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SIRT1 as a therapeutic target in inflammaging of the pulmonary disease

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Abstract

Objective—Chronic inflammation and cellular senescence are intertwined in the pathogenesis of premature aging, which is considered as an important contributing factor in driving chronic obstructive pulmonary disease (COPD). SIRT1, a NAD⁺-dependent protein/histone deacetylase, regulates inflammation, senescence/aging, stress resistance, and DNA damage repair via deacetylating intracellular signaling molecules and chromatin histones. The present review describes the mechanism and regulation of SIRT1 by environmental agents/oxidants/reactive aldehydes and pro-inflammatory stimuli in lung inflammation and aging. The role of dietary polyphenols in regulation of SIRT1 in inflammaging is also discussed.

Methods—Analysis of current research findings on the mechanism of inflammation and senescence/aging (i.e., inflammaging) and their regulation by SIRT1 in premature aging of the lung.

Results—COPD is a disease of lung inflammaging, which is associated with the DNA damage response, transcription activation and chromatin modifications. SIRT1 regulates inflammaging via regulating FOXO3, p53, NF- κ B, histones and various proteins involved in DNA damage and repair. Polyphenols and its analogs have been shown to activate SIRT1 although they have anti-inflammatory and antioxidant properties.

Conclusions—Targeting lung inflammation and cellular senescence as well as premature lung aging using pharmacological SIRT1 activators or polyphenols would be a promising therapeutic intervention for COPD/emphysema.

Keywords

Inflammaging; COPD; SIRT1; Tobacco smoke; Oxidative stress; NF- κ B; DNA damage response; FOXO3; Histone modifications; Polyphenols

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Introduction

The word “inflammaging” is coined by C Franceschi in 2000, which refers to a progressive increase in proinflammatory status, a major characteristic of the aging process. This can be reflected in diseases where underlying chronic abnormal inflammation exist (Franceschi et al., 2000). For example, chronic inflammation is associated with aging and its related diseases, such as diabetes, atherosclerosis, cancer, and chronic obstructive pulmonary disease (COPD). The inflammation and cellular senescence are intertwined in the process of accelerated or premature aging. The causal role of inflammation and aging in certain conditions and diseases remains unknown. COPD is the fourth leading cause of chronic morbidity and mortality in the United States and globally, affecting an estimated 23 million people. It includes airway obstruction/chronic bronchitis and emphysema, which is linked with lung inflammaging and premature aging (accelerated decline in lung function) due to inhaled cigarette smoke-derived oxidants and free radicals, and noxious gases. However, in certain conditions, such as in pulmonary emphysema inflammation is almost absent but the disease/lung destruction progresses.

The NAD⁺-dependent protein deacetylase, sirtuin1 (SIRT1), has been reported as an important regulator of aging phenomena, such as apoptosis/senescence, stress resistance, and inflammation through the deacetylation of intracellular signaling molecules and chromatin histones (Chung et al., 2010). The level/activity of SIRT1 deacetylase is decreased in chronic lung inflammatory conditions and premature aging where sustained oxidative/carbonyl (due to reactive aldehydes-acrolein and 4-hydroxy-2-nonenal) stress occurs. SIRT1 is oxidatively down-regulated by cigarette smoke/aldehydes, leading to post-translational modifications, inactivation and protein loss via the proteasome (Caito et al., 2010b). However, very little is known whether SIRT1 regulates inflammaging, particularly in the development of COPD. In this review, we describe the mechanism and regulation of SIRT1 by oxidants/aldehydes generated by environmental and pro-inflammatory stimuli in lung inflammaging, particularly in pathogenesis of COPD, a disease of accelerated premature aging and inflammation of the lung. We also discuss the role of dietary polyphenols and pharmacological analogs in regulation of SIRT1 in inflammaging.

Etiology and comorbidities of COPD

COPD is characterized by destruction of the alveolar wall, decline in lung function, and chronic lung inflammatory response. An estimated 10^{15-17} oxidants/free radicals and ~4,700 different highly reactive chemical compounds/aldehydes are present in per puff of cigarette smoke, which is the major risk factor in the development of COPD. It accounts for ~80%-90% of COPD cases in USA (Sethi and Rochester, 2000). Additionally, noxious environmental gases/particles, such as NO₂, SO₂, and particulate matters, as well as exposure to second-hand tobacco smoke and smoke derived from burning of biomass fuels can trigger inflammatory response in lungs of a susceptible population. Maternal smoking is another contributing factor in promoting COPD in the offspring during the later stages of life (Beyer et al., 2009). Tobacco smoking has also been associated with cardiovascular disease, skin wrinkling, as well as several types of cancer (*e.g.* lung) and premature aging of the lungs (accelerated decline in lung function). Chronic inflammation, oxidative/carbonyl stress and protease/antiprotease imbalance resolve very slowly after smoking cessation, the resolution demanding from months to years (Louhelainen et al., 2009; Louhelainen et al., 2010; Nagai et al., 2006). This may explain why smoking cessation alone is not the only “therapy” to prevent COPD progression. COPD also can develop in non-smokers especially in women, or in those with childhood respiratory problems, asthma, as well as long exposure to smoke-derived from biomass fuel burning and environmental pollutants (Lamprecht et al., 2011; Salvi and Barnes, 2009).

In addition to intra-pulmonary manifestations, comorbidities, such as lung cancer, cardiovascular disease, diabetes, metabolic syndrome, osteoporosis, muscle atrophy, skin wrinkling/aging and depression, are the major causes for mortality in COPD. For example, the skeletal muscle wasting and depression negatively affect the quality of life in COPD patients. Although COPD increases the susceptibility for lung tumorigenesis up to 4.5-fold (Sundar et al., 2011; Yao and Rahman, 2009), the causal pathways that links COPD and other comorbid conditions remains to be studied. It is apparent that besides local inhaled therapies, systemic/oral therapies with minimal side effects are necessary to slow the COPD lung disease and its systemic manifestations.

Inflammaging phenotype in COPD

A variety of cellular processes, such as inflammation, aging/senescence, oxidative stress, apoptosis/proliferation, autophagy, and autoimmunity, are involved in the pathogenesis of COPD/emphysema (Yao and Rahman, 2009, 2011). Hence, the specific molecules that regulate aging/senescence and inflammatory/immune events will provide the possible therapies for intervention in COPD.

Lung function decreases with age along with additional age-related alterations, such as changes of the elastic recoil of the lung, increased alveolar size, and reduced defense mechanisms. The prevalence of COPD increases with aging, and upregulation of pro-inflammatory genes occurs in lungs of COPD patients, suggesting the association of inflammation and aging/senescence in the pathogenesis of COPD/emphysema. Lung cellular senescence is accelerated in COPD, which has been found to be independently associated with lowered antioxidant defense, elevated oxidative stress, protease/antiprotease imbalance, and elastolysis (Ito and Barnes, 2009; MacNee, 2009). The telomere length in circulating lymphocytes is shortened (i.e., replicative senescence) in patients with COPD as compared to non-smokers (Houben et al., 2009; Morla et al., 2006; Mui et al., 2009; Savale et al., 2009). Furthermore, the telomere length was positively correlated with PaO₂, SaO₂, 6-minute walking distance, and lung function in patients with COPD (Mui et al., 2009; Savale et al., 2009). It is postulated that these senescent immune cells have downregulated humoral and cellular immunity, or lose the ability to self-recognition, thereby leading to impaired host defense and autoantibody generation. Cigarette smoke/oxidants/aldehydes exposure has been shown to induce senescence (i.e., stress-induced premature senescence, SIPS) in both alveolar epithelial cells and fibroblasts, which is independent of telomere shortening (Muller et al., 2006; Nyunoya et al., 2006; Nyunoya et al., 2009; Tsuji et al., 2004, 2006, 2010). In addition to type II epithelial cells, the number of senescent Clara cells is also increased in patients with COPD as compared to nonsmokers (Aoshiba and Nagai, 2009). Both Type II epithelial cells and Clara cells are the progenitors of alveolar and airway epithelial cell for regeneration, respectively. Hence, the senescence of these progenitor cells may dampen the repair of damaged lung tissue, which explains why COPD progresses even after cessation of smoking.

The role of cellular senescence in COPD/emphysema is further attested by the animal studies. The deficiency of Klotho or senescence marker protein-30 gene leads to emphysematous phenotype in mouse lung (Sato et al., 2006; Suga et al., 2000). Knockout of telomerase, a holoenzyme required for maintaining telomere length, also increases the mean linear intercept of airspace in mouse (Lee et al., 2009). These findings implicate that cellular senescence is an essential process contributing to the development/progression of COPD/emphysema. Nevertheless, further study is required to which phenomenon drives the progression of COPD/emphysema, replicative senescence, SIPS, or both. It is also important to bear in mind that the telomere length is longer in mice than that in long-living mammals due to high levels of telomerase, suggesting caution when extrapolating the data from mouse to human.

Cellular senescence is a permanent state of cell cycle arrest, which prevents the growth of cells exposed to potential oncogenic stimuli. However, the senescent cells are metabolically active, and prone to secrete pro-inflammatory cytokines (i.e., IL-6 and IL-8) and matrix metalloproteinases (i.e., MMP-3 and MMP-9) involved in inflammaging (Freund et al., 2010; Rodier et al., 2009). These pro-inflammatory mediators may in turn initiate and maintain cellular senescence as the deficiency of IL-6, IL-6R, or CXCR2 prevented SIPS (Acosta et al., 2008; Kuilman et al., 2008) (Figure 1). Thus, the low grade of chronic inflammation and cellular senescence form a vicious cycle via an autocrine and paracrine manner, which may render lung progenitor cells unable to repair the damaged lung tissues, leading to aggressive lung destruction. Indeed, the increased percentage of pro-inflammatory senescent type II cells expressing both p16 and phosphorylated NF- κ B (i.e., senescent-associated secretory phenotype, SASP) was observed in lungs of patients with COPD as compared to smokers and nonsmokers (Tsuji et al., 2010). Furthermore, cellular senescence is also associated with apoptosis/autophagy (Vicencio et al., 2008). Thus, the cellular senescence is an important cellular status that allows the damaged cells to adapt to stress or undergo programmed cell death in the pathogenesis of COPD/emphysema. The cellular senescence also facilitates bacterial adhesion to the lung cells under the persistent SIPS leading to exacerbations of the disease (Shivshankar et al., 2011; Zhou et al., 2011).

Mechanism of inflammaging in COPD

A variety of molecules have been shown to regulate the inflammaging or in other word SASP, which includes DNA damage response (DDR), transcription factors, and epigenetic (more specifically epigenomic) modifications. Thus, the study of these molecules/pathways particularly in response to cigarette smoke will provide an avenue in preventing the progression of COPD/emphysema.

DNA damage response—Cigarette smoke/oxidative stress has been shown to cause DNA damage, which is increased in patients with COPD/emphysema (Caramori et al., 2011). Recent studies have demonstrated that persistent DNA damage causes SIPS with increased pro-inflammatory mediators release (Coppe et al., 2008; Rodier et al., 2009) (Figure 1). It seems that SASP is induced by genotoxic stress, such as oxidants/reactive aldehydes (reactive oxygen species, ROS)/smoking and ionizing radiation, rather than proliferative arrest *per se* (Coppe et al., 2008; Rodier et al., 2009). The upstream signals of DDR, including ataxia telangiectasia mutated (ATM) and its substrates Nijmegen breakage syndrome 1 (NBS1), Werner syndrome protein as well as checkpoint kinase 2 (CHK2), are required for inflammatory cytokines secretion in senescent cells (Rodier et al., 2009). The mechanism of ATM signal-mediated pro-inflammatory release is associated with NF- κ B activation (Elkon et al., 2005; Wu et al., 2006).

The double-strand break (DSB) is the most dramatic form of DNA damage, which can be repaired either by homologous recombination (HR), classic or alternative non-homologous end joining (NHEJ). The former corrects DSB damage in a precise manner using a way that retrieves information from a homologous and undamaged DNA, whereas the latter is a primary pathway to repair DSB defects in an error-prone manner which does not require a homologous template. Usually, the classic NHEJ has faster kinetics than alternative NHEJ and HR to monitor end joining (Han and Yu, 2008; Mao et al., 2008a). The HR-based repair usually happens in late S-and G2-phases of cell cycle while the early rapid repair is active throughout the cell cycle (Mao et al., 2008b; Neal and Meek, 2011). The decision that damaged cells choose HR or NHEJ for DSB repair depends on the factors/situations including the cell cycle stage and available undamaged sister chromatid as well as the availability of repairing proteins/enzymes at the time of damage acquisition. Cigarette smoke/oxidative/carbonyl stress has been shown to decrease the NHEJ repair proteins such

as Ku70, Ku80 and Ku86 directly or indirectly (Caramori et al., 2011; Song et al., 2003), which may lead to sustained DNA damage and account for SASP observed in patients with COPD.

Transcription regulation—NF- κ B is a key transcription factor responsible for pro-inflammatory genes transcription, which is significantly increased in patients with COPD (Caramori et al., 2003; Di Stefano et al., 2002). Interestingly, it also regulates cellular senescence, DNA repair as well as genome stability via an oxidative stress-related mechanism (Acosta et al., 2008; Bernard et al., 2004; Kawahara et al., 2009; Wang et al., 2009). This is important for preventing further DNA damage in the earlier phase of smokers/COPD, although DNA damage was not changed between RelA/p65 deficient and wild-type mouse embryonic fibroblasts (Wang et al., 2009). However, the deletion of RelA/p65 decreases the production of CXCR2 ligands (i.e., IL-8 and GRO γ) during SIPS. Similarly, transcription factor C/EBP β is also involved in SASP (Acosta et al., 2008). Hence, the sustained activation of NF- κ B triggered by cigarette smoke/oxidants/aldehydes will dampen the re-epithelialization of damaged airways and alveolar walls due to epithelium senescence, as well as will result in chronic inflammatory response via increasing expression of SASP factors in lungs.

Chromatin/histone modifications—Chromatin remodeling, including DNA methylation and histone modifications (histone acetylation/acetylation and methylation/demethylation), has been shown to regulate cellular senescence (Dimauro and David, 2009). Cigarette smoke and oxidants cause histone acetylation (e.g., H3K9, H3K14, H4K5, H4K8, H4K12, H4K16) and increased expression of NF- κ B-dependent pro-inflammatory cytokines in rodent lungs (Yang et al., 2008; Yao et al., 2010). Similarly, increased histone acetylation (specifically histone H4) occurs in lungs of smokers, and in bronchial biopsy/peripheral lung tissue (acetylation of histone H4 on pro-inflammatory gene promoter but no change in global increase in HAT activity) obtained from patients with COPD (Ito et al., 2005). Histone acetylation is dynamic reversible and is regulated by both histone acetyltransferases (HATs) and deacetylases (HDACs). Furthermore, histone modifications, such as H3K9 acetylation and H4K20 methylation, are associated with aging (Michishita et al., 2008; Sarg et al., 2002). The enzymes responsible for histone acetylation/deacetylation (e.g., p300, CBP, SIRT1, and SIRT6) and methylation/demethylation (e.g., SUV39h1, KMD, and EZH2) have been shown to regulate cellular senescence and aging (Bandyopadhyay et al., 2002; Braig et al., 2005; Longo and Kennedy, 2006; Michishita et al., 2008; Mostoslavsky et al., 2006). However, no information is available regarding the regulation of histone modifications in SIPS/SASP particularly in response to cigarette smoke/oxidants/aldehydes exposure in lung cells.

SIRT1 as a target for inflammaging

Unlike class I and II histone deacetylases (HDACs), which require a water molecule for deacetylation, type III SIRT1s require NAD⁺ as a cofactor and are not inhibited by trichostatin A. The deacetylase activity of sirtuins is inhibited by the reaction product, nicotinamide. SIRT1s have five homologues in yeast (ySir2 and Hst1–4) and seven in humans (SIRT1–7). The best characterized and well-studied among the human sirtuins is SIRT1, a nuclear protein reported to regulate critical metabolic and physiological processes (Alcendor et al., 2007; Finkel et al., 2009; Lavu et al., 2008; Michan and Sinclair, 2007; Yang and Sauve, 2006). SIRT1 removes 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. Activation or overexpression of SIRT1 (sir2) has been shown to increase the lifespan of *Drosophila*, *S. cerevisiae* and *C. elegans* up to 70% although resveratrol used in these studies is non-specific activator of SIRT1.

Furthermore, the role of resveratrol (via SIRT1) in prolonging lifespan in mammals remains unclear (Bordone et al., 2007; Wood et al., 2004). SIRT1 regulates numerous processes, including inflammation and cellular senescence/aging, due to its ability to deacetylate NF- κ B, forkhead box class O (FOXO)3, p53, Werner syndrome protein, Klotho, β -catenin/Wnt, Notch, endothelial nitric oxide synthase (eNOS), and histones (Finkel et al., 2009; Lavu et al., 2008; Michan and Sinclair, 2007) (Figure 2).

Recent studies have shown five single nucleotide polymorphisms of SIRT1 in a population-based study, suggesting SIRT1 variability in the human population (Flachsbart et al., 2006; Zillikens et al., 2009). However, it is unknown whether SIRT1 (SNPs or allelic variants) is a susceptibility factor for development of COPD in smokers. It would be interesting in future study to determine SIRT1 polymorphisms in COPD and link to susceptibility to the disease.

SIRT1 modification by oxidative/carbonyl stress

In addition to NAD⁺ and nicotinamide, SIRT1 protein level and activity can be affected by posttranslational modifications. There are five known phosphorylation sites in SIRT1 on serine residues S14, S16, S26, S27, and S47. SIRT1 can be phosphorylated or dephosphorylated by PKC, CK2 or PI3K-and *ser/thr* phosphatase-dependent mechanisms, and possibly by other members of the MAP kinase family. Oxidants/aldehydes derived from tobacco smoke caused SIRT1 phosphorylation in macrophages, epithelial cells as well as in mouse lungs (Caito et al., 2010b). Proteasome inhibitors inhibited SIRT1 phosphorylation, suggesting that phosphorylation in addition to covalent carbonyl/oxidative/nitrosative modifications of SIRT1 cause its irreversible modifications and subsequent proteasomal degradation (Arunachalam et al., 2010;

Caito et al., 2010a; Caito et al., 2010b). Furthermore, SIRT1 is also subject to S-glutathionylation and its enzymatic activity is modulated by intracellular redox GSH status, and is reversed by glutaredoxin1, an enzyme that reverses glutathionylated proteins (Caito et al., 2010b; Zee et al., 2010) (Figure 2). Thus, SIRT1 posttranslational modifications can modify its activity, and cause its nucleocytoplasmic shuttling and subsequent ubiquitination-proteasomal degradation as well as inhibition of *ser-thr* phosphatases particularly in response to CS exposure. These findings advance the emerging field of research on SIRT1 regulation by suggesting that a simple activation of SIRT1 by pharmacological agents may not be effective since SIRT1 is covalently modified in carbonyl/oxidative/inflammatory conditions. Indeed, increasing cellular NAD⁺ by PARP-1 inhibitor or NAD⁺ precursor was unable to restore SIRT1 activity, particularly in response to genotoxic stress caused by cigarette smoke/oxidants/reactive aldehydes (Caito et al., 2010a). Therefore, the reversal of oxidative post-translationally modified SIRT1 may be an avenue before effective therapeutic strategies can be designed for chronic inflammatory diseases.

SIRT1 and regulation of NF- κ B

SIRT1 protein directly interacts with RelA/p65 subunit of NF- κ B, and deacetylates lys310 residue of RelA/p65, a site that is critical for NF- κ B transcriptional activity (Chen et al., 2002; Yeung et al., 2004). We have shown that cigarette smoke-mediated pro-inflammatory cytokine release is regulated by SIRT1 via its interaction with NF- κ B in monocytes and mouse lung, as well as in smokers and patients with COPD (Rajendrasozhan et al., 2008; Yang et al., 2007). Both sirtinol (an inhibitor of SIRT1) and SIRT1 knockdown augmented, whereas SRT1720 (a potent SIRT1 activator) inhibited cigarette smoke-mediated pro-inflammatory cytokine release (Nakamaru et al., 2009; Rajendrasozhan et al., 2008; Yang et al., 2007). Furthermore, the level and activity of SIRT1 were decreased in lung of patients with COPD (Nakamaru et al., 2009; Rajendrasozhan et al., 2008). Hence, downregulation of SIRT1 would lead to increased lung inflammatory via regulating NF- κ B. Recent studies

have shown that SIRT1 also deacetylates and suppresses the transcription activity of activator protein-1 leading to down-regulation of cyclooxygenase-2 gene expression (Gao and Ye, 2008; Zhang et al., 2009; Zhang et al., 2010a), suggesting the multiple targets of SIRT1 in regulating inflammation.

SIRT1 and cell senescence/aging

McBurney *et al.* have shown that mice lacking SIRT1 were smaller and aged faster than their wild-type littermates (McBurney et al., 2003). Senescent mouse embryonic fibroblasts and human endothelial cells have decreased levels of SIRT1 (Orimo et al., 2009; Sasaki et al., 2006). SIRT1 is therefore considered a novel anti-aging protein involved in regulation of cell senescence and proliferation due to its ability to deacetylate FOXO3 and p53 proteins, which is involved in a variety of cellular responses, such as cell cycle arrest, cellular senescence, proliferation, and resistance to oxidative stress and apoptosis (Brunet et al., 2004; Kops et al., 2002; Kyoung Kim et al., 2005; Willcox et al., 2008).

The mechanism of SIRT1/FOXO3 or SIRT1/p53 in cellular proliferation and senescence is associated with altered transcription of downstream cell cycle inhibitors (e.g. p16, p21, and p27) (Furukawa et al., 2007; Ota et al., 2007). Recently, it has been shown that FOXO3 and p53 are acetylated when SIRT1 is reduced in mouse lung exposed oxidants/aldehydes/cigarette smoke, as well as in lungs of patients with COPD (Caito et al., 2010a; Caito et al., 2010b; Hwang et al., 2011). Furthermore, the level of FOXO3 was significantly decreased in lungs of patients with COPD (Hwang et al., 2011; MacNee and Tuder, 2009). Genetic ablation of FOXO3 leads to emphysema and exaggerated inflammation by NF- κ B activation and downregulation of antioxidant defense (Hwang et al., 2011). It can be speculated that FOXOs maintenance would offer an alternative insight for SIRT1's function in COPD (inflammaging/SIPS), but so far this kind of manipulation has not been published in human diseases. Therefore, the study of SIRT1-FOXO3/p53 pathway will provide more insight into the imbalance of cellular proliferation/senescence and apoptosis in response to oxidative stress, and whether polyphenols have any effect on this pathway, since polyphenols (e.g. resveratrol) have been shown to regulate cellular senescence (Stefani et al., 2007; Zamin et al., 2009). It is also possible that SIRT1 regulates the function of p21 by posttranslational modification since p21 itself can be subject to acetylation/deacetylation (Chen et al., 2004). However, it remains to be seen whether SIRT1 is also involved in p21-mediated regulation of cell proliferation/senescence, although p21 is a sensor of cellular stress to trigger lung inflammation and injury (Tuder et al., 2008; Yao et al., 2008).

The functional link between emphysema and aging implied by the findings on regulation of Klotho and senescence marker protein-30 which are implicated in both of these processes (Afanas'ev, 2010; Koike et al., 2010; Sato et al., 2006; Suga et al., 2000). It remains to be known whether SIRT1 regulates these genes and proteins in response to CS exposure. Several other SIRT1 protein substrates involved in cell stress response signaling and cellular senescence have been identified, including ku70, Wnt/ β -catenin, Notch, and Werner syndrome protein (Guarani et al., 2011; Holloway et al., 2010; Li et al., 2008; Uhl et al., 2010; Vaitiekunaite et al., 2007) (Table 1). Hence, the study on these molecules in condition of oxidative stress/cigarette smoke will further enhance the understanding of inflammaging in pathogenesis of COPD.

SIRT1 and regulation of DNA damage and repair

Accumulating evidence suggests that SIRT1 relocates to the sites of DNA damage and promotes DNA damage repair via deacetylating DSB repair and recombination proteins, such as ku70, NBS, Werner helicase, and nibrin (Gorospe and de Cabo, 2008; Jeong et al., 2007; Uhl et al., 2010; Yuan and Seto, 2007; Yuan et al., 2007). Interestingly, inhibition of

type I and II HDACs did not repress HR, but they function in the DDR to promote DNA NHEJ (Miller et al., 2010; Uhl et al., 2010), suggesting the differentiated role of HDACs (HDAC1 and HDAC2) in DNA damage and repair. SIRT1 also deacetylates histone H3K56 thereby regulating DNA damage and genomic instability (Vempati et al., 2010; Yuan et al., 2009). Histone methylation (e.g., H3K9me3) can also be regulated by SIRT1 via increasing/deacetylating Suv39h1, or enabling histone H3 toward Suv39h1 (Vaquero et al., 2007). Further study is required to investigate which histone residue(s) are modified and how these modifications affect genomic stability, DNA damage repair, and subsequent cellular senescence.

SIRT1 and lung stem cells: regenerative processes

SIRT1 levels have been found to be significantly higher in embryonic stem cells than in differentiated tissues (Saunders et al., 2010). However, SIRT1 deficiency in the embryonic cells leads to embryonic and developmental abnormalities including defects in the formation of the primitive vascular network (Mantel and Broxmeyer, 2008; Ou et al., 2011). COPD represents a disease with premature ageing and cellular senescence in Clara cells and type II epithelial cells, the progenitor cells of airway and alveolar epithelium. Therefore, the regulation of SIRT1 in these progenitor cells would be a promising therapeutic avenue in treatment of COPD.

SIRT1 and cardiovascular homeostasis

SIRT1 interacts eNOS-nitric oxide generating system thereby regulating vascular senescence and dysfunction as well as atherosclerosis (Arunachalam et al., 2010; Ota et al., 2010). SIRT1's protection on aging and premature senescence in cardiomyocytes and endothelial cells is due to antioxidant property through FOXO3 (Alcendor et al., 2007; Tanno et al., 2010). Overexpression of SIRT1 in mouse heart regulates aging and resistance to oxidative stress by inhibition of apoptosis and expression of senescence markers (Alcendor et al., 2007). A recent study has shown that resveratrol and other dietary polyphenols attenuate mitochondrial oxidative stress in endothelial cells via activation of SIRT1 (Ungvari et al., 2009). Activation of SIRT1 by resveratrol led to lysine deacetylation in ischemic preconditioning and protects cardiac ischemic-reperfusion (Nadtochiy et al., 2011). Therefore, SIRT1 exhibits a beneficial role in cardiovascular function, which is damaged in patients with COPD.

Clinical implications of SIRT1 activation in inflammaging

Dietary polyphenols

Naturally occurring dietary polyphenols, such as resveratrol, curcumin, quercetin, and catechins, have been shown to activate SIRT1 directly or indirectly in addition to their antioxidant and anti-inflammatory properties. Resveratrol is beneficial in many other cellular dysfunctions that are known to be associated with COPD including diabetes as SIRT1 is antihyperglycemic and protects against diabetic nephropathy (Sharma et al., 2011). Resveratrol prevents ATP decline, lowers the Km of SIRT1 for NAD⁺, HIF-1 α expression and autophagy providing an additional insight into the role of SIRT1/resveratrol in systemic inflammation and metabolic homeostasis (Zhang et al., 2010b). Resveratrol also indirectly regulates SIRT1 via activating nicotinamide phosphoribosyltransferase and AMP-activated kinase (AMPK) leading to increased intracellular level of NAD⁺ (Canto et al., 2009; Fulco et al., 2008; Hou et al., 2008; Mukherjee et al., 2009; Suchankova et al., 2009; Um et al., 2010). Furthermore, activation of AMPK by 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside (AICAR) increased the SIRT1 protein in skeletal muscle and attenuated LPS-induced lung inflammation (Suwa et al., 2011; Zhao et al., 2008). Recent studies demonstrated that resveratrol is not a specific activator of SIRT1, and treatment with

resveratrol reduces SIRT1 levels as well as induces DNA damage (Beher et al., 2009; Pacholec et al., 2010; Pizarro et al., 2011; Tyagi et al., 2011), suggesting the controversial beneficial role of resveratrol in inflammaging.

There are some scanty reports available that quercetin and catechins also activate mammalian SIRT1 or yeast Sir2 albeit to a lesser extent as compared to resveratrol (Davis et al., 2009; de Boer et al., 2006; Howitz et al., 2003). Therefore, the activation of SIRT1 by polyphenols may be beneficial for regulation of inflammaging (Celik and Arinc, 2010). However, the separate studies show that polyphenols, such as epigallocatechin gallate (EGCG) and quercetin did not exhibit any ability to activate SIRT1 in cellular system (Choi et al., 2009; de Boer et al., 2006; Feng et al., 2009). On the contrary, these polyphenols inhibit SIRT1 activity (de Boer et al., 2006). This is due to their instability leading to formation of oxidized form to produce ROS in the medium in particular with reaction with aldehydes/quinones (i.e. resveratrol, EGCG) or SIRT1-inhibitory metabolites (i.e. quercetin and its metabolites) (de Boer et al., 2006). Understanding the role and mechanisms of polyphenols in SIRT1 regulation and cellular functions will help in identification of pharmacological agents for their possible use as nutraceuticals in prevention/management of inflammaging.

Synthetic pharmacological SIRT1 activators

Multiple SIRT1 activators have been developed, and these molecules increase SIRT1 activity by lowering the K_m of SIRT1 for the substrates (Milne et al., 2007; Smith et al., 2009). SRT1720 has been reported to be 800–1000-fold more effective than resveratrol in activating SIRT1 (Milne et al., 2007). As compared to resveratrol, SRT2172 is more effective in inhibiting MMP-9 production in monocytes (Nakamaru et al., 2009). The efficiency of the SIRT1 activating compounds is strongly dependent on structural features of the peptide and probably on allosteric regulation (Dai et al., 2010; Pacholec et al., 2010). These molecules such as SRT2104, SRT2172, SRT2183 and SRT2379 are undergoing clinical testing in several metabolic diseases including diabetes, obesity and metabolic syndrome (where increased body mass versus lower oxygen consumption plays an important role in metabolic disorders and hence abnormal aging), and appear to be safe in human healthy volunteers and to be promising against these diseases. Further studies are urgently needed to investigate the efficacy of these molecules in COPD/emphysema and normal aging. However, recent studies showed that SRT1720, SRT2183, and SRT1460 are non-specific for SIRT1 activation (Pacholec et al., 2010). Therefore, development of a specific pharmacological SIRT1 activator is crucial in understanding the role of SIRT1 in cellular function and potentially clinical application of SIRT1 activators in diseases associated with inflammaging.

Other modulators of SIRT1 activity

NAD^+ and its dependent deacetylases (e.g., SIRT1) have been linked to lifespan. Due to the wide presence of NAD^+ degrading enzymes, the bioavailability of exogenously given NAD^+ is low and on the other hand may lead to harmful effects when given systemically. A vitamin B3 component represents a NAD^+ precursor, which has low *in vivo* toxicity. However, it has dual effects of SIRT1: either activation or inhibition (Denu, 2005). Administration of nicotinamide mononucleotide may present potential alternative since it does not activate NAD^+ consuming pathways or lead to SIRT1 inhibition. PARP-1 activation drains cellular NAD^+ thereby compromising SIRT1 activity. Hence, inhibition of PARP-1 maintains intracellular NAD^+ pool with elevated SIRT1 activity though controversial results have also been obtained (Caito et al., 2010a; Hwang et al., 2010). Interestingly, an old drug theophylline prevents NAD^+ depletion (Moonen et al., 2005). The NAD^+ maintaining compounds have multiple other functions, which can be independent as well, but there is a

potential in developing compounds that activate SIRT1 by promoting NAD⁺ synthesis, though their clinical testing and possible toxicities have not been yet evaluated.

Metformin is a widely used drug especially for adult onset type II diabetes. Recent study has shown that the mechanisms associated with metformin include SIRT1 activation, which is associated with reduced TORC2 protein (Caton et al., 2010). It appears that at least in muscle cells the inhibitory effects of metformin on fatty acid metabolism occur via phosphorylation of AMPK- α (Bogachus and Turcotte, 2010; Caton et al., 2010). Several studies are ongoing on metformin and its effects especially during COPD exacerbations with diabetes.

Conclusions and future directions

Cigarette smoke is the primary cause of COPD characterized by accelerated decline in lung function, abnormal inflammation and premature lung aging. Targeting lung inflammation and cellular senescence as well as premature lung aging would be a promising therapeutic intervention for COPD/emphysema. SIRT1 plays a pivotal role in protecting inflammatory response and cell senescence, which is significantly decreased in lungs of patients with COPD. It is interesting to note that mouse sir2 homolog SIRT6 is also involved in the genomic stability, DNA damage response, inflammation, cellular senescence and aging (Kawahara et al., 2009; Lombard et al., 2008; Michishita et al., 2008; Mostoslavsky et al., 2006; Yang et al., 2009). We have recently shown that SIRT6 in fact promotes DNA repair by activating PARP-1 via lys521 residue, thereby stimulating poly-ADP-ribosylase activity and enhancing DSB repair under oxidative stress (Mao et al., 2011). Hence, the regulation of SIRT1 or SIRT6 activity by dietary polyphenols, specific activators (e.g., SRT2172 and SRT1720), or AMP-activated protein kinase activators (e.g., AICAR), and/or other specific activators of SIRT6 is a promising therapeutic strategy against many chronic inflammatory diseases including the diseases which are associated with inflammaging (e.g., COPD and its comorbidities) (Nakamaru et al., 2009; Tang et al., 2011; Wang et al., 2011). However, the most polyphenols are poorly absorbed, rapidly metabolized and oxidized, and undergo sulfation and glucuronidation, and also lead to formation of their own oxidation products. The biochemical mode of action of dietary polyphenols on activation of SIRT1 is an important area for further research. Further studies are required to validate the involvement of SIRT1 in inflammaging of lung, and whether pharmacological activation of SIRT1 protects lungs against inflammaging triggered by environmental pollutants, cigarette smoke and other inhaled aldehydes/oxidants.

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Abbreviations

AICAR	5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside
AMPK	AMP-activated kinase
ATM	ataxia telangiectasia mutated
CHK2	checkpoint kinase 2
COPD	chronic obstructive pulmonary disease

DDR	DNA damage response
DSB	double-strand break
EGCG	epigallocatechin gallate
eNOS	endothelial nitric oxide synthase
FOXO3	forkhead box class O 3
HATs	histone acetyltransferases
HDACs	histone deacetylases
HR	homologous recombination
NBS1	Nijmegen breakage syndrome 1
NHEJ	non-homologous end joining
SASP	senescent-associated secretory phenotype
SIPS	stress-induced premature senescence
SIRT1	sirtuin1

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Research Highlights

- Chronic inflammation and cellular senescence occur in premature lung aging.
- Cigarette smoke/oxidative stress causes stress-induced premature senescence.
- Shortening of telomere and alteration in telomerase occur in patients with COPD.
- SIRT1 regulates senescence and inflammaging via telomere, FOXO3, p53, and histones.
- Pharmacological or polyphenol activation of SIRT1 would halt lung inflammaging.

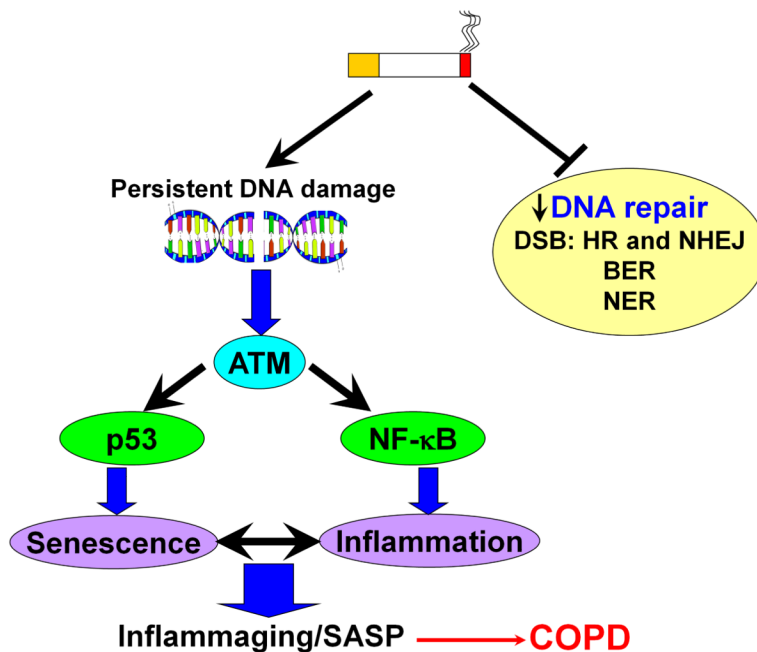


Figure 1. Oxidative stress induces persistent DNA damage leading to cellular senescence and inflammation

Sustained or persistent DNA damage from oxidative/carbonyl stress recruits checkpoint kinase ataxia telangiectasia mutated (ATM) leading to cellular senescence and inflammatory response through activation of p53 and NF- κ B, respectively. Oxidative/carbonyl stress also damages the DNA repair pathways, such as double-strand break (DSB), base excision repair (BER), and nucleotide excision repair (NER), which further cause DNA damage. The cellular senescence and inflammation will form a positive feedback to compromise normal cellular homeostasis.

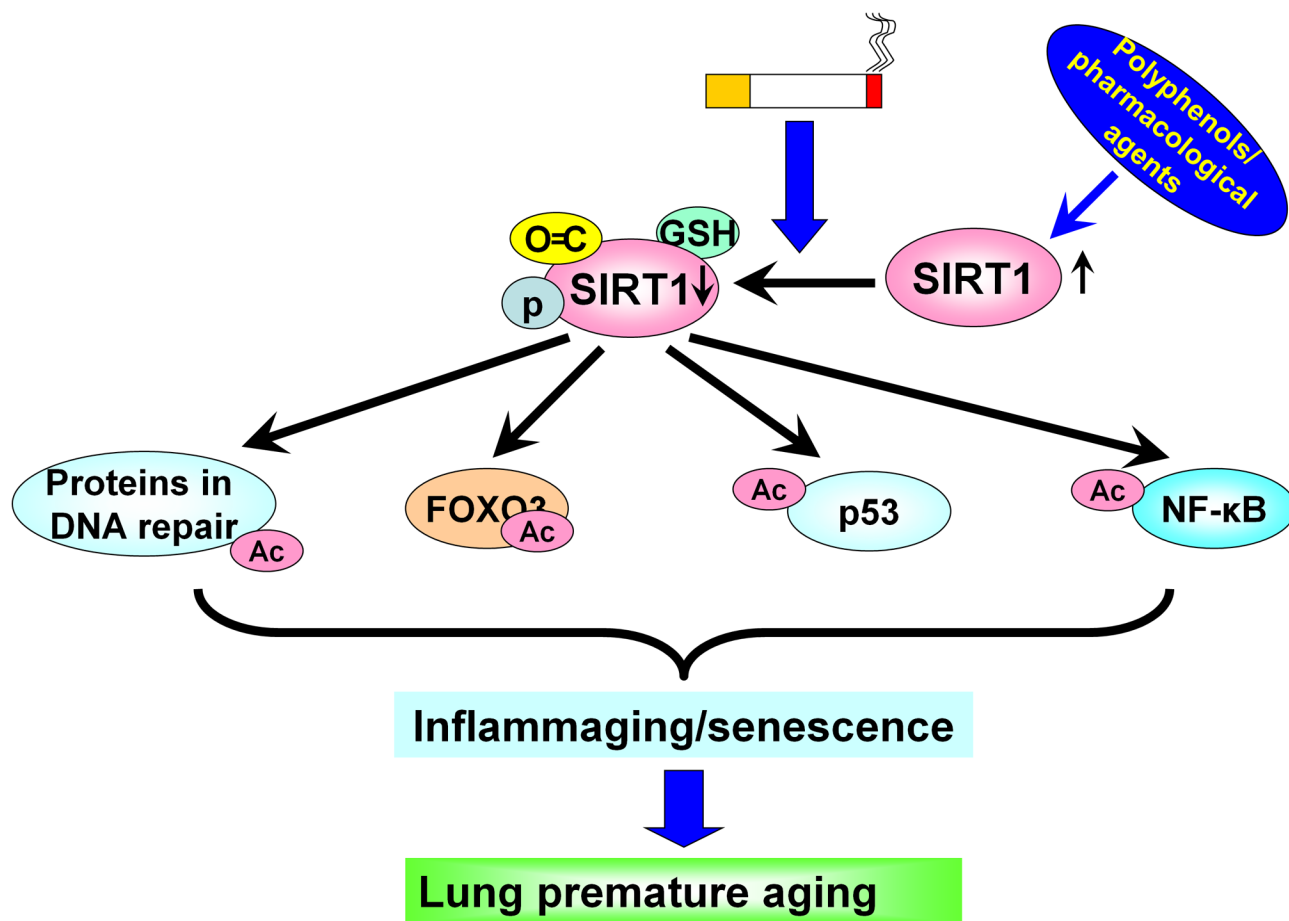


Figure 2. SIRT1 reduction caused by cigarette smoke results in deacetylation of proteins in DNA repair, FOXO3, p53 and NF-κB leading to premature lung aging
 SIRT1 is subjected to posttranslational modifications in response to oxidative/carbonyl stress, which causes the acetylation of various substrates, including ku70, Werner syndrome protein, FOXO3, p53 and NF-κB. These molecules play an important role in initiating and causing inflammation, cellular senescence and DNA damage, which is a major characteristic of lung premature aging. Activation of SIRT1 by polyphenols and its analogs (pharmacological activators) may attenuate lung inflammaging.

Table 1
SIRT1-regulated proteins and their involvements in cellular senescence and DNA damage repair process

Proteins	Cellular senescence	DNA damage repair	Alteration in response to oxidative stress
FOXO3	Inhibits cellular senescence	Promotes DNA damage repair via interacting with ATM	Acetylated and degraded
p53	Induces cellular senescence	Causes DNA damage	Acetylated and increased
NF- κ B	Induces SASP after sustained activation	Protects DNA damage at earlier phase	Acetylated and activated
eNOS	Delays endothelial cell senescence	-	Acetylated and deactivated
Notch	Induces cellular senescence	Protects DNA damage	Acetylated and destabilization
Werner syndrome protein	Protects cellular senescence	Stimulates repair of DNA damage	Degraded
Klotho	Suppresses cellular senescence	Reduces DNA damage	-
SMP-30	Protects cellular senescence	Reduces DNA damage	Decreased with aging
Wnt/ β -catenin	Promotes cellular senescence	-	No significant change in
Ku70	Attenuates cellular senescence	Involved in NHEJ pathway	lungs of COPD patients
Ku86	Suppresses cellular senescence	Involved in NHEJ pathway	Decreased