REDOX REGULATION OF SIRT1 IN INFLAMMATION AND CELLULAR SENESCENCE

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Abstract

Sirtuin1 (SIRT1) regulates inflammation, aging (lifespan and healthspan), calorie restriction/ energetics, mitochondrial biogenesis, stress resistance, cellular senescence, endothelial functions, apoptosis/autophagy, and circadian rhythms through deacetylation of transcription factors and histones. SIRT1 level and activity are decreased in chronic inflammatory conditions and aging where oxidative stress occurs. SIRT1 is regulated by a NAD^+-dependent DNA repair enzyme poly(ADP-ribose)-polymerase-1 (PARP-1), and subsequent NAD^+ depletion by oxidative stresses may have consequent effects on inflammatory and stress responses as well as cellular senescence. SIRT1 has been shown to undergo covalent oxidative modifications by cigarette smoke-derived oxidants/aldehydes, leading to post-translational modifications, inactivation, and protein degradation. Furthermore, oxidant/carbonyl stress-mediated reduction of SIRT1 leads to the loss of its control on acetylation of target proteins including p53, RelA/p65 and FOXO3, thereby enhancing the inflammatory, pro-senescent and apoptotic responses, as well as endothelial dysfunction. In this review, the mechanisms of cigarette smoke/oxidant-mediated redox post-translational modifications of SIRT1 and its role in PARP1, NF-κB activation, FOXO3 and eNOS regulation, as well as chromatin remodeling/histone modifications during inflammaging are discussed. Furthermore, we also discussed various novel ways to activate SIRT1 either directly or indirectly, which may have therapeutic potential in attenuating inflammation and premature senescence involved in chronic lung diseases.

Keywords

SIRT1; Redox signaling; Inflammation; Senescence; NF-κB; FOXO3; Tobacco smoke; Oxidants; GSH; COPD

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Introduction

Intracellular reduction-oxidation (redox) status, which refers to the ratio of the reversible oxidized and reduced form of a specific redox couple, maintains cellular homeostasis through the balance of oxidants and antioxidants. Oxidative stress reflects an imbalance between reactive oxygen species (ROS) production and antioxidant defense, favoring the oxidant environment [1, 2]. Both intracellular redox status and oxidative stress are known to be involved in inflammation and aging [3–6]. Redox post-translational modifications and consequent altered functions of a targeted protein are important signal transduction processes. During a redox response, reversible or irreversible post-translational modifications on proteins occur through either direct oxidation of amino acid side chains or addition of reactive intermediates from the oxidation of other cellular components on cysteine, histidine, and lysine residues [7]. These modifications result in formation of disulfide bonds, S-nitrosylation, and S-glutathionylation, which can be reversed by thioredoxin and glutaredoxin enzymes [8]. However, irreversible covalent modifications, such as carbonylation and tyrosine nitration, can lead to protein dysfunction and folding, as well as degradation.

Sirtuins (SIRTs) are a family of deacetylases with homology to *Saccharomyces cerevisiae* silent information regulator 2 (Sir2) that requires NAD^+ as a cofactor for the deacetylation reaction. There are seven sirtuins in mammals, and each comprises a conserved central core deacetylase domain flanked by variable length N- and C-terminus. Interestingly, as sirtuins require NAD^+ cofactor for their enzymatic activity, it is thought that these deacetylases respond to changes in environment, oxidative stress, and metabolism [9]. SIRT1 is the most extensively studied sirtuin in mammals, primarily due to its regulation of diverse cellular targets and functions as well as its therapeutic potential.

SIRT1 has been increasingly recognized to play diverse roles in gene silencing, stress resistance, apoptosis, senescence, aging, and inflammation [10–13]. These physiological functions of SIRT1 are mainly mediated by deacetylation of histones, transcription factors or co-activators, such as p53, forkhead box O (FOXO), nuclear factor-kappaB (NF-κB), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and Ku70 [10–14]. In addition to its well-known function as molecular sensors of nutritional status in cells, several lines of evidence indicate that SIRT1 is a possible candidate for redox modulation because its activity is regulated by NAD^+ and it is therefore, sensitive to the redox state [15, 16]. Recently, we found that SIRT1 protects against lung cellular senescence and inflammatory response to oxidative stress imposed by cigarette smoke [13]. Though some aspects of this review have been discussed and reviewed previously in light of prior themes [10-12, 17], this review provides an updated interpretation and review of literature based on current knowledge and perspective on free radical biology and diseases. In this review, we discuss the recent studies on the regulation of SIRT1 by redox state, and related signaling pathway involved in inflammation and premature senescence.

Posttranslational modifications of SIRT1 by oxidative stress

The regulation of SIRT1 by oxidative stress seems to be complex since SIRT1 is involved in diverse redox-dependent cellular processes. SIRT1 either directly or indirectly can influence the redox functions of the cells. However, cellular redox status can also affect SIRT1 level and activity through its post-translational modifications.

SIRT1 and oxidative stress

SIRT1 has been shown to regulate cellular oxidative stress burden and its toxicity [17–20]. This may be, in part, due to SIRT1-mediated induction of manganese superoxide dismutase (MnSOD) via deacetylation and activation of FOXO3 transcription factor. This induction is augmented by resveratrol, leading to increased resistance to oxidative stress in myoblasts [21]. These findings have been confirmed by other studies that FOXO3 activation protects against oxidative stress through induction of MnSOD expression [22, 23]. Alcendor *et al.* also reported that a moderate overexpression of SIRT1 protected the heart from oxidative stress with increased expression of catalase, which results from deacetylation of FOXO3 in mice [24]. A recent study reports that liver-specific SIRT1 deficiency caused increase in ROS production, which disrupted the mTOR/Akt signaling in other insulin-sensitive organs leading to insulin resistance [25]. This is in agreement with the findings that SIRT1 attenuates oxidative stress-induced mesangial cell apoptosis via p53 deacetylation [18]. However, it has been reported that SIRT1 deficiency in mouse embryonic fibroblasts showed higher replicative life span under oxidative stress [19]. Li *et al.* also reported the pro-oxidative stress role of SIRT1 in neurons and in mouse brain [20]. Thus, the involvement of SIRT1 in regulation of cellular oxidative stress may depend on the availability of its direct substrates.

In addition to the role of SIRT1 in regulation of cellular oxidative stress burden, SIRT1 *per se* is also regulated by oxidative stress. SIRT1 protein levels are altered during metabolic reactions/changes, aging, chronic diseases, and diverse extracellular stimuli (reviewed in [26]). We have shown that the levels of SIRT1 protein are decreased *in vitro* in lung epithelial cells, endothelial cells, and macrophages in response to oxidants derived from cigarette smoke extract, as well as in lungs of smokers and patients with chronic obstructive pulmonary disease (COPD) [13, 27–31]. The reduction of SIRT1 abundance by oxidative stress preceded its transcriptional alteration [29], suggesting post-translational regulation of SIRT1 by oxidative stress. H_2O_2 has also been shown to accelerate cellular senescence by decreasing NAD^+ and subsequent SIRT1 activity in human lung fibroblasts [32]. Treatment of human promyelocytic leukemia cells with buthionine sulfoximine, an inhibitor of glutathione biosynthesis, and H_2O_2 significantly decreases SIRT1 mRNA [33]. Similarly, H_2O_2 treatment reduces SIRT1 abundance in human lung epithelial cells [31]. These findings suggest that intracellular thiol plays a critical role in regulation of SIRT1 activity. However, H_2O_2 treatment up-regulates SIRT1 expression and induction of catalase, although SIRT1 overexpression rescues H_2O_2-induced cellular apoptosis in renal tubular cells [34]. Such dual effects of oxidative stress on SIRT1 are further supported by the findings that SIRT1 is up-regulated under oxidative conditions, leading to inhibition of pro-neuronal transcription factors and decreased neurogenesis [35]. However, the exact

mechanism for the up-regulation of SIRT1 expression level or activity by oxidants is not known.

Oxidative stress and post-translational modifications of SIRT1

Mammalian SIRT1 is comprised of 747 amino acids and consists of three regions; the central core possessing the deacetylase domain (amino acids 273-517), as well as the N- and C-terminal regions flanking the enzymatic core [14] (Fig. 1). The catalytic domain is comprised of 250 amino acids and is highly conserved among species. The catalytic domain constitutes of a substrate binding pocket and a NAD^+ binding pocket, consisting of a structural Zn^{2+} complexed to 4 cysteine residues, a Rossmann fold domain, a classical NAD-binding motif, and other serine residues [14]. The N- and C-terminus contain regulatory elements and binding domains for SIRT1 co-activators/co-repressors and substrates.

To date, SIRT1 has been shown to contain fifteen phosphorylation sites [36–39], one SUMOylation residue [40] and two S-nitrosylation residues [41]. The putative sites of the other post-translational modifications, such as carbonylation and S-glutathionylation, remain to be characterized [31, 42]. Oxidative stress-mediated post-translational modifications of SIRT1 may be due to the adaptive response to environmental stress in acute conditions. However, under a chronic oxidative/environmental stress, these modifications can be deleterious. The effects of post-translational modifications on SIRT1 are summarized in Fig. 2.

SIRT1 undergoes serine phosphorylation, and the phosphorylation/dephosphorylation affects its activity and protein levels through proteasome-dependent or independent degradation [28, 31, 36, 43]. SIRT1 contains several post-translational modification sites for phosphorylation, of which 7 are localized within the N-terminus, and 8 within the C-terminus. Serine phosphorylation sites on SIRT1 (Ser27, Ser47, Ser659, and Ser661) are identified, which are regulated by various protein kinases under basal physiological conditions [36–38, 43, 44]. Phosphorylation of SIRT1 on Ser27 by JNK2 kinase increases the stability of SIRT1 in cancer cell lines [45]. Similarly, mIGF-1/JNK1 regulation of SIRT1 protects against oxidative stress in the heart [46]. The separate studies have demonstrated that JNK1-dependent SIRT1 phosphorylation promotes its enzymatic activity, but leads to proteasome-mediated degradation [44, 47], suggesting the dual effects of JNK1-dependent phosphorylation on SIRT1. Phosphorylation on Thr530 and Ser540 by cyclinB/Cdk1 is required for normal cell cycle progression [36]. SIRT1 is phosphorylated on Ser154, Ser649, Ser651 and Ser683 by caseine kinase 2 (CK2) in response to ionizing radiation-induced DNA damage, which increases SIRT1 deacetylase activity and substrate binding affinity [43]. We have shown that oxidants/aldehydes derived from cigarette smoke caused SIRT1 phosphorylation in macrophages, epithelial cells, as well as in mouse lungs [31]. Proteasome inhibitors block cigarette smoke-induced reduction of SIRT1 suggesting that phosphorylation, in addition to covalent oxidative/nitrosative modifications, of SIRT1 leads to its irreversible modifications and subsequent proteasomal degradation [27, 31].

SUMO is a small ubiquitin-like protein that has the opposite effect of ubiquitin. Ubiquitination has classically been shown to increase protein degradation, whereas SUMOylation has been shown to increase protein stability [48]. Both SUMOylation and

ubiquitination can occur under oxidative stress conditions, and these effects are regulated by the intracellular thiol levels. SUMOylation of SIRT1 has also been reported [40]. When SIRT1 is SUMOylated at Lys734, its deacetylase activity is increased. In response to oxidative stress and DNA damage induced by UV radiation, SIRT1 associates with Sentrin-specific protease 1 (SENP1), and becomes deSUMOylated and less active [40].

Oxidants/electrophiles covalently modify SIRT1 post-translationally, decreasing its enzymatic activity and marking the protein for proteasomal degradation [31]. SIRT1 is a redox-sensitive molecule, and intracellular thiols regulate SIRT1 level and activity. Treatment with buthionine sulfoximine, an inhibitor for glutathione (GSH) biosynthesis, further decreased SIRT1 levels in response to oxidative/carbonyl stress, whereas elevation of intracellular thiol pools by GSH monoethylester rescued cigarette smoke extract-induced reduction of SIRT1 abundance in epithelial cells. Further study is required to investigate whether treatments of buthionine sulfoximine and GSH monoethylester influence SIRT1 glutathionylation. Zee *et al.* has shown that SIRT1 is also subject to S-glutathionylation of specific cysteine residues (e.g., cys67, cys268 and cys623) leading to inhibition of resveratrol-induced SIRT1 activation [42]. It remains elusive how SIRT1 glutathionylation differentially affects its enzymatic activity and abundance. Aldehydes caused formation of carbonyl adducts on SIRT1 cysteine residues, which was reversed by increasing the intracellular thiols and N-acetyl-L-cysteine (NAC) [31]. SIRT1 was also carbonylated and glutathionylated *in vivo* in mice exposed to cigarette smoke. These modifications were attenuated by increasing intracellular thiols by NAC *in vitro* and *in vivo* in mice over-expressing glutaredoxin 1, an enzyme that repairs glutathionylated proteins.

S-nitrosylation is a covalent attachment of a nitric oxide group to a cysteine thiol/sulfhydryl, which leads to formation of a S-nitrosothiol derivative [49]. Kornberg *et al.* showed that nitrosylated glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is transported to the nucleus, which physiologically transnitrosylated SIRT1 and HDAC2 [41]. Since nitric oxide is a major mediator in inflammation, the S-nitrosylation of SIRT1 by GAPDH via nitric oxide synthase (NOS) may have clinical relevance in chronic inflammation and type 2 diabetes. Though this study showed that SIRT1 is nitrosylated at cysteine 387 and 390 residues by residue-specific mutation and the biotin switch assay, further confirmation by proteomics is required to affirm these S-nitrosylation sites.

A recently study highlighted that 25 amino acid sequence in the C-terminal domain is essential for SIRT1 deacetylase activity [50]. The endogenous Sirt1 inhibitor Deleted in Breast Cancer 1 (DBC1) inhibits SIRT1 by inhibiting this domain. This is mediated by protein kinase A and AMP-activated protein kinase [51]. Similarly, SIRT1 activity is shown to be negatively regulated by DBC1 through direct binding, and this SIRT1-DBC1 interaction is increased following DNA damage and oxidative stress [52]. These data suggest a multiple mode of biochemical regulation of SIRT1 deacetylase activity.

Taken together, SIRT1 is a redox-sensitive protein, which is subject to post-translational modifications, such as phosphorylation, SUMOylation, S-nitrosylation, S-glutathionylation and carbonylation, leading to alteration of SIRT1 level and activity [27, 28, 31]. Oxidant/carbonyl stress-induced reduction of SIRT1 through post-translational modifications may

have implications in the pathogenesis of chronic inflammatory diseases where oxidative stress occurs.

Biology of SIRT1 in response to oxidative stress

Deacetylase function of SIRT1

Acetylation is a common post-translational modification, and many biological functions ranging from altering protein function to opening DNA for transcription are regulated by this modification. Acetylation occurs on the N-terminus of proteins or on the ε-amino group of lysines by histone acetyltransferases (HATs), such as p300, CREB-binding protein (CBP), and p300-CBP associated factor (PCAF). Acetylation is a reversible modification, as acetyl groups are removed from proteins by deacetylases, such as HDACs. SIRT1 reverses acetylation of lysine residues on their target proteins by hydrolyzing one NAD^+ and generating nicotinamide and a unique metabolite called 2′-O-acetyl-ADP-ribose. Nicotinamide is an inhibitor of SIRT1 and precursor for NAD^+ synthesis through the NAD^+ salvage pathway. Since this mechanism utilizes a NAD^+-dependent reaction, deacetylation by SIRT1 may be affected by NAD^+ salvage pathway, which is regulated by energy and redox status. Metabolic signals, including calorie restriction, alter the NAD^+/NADH ratio towards higher NAD^+ levels, thereby increasing SIRT1 deacetylase activity [15, 53]. Canto *et al.* supported this concept showing that AMP-activated protein kinase (AMPK) regulates energy expenditure by modulating NAD^+ metabolism and SIRT1 activity [54]. SIRT1 is able to deacetylate histone and non-histone proteins, which are summarized in Table 1.

In terms of redox response, a number of evidence has indicated that oxidative stress plays a significant role in regulation of SIRT1 deacetylase activity [55]. Earlier studies indicated that SIRT1 promotes cell survival under oxidative stress by inhibiting p53-dependent apoptosis, due to inhibition of p53 transactivation through its deacetylation [56]. Since then, Brunet *et al.* have shown that SIRT1 and FOXO3 bind together in response to oxidative stress, and SIRT1 deacetylates FOXO3 [57], which also occurs with FOXO4 in response to peroxide stress [58]. Cigarette smoke-induced oxidative stress augments acetylation of FOXO3 in lungs of both mouse and human smokers, which is attenuated by SIRT1 overexpression and pharmacological activator [13, 59]. Similarly, both SIRT1 overexpression and a specific pharmacological activator (SRT1720) decreases acetylation of RelA/p65 and NF-κB-dependent inflammation in mouse lungs by oxidative stress imposed by cigarette smoke [13, 29, 30]. Hence, both reduced SIRT1 abundance and activity under oxidative stress conditions can lead to increased acetylation of NF-κB and FOXO3. Though numerous studies regarding the tight relations between oxidative stress and NAD^+ salvage pathway have been reported, the plausible mechanism in which oxidative stress regulates SIRT1 is not well characterized. Recently, however, several compelling studies regarding the regulation of circadian rhythm provide a hint for this mechanism. NAMPT-mediated NAD^+ biosynthesis and intracellular NAD^+ levels display circadian oscillations that are regulated by negative feedback loop involving NAMPT/NAD^+ and CLOCK/SIRT1 [60, 61]. SIRT1 regulates the circadian clock oscillatory mechanisms via deacetylation of circadian clock components [62, 63]. Various organisms are subjected to endogenous circadian and exogenously driven daily rhythms. Substantial oscillation of antioxidant enzyme activity is

detected [64], suggesting the significance of circadian rhythmicity in avoiding excessive oxidative stress. Furthermore, it is reported that disruption of circadian rhythms by jetlag and night shift predisposes to inflammation [65]. Taken together, physiological and chronobiological relevance of SIRT1 activity in response to oxidative stress may provide new research directions regarding inflammation and its therapeutic strategies based on SIRT1 activation.

Transcriptional regulation of SIRT1

Oxidative stress-mediated post-translational modifications of SIRT1 can affect its stability and enzymatic activity, but little is known about the regulation of SIRT1 gene expression at transcriptional level. Transcription of SIRT1 is controlled by the p53 and FOXO3 transcription factors. When p53 is activated, p53 is phosphorylated and then acetylated by CBP/p300 acetyltransferases on Lys370, Lys372, Lys373, Lys381, and Lys382 residues, which exposes its DNA binding domain [66]. Activated p53 has been shown to bind to two p53-response elements on the SIRT1 promoter [67]. Under conditions of nutrient withdrawal and short-term starvation, activated FOXO3 is translocated into the nucleus of pheochromocytoma neuronal cancer cells, in which it binds and removes p53 from two p53-binding sites on the SIRT1 promoter [67]. As p53 represses SIRT1 gene expression, its removal by FOXO3 activates SIRT1 transcription. The repression of SIRT1 transcription by p53 may be attenuated by activation of endothelial nitric oxide synthase (eNOS) in endothelial cells. The eNOS produces NO˙, which activates guanylate cyclase to produce cGMP from GTP, thereby decreasing p53 stability [68]. SIRT1 is also able to deacetylate and activate eNOS [69]. Additionally, SIRT1 is capable of directly deacetylating p53 (p53 binds on the promoter region of SIRT1), which destabilizes and inactivates the transcription factor [56]; providing another twist to its mechanism by which SIRT1 can regulate its own transcription (Fig. 3). However, during DNA damage by etoposide, the regulation of SIRT1 is not controlled by p53 [70]. Furthermore, SIRT1 activity and transcription are increased during acute hypoxia in HIF-dependent manner [71]. SIRT1 deacetylates both HIF-1α on Lys674 and HIF-2α on Lys385, Lys685 and Lys741, changing their activities in opposing directions. Deacetylation by SIRT1 suppresses HIF-1α transactivation, whereas HIF-2α-mediated transcription of target genes is activated [16, 72]. Hence, SIRT1-HIF-2α/SIRT1-HIF-1α feedback loop which is active during hypoxia [73, 74] may affect SIRT1 stability in transcriptional level and have implications in other environmental stress related chronic inflammatory diseases.

Under conditions of oxidative stress, two other transcription factors, tumor suppressor hypermethylated in cancer 1 (HIC1) and the cell cycle regulator E2F1, have been identified to modulate SIRT1 transcription (Fig. 3). The HIC1 transcriptional repressor is shown to inhibit SIRT1 transcription in response to DNA damage response, leading to downregulation of pro-survival activities of p53 [70]. Despite its inactivating function under oxidative stress, HIC1 is also able to induce SIRT1 transcription upon calorie restriction. Conversely, SIRT1 transcription and its protein levels have also been shown to increase through activation of the E2F1 transcription factor in response to DNA damage [75]. Elevated SIRT1 deacetylates E2F1 and shuts down its own transcription as a feedback inhibitory mechanism, which may inhibit the pro-apoptotic activities of E2F1 [75]. Thus, SIRT1 plays a major role in its own

gene transcription. However, the cells may not be able to replenish SIRT1 levels if a significant amount of SIRT1 is lost. In post-transcriptional SIRT1 regulation, the Hu antigen R (HuR), which is a member of the embryonic lethal abnormal-vision family of mRNA-binding proteins, plays a critical role in stability of SIRT1 mRNA. HuR binds with the SIRT1 mRNA and maintains its steady-state levels. Abdelmohesn *et al.* reported that HuR-SIRT1 mRNA complex is rapidly dissociated in response to oxidative stress, leading to the destabilization of SIRT1 mRNA and reduction in SIRT1 protein levels [76] (Fig. 4).

SIRT1 nucleocytoplasmic shuttling

SIRT1 is a nuclear protein, which was first described in HeLa cells and human fibroblasts [77, 78]. However, its presence in the nucleus has been doubted due to several other experimental observations in different cell lines and organisms studied. For example, in *Drosophila*, SIRT1 homolog Sir2 was initially localized to the cytoplasm, but then shuttles to the nucleus during the blastoderm of embryonic development [79]. In mammalian cells, SIRT1 is present in both the nucleus and the cytoplasm (nucleocytoplasm) in neonatal rat cardiomycocytes, mouse striatum, ependymal cells of the testes in mouse, and human pancreatic β cells [80, 81]. Furthermore, two independent studies have confirmed that murine SIRT1 is indeed subjected to nucleocytoplasmic shuttling upon oxidative stress [81, 82].

Mammalian (mouse) SIRT1 possesses two Nuclear Localization Sequences (NLS; amino acid residues 31-38 and 223-230), and two NES (amino acid residues 138-145, 425-431) [81]. The two NLS are N-terminal to the central catalytic domain, whereas one NES is N-terminal to the catalytic domain and the second resides in the catalytic domain. Hence, catalytic domain is the key in recognizing the nucleocytoplasmic shuttling of SIRT1. In humans, SIRT1 has both NLS and NES, but their exact residues are not fully characterized [82]. Both of these sequences can be the targets of oxidative stress. It has been reported that oxidative stress regulates NLS and NES of many proteins such as yeast transcription factor Pap1, and yAP-1, as well as human pancreatic transcription factor PDX-1 [83–85]. It remains unknown whether the imbalance of GSH/GSSG ratio in the nucleus also has a profound effect on nucleocytoplasmic shuttling of SIRT1.

The nucleocytoplasmic shuttling of SIRT1 has been described in both physiological and pathological conditions where oxidative stress occurs (Fig. 5). Inhibition of phosphoinositide 3-kinase (PI3K) with LY294002 resulted in cytoplasmic localization of SIRT1, although the amino acid residue phosphorylated by this kinase is not known [81]. It has been shown that in *C. elegans* the homolog of SIRT1, Sir-2.1, binds to the 14-3-3 protein, which is a phosphoserine binding protein that can enhance nucleocytoplasmic shuttling [86–88]. However, it remains to be determined whether human SIRT1 can also bind to 14-3-3 protein. On the contrary, SIRT1 has been shown to shuttle from the cytoplasm to the nucleus during the differentiation of neural progenitor cells to neurons [89]. SIRT1 is shown to be localized in the nucleus, resulting in increased histone deacetylation and apoptosis in response to oxidative stress [81, 82, 90]. This suggests that SIRT1 nucleocytoplasmic shuttling and localization determine its function under oxidative stress. The activity of SIRT1 deacetylase can be present in the cytoplasm due to the presence of

many known SIRT1 substrates, including p53, FOXO proteins, and NF-κB. These molecules can also shuttle between both the compartments. Recently a few cytoplasmic targets of SIRT1 deacetylation have been identified, these include Atg proteins (Atg5, 7, and 8) involved in autophagy, the process of degrading cellular organelles and proteins [91]. Other cytoplasmic targets of SIRT1 remain to be identified. These targets may also be under the regulation of redox status of the cells.

Cigarette smoke extract induced a time- and dose-dependent shuttling of SIRT1 from the nucleus in human bronchial epithelial cells and other cell types [31]. H_2O_2 treatment also resulted in cytoplasmic localization of SIRT1 [31, 82]. Since cigarette smoke extract induces the loss of SIRT1, it is possible that nucleocytoplasmic shuttling of SIRT1 may facilitate proteasomal degradation in the cytoplasm, although H_2O_2 does not lead to SIRT1 protein loss [31, 82]. Recent studies have highlighted that cytoplasmic localization of SIRT1 occurs during apoptosis [82]; however, no cell death was seen in response to cigarette smoke extract and H_2O_2 treatments in lung epithelial cells [31]. This suggests that carbonyl stress rather than oxidative stress causes degradation of SIRT1, though both stresses cause the nucleocytoplasmic shuttling of SIRT1.

Nucleocytoplasmic shuttling of SIRT1 in response to oxidative stress could be reduced by pretreatment of cells with NAC (increasing the intracellular thiol pools) [31], suggesting that nucleocytoplasmic shuttling is mediated by a redox sensitive mechanism. This observation alluded that redox status of the cells also affects NES/NLS and other proteins involved in nucleocytoplasmic shuttling of SIRT1. Oxidative stress activates redox-sensitive kinases, such as IκB kinase (IKK), PI3K, and extracellular signal-related kinase 1/2 (ERK1/2) [92, 93]. PI3K has been shown to be involved in the nuclear localization of SIRT1, since inhibition of PI3K resulted in cytoplasmic localization of SIRT1 [81]. The phosphorylation by CK2 increases SIRT1 activity [37, 43], suggesting that a kinase-dependent redox mechanism is involved in SIRT1 nucleocytoplasmic shuttling. Cellular signaling, particularly the kinase-dependent phosphorylation is a key determinant of cellular localization for several proteins, which includes FOXO3 transcription factor [94, 95]. Cigarette smoke/oxidative stress-induced nucleocytoplasmic shuttling of SIRT1 can affect SIRT1-FOXO3 pathway, resulting in a loss of certain antioxidant defense mechanisms as FOXO3 regulates MnSOD and catalase (Fig. 6).

Signaling of SIRT1 in regulation of inflammation and cellular senescence

In the ensuing section, the signaling pathway in context that SIRT1 is involved in the regulation of inflammation and cellular senescence via several signaling molecules is discussed.

SIRT1 and RelA/p65

NF-κB is a key redox-sensitive transcription factor responsible for pro-inflammatory genes transcription [96]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-8 (IL-8) and IL-6, play an important role in activating cells of the immune system, and thus aid in the initiation of inflammatory response. One of the major sources of these pro-inflammatory mediators is the macrophages at the site of injury. In these cells, the

regulation of transcription of these cytokines is mediated by NF-κB. Under physiological and pathological conditions, NF-κB must undergo a variety of post-translational modifications, including phosphorylation and acetylation [97]. Acetylation (along with phosphorylation) plays a prominent role in regulating the nuclear action of NF-κB. It has been reported that both p300 and CBP acetyltransferases acetylate RelA/p65 subunit of NF-κB at Lys218, Lys221, and Lys310 [98]. Acetylation of discrete lysine residues in RelA/p65 modulates distinct functions of NF-κB, including transcriptional activation, DNA binding, and assembly with its inhibitor IκBα [99]. Upon acetylation by master co-activator CBP/p300, the RelA/p65 subunit of NF-κB is unable to bind to IκBα, and thus remains bound to DNA and able to stimulate gene expression. Deacetylation allows NF-κB/IκBα interaction and suppression of NF-κB activity. The amplitude and duration of the cycles of NF-κB/IκB association and dissociation appear to be critical for the induction of pro-inflammatory genes, particularly in response to oxidative stress.

SIRT1 can interact with RelA/p65 protein in the NF-κB complex and specifically deacetylates lysine 310, and potentiates the transactivation capacity of the NF-κB complex [100]. Similar observation is seen in response to other stresses including cigarette smoke. Cigarette smoke-mediated oxidative stress induces reduction of SIRT1 associated with increased acetylation and activation of RelA/p65 NF-κB [13, 29]. Depletion of SIRT1 by siRNA leads to augmentation of cigarette smoke-mediated acetylation of RelA/p65 NF-κB [29]. Oxidants/cigarette smoke-mediated pro-inflammatory cytokine release is regulated by SIRT1 via its interaction with NF-κB in a monocyte-macrophage cell line (MonoMac6), in lung tissue of mouse, and in smokers and patients with COPD [13, 29, 30]. Cigarette smoke extract caused a dose- and time-dependent decrease in SIRT1 levels and activity concomitant with increased NF-κB-dependent release of pro-inflammatory mediators in MonoMac6 cells and in mouse lungs [29, 30]. Sirtinol (an inhibitor of SIRT1) augmented, whereas SRT1720 (a specific and potent SIRT1 activator) inhibited cigarette smoke-mediated pro-inflammatory cytokine release [13, 29]. Furthermore, SIRT1 interacts with the RelA/p65 subunit of NF-κB, and this interaction is disrupted by cigarette smoke, leading to increased acetylation of RelA/p65 in MonoMac6 cells [29]. A recent study has demonstrated the functional regulation of SIRT1 through NF-κB-dependent STAT3 expression in mitochondrial function [101]. Genetic ablation of SIRT1 contributes to heightened cellular respiration through induction and activation of STAT3, via phosphorylation (Ser727), and subcellular localization of STAT3 in mitochondria implicating the interplay between STAT3 and SIRT1 in pro-inflammatory conditions [101]. In addition to regulating the pro-inflammatory response, NF-κB also regulates pro-survival pathways mainly in transformed cells [102, 103]. However, it remains to be known what forms of RelA/p65 (phosphorylated and/or acetylated) impart these effects in non-transformed versus transformed cells, whether one or both of these aspects are regulated by oxidants/redox status of the cells. Yao and co-workers have recently shown that genetic ablation of SIRT1 in mice leads to increased NF-κB activation and pro-inflammatory cytokine release in response to cigarette smoke, implying a key role for SIRT1 in regulation of NF-κB-regulated genes [13]. SIRT1 is also shown to play an important role in IL-2-mediated reversal of T-cell tolerance [104]. Hence, downregulation of SIRT1 would have dual effects leading to increased lung inflammation

and decreased cytoprotective effects of lung cells. This may be a vicious cycle leading to increased oxidative stress.

SIRT1 and FOXOs

FOXO transcription factor, which contains forkhead DNA-binding domains, is the mammalian homolog of the *Caenorhabditis elegans* longevity gene DAF-16. FOXOs are involved in mediating the response to oxidative stress, and enhanced oxidative stress resistance has been frequently correlated with increased lifespan [105]. Furthermore, FOXO3 protects quiescent cells from oxidative stress by directly increasing the transcription of MnSOD mRNA and protein levels [22]. Oxidative stress can also regulate FOXOs through the small GTPase/JNK-dependent mechanism [106]. In addition to oxidative stress, accumulating studies suggest that FOXOs participate in the pathogenesis of multiple inflammatory diseases. FOXO3 deficiency leads to spontaneous lymphocyte proliferation associated with inflammation due to the loss of NF-κB inhibition [107]. FOXO1 deficiency induces inflammatory bowel diseases [108], which is also shown in FOXO4 deficient mice [109]. However, in neutrophilic inflammation, such as rheumatoid arthritis and peritonitis, FOXO3 levels are elevated and required to suppress pro-apoptotic response in neutrophils [110, 111]. Such observations indicate that FOXOs play a critical role in the pathogenesis of inflammation, but the mechanism underlying both pro-inflammatory and anti-inflammatory effects of FOXOs remains elusive.

Transcriptional activity of FOXOs is generally regulated by their post-translational modifications, such as phosphorylation and acetylation. Several studies have shown that FOXO1, FOXO3, and FOXO4 are acetylated in response to cellular stress by the acetyltransferase of CBP/p300, and FOXOs physically associated with SIRT1 [57, 58, 112]. These studies noted that FOXOs were deacetylated and their transcriptional activity was repressed by SIRT1 [112]. Interestingly, SIRT1 can also stimulate FOXO activity. For example, this is the case for FOXO1, following deacetylation of lysines Lys242, Lys245 and Lys262 [113], or for a subset of FOXO3 and FOXO4 genes controlling resistance to oxidative stress [57, 58]. Recent studies have shown that cigarette smoke and oxidative stress induce a significant reduction in protein abundance of SIRT1 and FOXO3, leading to excessive and persistent inflammation and emphysema/COPD by increased acetylation of FOXO3 [59]. Cigarette smoke-induced acetylation of FOXO3 due to the loss of SIRT1 enhances the transcription of antioxidants genes to counteract oxidative stress. In other inflammatory diseases, such as myocardial infarction, tyrosol activates FOXO3 and SIRT1, resulting in cardioprotection [114]. NAD-NAMPT pathway is shown to be involved in the FOXO3-mediated regulation of growth arrest and DNA damage-inducible gene (GADD45A) [115], implicating the role of this pathway in cigarette smoke-induced cellular senescence. A recent study has shown the role of SIRT1-FOXO3 axis in cellular adaptation to hypoxia-associated oxidative stress. Kume *et al.* have shown that hypoxia inhibited SIRT1 activity and failed to enhance nuclear translocation of FOXO3, subsequent autophagy, and cell cycle arrest, which increased mitochondrial oxidative damage in kidneys of aged mice [116]. SIRT1 is also required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function have recently been shown [117]. Studies have shown that FOXO3 plays an important role in endothelial function as well [118, 119].

Despite the knowledge of SIRT1-mediated regulation of FOXOs, the role of SIRT1 and FOXOs on cellular metabolism and disease pathogenesis are still controversial. There seem to be contradictory effects of deacetylation on FOXO function which cannot easily be reconciled. Further studies are required to understand the role of oxidative stress or redox status of the cells in regulation of SIRT1-FOXOs in various inflammatory conditions, and also in cell differentiation, senescence, and metabolism.

SIRT1 and PARP-1

Poly(ADP-ribose)-polymerase-1 (PARP-1) is the key member of the PARP family, and is known as a DNA-bound enzyme that protects the genome stability by DNA repair and regulates chromatin structure, transcription, cell proliferation, and apoptosis. Several studies have shown that PARP-1 is rapidly activated in diverse inflammatory conditions and in response to oxidant and genotoxic stress. PARP-1 suppression by genetic deletion or pharmacological inhibitors reduces the extent of inflammatory responses. The role of PARP-1 in inflammation is demonstrated by the observations that PARP-1 facilitates the inflammatory responses by promoting gene expression of inflammatory mediators, such as cyclooxygenase-2, IL-1β, IL-6, TNF-α, and monocyte chemotactic protein-1, although PARP-1 has anti-inflammatory effect [120, 121].

PARP-1 is involved in regulation of poly(ADP-ribosyl)ation using NAD^+ as a donor of ADP-ribose units. Poly(ADP-ribose) are negatively charged and non-covalently bind to nuclear proteins, such as histones and other transcription factors. Due to this function, poly(ADP-ribose) can act as a scaffolding to allow for chromatin remodeling and DNA repair processes. In response to oxidative and genotoxic stresses, PARP-1 is activated converting NAD^+ into poly(ADP-ribose) chains, which non-covalently modifies nuclear proteins (Fig. 7). Since PARP-1 and SIRT1 both require NAD^+ as a substrate, it is expected that PARP-1 could have profound effects on SIRT1 activity. This is true since PARP-1 and SIRT1 interact and are involved in apoptosis-inducing factor (AIF)1-mediated apoptosis [122]. The inhibition of SIRT1 by PARP-1 activation and subsequent NAD^+ depletion has been shown in response to H_2O_2-induced cell senescence [32], but the effect of oxidative/genotoxic stimuli on PARP-1 activation and SIRT1 activity still remains to be studied. Cigarette smoke induces PARP-1 and reduces the levels of SIRT1 perhaps due to depletion of intracellular NAD^+ pool.

A methylxanthine derivative (a component of tea polyphenols) theophylline, an anti-inflammatory agent, protects against intracellular NAD^+ depletion via PARP-1 inhibition and associated sparing of SIRT1 activity in macrophages and lung cells of patients with COPD [123–125]. Furthermore, PARP-1 was activated in response to cigarette smoke and oxidative stress, as evidenced by increased formation of poly(ADP-ribose), which is due to depletion of NAD^+ and subsequent reduction of SIRT1 activity (Fig. 7) [126]. Interestingly, a PARP-1 pharmacological inhibitor, 3-aminobenzimide, attenuated cigarette smoke- and oxidative stress-induced autophagy. This phenomenon occurs through a partial increase in SIRT1 activity implicating the role of PARP-1 in pulmonary inflammation and senescence [126]. Interestingly, inhibition of PARP-1 did not fully restore cigarette smoke-induced decrease in SIRT1 activity in lung epithelial cells even in the presence of SIRT1 activator

resveratrol. This may be due to SIRT1 post-translational modifications, such as carbonylation/alkylation, thereby impairing (due to covalent modifications) the restoration of SIRT1 activity even the levels of NAD^+ is elevated after PARP-1 inhibition [27]. These studies show that a functional link exists between PARP-1 and SIRT1 through NAD^+ cofactor availability in inflammatory conditions where oxidative stress occurs.

Any changes in levels of intracellular NAD^+ and/or PARP-1 activity, particularly in response to oxidants and environmental stimuli/inhaled pollutants, may influence SIRT1 activity. This is supported by a study showing that SIRT1 protects against thrombomodulin downregulation via regulation by KLF2 at transcriptional level, and lung coagulation following particulate matter exposure [127].

The role of PARP-1 and SIRT1 in regulation of cellular function has been confirmed in genetic mouse models. Double mutation of PARP-1 and SIRT1 showed genome instability and chromatin modifications and increased lethality in mice [128]. PARP-1 was subjected to acetylation and subsequent activation under stress conditions (UV irradiation, oxidative and genotoxic stresses), which is regulated by SIRT1 [129]. Recent studies with PARP-1$^{-/-}$ and PARP-2$^{-/-}$ mice show a direct functional link with SIRT1 in metabolic homeostasis, suggesting a potential antagonism between PARP-1 or PARP-2 and SIRT1 [130, 131]. There seem to be a feedback loop between SIRT1 and PARP-1 in response to various stimuli, but the role of SIRT1 and PARP-1 is complex and may not be dependent on each other in pro-inflammatory, oxidative and/or genotoxic conditions. Nevertheless, SIRT1 and PARP-1 are emerging as one of the major therapeutic targets against diverse inflammatory response and premature senescence, and hence understanding the mechanisms in regulation of their functions by environmental/oxidative stress is crucial.

SIRT1 and endothelial nitric oxide synthase (eNOS)

The pathophysiology of endothelial dysfunction involves multiple mechanisms including dysregulation of NO by vascular/endothelial eNOS. Recent studies have suggested that endothelial cell dysfunction is one of the key pathological alterations seen in pathogenesis of COPD/emphysema [132]. Animal studies have shown that cigarette smoke-induced emphysematous alveolar septa are almost avascular, which is associated with reduced expression of eNOS and endothelium dysfunction [133]. SIRT1 is highly expressed in vascular endothelial cells including microvascular endothelial cells of the lungs, and has shown to regulate endothelial functions [28]. Hence, any alteration in endothelial SIRT1 will affect normal endothelial function and thereby vascular physiology. Recent studies have highlighted an emerging role of SIRT1 in cardioprotection [46, 134, 135]. Cigarette smoke-induced apoptosis of coronary arterial endothelial cells and inflammatory response were attenuated by SIRT1 overexpression [136]. One plausible mechanism for SIRT1's regulation on endothelial function involves a reduction in activity of eNOS and caveolin-1. This may be due to endogenous or exogenous inhibition or reduction in the availability of its substrate L-arginine and/or decreased bioavailability of NO. Nisoli *et al.* have shown that the levels of cGMP and eNOS are elevated in tissues of calorie restricted mice, and the production of NO increases SIRT1 expression, which was blunted in eNOS-deficient mice [137]. SIRT1 has shown to bind to eNOS, and to deacetylate lysines K496 and K506 residues in the

calmodulin-binding domain of eNOS leading to enhanced production of NO (Fig. 8). This binding is essential for endothelial-dependent vasorelaxation, endothelial cell survival, migration, and postnatal neovascularization, whereas SIRT1 knockdown resulted in decreased NO production and impaired endothelial-dependent vasodilatation [69]. Interestingly, NO has been shown to activate the SIRT1 promoter leading to an increase of SIRT1 mRNA and protein indicating that a positive feedback mechanism exists between SIRT1 and eNOS (Fig. 3). SIRT1 activation through small molecules may help to reset the activity of eNOS by keeping the Lys496 and Lys506 deacetylated during the conditions of endothelial dysfunction where NO availability is limited, particularly in susceptible chronic smokers.

Activation of SIRT1 by resveratrol protects endothelial cells against cigarette smoke-mediated oxidative stress [136]. Furthermore, cigarette smoke extract and H_2O_2 treatments caused dose- and time-dependent decrease in SIRT1 level and its deacetylase activity in human umbilical vein endothelial cells [28], and in mice exposed to cigarette smoke [13, 138]. These findings are in agreement with the recent reports showing that cigarette smoke-mediated oxidative stress decreased SIRT1 levels and its deacetylase activity associated with increased acetylation eNOS, which was associated with increased pro-inflammatory gene expression [28, 31]. This observation is further substantiated that cigarette smoke extract-induced oxidative stress resulted in increased eNOS acetylation in endothelial cells (acetylation leads to inactivation of eNOS activity) [28]. This study has also shown that SIRT1 activation by a nonspecific SIRT1 activator resveratrol attenuated cigarette smoke-induced eNOS acetylation, whereas SIRT1 inhibition by splitomicin further increased eNOS acetylation. These observations support the concept that activation of SIRT1 pharmacologically or by dietary polyphenol resveratrol may protect against deleterious effects of cigarette smoke/oxidants/carbonyls on endothelial dysfunction (presumably via deacetylation of eNOS resulting in availability of NO). This may be one of the possible mechanisms of resveratrol in maintaining or improving endothelial function. Furthermore, the levels and activity of SIRT1 are significantly decreased in lungs of atherosclerosis-prone ApoE$^{-/-}$ mice with further reduction in response to cigarette smoke. This will lead to increased acetylation and inactivation of eNOS in the lungs of ApoE$^{-/-}$ mice exposed to cigarette smoke resulting in endothelial dysfunction [138]. Further studies are required to determine whether oxidative stress or change in redox status of the cells can influence eNOS acetylation via SIRT1 and hence the NO bioavailability in endothelial cells. This will have implications in endothelial dysfunction and alterations in proliferation, migration, and angiogenesis in smokers and other inflammatory conditions where oxidative/carbonyl stress occurs.

SIRT1 and histone modifications

The post-translational modifications on the complex structure of histone tails is a central mechanism for regulation of gene expression and is known as epigenetic chromatin remodeling [139]. These post-translational modifications may facilitate the activation or repression of chromatin-mediated gene expression for inflammatory mediators, cell cycle arrest, apoptosis, senescence, antioxidants, growth factors, and tumor suppressor genes. Generally, acetylation of the histone tails correlates with activation of gene expression,

whereas deacetylation is associated with gene silencing. The possible link for specific epigenetic modifications (e.g. acetylation of histones) on pro-inflammatory genes in different disease phenotype might be due to the environment and alterations in patterns of gene expression.

SIRT1 is a histone/protein deacetylase and has been shown to be involved in deacetylation of histone proteins. In yeast, SIRT1 homologue Sir2 associates with inactive telomeric chromatin, and silences the transcription of ribosomal DNA and of mating-type loci [140]. It has also been reported that oxidative stress leads to redistribution of Sir2 on chromatin and increases cellular aging [141]. In mammals, only SIRT1, SIRT2, SIRT3, and SIRT5 have a conserved deacetylase domain [140, 142], and deacetylase activity seems to be restricted to SIRT1-SIRT3. SIRT1 can affect the acetylation of the four core histones *in vitro*, but seems to preferentially deacetylate histone H3 on Lys9 and Lys14 (H3K9 and H3K14) and histone H4 on Lys16 (H4K16) [143, 144]. Recently, SIRT1 was reported to form complex with RelA/p65 and p300 at the Bcl2-associated factor 1 (Bclaf1) promoter region to regulate Bclaf1 expression by suppressing H3K56 acetylation, thereby reducing T cell activation, but has no effect on B cell activation demonstrating the cell-type specific effect. Nevertheless, these findings suggest that SIRT1 via H3K56 deacetylation may have significant impact on innate and adaptive immune response [145].

Histone H3K4 trimethylation opens chromatin for active gene transcription, whereas histone H3K9 and H3K27 trimethylation silences/represses gene transcription by closing the active chromatin [146]. The direct histone deacetylation activity of SIRT1 synergizes with facilitated trimethylation of H3K9 [143]. Trimethylation of H3 is a well-established mark of facultative heterochromatin and transcriptional repression and can occur under oxidative stress conditions. The mechanistic basis of the positive action of SIRT1 on H3K9 methylation to further repress transcription involves the activation of the histone methyltransferase SUV39H1 by SIRT1-mediated deacetylation [147]. SUV39H1 is regulated under oxidative stress conditions when SIRT1 is depleted in inflammation. Hence, in addition to histone acetylation, SIRT1 also indirectly regulates methylation of histone by deacetylation of histone methyltransferase. SIRT1 interacts directly with, recruits and deacetylates SUV39H1, which is the principal enzyme responsible for the accumulation of histone H3 containing a tri-methyl group at its Lys9 position (H3K9me3). Elevated levels of SUV39H1 activity by SIRT1 result in increased levels of the H3K9me3 modifications [147]. Recently, it is reported that SIRT1 physically associates and deacetylates the DNA methyltransferase 1 protein and alters its activities [148]. SIRT1 also deacetylates methyl-CpG binding protein 2 (MeCP2) [149], further highlighting the role of SIRT1 in genomic stability and epigenetic regulation. SIRT1 is shown to dynamically interacts with and regulates hMOF and TiP60 through deacetylation, implicating the regulatory role of SIRT1 in DNA damage response [150]. Any alterations of SIRT1 under oxidative stress may cause genomic instability leading to inflammatory response and cellular senescence.

The role of other sirtuins (e.g. SIRT2, SIRT3 and SIRT6) in regulation of histone acetylation is ascribed. SIRT2, despite its cytoplasmic localization, can deacetylate H4K16, and to a lesser extent H3K9, during mitosis when the nuclear envelope disassembles [151]. This suggests that SIRT2 could promote cell cycle progression by favoring the condensation of

chromatin prior to chromosome segregation during mitosis. SIRT3 also exhibits histone deacetylase activity directed towards H3K9 and H4K16 *in vitro* [152]. Similarly, SIRT6 deacetylates H3K56, and has deacetylase-independent polyADP-ribosylation function during oxidative stress mediated DNA damage [153-155]. However, the functional relevance of these modifications by SIRT2, SIRT3, or SIRT6 in maintaining genomic stability (deacetylation at the genome wide level) under oxidative stress is not known. Recent studies have shown that SIRT6 regulates lifespan in male mice [156], and rescues the decline of homologous recombination repair during replicative senescence [157]. However, the role of SIRT6 in premature senescence is not known. SIRT1 is regulated by several miRNAs, such as miR-34a and miR-22, which are involved in cellular senescence via histone modifications [158]. Altogether, these studies have demonstrated that histones are the targets of sirtuin-mediated deacetylation facilitating heterochromatin formation as senescence-associated heterochromatin foci. Further work is required to understand how the promoter-specific deacetylation of histones by sirtuins, particularly by SIRT1, can regulate histone acetylation/methylation during inflammatory response and cellular senescence.

SIRT1 and cellular senescence

Oxidative stress causes cellular senescence, and SIRT1 protects against premature aging/ cellular senescence via regulating FOXOs, p53, and p21 as well as molecules involved in DNA damage and repair [12, 32, 159, 160]. This is corroborated by a recent study showing that SIRT1 protects against cigarette smoke/oxidative stress-induced lung cellular senescence by regulating FOXO3 and pro-senescence gene p21 [13]. In addition to FOXO3 and p21, SIRT1 prevented cellular senescence by deacetylation and repression of p53 [161]. Furukawa et al. also reported that SIRT1 deficiency caused accumulation of p53 acetylation, thereby enhancing oxidative stress-induced cellular senescence [32]. In stem and progenitor cells, SIRT1 also has an ability to regulate senescence and aging. Proteases, such as cathepsin, can cleave SIRT1 in endothelial progenitor cells, leading to stress-induced premature senescence [162]. The involvement of SIRT1 in maintaining the stem cell homeostasis is supported by a study showing requirement of SIRT1 for long-term growth of human mesenchymal stem cells without undergoing cellular senescence [163]. Also, SIRT1 is shown to play an essential role in the maintenance of hematopoietic stem/progenitor cells [164]. Similarly, Homma *et al* have shown that SIRT1 plays an important role in mediating greater functionality of human embryonic stem (ES)/induced pluripotent stem (iPS)-derived vascular endothelial cells [165]. This highlights a novel avenue for ES- and iPS-derived vascular endothelial cells as the cell source for regenerative medicine in inflammaging and cellular senescence [166], particularly in response to oxidative and sheer stresses [167]. SIRT1 also prevents replicative senescence of normal human umbilical cord fibroblasts through potentiating the transcription of human telomerase reverse transcriptase gene [168]. Another study has reported the maintenance of telomere by SIRT1 and DNA repair enzyme XRCC6 [169]. These findings suggest a pivotal role of SIRT1 in regulating both replicative and premature senescence in stem and differentiated cells in the conditions of oxidative stress. Therefore, the activation of SIRT1 in stem/progenitor cells or iPS-EPCs would be a promising therapeutic way in intervening chronic inflammatory diseases associated with aging.

Dietary and pharmacological activation of SIRT1

Dietary phytochemicals

SIRT1 activators are emerging as key regulators in many diseases involved in inflammation including type 2 diabetes, cancer, cardiovascular diseases, and COPD [11–13, 140, 170–173]. SIRT1 is responsible for the beneficial effects of caloric restriction, and resveratrol mimics the effects of caloric restriction. Resveratrol was identified as the first natural chemical activator of SIRT1. Resveratrol (3, 4′-5- trihydroxystilbene), a phytoalexin found in the skin and seeds of grapes, other plants, and plant-derived products (like red wine) increases SIRT1 activity up to 8-fold ($EC_{1.5}$ = 46.2 μM, and maximum activation of SIRT1 of 201%), lowering the K_m value for acetylated substrate by 35-fold and NAD^+ by 5-fold [174]. However, resveratrol is a non-selective and non-specific compound that can regulate other pathways, such as Nrf2 and NF-κB [175, 176]. Thus, doubt has been casted on whether resveratrol is an actual activator of SIRT1. One study has shown that increased SIRT1 deacetylation by resveratrol occurs only when the deacetylated protein substrate had a fluorophore attached, substrates lacking the fluorophore did not show increased deacetylation by resveratrol, suggesting that resveratrol may not be a direct activator of SIRT1 [177]. Recent studies have highlighted that resveratrol may regulate aging-phenotype by an indirect mechanism independent of SIRT1 activation. For example, resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases leading to elevation of cAMP levels, which then indirectly increases NAD^+ and SIRT1 activity [178]. Similarly, another study reported that the cAMP/PKA pathway controls SIRT1 enzymatic activity independently of changes in NAD^+ levels [179]. This may have implication in treatment of patients with COPD, as PDE4 inhibition is known to play an important role in inhibiting inflammation in these patients. Resveratrol reduces vascular cell senescence through attenuation of oxidative stress by SIRT1/NADPH oxidase-dependent mechanisms [180]. Furthermore, red wine extract protects against oxidative stress-induced endothelial senescence via NO and COX-2-dependent mechanisms [181]. Calorie restriction-like effects of resveratrol supplementation on energy metabolism and metabolic profile have been shown in obese humans [182]. SIRT1 activation by resveratrol is also known to modulate matrix metalloproteinases (MMP1, MMP3, MMP9) activity in fibroblasts [183–186]. MMPs play an important role in inducing cellular senescence, and hence inhibition of MMPs will delay senescence-associated secretory phenotype. Other polyphenolic plant-derived compounds, such as butein, quercetin, piceatannol, and myrcetin, have also been shown to activate SIRT1 activity [10, 12, 73]. These compounds have a modest ability to activate SIRT1 ranging from 3.19–8.53 folds, especially under oxidative stress conditions. Other dietary compounds may have also beneficial effects in activation of SIRT1 which are yet to be explored. One notable example is sulforaphane, an activator Nrf2, may indirectly restore SIRT1 activity by reversing oxidative/carbonyl modifications of SIRT1 via activation of phase II detoxifying/antioxidant enzymes (carbonyl reductases, thioredoxin reductases), and hence possibly will reverse steroid resistance in patients with COPD and severe asthmatics. However, studies are required to attest this functional activity of SIRT1 by dietary natural products.

Pharmacological compounds

Recently, several selective SIRT1 activators have been commercially developed for the treatment of type 2 diabetes by Sirtris pharmaceuticals, which are acquired by GSK [187–189]. These activators are analogs of resveratrol, which include SRT1720, SRT2183, SRT501, SRT2104, SRT2379, and SRT1460, resVida, Longevinex[R] [190], and a related compound pyrroloquinoxaline. The most potent of the compounds was SRT1720 ($EC_{1.5}$ = 0.16 μM and maximum activation of SIRT1 of 781%), which improved glucose homeostasis and insulin sensitivity in three different animal models of type 2 diabetes and obesity [9, 188]. Furthermore, the efficacy and bioavailability of these compounds in humans are not known. A recent study by Hoffmann has shown the pharmacokinetics and tolerability of SRT2104 for activation of SIRT1 after single and repeated oral administration in humans [191]. Yao and colleagues have recently shown that SRT1720 protects against cigarette smoke-mediated premature senescence and pulmonary emphysema in mice independently of inflammation [13]. However, the effectiveness of these drugs for the treatment of diseases caused by oxidative/carbonyl stress, where SIRT1 levels are decreased, remains to be determined.

Conclusions

SIRT1 regulates inflammation, aging, calorie restriction/energetics, stress resistance, senescence, endothelial functions, apoptosis/autophagy, and other cellular functions through deacetylation of transcription factors and histones. SIRT1 undergoes reversible/irreversible covalent oxidative modification by cigarette smoke-derived oxidants and aldehydes, leading to inactivation and degradation. The carbonylation, S-nitrosylation, and S-glutathionylation of SIRT1 are attenuated by increasing intracellular thiols by NAC and glutaredoxin1. Hence, SIRT1 is a redox sensitive molecule. SIRT1 is regulated by PARP-1 activation and subsequent NAD^+ depletion in response to environmental/oxidative stresses, which may have subsequent effects on inflammatory and stress responses, as well as cellular senescence via regulating RelA/p65, FOXO3, p21, and p53. SIRT1 is also known to deacetylate eNOS and hence restoring NO-mediated endothelial function. Overall, cigarette smoke/oxidant-mediated redox post-translational modifications of SIRT1 via the loss of its function on its interacting molecules, such as PARP1, NF-κB, FOXO3 and eNOS, as well as chromatin remodeling/histone modifications play a crucial role in inflammatory response and cellular senescence.

SIRT1 activation by pharmacological activation is important, but it must be kept in mind that SIRT1 is a redox-sensitive protein, and that a simple activation of SIRT1 by pharmacological agents may not be effective. SIRT1 is covalently modified under oxidative/inflammatory conditions, hence a redox regulating agent to stabilize SIRT1 (e.g. reversal of carbonylation of SIRT1) may be an avenue before effective therapeutic strategies (pharmacological activation of SIRT1 along with stabilization of SIRT1) can be designed for chronic inflammatory diseases where oxidative/carbonyl stress occurs. Furthermore, understanding the oxidant/carbonyl-mediated reduction and redox regulation/modifications of SIRT1 will have widespread implications in understanding mechanism of premature

cellular senescence and the pathogenesis of various chronic inflammatory diseases where oxidative/carbonyl stress occur.

Acknowledgments

Abbreviations

AMPK	AMP-activated protein kinase
CBP	CREB-binding protein
CK2	caseine kinase 2
COPD	chronic obstructive pulmonary disease
CREB	cAMP-response-element-binding protein
CRM1	chromosome region maintenance-1
eNOS	endothelial nitric oxide synthase
ERK	extracellular signal-related kinase
FOXO	forkhead box O
GAPDH	glyceraldehydes-3-phosphate dehydrogenase
GSH	glutathione
HAT	histone acetyltransferase
HDAC	histone deacetylase
HIC1	hypermethylated in cancer 1
HIF	hypoxia-inducible factor
IKK	I kappaB kinase
IL-8	interleukin-8
JNK	c-Jun N-terminal protein kinase
LPS	lipopolysaccharide
MnSOD	manganese superoxide dismutase
NAC	N-acetyl-cysteine
NAMPT	nicotinamide phosphoribosyltransferase
NES	Nuclear export sequences
NF-κB	nuclear factor κB
NLS	nuclear localization sequences
NPC	nuclear pore complexes

PARP-1	poly (ADP-ribose) polymerase-1
PCAF	p300-CBP associated factor
PGC-1α	peroxisome-proliferator-activated receptor gamma coactivator 1-alpha
PI3K	phosphoinositide 3-kinase
SENP1	Sentrin-specific protease 1
Sir2	silent information regulator 2
SIRT	sirtuin
STAT3	signal transducer and activator of transcription 3
SUV39H1	suppressor of variegation 3-9 homologue 1
TGF-β1	transforming growth factor-β1

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Highlights

SIRT1 regulates inflammaging and cellular senescence.

SIRT1 is a redox sensitive protein which undergoes posttranslational modifications.

SIRT1 is regulated by PARP-1 in response to redox changes and oxidative stress

SIRT1 regulates RelA/p65, p53, and FOXO3-mediated inflammation and senescence.

Activation of SIRT1 attenuates inflammaging in chronic inflammatory diseases.
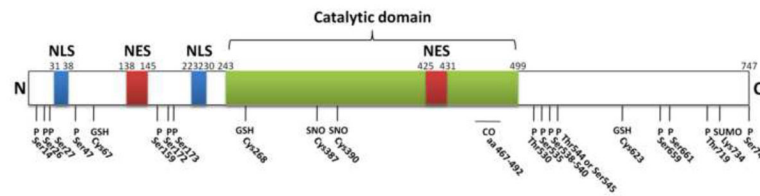
Figure 1. Schematic of SIRT1 residues for post-translational modifications

Mammalian SIRT1 comprises 747 amino acids, which contains a central catalytic domain (green), two nuclear localization sequences (NLS, blue), and two nuclear export sequences (NES, red). P: phosphorylation, GSH: S-glutathionylation, SNO: S-nitrosylation, CO: carbonylation, SUMO: SUMOylation, Ser: serine, Cys: cysteine, aa: amino acids, Thr: threonine, Lys: lysine. N: N-terminal end, and C: C-terminal end.
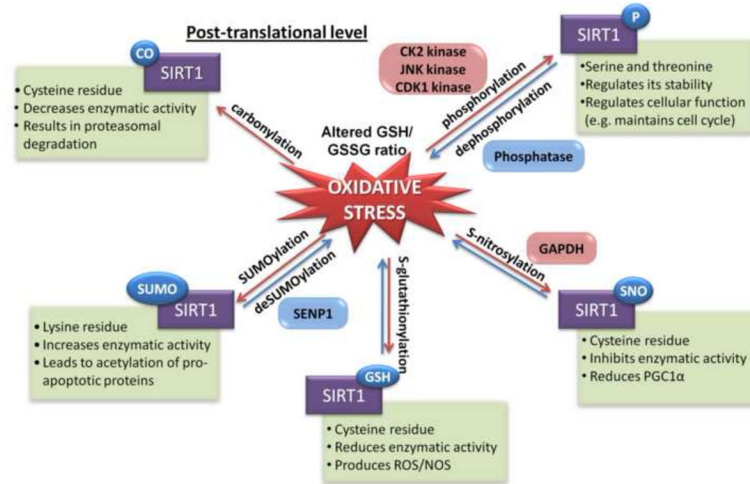
Figure 2. Post-translational modifications of SIRT1
In response to oxidative stress, SIRT1 undergoes post-translational modifications, such as phosphorylation (P), S-nitrosylation (SNO), S-glutathionylation (GSH), carbonylation (CO), and SUMOylation (SUMO). SIRT1 deacetylase activity and subsequent cellular responses are affected by these post-translational modifications. Alteration in intracellular GSH/GSSG ratio by oxidative stress can also affect these modifications.
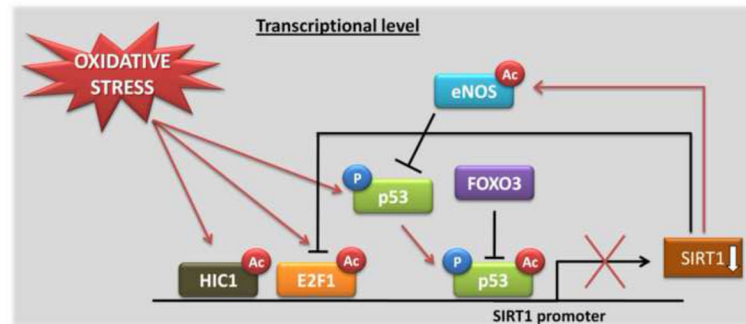
Figure 3. Transcriptional regulation of SIRT1 in response to oxidative stress
Transcription of SIRT1 is repressed by activation of p53, HIC1, and E2F1 in response to oxidative stress. FOXO3 removes p53 from two p53-binding sites on the SIRT1 promoter. Repression of SIRT1 transcription by p53 may reduce the activation of endothelial nitric oxide synthase (eNOS) through eNOS acetylation. SIRT1 also deacetylates p53 and FOXO3, and in turn modulates their transcriptional activity.
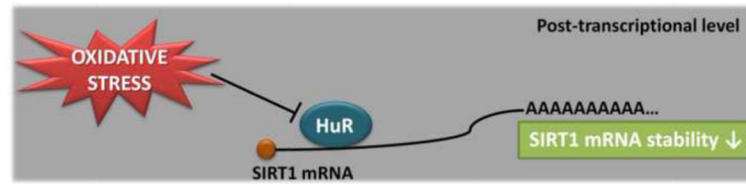
Figure 4. Translational regulation of SIRT1 stability in response to oxidative stress
The Hu antigen R (HuR) plays a critical role in stability of SIRT1 mRNA. Under oxidative stress, HuR-SIRT1 mRNA complex is rapidly dissociated, leading to reduction of SIRT1 mRNA stability.
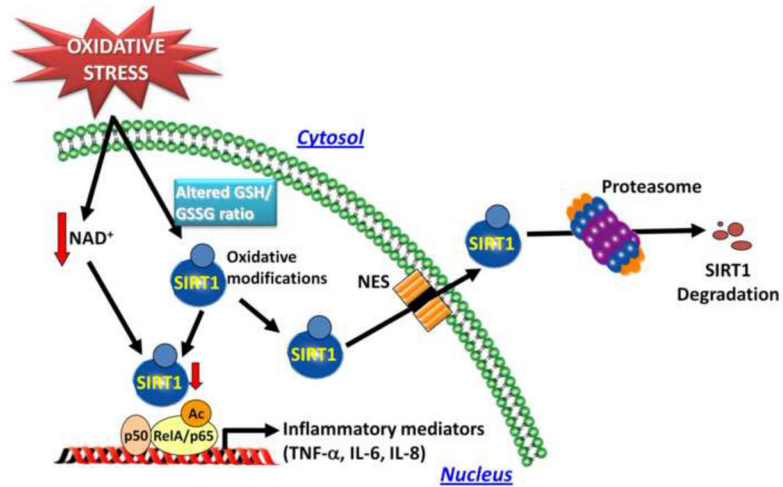
Figure 5. Regulation of SIRT1 nucleocytoplasmic shuttling by oxidative stress
Oxidative stress causes oxidative and carbonyl modifications as well as nucleocytoplasmic shuttling of SIRT1 to the cytoplasm. This will decrease SIRT1 protein levels through proteasomal degradation in the cytoplasm. At the same time, the transcription of NF-κB-dependent pro-inflammatory genes is increased once SIRT1 is reduced. Intracellular redox status (i.e., GSH/GSSG ratio) can also affect nucleocytoplasmic shuttling of SIRT1. NES, Nuclear export sequences.
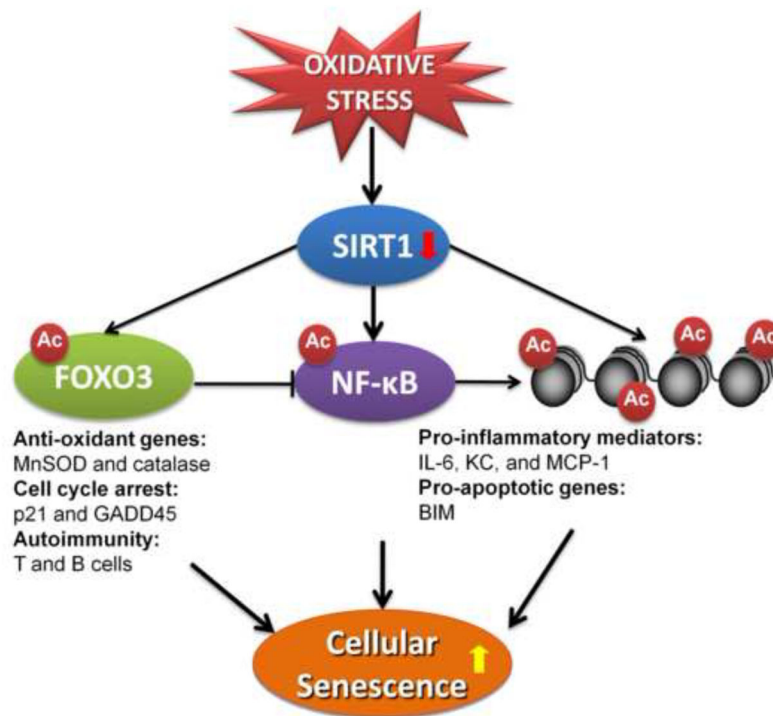
Figure 6. SIRT1 in regulating inflammation and cellular senescence under oxidative stress
Oxidants derived from cigarette smoke inhibit SIRT1 activity, and reduce its levels by post-translational modifications. SIRT1 reduction leads to RelA/p65 and FOXO3 acetylation, as well as modifications of histones H3 and H4. The acetylation of these molecules by SIRT1 reduction causes the abnormal transcription of pro-inflammatory, antioxidant, pro-senescent and pro-apoptotic genes involved in oxidative stress, inflammation, and premature cellular senescence.
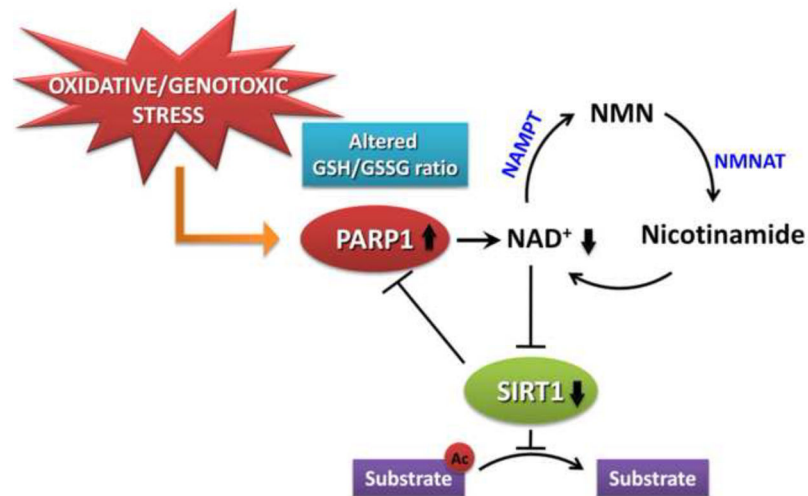
Figure 7. Interplay between SIRT1 and PARP1 under oxidative stress
Oxidative or genotoxic stress and abnormal redox status activate PARP1, leading to the depletion of NAD^+ and subsequent inactivation of SIRT1 deacetylase activity. PARP1 activation is also regulated by intracellular levels of GSH/GSSG. Furthermore, SIRT1 regulates PARP1 activity via deacetylating PARP1 in response to oxidative stress. NMN: nicotinamide mononucleotide, NAMPT: nicotinamide phosphoribosyltransferase, NMNAT: nicotinamide/nicotinic acid mononucleotide adenylyltransferase, PARP1: poly (ADP-ribose) polymerase-1.
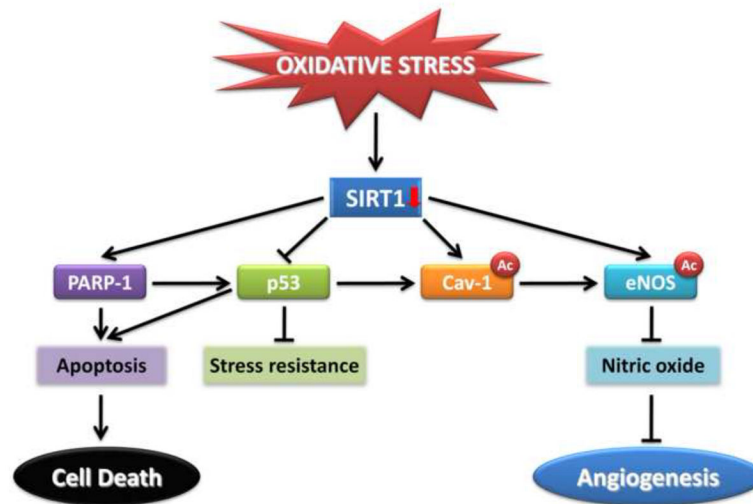
Figure 8. SIRT1-mediated regulation of eNOS

Oxidant/carbonyl stress down-regulates the SIRT1 activity and level. This will regulate PARP1, and cause acetylation of CAV-1 and eNOS, which influences several cellular processes, such as apoptosis, angiogenesis and vascular homeostasis in endothelial cells. PARP1: poly (ADP-ribose) polymerase-1, CAV-1: caveolin-1: eNOS: endothelial nitric oxide synthase, Ac: acetylation.

Table 1

Targets of SIRT1 which are regulated under oxidative stress

SUBSTRATES/TARGETS	FUNCTIONS
Histones H1K26, H3K9, H3K14, H3K56, H4K16	Reduces T cell activation, reduces transcriptional silencing, role in innate and adaptive immune function.
Non-histones p53, RelA/p65, FOXO3, STAT3, p73, E2F1, PTEN, Bax, HIF-1α, HIF-2α, β-catenin, PGC1α, CLOCK, BMAL1, Per2, Ku70, SMAD7, TORC2, p300, SUV39H1, PPARγ	DNA damage and repair response, oxidative stress response, autophagy, energy metabolism, cell cycle, cell survival, growth arrest, apoptosis, immune function, inflammation, circadian rhythm, NF-κB, NOTCH, WNT, TGF-β-induced signaling, insulin sensitivity and signaling, genomic stability, mitochondrial biogenesis, and adipogenesis.