Published in final edited form as:

Biochem Pharmacol. 2012 November 15; 84(10): 1332–1339. doi:10.1016/j.bcp.2012.06.031.

Perspectives on translational and therapeutic aspects of SIRT1 in inflammaging and senescence

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Abstract

SIRT1, a type III protein deacetylase, is considered as a novel anti-aging protein involved in regulation of cellular senescence/aging and inflammation. SIRT1 level and activity are decreased during lung inflammaging caused by oxidative stress. The mechanism of SIRT1-mediated protection against inflammaging is associated with the regulation of inflammation, premature senescence, telomere attrition, senescence associated secretory phenotype, and DNA damage response. A variety of dietary polyphenols and pharmacological activators are shown to regulate SIRT1 so as to intervene the progression of type 2 diabetes, cancer, cardiovascular diseases, and chronic obstructive pulmonary disease associated with inflammaging. However, recent studies have shown the non-specific regulation of SIRT1 by the aforementioned pharmacological activators and polyphenols. In this perspective, we have briefly discussed the role of SIRT1 in regulation of cellular senescence and its associated secretory phenotype, DNA damage response, particularly in lung inflammaging and during the development of chronic obstructive pulmonary diseases. We have also discussed the potential directions for future translational therapeutic avenues for SIRT1 in modulating lung inflammaging associated with senescence in chronic lung diseases associated with increased oxidative stress.

Keywords

SIRT1; inflammation; cellular senescence; telomere attrition; senescence associated secretory phenotype; DNA damage and repair

Introduction

Sirtuin1 (SIRT1), a type III histone deacetylase, requires NAD⁺ as a cofactor to remove the acetyl moieties from the ϵ -acetamido groups of lysine residues of histones and other signaling proteins, thus facilitating chromatin condensation and silencing of gene transcription. SIRT1 regulates a variety of signaling pathways involved in metabolism, inflammation, cellular senescence, proliferation, apoptosis, and DNA damage response (DDR), due to its ability to deacetylate forkhead box class O (FOXO)3, NF- κ B, p53, Werner syndrome protein, Klotho, β -catenin/Wnt, Notch, PARP-1, and histones [1–3]

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(Figure 1). This suggests the involvement of SIRT1 in the pathogenesis of type 2 diabetes, cancer, cardiovascular diseases, and chronic obstructive pulmonary disease (COPD). Indeed, five single nucleotide polymorphisms (SNPs) of SIRT1 are identified in a population-based study, indicating its variability in the human population [4, 5]. However, it remains unknown whether SNPs or allelic variants of SIRT1 is a susceptibility factor for the development of these diseases associated with inflammaging that characterized by aging accompanying with a low-grade chronic inflammation. In this review, we have discussed the role of SIRT1 in inflammaging in translational research and its pharmacological activators in intervening chronic diseases with lung inflammation and senescence.

SIRT1 and premature senescence

SIRT1 is considered a novel anti-aging protein involved in regulation of cell senescence and premature aging. The levels of SIRT1 are decreased in senescent mouse embryonic fibroblasts as well as in lung epithelial cells, human endothelial cells and macrophages exposed to oxidants [6–11]. We and others have shown that SIRT1 also exhibits an age-dependent reduction in rodents [12–14]. Mice deficient in SIRT1 are smaller and age faster than their wild-type littermates [15]. SIRT1 protects against endothelial dysfunction by preventing stress-induced premature senescence (SIPS), thereby modulating endothelial dysfunction in the progression of cardiovascular diseases [16–20]. Genetic overexpression of SIRT1 protects against SIPS in the lungs, which is an important contributing factor for the development of COPD [12]. The mechanism for SIRT1-mediated protection against cellular senescence is due to the regulation of a redox-sensitive transcription factor FOXO3, since SIRT1 activation by a pharmacological activator SRT1720 has no effect on increased lung cellular senescence and emphysema in FOXO3 knockout mice [12]. It is interesting to note that SIRT1 also represses FOXO transcriptional activity, suggesting their cell- and/or FOXO isoform-specific roles in regulating senescence and angiogenesis as well as cell cycle arrest under certain conditions of stress [21, 22]. The levels of p21 and p16 are significantly increased in mice deficient in SIRT1 or FOXO3 in response to cigarette smoke [12]. Moreover, deletion of pro-senescent gene p21 protected against cigarette smoke-induced cellular senescence in lung cells and subsequent pulmonary emphysema in mice [12, 23]. These findings are in agreement with the association among increased acetylation and degradation of FOXO3, increased p21 expression, as well as SIRT1 reduction in lungs of COPD patients [12, 24–26]. Indeed, a link between cellular senescence and premature lung aging has been proposed in the pathogenesis of COPD [27–33]. Cigarette smoke induces senescence in lung epithelial cells, fibroblasts, and endothelial cells *in vitro* [34–40]. The involvement of cellular senescence in the pathogenesis of emphysema has been shown in various studies using genetically altered mouse strains [12, 41–43]. Therefore, the study of SIRT1/FOXO3/p21 signaling will provide more insights in tipping the imbalance of cellular senescence towards proliferation in lung cells during inflammaging caused by cigarette smoke and oxidants. Furthermore, it remains to be known whether the clearance of p21 or p16 positive senesced cells using a newly developed p16-INK technique protects against oxidative stress-induced lung inflammaging and subsequent emphysema [44]. It is also unknown which cells preferentially first undergo cellular senescence which thereby can trigger a cascade of senescence phenotype of neighboring cells in the lungs.

Apart from FOXO3, several other protein substrates for SIRT1, which are involved in cell stress response signaling and cellular senescence, have been identified. This includes Ku70/Ku80, Wnt/ β -catenin, Notch, and Werner syndrome protein [45–49] (Figure 1). A recent study has identified XRCC5/Ku80 as a potential COPD-susceptibility gene through the multi-study fine-mapping strategy [50]. Indeed, the Ku80 knockout mice develop early aging [51]. Hence, further studies on these molecules in a condition of oxidative stress/

cigarette smoke will enhance the understanding of lung inflammaging and cellular senescence in the pathogenesis of COPD.

SIRT1 in telomere attrition

SIRT1 has been shown to prevent telomere shortening, which is a susceptible factor for developing emphysema [52–54]. Indeed, the telomere length is shortened in blood cells, alveolar macrophages, pulmonary vascular endothelial cells, and lung epithelial cells of patients with COPD [38, 55–60]. Furthermore, telomere exhaustion/attrition leads to cellular senescence in vascular smooth muscle cells and endothelial cells, which plays an important role in pathogenesis of cardiovascular diseases, such as atherosclerosis and pulmonary hypertension [61–64]. The mechanism underlying the protection of SIRT1 against telomere attrition and replicative senescence is due to the regulation in the gene transcription of telomerase reverse transcriptase, which is used as a template for elongating telomeres [65]. Telomere length can also be maintained through alternative mechanisms in the absence of telomerase activity. Hence, another possibility is that SIRT1 modulates histone acetylation/deacetylation (e.g., H3K9 and H3K56), as well as the recruitment of PARP-1 and Ku70/Ku80 at telomere chromatin, thereby maintaining the telomeric integrity [53, 66–68] (Figure 1). However, it remains to be seen whether SIRT1 protects against oxidant/cigarette smoke-induced telomere attrition and shortening during lung inflammaging.

SIRT1 and senescence associated secretory phenotype/inflammation

The senescent cells are prone to secrete pro-inflammatory mediators, such as IL-6, IL-8 and MMPs, which are dependent on NF- κ B activation. This phenomenon refers to senescence associated secretory phenotype (SASP) [69, 70]. Indeed, increased RelA/p65 phosphorylation was increased in p16-positive senescent cells in lungs of COPD patients as compared to smokers [37]. SIRT1 interacts with RelA/p65 subunit of NF- κ B, and deacetylates its lys310 residue, a site that is critical for NF- κ B transcriptional activity [71, 72] (Figure 1). We have shown that cigarette smoke-mediated pro-inflammatory cytokine release is reduced by SIRT1 via deacetylating RelA/p65 in monocytes and mouse lung, as well as in smokers and patients with COPD [9, 10, 24]. Both sirtinol (an inhibitor of SIRT1) and SIRT1 knockdown augmented, whereas SRT1720 (a potent SIRT1 activator) inhibited cigarette smoke-mediated pro-inflammatory cytokine release [9, 24, 25]. SIRT1 genetic overexpression or activation by a pharmacological activator SRT1720 attenuated cigarette smoke-induced NF- κ B activation and lung inflammation [12]. However, the treatment of NF- κ B inhibitor had no effect on lung cellular senescence or airspace enlargement in mouse with emphysema [12]. This suggests that SIRT1 protects against emphysema via reducing lung cellular senescence, independently of NF- κ B-dependent inflammation. Further study is required to investigate whether other signals, such as CXCR2-mediated inflammatory pathway reinforce cellular senescence during lung premature aging [73]. It would be interesting to determine whether SIRT1 activation reverses cellular senescence during lung inflammaging.

SIRT1 and DDR

Cigarette smoke causes DNA damage and impairs double-strand break (DSB) repair, which is aggravated in patients with COPD/emphysema [74–79]. Recent studies have shown that persistent DNA damage causes SIPS and SASP [70, 80]. Thus, cigarette smoke-mediated DNA damage may be one of the important mechanisms in initiating and maintaining SIPS and SASP. In response to DNA damage, SIRT1 can relocate to the damaged sites and promote DNA repair via deacetylating DNA repair proteins, such as Ku70, NBS, Werner helicase, and nibrin [47, 68, 81–83] (Figure 1). Indeed, the increased acetylation of Ku70 caused by oxidative and genotoxic stress reduces its DNA-binding affinity during DNA

repair. Further study is required to determine whether Ku70 and other DNA repair proteins undergo acetylation/deacetylation under oxidative stress imposed by cigarette smoke, and if SIRT1 has any effect on their posttranslational modification status and ability to bind the damaged DNA with its repair proteins.

SIRT1 interacts with PARP-1 and reduces its acetylation that is required for full NF- κ B-dependent transcriptional activity [84]. PARP-1 is an important signal that activates DNA repair programs, and PARP-1/NF- κ B signaling cascade is activated during cellular senescence [85, 86]. Therefore, it is possible that SIRT1 regulates SIPS and SASP via PARP-1-dependent mechanisms on DDR and telomere function in response to cigarette smoke/oxidants. This contention requires further studies to translate the findings of SIRT1 regulation in replicative senescence in pathogenesis of COPD which is associated with lung inflammaging.

SIRT1 and histone modifications in inflammaging

Histone modifications play an important role in regulating DNA damage/repair, pro-inflammatory gene transcription, genomic instability, and premature aging [87–91]. Histone methylation at H3K79 and H4K20 recruits 53BP1 and Crb2 to DNA damage foci after DSB induction [92–95]. Moreover, H3K36 dimethylation has been shown to increase the rate of the association of Ku70 and NBS1 with DSB sites [96, 97]. Furthermore, H3K79 dimethylation is required for ionizing radiation-induced 53BP1 foci formation when H4K20 dimethylation is low [95, 98], suggesting the cross-talk of histone acetylation and methylation regulate DDR. Opening, repairing, and closing of chromatin occur in order to repair the damaged DNA [99]. Hence, these histone acetylation and methylation after DNA damage will alter chromatin status between euchromatin and heterochromatin so as to recruit DNA repair factors and cofactors (e.g., HP1) to damaged sites. SIRT1 also deacetylates histone H3K56, thereby regulating DNA damage and genomic instability [90, 91]. This may be due to SIRT1-mediated transcriptional repression, which prevents transcription from interfering with the repair process. Histone methylation (e.g., H3K9me3) can also be regulated by SIRT1 via deacetylating Suv39h1, or enabling histone H3 toward Suv39h1 [100]. However, studies are required to determine which histone residue(s) are modified and how these modifications affect genomic stability, DNA damage repair, and subsequent cellular senescence. SIRT1 is regulated by several miRNAs, such as miR-34 and miR-22, which are involved in cellular senescence via histone modifications [101–103]. It also remains to be seen if cigarette smoke-induced SIRT1 reduction alters histone acetylation and methylation, as well as their cross-talks with histone modifications and DNA methylation, thereby regulating DDR and cellular senescence. Furthermore, pharmacological activation of SIRT1 may ameliorate histone modifications and intervene formation of senescence associated with heterochromatin foci (SAHF) in inflammaging.

SIRT1 and oxidative stress in inflammaging

Apart from the posttranslational modifications by oxidative stress [10], SIRT1 itself protects against oxidative stress by up-regulating FOXO3-dependent antioxidant genes (i.e., catalase and MnSOD) [104–108]. A recent study has shown that SIRT1 can deacetylate Nrf2, a master regulator of the cellular redox state, thereby decreasing Nrf2 transcriptional activity and nucleo-cytoplasmic localization in human cancer line [109] (Figure 1). However, it remains elusive whether SIRT1 (direct replenishment of NAD⁺ or via activation of AMPK) protects against oxidative stress via regulating Nrf2 acetylation and deacetylation in primary cells during aging [109, 110]. Oxidative stress and inflammation are key events in premature aging, and both play an important role in the development of COPD/emphysema [111–113].

Hence, it is likely that SIRT1 activation ameliorates lung inflammaging via down-regulating oxidative stress-mediated cellular senescence.

SIRT1 and lung stem/progenitor cells

The level of SIRT1 is higher in embryonic stem cells than that in differentiated tissues [114]. SIRT1 is required for the long-term growth of human mesenchymal stem cells, whereas its cleavage causes SIPS in endothelial progenitor cells [115, 116]. SIRT1 deficiency in the embryonic cells leads to embryonic and developmental abnormalities including defects in the formation of the primitive vascular network, which may be due to the regulation of developmental genes, such as NANOG and Notch [46, 117–119]. SIRT1 is known to regulate endothelial function via eNOS acetylation/deacetylation [8]. Increased loss of endothelial cells occurs in progression of COPD/emphysema [120]. It has been shown that endothelial progenitor cells (EPC), which promote revascularization (angiogenesis), are senesced in response to high levels of glucose which is seen in patients with diabetes, due to SIRT1 reduction [21, 115, 121]. Hence, it will be interesting to see if SIRT1 regulates lung tissue regeneration via angiogenesis by increasing the function of EPCs or induced pluripotent stem (iPS) cells-derived EPCs. COPD represents a disease with premature aging and cellular senescence in Clara cells and type II epithelial cells, which are the progenitor cells of airway and alveolar epithelium. We found that SIRT1 deletion in Clara cells renders mice susceptible to the development of pulmonary emphysema associated with increased lung cellular senescence [12]. A recent study has shown that human lung contains stem cells [122]. Therefore, the regulation of SIRT1 in lung stem/progenitor cells or iPS-EPCs would be a promising therapeutic avenue in the treatment of COPD and its comorbid cardiovascular diseases.

There are cancer stem cells (CSCs) in lungs of patients with lung tumor, which has the ability to form colonies and develop region-specific lung cancers [123]. Furthermore, EPCs control the angiogenic switch in mouse lung metastasis, suggesting selective inhibition of EPCs may be beneficial for cancer patients with lung metastases [124]. However, it remains to be known whether SIRT1 regulates these CSCs and EPCs in lung tumorigenesis and metastases, despite the SIRT1 function is abnormal in lung cancer [125].

SIRT1 activation by dietary polyphenols and pharmacological activators

Resveratrol

Resveratrol, a phytoalexin found in the skin and seeds of grapes, has been shown to possess anti-inflammatory and antioxidant properties. Since 2003, resveratrol was identified as a potent SIRT1 activator and mimicked the effect of calorie restriction in regulating longevity in yeast, worms, flies, and short-lived fishes, as well as in mice [126–134] (Table 1). However, the beneficial effects of activation of SIRT1 in higher mammals are lacking. In obese humans, one month of resveratrol supplementation also induces metabolic changes, mimicking the effect of calorie restriction [135]. This is in part due to the effect of resveratrol on cellular senescence and inflammation via activating SIRT1 [136–138]. A recent study has shown that SIRT1 may not increase the longevity in *C. elegans* and *drosophila* [139], which cast doubts on whether resveratrol is an actual activator of SIRT1. Indeed, resveratrol increases SIRT1 deacetylase activity only when the deacetylated protein substrates have a fluorophore attached, whereas substrates lacking the fluorophore did not show increased deacetylation by resveratrol [140]. These findings suggest that resveratrol is not a direct activator of SIRT1 [140–142]. This is confirmed by the studies that resveratrol indirectly regulates SIRT1 via activating nicotinamide phosphoribosyltransferase (NAMPT) and cAMP-Epac1-AMP-activated kinase (AMPK), leading to an increase in intracellular level of NAD⁺ [143–149]. Inhibition of phosphodiesterase (PDE)4 (elevation of intracellular

cAMP) reproduces all of the metabolic benefits of resveratrol, which is due to an increase in intracellular levels of cAMP leading to AMPK and subsequent SIRT1 activation [149]. Furthermore, AMPK activation induces the disassociation of SIRT1 from its endogenous inhibitor deleted in breast cancer-1 (DBC1), thereby activating SIRT1 [150–152]. It remains to see whether resveratrol has any effect on the association of SIRT1 with DBC1. Furthermore, treatment with resveratrol has no effect or reduced SIRT1 levels during oxidative stress [153, 154], suggesting the controversial ‘beneficial’ role of resveratrol in inflammaging. Nevertheless, resveratrol does delay or attenuate the progression of age-associated disease model in rodents [155]. Further studies are required to investigate if resveratrol inhibits inflammation and cellular senescence via the involvement of SIRT1 in specific lung cells including stem cells.

Quercetin and other polyphenols

Quercetin, 3,3',4',5,7-pentahydroxyflavone, is a plant-derived flavonol found in apples, tea, capers, and onion. It has been shown that quercetin protects against emphysema, which is associated with the increased expression of SIRT1 [156] (Table 1). This is in agreement with the previous reports that quercetin and catechins activate mammalian SIRT1 or yeast Sir2 [126, 157, 158]. Other polyphenolic compounds, such as butein, quercetin, piceatannol, and myricetin, can also activate SIRT1 [159]. These compounds have a modest ability to activate SIRT1 ranging from 3.19–8.53 fold as compared to resveratrol. Nevertheless, these polyphenols may be beneficial in regulation of lung inflammaging through SIRT1 [160]. Interestingly, some polyphenols, such as epigallocatechin gallate (EGCG) and quercetin, did not exhibit any ability to activate SIRT1 (perhaps do not lower the K_m for NAD^+) in a variety of cellular systems [158, 161, 162]. On the contrary, these polyphenols inhibit SIRT1 activity [158]. This is due to their instability leading to formation of oxidized form of polyphenols to generate reactive oxygen species (ROS) in the medium in particular their reactions with aldehydes/quinones (via resveratrol, EGCG) or due to SIRT1-inhibitory metabolites (i.e. via quercetin and its metabolites) [158].

Sulforaphane

We and others have shown that SIRT1 undergoes posttranslational modifications, such as phosphorylation, carbonylation, nitrosylation and S-glutathionylation by oxidative/carbonyl stress [8, 10, 163–165]. Increasing cellular NAD^+ levels by PARP-1 inhibition or NAD^+ precursors was unable to restore the loss of SIRT1 activity caused by cigarette smoke, due to oxidative/carbonyl posttranslational modifications of SIRT1 [163]. Sulforaphane, an activator Nrf2, may indirectly restore SIRT1 activity by reversing oxidative/carbonyl modifications of SIRT1 via activation of phase II detoxifying/antioxidant enzymes (aldehyde/carbonyl reductases, thioredoxin reductases) in primary cells, although sulforaphane decreases the total activity of HDAC *in vivo* [166]. Therefore, the studies are required to attest this functional activity of SIRT1 by dietary natural products including Nrf2 activators.

Pharmacological compounds

Several SIRT1 activators, which are analogs of resveratrol, have been developed for the treatment of aging-associated diseases including type 2 diabetes [167–169]. These activators include SRT1720, SRT1460, SRT2183, SRT2104, SRT2172, and SRT2379 (Table 1). The most potent of the compounds is SRT1720 ($EC_{1.5} = 0.16 \mu M$ and maximum activation of SIRT1 of 781%), which is 800–1000 fold more effective than resveratrol in activating SIRT1 [168]. SRT2172 is more effective in inhibiting MMP-9 production in monocytes as compared to resveratrol [25]. This may be via activation of TIMPs (TIMP-1) via its acetylation/deacetylation. The efficiency of these SIRT1 activators is strongly dependent on structural features of the peptide and probably on allosteric regulation [141, 170]. SRT1720

improves glucose homeostasis and insulin sensitivity in animal models of type 2 diabetes [168]. We found that SRT1720 treatment reduces cigarette smoke-induced lung cellular senescence due to SIRT1 activation. Consequently, the lung inflammatory response and airspace enlargement were significantly improved by SRT1720 administration [12]. In addition, SRT1720 improves survival and healthspan of obese mice [171], suggesting the feasibility of designing novel molecules that are safe and effective in promoting longevity and preventing multiple age-related diseases in mammals. As above described, SRT1720, SRT2183, and SRT1460 are non-specific for SIRT1 activation [141]. Therefore, the development of a specific selective pharmacological SIRT1 activator is crucial in understanding the role of SIRT1 in cellular functions and potential clinical application of SIRT1 activators in diseases associated with lung inflammaging.

Other SIRT1 modulators

SIRT1 requires NAD⁺ as a cofactor in deacetylating substrates. Theophylline prevents NAD⁺ depletion [172]. PARP-1 activation drains cellular NAD⁺, which compromises SIRT1 activity. Hence, theophylline or PARP-1 inhibitor would maintain intracellular NAD⁺ pool, thereby activating SIRT1. A recent study has shown that there is no alteration of SIRT1 activity after PARP-1 inhibitor treatment in the condition of oxidative stress, which is due to SIRT1 carbonylation and oxidation [11, 163]. Hence, the reversal of SIRT1 posttranslational modifications, such as carbonylation and oxidation, would be important before the pharmacological activation of SIRT1 in regulating lung inflammaging.

Metformin is a widely used drug especially for adult onset type 2 diabetes. A recent study has demonstrated that the beneficial effect of metformin is associated with the activation and induction of SIRT1 [173] (Table 1). Further studies revealed that metformin targets AMPK, an upstream kinase for activating SIRT1 [173–177]. The effectiveness and mechanism of metformin in lung inflammaging/senescence remains elusive, although several clinical trials are ongoing to study the effect of metformin in treatment of COPD and its exacerbations.

Translational impact

SIRT1 exhibits an age-dependent reduction. It is also reduced in aging-associated diseases, such as COPD and diabetes. A variety of pharmacological and dietary compounds, such as resveratrol and SRT1720, are shown to target SIRT1 in order to delay inflammaging or attenuate the progression of aging-associated diseases. However, recent studies have revealed that most of the above dietary compounds are non-specific activators of SIRT1. Hence, the development of specific and selective SIRT1 activator is urgently required to delay or ameliorate the progression of lung inflammaging.

Conclusions and future directions

SIRT1 regulates cellular senescence/premature aging, inflammation, stress resistance, and apoptosis/autophagy via deacetylating transcription factors (e.g., FOXO3), signaling molecules (e.g., PARP-1), and histones. However, a recent study revealed that there is no effect of SIRT1 on longevity in *C. elegans* and *Drosophila* [139], which cast a doubt on beneficial role of SIRT1 activation in human aging and aging-associated diseases. It has been shown that SIRT6 also regulates cellular senescence, aging, inflammation, and DDR [178–183]. However, it remains to be seen whether there is an overlapping function between SIRT1 and SIRT6 in regulating lung inflammaging. It would also be interesting to determine if SIRT1 and other histone deacetylases have differential roles in regulating premature and replicative senescence during the progression of COPD. The involvement of specific cell types in cellular senescence and their regulation by SIRT1 in the lung is not known. The

development of SIRT1 or SIRT6 activity by dietary polyphenols, specific activators (e.g., SRT1720), or AMP-activated protein kinase activators (e.g., AICAR) is a promising therapeutic strategy against senescence/aging-associated diseases associated with lung inflammaging (e.g., COPD, cancer, diabetes, and cardiovascular diseases) [25, 184, 185]. It is also important to study how these dietary polyphenols and putative pharmacological activators activate SIRT1, and to develop the direct and specific SIRT1 activators. In addition, most of the polyphenols are poorly absorbed and rapidly metabolized as well as oxidized, which affect their regulation in SIRT1 function. Hence, further study is required to study the biochemical mode of action of dietary polyphenols on SIRT1 activation and in modulation of senescence in inflammaging.

Acknowledgments

This study was supported by the NIH 1R01HL085613, 1R01HL097751, 1R01HL092842, and NIEHS Environmental Health Science Center grant P30-ES01247.

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Figure 1. SIRT1 regulates protein acetylation and deacetylation in inflammaging

SIRT1 removes the acetyl moieties from the ϵ -acetamido groups of lysine residues of proteins that include FOXO3, p53, Nrf2, NF- κ B, PARP-1, Ku70 and Notch. The acetylation and deacetylation of these proteins alter their transcriptional and enzymatic activities, as well as protein levels, thereby regulating cellular senescence, apoptosis, inflammation, ROS production, DNA damage and repair, and angiogenesis. All these cellular processes are involved in the inflammaging that occurs in aging-associated diseases such as COPD, diabetes, and cancer.

Table 1

Putative SIRT1 activators in inflammaging

Putative activator	Potency to activate SIRT1	Function	Reference
<i>Polyphenols</i>			
Resveratrol	Increases SIRT1 activity up to 8-fold ($EC_{1.5} = 46.2 \mu\text{M}$)	Delays the progression of aging-associated diseases Antioxidant and anti-inflammatory effects	[155, 158]
Quercetin	Increases SIRT1 activity up to 2-fold	Prevents the progression of emphysema	[156, 158]
EGCG	Increases SIRT1 activity up to 1.6-fold	Reduces lung inflammation	[158, 186]
<i>Pharmacological activators</i>			
SRT1720	$EC_{1.5}=0.16 \mu\text{M}$ in increasing SIRT1 activity	Protects against lung inflammaging Extends lifespan of adult mice	[12, 171]
SRT2172	$EC_{50}=0.136 \mu\text{M}$ in increasing SIRT1 activity	Inhibits MMP-9 production	[25]
<i>Metformin</i>	Increases SIRT1 activity up to 1.2-fold	Suppresses hepatic gluconeogenesis	[173]