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Review

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). Sirtuin1 (SIRT1), a nicotinamide adenine dinucleotide (NAD^+)-dependent protein/histone deacetylase, regulates inflammation, senescence/aging, stress resistance, and deoxyribonucleic acid (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 the lung inflammaging, which is associated with the DNA damage response, transcription activation and chromatin modifications. SIRT1 regulates inflammaging via regulating forkhead box class O 3, p53, nuclear factor kappa 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 anti-oxidant 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.

Contents

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 jointing; SASP, senescent-associated secretory phenotype; SIPS, stress-induced premature senescence; SIRT1, sirtuin1.

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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 exists (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 are 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 aldehyde-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 ~4700 different highly reactive chemical compounds/aldehydes are present in per puff of cigarette smoke, which are the major risk factors in the development of COPD. They account for ~80%–90% of COPD cases in USA (Sethi and Rochester, 2000). Additionally, noxious environmental gases/particles, such as NO_2, SO_2, 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 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 requiring from months to years (Louhelainen et al., 2009, 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 abnormalities 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 link COPD and other comorbid conditions remain to be studied. It is apparent that, besides local inhaled therapies, systemic and oral therapies with minimal side effects are necessary to slow the progression of COPD 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 Pa_{O2}, Sa_{O2}, 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/oxidant/aldehyde exposure has been shown to induce senescence (i.e., stress-induced premature senescence, SIPS) in both alveolar epithelial cells and fibroblasts as well as in endothelial cells, which is independent of telomere shortening (Muller et al., 2006;