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Sirtuins and Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is one of the world leading causes of death. It has been recently related to aging and inflammation, as well as sirtuins are actually recognized to be involved in both these phenomena. Sirtuins are a family of highly conserved protein deacetylases and they influence the factors that worsen physiological aging such as glucose metabolism, DNA stability and cancer, neurodegenerative processes, etc. Among the seven sirtuins, SIRT1 and SIRT6 have been deeply investigated in COPD. Actually researchers hypothesize that SIRT 1 activators could play a fundamental role in counteract COPD. Natural compounds as Resveratrol are actually retained SIRT1 activators and could be indicated as powerful weapons against this complex disease.

Keywords

Sirtuins, Chronic Obstructive Pulmonary Disease, Resveratrol, Wine

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the ten leading causes of total years life lost in 2016 [1].

It also requires the greatest amount of health care utilization [2] also because patients frequently undergo exacerbations [3] and almost all of them have comorbidities [4], thus negatively influencing their work ability and global social costs [5].

In the last decade, a growing body of evidences lead researchers to consider COPD as an age-related disease: In fact an increased prevalence in elder population along with the presence in COPD of morpho-structural alterations similar to what observed in old lung, has been widely described [6].

Many aging features such as telomere shortening, cellular senescence, impaired

autophagy, mitochondrial dysfunction, stem cell lost, genetic and epigenetic modifications, and a low-grade chronic inflammation (the so-called inflammaging) [7] are evident in COPD and some of them are strictly correlated with smoke habit and number of pack-years [8].

The most of the above mentioned processes are strictly interrelated and in different manners they are involved in pathophysiology of COPD [9].

Along with these observations, antiaging molecules have been widely recognised to be reduced in COPD. As a consequence, cell agents that regulate these phenomena have been deeply investigated. Among them, Sirtuins are worthy of consideration.

2. Sirtuins

Sirtuins are a family of highly conserved protein deacetylases that depend on nicotinamide adenine dinucleotide for their activity. They catalyze the removal of acetyl groups from lysine residua. They may promote different post translational modifications in many different proteins so they are actually known as deacylases [10].

Up to now, seven sirtuins have been recognized, listed from 1 to 7. Each of them shows a catalytic domain (present in all sirtuins) whilst different N- and C-ends give selective biological features to every sirtuin.

In a previous paper [11] we examined the role of sirtuins in influencing the factors that worsen physiological aging such as glucose metabolism, DNA stability and cancer, neurodegenerative processes, etc.

Now our aim was to clarify the role of sirtuins as pathophysiological agents and therapeutical targets in COPD.

3. Sirtuins and COPD

Among the different Sirtuins, SIRT1 (the most deeply investigated sirtuin in mammals) plays a fundamental role in influencing oxidative cell damage and, as a consequence, health and life duration [12]. In fact, it is involved in glucose metabolism, DNA reparation, etc. by modulating oxidative stress response, endothelial dysfunction and inflammation.

Many years ago, Sirt1 levels were found to be reduced in lungs of smokers and COPD patients [13] and this finding was inversely related to increased amounts of oxidative and nitrosative markers. A few years later, another group of authors demonstrated that while SIRT1 decreases, prosenescent factors, such as ciclin-dependent kinase inhibitor 2 and caveolin 1, increase in COPD severity-dependent manner [14] whilst SIRT1 overexpression modulates this phaenomenum [15] and protects against emphysema by counteracting the premature senescence in mice.

In this animal model, these researchers demonstrated the leading role of SIRT1 in attenuating aging-associated manifestations of COPD: interestingly, SIRT1 expression and functional acivity decrease along with age progression.

Last year, for the first time, serum SIRT1 levels were found to be decreased in COPD patients and this reduction was positively correlated with airway obstruction entity, severity of lung emphysema and frequency of exacerbations [16].

More recently, SIRT1 has been demonstrated to protect lungs in the early and late stages of pulmonary fibrosis in patients with systemic sclerosis by reducing proinflammatory and profibrotic processes [17]. Also SIRT7 has been involved in pulmonary fibrosis: in fact its levels are reduced in rat model of this disease and are associated with a profibrotic fenotype of lung fibroblasts [18].

Also cardiovascular function, which is impaired in COPD patients, is positively influenced by SIRT1 which is able to regulate vascular senescence and atherosclerosis development [19].

In addition to SIRT1, SIRT6 have also been shown to improve COPD. SIRT6 is associated with redox state and inhibits cellular senescence and fibrosis [20] [21]. It is also involved in genomic stability, DNA damage response, inflammation, cell senescence and aging [22] so it could be another putative therapeutical target for natural and synthetic compounds.

For all the above described pathophysiological implications, SIRT1 and SIRT6 have been recently identified as the leading targets for a new therapeutical approach in the treatment of COPD [23].

4. Sirtuin Modulation

Different dietary polyphenols such as quercetin, curcumin, catechins and resveratrol have been demonstrated to be able in activating (both directly and indirectly) SIRT1 in addiction to their well known antioxidant and antiinflammatory properties.

Among these natural compounds, Resveratrol plays a leading role. In fact it lowers the Km of SIRT1 for NAD+ [24].

In rat models of COPD, treatment with Resveratrol leads to a significant ($p < 0.05$) reduction of inflammation markers levels (such as IL-6 and IL-8) and reconstruction of small airways [25].

As you know, Resveratrol is a fundamental part of grape. Previously [26] [27] [28] we underlined the beneficial effects of moderate wine consumption in different clinical conditions. In general population [29] wine intake is positively associated with the Forced Expiratory Volume in 1 second (FEV1) [30]. Among wines, the white ones exhibit a positive association with higher levels of FEV1 and FEV1/FVC (Forced Vital Capacity) ratio [30].

These beneficial effects could be enhanced by quercetin, a powerful catechin which was demonstrated to prevent progression of emphysema in mice by reducing oxidative stress, inflammation and lung expression of matrix metalloproteinase activity via an increase of SIRT1 levels [31].

Many Authors investigated about synthetic pharmacological SIRT1 activators and their effects in lung diseases. Interesting results show positive influence of these compounds on septic-associated lung injury [32] [33] emphysema [34] and

asthma [35]

5. Conclusions

SIRT1 activators are promising therapeutical weapons to counteract COPD, as demonstrated by ITO [36] who created the fascinating word "Geroprotectors" to indicate all these agents that fight aging and aging-related disorders.

Could Resveratrol also be considered a Geroprotector? This topic needs further investigations but is undoubtedly worthy of our future attention.

If we consider that "prevent is better than cure", it is reasonable to imagine that a healthy lifestyle, with salubrious foods and beverages, along with a regular exercise, will be a cheap and smart medical prescription in a general population who is always older.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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