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Short Communication

Research Progress of Sirt1 in Lung Injury

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1. Abstract

Recently lung injury has a high clinical morbidity and mortality due to the destroyed alveolar epithelial barrier and endothelial dysfunction. If there is no further treatment, it will be deteriorated into pulmonary fibrosis and even lung cancer. Silencing regulator 2 related enzyme 1 (Sirt1) is a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase, associated with various cellular processes, such as proliferation, apoptosis and inflammation, through deacetylated histones and some non-histone proteins, such as the fork head transcription factor (FOXO) and nuclear factor κB (NF-κB), et al. Sirt1 plays a key role in smoking-induced lung injury, bronchial asthma, and oxidative stress-induced lung disease. It has been found that resveratrol, as a strongest agonist of polyphenols Sirt1, plays an obvious anti-inflammatory effect by de acetylation of several inflammatory related transcription factors, such as NF-κB. Therefore, Sirt1 is a negative regulatory target of inflammatory factors, and Sirt1 signaling pathways can provide a new direction for the treatment of lung injury. In this review, we will discuss about the research progress of Sirt1 in lung injury.

3. Introduction

Sirtuins is a family of Histone De Acetylase (HDACs) family, which catalyzes the de acetylation of histone and non- histone lysine residues [1]. The human Sirt1 gene is located in the chromosome 10q21.3 and gene length is 33.72kb, which mainly located in the nucleus and expressed in the eukaryotes and prokaryotes. The mammalian Sirtuins family has seven members (Sirt1-Sirt7), which share a common highly conserved catalytic domain with different N- and C-terminal structures, and different terminal extensions determine their subcellular localization and distribution [2], distributed in mitochondria, cytoplasm, nucleus and tissues. Sirt1, 6 and 7 are mainly located in the nucleus, where Sirt1 and Sirt2 can be located in the nucleus or in the cytoplasm [3,4]. Sirt3, 4 and 5 are mainly located in mitochondria, mainly involved in stress response, aging, cardiac metabolic diseases and liver metabolic pathways [5-8]. In addition, Sirtl also has a certain expression in the cytoplasm, and there is a nuclear-cytoplasmic shuttle movement to adjust the balance and homeostasis of all aspects in vivo. Studies have shown that Sirt1-3 has strong deacetylase activity, while SIRT4-7 has weaker deacetylase activity [9]. Sirt1 is involved in chromatin modification, epigenetics, inflammation, and stress responses, interacting with histones and some non-histone substrates. Among them, non-histone substrates include that tumor suppressor gene p53, nuclear factor-κB (NF-κB), peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α), FOXO, liver x (LXR), PARP, Ku70 and hypoxia-inducible factor (HIF)-1α, and so on [10]. Moreover, Sirt1 regulates metabolism by de acetylation of PGC-1α, which plays an important role in glucose and lipid metabolism during fasting, and is involved in regulating glucose metabolism, lipid metabolism, cell differentiation, cell stress, apoptosis and inflammatory reactions and so on. Sirt1 regulates glucose metabolism because FOXO1, as a de acetylating transcription factor and co-activating factor peroxisome proliferator, activates receptor gamma co-activator 1α (PGC1α), and enhances the process of sugar isogenesis. Meanwhile, Sirt1 is also expressed in degenerative diseases, acute myeloid leukemia, colon cancer, prostate cancer, ovarian cancer, breast cancer, melanoma and lung adenocarcinoma; Sirt2 is mainly expressed in neurodegenerative diseases, brain tissue and glioma; Sirt3 is mainly expressed in neurodegenerative diseases, B-cell chronic lymphocytic leukemia, mantle cell lymphoma, chronic lymphocytic leukemia, breast

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cancer and gastric cancer; Sirt4 and Sirt6 are mainly expressed in breast cancer and colon cancer Sirt5 is mainly expressed in pancreatic cancer, breast cancer and non-small cell carcinoma; Sirt7 is mainly expressed in cancer: liver, testis, spleen, thyroid and breast [11]. Studies have shown that rs12413112 and rs1467568 polymorphisms have a protective effect on cardiovascular diseases, regarding the location of this polymorphism in the 3′UTR, and many studies have revealed an association between the nucleotide variations in this position and change in the expression pattern of their flanking genes. Hence, it seems that the A-allele of this polymorphism increases Sirt1 expression that results in reduced risk of developing cardiovascular diseases. A significant association between the rs1467568 polymorphism and the risk of type II diabetes during a fatal confrontation with famine, hence Sirt1 is a crucial genetic factor that effects fetal programming during malnutrition.

Alveolar epithelial cells are the first protective barrier, which are also an important respiratory barrier for gas exchange. When inhaled toxic gases and particles by cigarette smoke, epithelial cells cause inflammation and further form a feedback loop for chronic inflammation [12,13]. Pulmonary inflammatory response is a feature of many lung diseases, such as Chronic Obstructive Pulmonary Disease (COPD) [14]. It is widely studied in clinical and scientific research as well as in the mechanism of lung injury. In clinical practice, lung injury occurs mainly due to bacteria or viral infections, inhalation syndrome and severe shock [15]. Inflammation activates alveolar macrophages, which in turn produce cytokines and inflammatory chemokines, which produce reactive oxygen species and reactive nitrogen-induced pulmonary edema [16,17]. Severe pneumonia causes the production of cytokines and chemokines, as well as polymorphonuclear leukocyte infiltration and reactive oxygen species, which in turn leads to damage to the epithelium and endothelium of the lungs, and leads to increased alveolar permeability and hinder to alveolar gas exchange [18]. Changes in the permeability of the alveolar epithelium and endothelial barrier are the pathophysiological features of lung injury, and the pulmonary endothelium plays a key role in lung injury [19,20]. Once activated, endothelial cells secrete cytokines and inflammatory chemokines, such as tumor necrosis factor TNF-α, interleukin IL-1β, and MCP-1 cause the accumulation of neutrophils and macrophages, which in turn leads to dysfunction of cells and organs. The recovery of lung injury requires a complete endothelial barrier and reconstruction as well as alveolar epithelial barrier repair. Sirt1 inhibits the process of inflammation by regulating a variety of mediators, which expression increase can inhibit the release of inflammatory factors, such as the release of tumor necrosis factor-α and interleukin (IL)-8. Therefore, Sirt1 becomes a process that inhibits the development of inflammation and potential targets [21].

3.1. The role of Sirt1 in Chronic Obstructive Pulmonary Disease (COPD)

COPD is one of the global public health challenges at present. Smoking induces oxidative stress, endoplasmic reticulum stress and apoptosis [22], which is the main cause of Chronic Obstructive Pulmonary Disease (COPD) and lung cancer [23]. COPD refers to chronic airflow limitations that cause permanent alveolar wall loss and alveolar space enlargement, thus the deletion of alveolar junction Structural and alveolar space enlargement are the most important pathological changes in COPD. Sirt1 is a transcriptional regulator that inhibits the expression of pro-apoptotic proteins [24], which can de acetylation a variety of transcription factors, for example, it can de acetylation p^{53}, causing p^{53} homeostasis imbalance and reducing the expression of Bax in the downstream gene [25], and then inhibits apoptosis. If the down regulation of Sirt1 expression can increase the level of p^{53} acetylation, and then promote apoptosis and senescence [26,27]. Studies have shown that Sirtl is a key factor in regulating oxidative stress in organisms, and can de acetylation of non -histone proteins such as antioxidants in cells. If the expression is suppressed, oxidative stress in cells will increase, which accelerate cell aging and damage oxidative stress to accelerate the aging process, and Sirt1 can inhibit oxidative stress, endothelial dysfunction and inflammatory response, and also participate in the development of COPD. It is reported that Sirt1 is a long-lived factor, which involve in the development of COPD through regulating oxidative stress, inflammation and senescence [28]. The latest research shows that Sirt1 protects the oxidative stress induced by smoking and de acetylation of FOXO3 [29]. Because FOXO3 is the substrate of Sirt1 non-histone, Sirtl can regulate the expression of antioxidant genes and enzymes in vivo by de acetylation of FOX03, thus reducing the damage of oxidative stresses products to cells and delaying cell apoptosis and aging. Because Sirt1 can de acetylate FOXOs, p53 and NF-κB, which can control the development process of COPD [30]. The up-regulated expression of Sirt1 reduces the level of acetylation of FOXO3 and protects the acute lung injury by regulating the downstream of antioxidant and anti-apoptotic factors [31-34]. The histopathological changes in acute lung injury include the following aspects: (1) the accumulation of neutrophils and macrophages after being activated; (2) apoptosis; (3) the increase of pro inflammatory and pulmonary capillary of permeability [35-37]. The expression of Sirt1 in the lung tissue of smokers was reduced in the nucleus [38], and the expression of Sirt1 was significantly reduced in smokers and COPD patients. In clinical, monitoring the level of Sirtl in the lung tissue of patients may provide a new way of thinking for the treatment of COPD.

3.2. The role of Sirt1 in lung fibrosis

Fibrosis is usually associated with aging and disease, all over the body and the formation of excessive fibrous connective tissue, which is caused by typical organ damage and eventually leads to organ failure [39]. The development process of fibrosis is usually divided into four main stages [40]. The first stage is primarily injury of organs and tissues that is the injury of epithelial cells and main cells; the second stage is the activation of the fibrous effector cells; the third stage is the deposition of the extracellular matrix; the fourth stage is the promotion of the dynamic deposition of extracellular matrix. The development of fibrosis eventually leads to organ failure and even death [25,41]. At the early stage of lung injury, lung tissue is surrounded by chronic inflammation, and subsequently the outer tissue wall is damaged by collagen [1,42]. Different pathological findings show that accumulation of extracellular matrix components is a common feature of fibrosis [7,43]. The abnormal accumulation of extracellular matrix, which is a typical fibrosis feature, leading to damage of tissue structure and function of [43,44]. Clinical chemical poisoning causes high morbidity and mortality worldwide. It is reported that there are more than two million cases, dying of parquet poisoning each year in China [45-48], in which parquet poisoning death is due to acute lung injury and multiple organ failure [49], however, parquet poisoning is the main cause of lung injury caused by oxygen free radicals [50,51]. As an inflammatory disease, lung injury can leading to alveolar damage, aeration perfusion to varying degrees, and non-cardiogenic pulmonary edema, and eventually leads to death [52]. There are various causes of fibrosis, including acute lung injury, chronic inflammation, autoimmune reaction and genetic changes.

Clinically, chemical poisoning causes high morbidity and mortality worldwide. It is reported that China has died of parquet poisoning more than two million cases each year[45-48], among which parquet poisoning death is due to acute lung injury and more Organ failure[49], lung injury caused by parquet poisoning is mainly the production of oxygen free radicals [50,51]. As an inflammatory disease, lung injury lead to alveolar damage, varying degrees of ventilatory perfusion, and non-cardiogenic pulmonary edema, and ultimately death [52]. The FOXO family belongs to the fork head transcription factor family and is an important cell fate regulator [53], which transfers from cytoplasm to nucleus and plays a transcriptional role by binding to promoter of target gene. It has been shown that acetylation of FOXO increases nuclear transcription and promotes transcriptional activity [54], and FOXO can be deacetylated by Sirt1 to enhance binding and transcriptional activity with DNA [55]. Therefore, Sirt1 can inhibit the development of pulmonary fibrosis through de acetylation of FOXO, which may provide a new strategy for the treatment of pulmonary fibrosis.

3.3. The role of Sirt1 in lung cancer

Among all cancers, lung cancer is one of the highest morbidity and mortality worldwide [56], of which approximately 80% are Non-Small Cell Lung Cancer (NSCLC) [57]. The role of Sirt1 in the mechanism of tumorigenesis and development has been paid more and more attention. Sirt1 may play a role in inhibiting cancer and promoting cancer in cancer. Recently, Sirtl is closely related to the metastasis of tumor cells, which can be used as a target for the treatment of lung cancer patients and its expression can also be one of the prognostic indicators of NSCLC treatment. Sirt1 and AMPK are closely related to the development of non-small cell lung cancer [58,59]. AMPK widely exists in organisms and plays a key role in cell energy metabolism and cell growth and differentiation. It is widely believed that AMPK has great potential in the treatment of cardiovascular diseases, diabetes, obesity, central nervous system diseases and cancer [60,61]. However, by H&E staining, Western blot, RT-PCR and immunofluorescence test, it was proved that the expression of Sirt1 and AMPK in NSCLC decreased significantly compared with in normal group [62]. Further exploration of the role of Sirt1 and AMPK in NSCLC provides a new direction for the treatment of NSCLC. Sirt1 may be a new target for the treatment of NSCLC, which brings new ideas for the clinical targeting therapy of NSCLC and the research and development of related targeted drugs. Furthermore, Sirtl plays an important role in the occurrence, development, treatment and prognosis of lung cancer, but its accurate mechanism is still not clear, which still needs further study. Whether Sirt1 has been used as an accelerator or inhibitor in the process of tumor formation and development has yet to be conclusive. However, it is believed that with the continuous discovery of the molecules interacting with SIRT1 and the deepening of the research on the correlation between SIRT1 and tumor, the mechanism of SIRT1 in the formation of tumor may be a new target for the treatment of tumor.

4. Conclusions

In short, the increase of the pro inflammatory mediators leads to lung injury [63]. It is reported that IL-6 is the medium for inducing acute lung injury and pulmonary edema, and Sirt1 plays a key role in regulating the development of inflammation, and it plays an anti-inflammatory effect by controlling the release of pro-inflammatory factors [64,65]. Oxidative stress is considered to be an important factor in cell damage. Oxygen free radicals can cause membrane lipid peroxidation and protein oxidation to destroy cell integrity and induce apoptosis. Sirtl is a deacetylase dependent on NAD^+, which plays a role in antioxidant stress, anti-inflammatory, and inhibition of apoptosis through the role of histone / non histone de acetylation group. A large number of studies have found that Sirtl has a strong anti-oxidative stress in neurodegenerative diseases, cardiovascular system diseases and renal system

diseases, which mechanism is still unclear, and further discussion is needed. Sirt1 plays a key role in the death of apoptotic cells, cell senescence and endothelial growth in the stress response pathway [66], but the mechanism of protecting blood vessels from stress induced endothelial dysfunction should be further explored. However, there are not many researches on Sirt1 in lung injury, so further exploration is needed. Research on the treatment strategies of Sirt1 agonists for lung injury and other diseases will be the direction of future research, and actively explore the pathogenesis of Sirtl in the regulation of respiratory diseases and the accurate target of its role, and actively develop its agonists and inhibitors in the clinical appliance of the broad prospects.

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