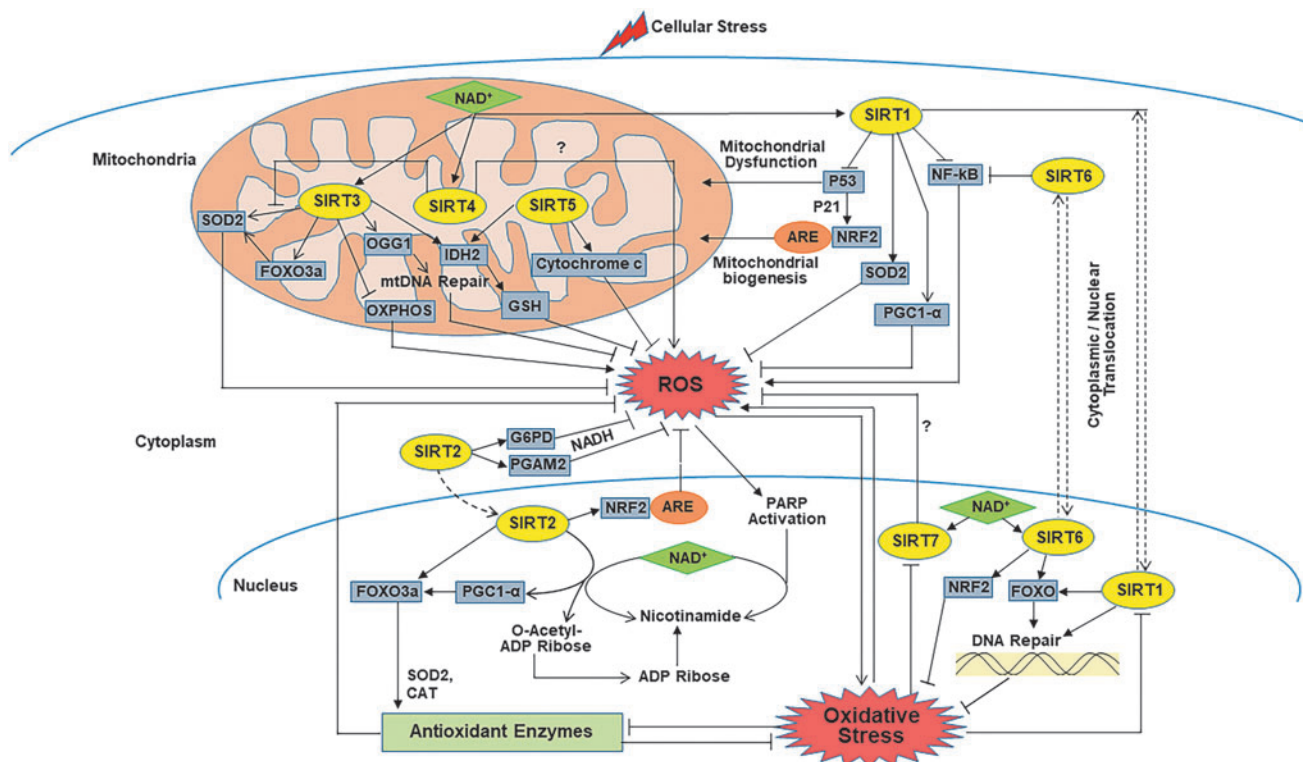Studies have shown that targets of SIRT2 deacetylation have important roles in antioxidant- and redox-mediated

FIG. 2.   Mechanistic illustration of the sirtuins in ARS pathways. Sirtuins are involved in regulating ARS in numerous ways. SIRTs 1–7 have been found to be involved in modulating levels of ROS, antioxidant enzymes, DNA repair, mitochondrial dysfunction, and oxidative stress in the cell through key transcription factors such as NRF2, p53, NF-κB, FOXO, and PGC-1α. *Question marks* (?) indicate that exact mechanism is unknown. When cells become stressed, ROS production is increased, and coenzyme NAD$^+$ (*green diamond*) activates various sirtuins (*yellow ovals*). In addition, sirtuins regulate the activity of the ARE (*orange ovals*), which in turn modulates the transcription of pro- and antioxidant genes to maintain redox signaling cascades. ADP, adenosine diphosphate; ARS, antioxidant and redox signaling; CAT, catalase; FOXO, class O of forkhead box transcription factors; G6PD, glucose 6-phosphate dehydrogenase; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa B subunit; PARP1, poly (ADP-ribose) polymerase 1; PGAM2, phosphoglycerate mutase; SIRT, sirtuin.

cellular homeostasis [reviewed in Ref. (47)]. One of these targets, PGC-1α, is deacetylated by SIRT2, which thereby modulates mitochondrial biogenesis and has been associated with upregulation of antioxidant enzyme expression and a reduction in ROS levels (77). SIRT2 has also been shown to deacetylate FOXO3a in response to oxidative stress, which is helpful because FOXO3a is a transcriptional activator of the *SOD2* gene that encodes MnSOD protein, a powerful antioxidant (168).

Other targets of SIRT2, which also play a role in ROS mediation, are metabolic enzymes such as glucose 6-phosphate dehydrogenase (G6PD), phosphoglycerate mutase (PGAM2), and nuclear factor kappa B subunit (NF-κB) (47). Under oxidative stress conditions, SIRT2 has been shown to deacetylate and activate G6PD, a key enzyme in the pentose phosphate pathway that produces NADPH in the cytosol (171). NADPH is an essential molecule that counteracts oxidative damage by keeping GSH in its reduced form. In the cell, GSH scavenges unsafe oxidative metabolites by converting H_2O_2 to water with the help of GPX [reviewed in Ref. (90)]. Interestingly, NADPH is the final reductant for PRDX, and SIRT2 has been shown to deacetylate and inhibit the peroxidase activity of PRDX-1, thereby sensitizing breast cancer cells to oxidative stress-inducing agents (42). Oxidative stress conditions also lead to deacetylation and activation

of PGAM2 by SIRT2, which allows the cell to respond to stress more easily (181). In addition, SIRT2 has been shown to activate NF-κB, which plays an important role in regulating ROS in the cell (121). Regulation of ROS by NF-κB is a complex process. The transcription of several NF-κB-dependent genes has been shown to influence the levels of ROS in the cell and, in turn, NF-κB activity has also been shown to be regulated by the levels of ROS [reviewed in Ref. (99)]. NF-κB plays a dual role in regulating ROS by targeting enzymes that promote the production of ROS, such as NADPH oxidase, xanthine oxidoreductase, inducible NO synthase, cyclooxygenase-2, and cytochrome p450 enzymes. On the contrary, NF-κB also targets those enzymes that may contribute to inhibition of ROS, such as SODs 1 and 2, thioredoxins, and glutathione S-transferase (99). Collectively, this suggests that SIRT2 has a critical role in the modulation of the oxidative stress response, implicating SIRT2 in the protection of organisms from metabolic disruption through mechanisms dependent on oxidative stress (Fig. 2).

SIRT3

SIRT3 is designated as a mitochondrial sirtuin since its active form is localized in the mitochondria. Full-length SIRT3 resides in the nucleus but translocates to the

mitochondria in response to stress (*e.g.,* DNA damage), where it is cleaved at its active site by the mitochondrial matrix processing peptidase (63). Although much of the research done on SIRT3 focuses on the roles played within the mitochondria, this enzyme has been implicated in a wide range of diseases, including cardiovascular, renal, and neurodegenerative diseases, as well as cancer (46, 58, 118, 125, 139). Recent studies indicate that SIRT3 modulates mitochondrial metabolism and works together with SIRT1 to increase the life span of experimental animals. In fact, SIRT3 is the only member of the sirtuin family for which direct evidence exists regarding the increase of longevity in humans [reviewed in Ref. (48)]. As SIRT3 is a mitochondrial sirtuin and most of the conditions mentioned above are intimately tied with oxidative stress, it seems reasonable to assume that there may be numerous links between SIRT3 and oxidative stress.

Based on a number of studies, SIRT3 is known to mediate the flow of mitochondrial oxidative pathways and therefore regulate the production of ROS [reviewed in Ref. (166)]. Loss of SIRT3 has been shown to increase the production of ROS, which leads to stabilization of the protumorigenic transcription factor HIF-1α (41). Furthermore, a study by Bell *et al.* found that increased ROS, in the absence of SIRT3, led to increased HIF-1α activation, and SIRT3 knockdown was associated with increased tumor growth in mouse xenografts in an HIF-1α-dependent manner (13). This illustrates that SIRT3 is able to inhibit HIF-1α as well as prevent ROS-mediated genomic instability, suggesting that SIRT3 may have tumor suppressive capabilities through ROS modulation pathways. In addition to its potential roles in tumorigenesis, SIRT3 can affect cellular health directly by influencing the production of ROS through modulation of enzymes involved in the mitochondrial oxidative phosphorylation (OXPHOS) pathway (51). Human mitochondrial DNA (mtDNA) encodes for 13 proteins, which are known to have a role in regulating respiration and OXPHOS in the mitochondria, and is significantly more susceptible to oxidative damage than nuclear DNA (133, 146). In the cell, ROS generated by OXPHOS, ionizing radiation, or chemicals are responsible for DNA damage, including changing purine and pyrimidine bases to 8-oxo-7,8-dihydroguanine (8-oxoG). Importantly, SIRT3 has been shown to target the enzyme that repairs this DNA damage, human 8-oxoguanine-DNA glycosylase 1 (OGG1) (32). SIRT3 has been shown to promote OGG1 by physically binding to it to prevent degradation and control its activation when DNA glycosylase becomes active. In addition, SIRT3 has been found to be crucial in the repair of mtDNA, protecting the integrity of mitochondria, and protecting the cell from apoptosis under conditions of oxidative stress by mediating the activity and replenishment of OGG1 (32). Together, these results suggest that SIRT3 has an important role in protecting the cell against genotoxic stress and oxidative damage, underlining its importance in ARS.

SIRT3 has also been shown to mediate the deacetylation of enzymes that are responsible for the reduction of ROS, leading to protection against oxidative stress-dependent developments and disorders such as cardiac hypertrophy and dysfunction, cancer, aging, and neural degeneration [reviewed in Ref. (4)]. For example, SIRT3 has been shown to activate isocitrate dehydrogenase (IDH2), SOD2, and CAT, all key enzymes in reducing the cellular burden of ROS (93,

154, 156). In addition, SIRT3 knockout mice have been found to have impaired ROS regulating capabilities and endothelial function when fed a high-cholesterol diet, suggesting an important role in ROS, especially in endothelial cell function (177). Interestingly, increased levels of ROS have been found to stimulate SIRT3 transcription and thereby may lead to deacetylation of SOD2 through an oxidative stress feedback loop [discussed in Ref. (93)]. For example, decreased SIRT3 levels have been found in human epidermal keratinocytes after ozone exposure, which was correlated with increased DNA damage, higher levels of cellular H_2O_2, and reduced SOD2 protein levels (91). This is important because lack of regulation of ROS in keratinocytes, which form and maintain the protective layer of the skin, is known to have an impact on their differentiation. When SIRT3 is knocked down in keratinocytes, levels of $O^{\bullet-}_2$ increase, promoting differentiation markers. The opposite is seen in keratinocytes with forced overexpression of SIRT3, which have decreased $O^{\bullet-}_2$ levels and expression of differentiation markers (11).

SIRT3 has been found to have roles in cellular metabolism as well. SIRT3 has also been found to modulate mitochondrial function by mediating levels of NAD^+, which can protect the liver and kidneys from acute diseases and injuries (71, 100). One study conducted on mice lacking SIRT3 found that compared to normal mice, the SIRT3 knockout mice exhibited decreased oxygen consumption, as well as an increase in ROS (65). These observations were also further confirmed through the knockout of SIRT3 *in vitro* using myoblasts, suggesting that the link between SIRT3 and cellular energy levels needs to be further explored. Taken together with SIRT3's obvious role in protecting cells from oxidative damage and genotoxic stress, these studies suggest the possible involvement of SIRT3 in multiple pathways associated with the regulation of oxidative stress (also outlined in Fig. 2).

SIRT4

SIRT4 is a mitochondrial sirtuin with the main function of ribosylation of adenosine diphosphate (ADP) (3, 48). It has been found to be highly expressed in the heart, kidneys, liver, and brain, suggesting that it may have enhanced roles in these tissues (52). Unlike other sirtuins, SIRT4 was initially thought to not have NAD^+-dependent deacetylase activity. Instead, it had been shown to use NAD to ADP-ribosylate glutamate dehydrogenase, which converts glutamate to α-ketoglutarate in mitochondria (52). Recently, however, SIRT4 was found to have the ability to deacetylate lysine, allowing it to control leucine metabolism and insulin secretion (3). In this study, SIRT4 knockout mice were shown to have dysregulated leucine metabolism, leading to elevated insulin secretion (3). This may be responsible for the mice developing accelerated age-induced resistance to insulin. Furthermore, a plethora of studies suggest that all the sirtuins except SIRT4 play a key role in the reduction of mitochondrial oxidative stress throughout the caloric restriction process [reviewed in Refs. (148, 172)]. This, however, does not minimize the role played by SIRT4 in oxidative stress regulation in the cell.

SIRT4 has been shown to be involved in the regulation of ROS production in mitochondria (Fig. 2), although it is

unclear if it affects the activation of antioxidant enzymes localized to the mitochondrial matrix. In a study of angiotensin II (Ang II)- induced cardiac hypertrophy in mice, it was found that overexpression and knockout of SIRT4 increased and decreased ROS, respectively, in both the heart and mitochondria (86). These same results were observed in rat cardiomyocytes, suggesting that SIRT4 may directly control the production of ROS to some extent in heart cells. The authors also found that SIRT4 inhibited the binding of SOD2 to SIRT3, resulting in increased acetylation and thereby reduced the activity of SOD2 (86). Together, these results suggest that SIRT4 may play an important role in managing the players involved in the antioxidant response, if not in actual regulation of the gene themselves.

Also, SIRT4 has been shown to be an integral factor in fatty acid oxidation in the liver and in muscle cells. A 2010 study found that SIRT4 knockdown increased fatty acid oxidation and oxygen consumption in primary mouse hepatocytes,

possibly *via* regulating SIRT1 expression (110). This is important because oxidation of fatty acids is a key source of mitochondrial ROS and has been linked to certain diseases, including kidney damage in diabetes (135). Interestingly, because of its role in oxidative metabolism, SIRT4 is being explored as a biomarker for coronary artery disease for certain populations. A 2014 study found that obese patients with hepatic steatosis had significantly lower levels of circulating SIRT4 than normal controls (157). The authors theorized that the lower SIRT4 levels may be in response to the lack of exercise and a high-calorie diet (both factors in increasing oxidative stress in many mammals) to reduce mitochondrial ROS, but this does not appear to fit with the previous research (110). It remains to be seen if SIRT4 can serve as a biomarker for coronary artery disease and what the exact role played by this sirtuin is. Also, the expression of SIRT4 has been found to differ depending on the cell type, which will need to be taken into consideration before using as a biomarker for
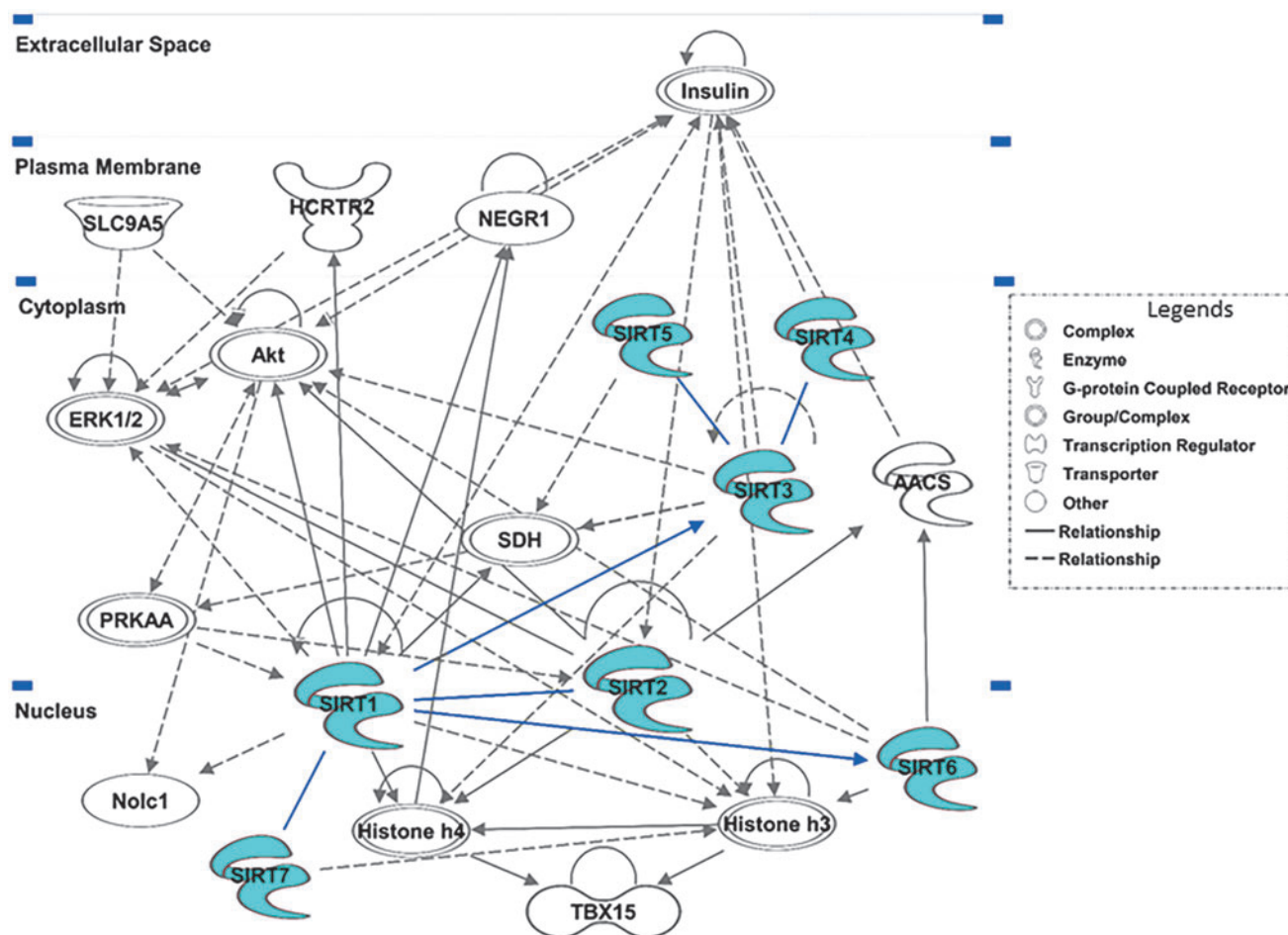

FIG. 3. **Dynamic interaction network of sirtuins.** A sirtuin interaction network was generated *via* Ingenuity Pathway Analysis (QIAGEN) to highlight how sirtuins interact among themselves. Molecular interactions are denoted by *arrows* with *solid lines* showing robust correlation and *dashed lines* showing less frequent correlations. In addition to SIRTs 1–7, several other proteins have also appeared as mediators in the sirtuin network (indicated with *uncolored background*). Blunt-ended lines indicate protein/protein interactions and arrowed lines indicate that one is affecting the expression of other. The interactions among sirtuins are denoted with *blue lines*. The illustration shows that sirtuins closely interact with each other, either directly or through very few intermediaries. This network suggests that the network of ARS molecules may be impacted by more than one sirtuin, and that understanding the interplay between sirtuins is crucial to understand sirtuin-mediated redox homeostasis. AACS, acetyl-CoA synthetase.

specific diseases. Clearly, additional studies are needed to determine the full capabilities and actions of SIRT4 in antioxidant response and oxidative stress as well as in oxidative stress-associated disease conditions.

SIRT5

SIRT5 is also localized in the mitochondria, where it functions to deacetylate, demalonylate, and desuccinylate multiple proteins (38, 48). SIRT5 has been found to be highly expressed in the tissues of the brain, heart, liver, and lymphoblasts, where it is shown to be accumulated heavily in the intermembrane spaces of the mitochondria (85, 107). SIRT5 has been described to have roles in cellular metabolism, detoxification, regulation of oxidative stress, energy production, and mediation of the apoptosis pathway (82). However, there is no definitive consensus on the roles of SIRT5 in these processes, and many conflicting views seem to exist in this regard. Although more research is needed to determine the exact roles played by SIRT5, it appears that its association with ROS and oxidative stress signaling is strong (Fig. 2).

SIRT5 is popularly known for the regulation of mitochondrial fatty acid oxidation, the urea cycle, and cellular respiration (106, 183). SIRT5 deacetylates and activates carbamoyl phosphate synthetase (CPS1), which catalyzes the first step of the urea cycle for the detoxification of ammonia. SIRT5 knockout mice have shown to have increased levels of ammonia during fasting (106). Ogura *et al.* have shown that mice overexpressing SIRT5 have increased the activity of CPS1, facilitating the conversion of ammonia to nontoxic urea (117). Here, it is important to mention that ammonia is known to induce ROS production and decrease antioxidant GSH content (16), suggesting the indirect involvement of SIRT5 in managing oxidative stress.

Interestingly, Liu *et al.* have shown that SIRT5 protects cardiomyocytes from oxidatively induced apoptosis, although the mechanism by which this protection occurs is unclear (82). Recent data have identified suppression of oxidative stress as being a possible mechanism by which SIRT5 may protect against apoptosis in SH-EP neuroblastoma cells (80). This finding is in accordance with previous data in lung tumor and epithelial cells (81, 170). Lin *et al.* have shown that SIRT5 binds to and desuccinylates SOD1, and that desuccinylation increases SOD1 activity. Furthermore, SOD1-mediated reduction in ROS was increased when SIRT5 was coexpressed, revealing a posttranslational regulation of SOD1 in lung tumor cells (81). SIRT5 has also been shown to deacetylate cytochrome c, which is an essential component of the electron transport chain (145). In a very recent study, cells that were transfected with SIRT5 were found to have decreased levels of ROS, suggesting that SIRT5 suppresses the progression of oxidative stress conditions in the cell (80). Overall, it appears that SIRT5 plays important roles in a response of cells to oxidative stress. However, this area of research needs further efforts aimed at elucidating the exact mechanism of SIRT5 functions.

SIRT6

SIRT6 is located within the nucleus of the cell and has been shown to function through NAD^+-dependent deacetylation of lysines 9 and 56 on histone 3 (H3K9 and H3K56) (95–97, 159, 160, 164). The delineation of SIRT6-mediated deacetylation on histone 3 uncovered the roles it possessed in chromatin regulation and gene expression through recruitment of certain transcription factors such as NF-κB (69, 70, 188). In addition to playing important roles in chromatin regulation and recruitment of transcription factors such as NF-κB, SIRT6 has also been suggested to have critical functions in other cellular processes such as gene expression, glucose homeostasis, and DNA repair (40, 64, 94, 160, 161). Research on SIRT6 knockout mice has provided the first evidence that it may be involved in regulating mammalian aging [reviewed in Ref. (48)]. SIRT6 knockout mice displayed shortened life span as well as premature aging phenotypes, including decrease in serum glucose and insulin-like growth factor (IGF-1) levels (103). Due to the essential roles SIRT6 has in cellular homeostasis, disruption of this enzyme appears to produce an effect on disease development (12, 53, 57, 101, 136, 161).

Based on recent research, SIRT6 is believed to be an important metabolic sensor that connects environmental signals to metabolic homeostasis and stress responses in mammals (12, 169). This underlines the role of SIRT6 as a mediator of oxidative stress and myocardial injury during ischemia/ reperfusion (I/R) (169). SIRT6 overexpression has been shown to protect cardiomyocytes against I/R injury by the reduction of oxidative stress and upregulation of endogenous antioxidants *via* an energy-sensing AMPK-FOXO3α axis that is necessary for oxidative stress resistance (169). Thus, SIRT6 appears to be vital in redox and antioxidant homeostasis as it seems to aid against oxidative stress damage. Similarly, SIRT6 has been shown to protect hMSCs from oxidative stress through coactivation of NRF2 (122). SIRT6-null hMSCs were shown to have dysregulated redox metabolism resulting in increased sensitivity to oxidative stress. It was also suggested that SIRT6 serves as a coactivator of NRF2 *via* interactions with the RNA polymerase II (RNAP II) complex in such a way that reduction of SIRT6 in hMSCs decreases the activation of the RNAP II complex (122). In addition, SIRT6 and NF-κB have also demonstrated protective roles in high glucose-mediated endothelial senescence (33). Downregulation of SIRT6 during a short-term exposure to high glucose increased expression of NF-κB, while overexpression of SIRT6 decreased NF-κB (9). Interestingly, research has shown that the protective effects of the antioxidant ergothioneine are associated with increases in SIRT1 and SIRT6, and their negative regulation of NF-κB, suggesting a strong dynamic regulation of both sirtuins in relation to redox signaling (33). SIRT6 has also been implicated in the control of inflammatory pathways in diabetic atherosclerotic lesions and endothelial levels (83). Moreover, epigenetic mechanisms in which stress represses SIRT6 expression have led to histone acetylation and gene expression, indicating a key role of SIRT6 in the stress response (187). Overall, SIRT6 expression and function seem to overlap with antiglycolytic and antioxidant mechanisms to aid against ROS (56) (Fig. 2). Indeed, our knowledge regarding the role and relevance of SIRT6 in oxidative stress and associated disease conditions is emerging and further research is needed in this direction.

SIRT7

The last member of the currently identified mammalian sirtuin family, SIRT7, is also primarily localized to the nucleus. Specifically, it is expressed in the nucleoli, where it binds to
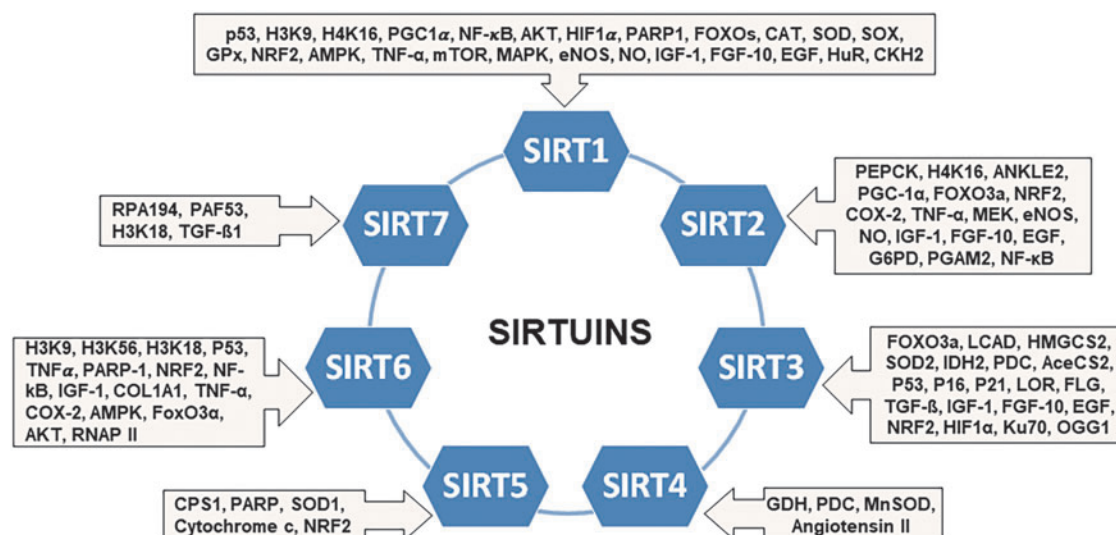
FIG. 4. Molecular associations of sirtuins with ARS-related targets. The figure illustrates the wide variety of ARS-related targets that have been shown to be regulated with sirtuins. Interestingly, several of the proteins appear to have common targets for SIRTs 1–7. For example, NRF2 appears to be a common target for SIRTs 1–3, 5, and 6, to mediate antioxidative genes. The large number of targets identified for SIRT1 suggests it may be more involved in ARS regulation than other sirtuins, although it may be a by-product of its popularity in research and early identification instead.

histones to positively regulate ribosomal DNA (rDNA) transcription [reviewed in Ref. (48)]. SIRT7 mRNA has been found to be expressed differentially in all tissues, with more expression in those with higher metabolic activities, and decreased expression has been correlated with age [reviewed in Refs. (43, 73)]. Interestingly, SIRT7 knockout mice have been characterized by lethal heart hypertrophy and a progeroid phenotype, manifesting as premature physiological aging, making affected individuals appear to be older than they are (163). This suggests that SIRT7 may have a role in aging and/or age-related dis-

eases. It is possible that these expression patterns and phenotypes are due to SIRT7's role in rDNA transcriptional regulation.

During replicative senescence, SIRT7 has been found to migrate to the chromatin and cytoplasm from the nucleoli, where it may reduce rDNA transcription (74). SIRT7 over-expression has shown to increase RNA polymerase I (RNA Pol I)-mediated transcription, while knockdown or inhibition of SIRT7 decreases it (43). This appears to be due to its ability to regulate subunits of RNA Pol I, specifically
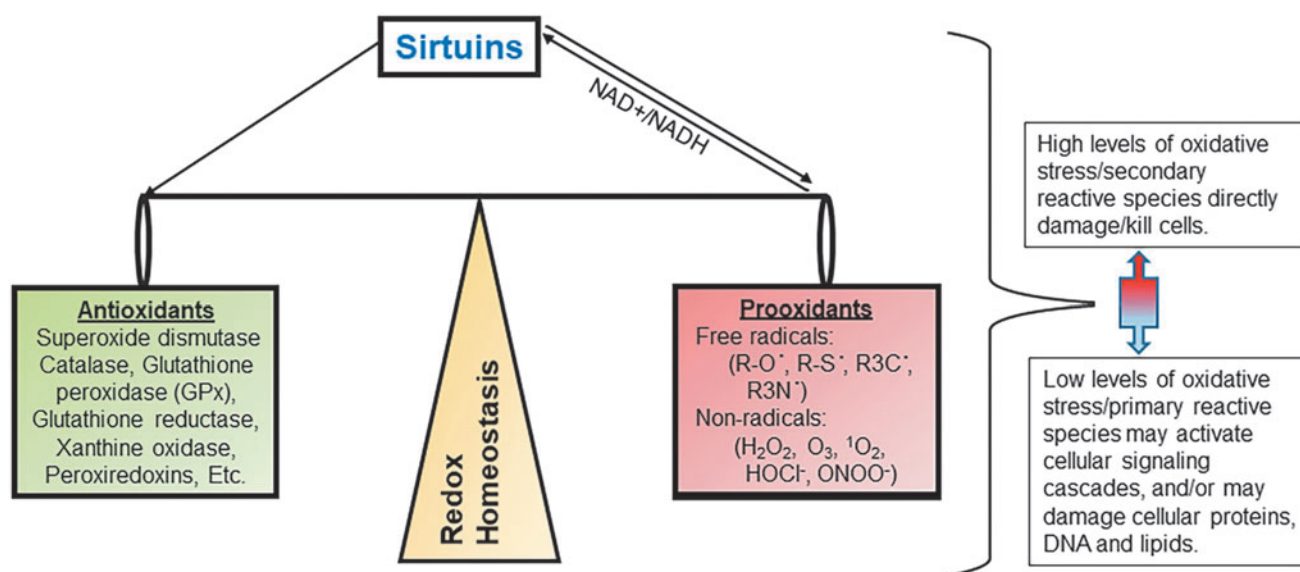

FIG. 5. A schematic representation of sirtuin-mediated redox homeostasis. Sirtuins contribute to redox homeostasis maintenance by balancing antioxidant enzymes and pro-oxidant radicals. As illustrated, sirtuins regulate the expression and activity of antioxidative enzymes and the production of pro-oxidants as well. Pro-oxidants also affect the activity of sirtuins through alteration of the $NAD^+/NADH$ ratio, allowing for a feedback loop that helps prevent the cell from entering or maintaining a state of oxidative stress. NAD, nicotinamide adenine dinucleotide.

Table 1. Chemical Modulators of Sirtuins

Modulators	Known actions	Ref.
SIRT1		
Asiatic acid	Increases SIRT1 and PGC-1, decreases apoptosis and ROS, stabilizes mitochondrial membrane potential in human neuroblastoma cells.	(180)
Baicalin	Upregulates SIRT1, reduces LDH, NO, caspase-3, and the apoptotic percentage of SH-SY5Y cells.	(26)
Exendin-4	Increases expression of SIRT1 and AMPK *in vivo*; induces fatty acid oxidation and glucose metabolism genes.	(79)
Ginkgolide B	Increases expression of SIRT1 in oxidized low-density lipoprotein-treated endothelial cells.	(88)
GLP-1-(7-34)-amide	Inhibits SIRT1 to stimulate pancreatic β-cell mass expansion.	(10)
Melatonin	Inhibits SIRT1 and has antitumor activity in osteosarcoma cells.	(31)
Pitavastatin	Increases SIRT1, eNOS, and CAT in streptozotocin-diabetic mice; decreases endothelial senescence.	(119)
Quercetin	Increases SIRT1 in mouse epididymal adipose tissue.	(36)
Telmisartan	Increases SIRT1 and AMPK phosphorylation in 3T3-L1 adipocytes.	(149)
Vitamin D	Upregulates SIRT1, rescues H_2O_2-induced SIRT1 reduction in endothelial cells.	(129)
SRT2104	Activates SIRT1 and extends mean and maximal life span of mice.	(92)
EX-527	Acts as potent and selective inhibitor of SIRT1.	(108)
SIRT2		
Clasto-lactacystin β-lactone	Inhibits 26S proteasome, which results in increase in SIRT2 protein in human cells.	(37)
Epoxomicin	Inhibits 26S proteasome, resulting in increases in SIRT2.	(37)
AGK2	Inhibits SIRT2, thereby rescuing α-synuclein-mediated toxicity in models of Parkinson's disease.	(120)
SIRT3		
Adjudin	Upregulates SIRT3 levels in rodent cochlear hair cells, exerting otoprotective effects.	(130)
Oroxylin A	Increases mitochondrial SIRT3, which mediates deacetylation of cyclophilin D in breast carcinoma.	(174)
Honokiol	Blocks and reverses cardiac hypertrophy in mice by activating SIRT3.	(128)
LC-0296	Inhibits SIRT3, cell proliferation, and promotes apoptosis of head and neck squamous cell carcinoma cells.	(2)
4′-Bromo-resveratrol	Binds to SIRT3 structures, revealing a mechanism for inhibition.	(112)
SDX-437	Selectively inhibits SIRT3 > 100-fold over SIRT1.	(123)
SIRT4		
None reported		
SIRT5		
Suramin	Binds to SIRT5, potentially inhibiting its deacetylase activity.	(147)
GW5074	Inhibits the desuccinylation activity of SIRT5.	(153)
SIRT6		
Quinazolinedione compounds	Inhibit SIRT6, reduce TNF production, increase glucose uptake, and increase H3K9 acetylation.	(152)
SIRT7		
None reported		
Multiple SIRTs		
D-glucose	Decreases SIRTs 1–7 expression in microvascular endothelial cells. Downregulates SIRT1, causing increase in ROS and decrease in mitochondrial antioxidant enzymes.	(102)

(continued)

TABLE 1. (CONTINUED)

Modulators	Known actions	Ref.
Nicotinamide (niacinamide)	Prohibits proliferation and enhances chemosensitivity of pancreatic cancer cells through inhibiting SIRT1 and Ras/Akt pathways.	(192)
	Inhibits SIRT3 *via* competition with the cofactor NAD$^+$.	(50)
Metformin	Increases SIRT1 and reduces expression of UCP2 in rat liver of type 2 diabetes mellitus with nonalcoholic fatty liver disease. Also decreases SIRT5 in mouse hepatocytes and liver.	(179) (20)
Resveratrol	Increases SIRT1 levels in RGC-5 retinal ganglion cells and 3T3-L1 preadipocytes. Decreases levels of SIRTs 3–4, as well as NAMPT in wild-type adult zebrafish liver.	(27, 29) (144)
Trichostatin A	Increases SIRTs 2, 4, and 7 in breast carcinoma cells expressing human Er alpha (ESR1) protein.	(132)
Valproic acid	Increases SIRTs 4 and 7 in human Er alpha (ESR1) protein-expressing breast cancer cells.	(132)
Pyrroloquinoline quinone	Increases expression and activity of SIRTs 1 and 3 in HepG2 cells.	(191)
Tenovin-1 and tenovin-6	Inhibits the protein-deacetylating activities of SIRTs 1 and 2.	(78)
Sirtinol and salermide	Inhibit SIRTs 1 and 2, resulting in increased cell death and p53 acetylation in breast carcinoma cells.	(124)
Thieno[3,2-d]pyrimidine-6-carboxamide	Derivatives of this compound inhibit SIRTs 1–3.	(34)
SRT1720	Activates SIRT1, but has potential to inhibit SIRT3 due to binding to the crystal structure of SIRT3 in complex with SRT1720.	(113)

Although this list consolidates the current research on sirtuin modulators, it may not be comprehensive and the classification(s) may be subject to further research.

CAT, catalase; eNOS, endothelial nitric oxide synthase; H$_2$O$_2$, hydrogen peroxide; LDH, lactate dehydrogenase; NAD, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; NO, nitric oxide; ROS, reactive oxygen species; SIRT, sirtuin; TNF, tumor necrosis factor.

RPA194 and PAF53 (28, 162). This action seems to involve NAD-dependent stimulation of SIRT7, which in turn deacetylates RPA194 and PAF53, leading to increased RNA Pol I activity and rDNA transcription. These studies suggest that SIRT7 plays a pivotal role in cellular responses to energy levels and allows the cells to undergo a mechanism for the cessation of rDNA transcription in stress conditions. Recent research has also uncovered a role for SIRT7 in the regulation of mitochondrial homeostasis *via* deacetylation of GABPβ1, one of the subunits of a complex involved in regulating several key mitochondrial genes (137). It is unclear, however, if SIRT7 activity is a cause or effect of NAD$^+$ availability, and further research is needed to ascertain the nature of SIRT7's connection to NAD$^+$ and mediation of the cellular energy level. It has been demonstrated that SIRT7 is slightly downregulated in response to H$_2$O$_2$-induced oxidative stress in embryonal heart-derived H9c2 cells of rats (189). This study also found that this decrease was mitigated by pre-exposure to the SIRT activator resveratrol. This suggests that other oxidative stress-related activities of resveratrol may be due to SIRT7 activity, at least in part, and that further work needs to be done to tease out the exact contributions of the other sirtuins to resveratrol's successes. Due to SIRT7 being a relatively recent subject of research, there is a lack of understanding about the substrates on which SIRT7 acts and therefore also the mechanisms by which it performs its various roles in the cell. However, preliminary studies suggest that it does play at least a small role in regulating the cell's response to oxidative stress (Fig. 2).

Mechanistic Interactions Among Sirtuins in ARS

As discussed above, each of the sirtuins has a distinct subcellular localization, which is important in rapidly sensing and responding to alterations in subcellular ROS within the mitochondria, nucleus, and cytoplasm. The toxic effects associated with altered levels of subcellular ROS are largely prevented by various antioxidants, many of which are regulated by sirtuins. Hence, sirtuins appear to be an integral part of an important cellular defense mechanism against oxidative stress and ROS formation. In Figure 2, the complexity of the cellular defense mechanism as it relates to the sirtuins can be seen. It is important to note that the subcellular localization of each of the sirtuins likely is a contributor to their ability to modulate ROS responses, and their interaction with ARS molecules can be seen in Figure 2 as well.

In general, research to date supports the notion that sirtuins play very important roles in maintaining proper cellular redox balance and in general seem to be protecting from the adverse effects of oxidative stress and associated diseases. This also suggests that the diseases involving redox imbalances may benefit from strategies aimed at sirtuin modulation. It is possible that while some conditions need targeting of specific sirtuins, others may need to target multiple sirtuins using pan activators.

To gain insight into the potential mechanisms and interacting partners of sirtuin regulation, we performed an ingenuity pathway analysis (IPA) to generate an interaction network focusing on redox signaling. As shown in Figure 3, all seven sirtuins appeared to interact with important molecules, such as acetyl-CoA synthetase (AACS), protein kinase B (popularly known as AKT), ERK1/2, HCRTR2, histone 3, histone 4, insulin, NEGR1, NOLC1, PRKAA, SLC9A5, SDH, and TBX15. Several of these molecules are known to be directly and/or indirectly linked with ARS. As an example, hyperactivation of AKT, a serine/threonine protein kinase, is known to occur in many cancer cell types. This raises metabolic activity in the mitochondria and inhibits FOXO transcriptional activity, resulting in greatly increased ROS levels, which sensitizes cancer cells to apoptosis induced by oxidative stimuli (35, 115).

Intriguingly, the IPA-generated sirtuin network showed interactions among sirtuins as well (Fig. 3). SIRT1 seems to interact directly with SIRTs 2, 6, and 7 as well as SIRT3, which further appears to interact with SIRTs 4 and 5. Also, SIRT1 has been found to regulate itself by several mechanisms, including initiating inhibition, degradation, ubiquitination, and stabilization. These interactions are defined based on experimental studies reported in the literature. For example, one direct link between SIRT1 and SIRT3 came from a report from Liu *et al.* where they have shown that SIRT1 inhibition decreases the expression of SIRT3 mRNA in TLR4-stimulated primary culture human monocytes as well as in cultured mouse splenocytes (a model that mimics the initiation and adaptation stages of sepsis) (84). SIRT1 has also been shown to regulate the expression of SIRT6 mRNA. Kim *et al.* have shown that SIRT1 forms a complex with NRF1 and FOXO3a in the promoter region of SIRT6 to regulate the levels of SIRT6. Consequently, this regulates the deacetylation of H3K9 by SIRT6 and the promoter regions of several genes involved in negative regulation of glycolysis, triglyceride synthesis, and fat metabolism (72). This evidence, in addition to others cited above, suggests that on top of the individual antioxidant and ROS-related activities that the SIRTs perform, they may interact closely enough with each other to coregulate the levels of oxidative stress. The idea that sirtuins interact so closely with each other has not been fully explored to date. This may uncover how activation or inhibition of one sirtuin may affect the regulation of others and allow for deeper understanding of sirtuin-mediated redox homeostasis in the cell.

Conclusion

The fact that sirtuins play important roles in maintaining cellular homeostasis to keep the cells healthy makes them an ideal candidate to be studied in redox regulation. Maintenance of redox homeostasis is accomplished *via* feedback mechanisms functioning at the various levels of complexity mostly related to transcriptional modulation. As discussed above and summarized in Figures 4 and 5, the sirtuins are involved in regulating many of the key genes and molecules integral to redox homeostasis and oxidative stress mitigation. The majority of the mammalian sirtuins appear to have protective activities, antioxidant-promoting actions, and/or ROS-suppressive effects in the cell. However, SIRT4 appears to have dual roles and is the only sirtuin shown to induce ROS production. Overall, the apparent protective effects of sirtuins

against oxidative stress support the theory that sirtuins could act synergistically *via* distinct mechanisms to enhance cellular homeostasis. This may serve as the mechanistic basis for the development and discovery of antioxidants and sirtuin modulators for the management of redox-related diseases. A list summarizing the chemical modulators of sirtuins with their known actions are detailed in Table 1. Further in-depth studies are required to ascertain and clarify the exact roles of each of the sirtuins, and to determine whether different sirtuins have functional redundancies, overlapping actions, or a dynamic equilibrium that may be important in regulating oxidative stress in the cell and as part of pathological manifestations. Given the interest in sirtuins as drug targets and their redox importance, the studies addressing these issues may provide therapeutic opportunities for the treatment of metabolic, age-related, and several other redox-related diseases.

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Abbreviations Used

4-HNE = 4-hydroxynonenal
8-oxoG = 8-oxo-7,8-dihydroguanine
ADP = adenosine diphosphate
Ang II = angiotensin II
ARE = antioxidant response element
ARS = antioxidant and redox signaling
CAT = catalase
CHK2 = checkpoint kinase 2
CPS1 = carbamoyl phosphate synthetase
CUL3 = cullin 3
DNA = deoxy acid
ERE = electrophilic response element
FOXO = class O of forkhead box transcription factors
G6PD = glucose 6-phosphate dehydrogenase
GCL = glutamate cysteine ligase
GPX = glutathione peroxidase
GSH = glutathione
H_2O_2 = hydrogen peroxide
HDAC = histone deacetylase
hMSCs = human mesenchymal stem cells
HO$^{\bullet}$ = hydroxyl radical
I/R = ischemia/reperfusion
IDH2 = isocitrate dehydrogenase
IPA = ingenuity pathway analysis
KEAP1 = kelch-like ECH-associated protein 1
mRNA = messenger RNA
mtDNA = mitochondrial DNA
NAD = nicotinamide adenine dinucleotide
NADPH = nicotinamide adenine dinucleotide phosphate (reduced form)
NAMPT = nicotinamide phosphoribosyltransferase
NF-κB = nuclear factor kappa B subunit
NO = nitric oxide
NRF2 = nuclear factor E2-related factor 2
$O^{\bullet}_2{}^-$ = superoxide anion radical
OGG1 = 8-oxoguanine-DNA glycosylase 1
ONOO$^-$ = peroxynitrite
OXPHOS = oxidative phosphorylation
PARP1 = poly (ADP-ribose) polymerase 1
PGAM2 = phosphoglycerate mutase
PRDX = peroxiredoxins
rDNA = ribosomal DNA
RNA Pol I = RNA polymerase I
RNA = ribonucleic acid
RNAP II = RNA polymerase II
RNS = reactive nitrogen species
ROS = reactive oxygen species
RS = reactive species
SIRT = sirtuin
SOD = superoxide dismutase