

Research Progress on the Role of SIRT1 in Obstructive Sleep Apnea

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Abstract: Obstructive Sleep Apnea (OSA) is a common sleep disorder. OSA is closely related to a variety of serious complications such as cardiovascular diseases, metabolic disorders, diabetes, cognitive impairment, and tumors. Silent information regulator 2 homolog 1 (SIRT1), a class III histone deacetylase, regulates key biological processes such as anti-oxidation, anti-inflammation, metabolic homeostasis and apoptosis. It plays a core protective role in a variety of pathophysiological mechanisms of OSA. This review systematically summarized the association of SIRT1 and its gene polymorphisms with the occurrence and development of OSA and its complications, elaborated the changes in the expression level of SIRT1 in OSA animal models and patients, and commented on the clinical research progress of targeted activation of SIRT1 as a potential treatment strategy for OSA. These findings provide an important theoretical basis and new ideas for the development of new strategies for clinical prevention, diagnosis and treatment of OSA based on SIRT1.

Keywords: SIRT1; Obstructive Sleep Apnea; Biomarkers; Genetic Polymorphism.

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder. During sleep, patients experience repeated narrowing or collapse of the pharyngeal airway, leading to upper airway obstruction, which in turn causes reduced inspiratory airflow or apnea. To restore ventilation, patients are often forced to awaken from sleep, resulting in a series of pathophysiological changes such as intermittent hypoxia, sleep fragmentation, and decreased blood oxygen saturation. These changes further contribute to symptoms such as daytime sleepiness and fatigue [1]. Numerous studies have indicated that inflammatory responses, oxidative stress, metabolic dysregulation, and autonomic nervous system dysfunction are intricately interconnected and collectively contribute to the pathogenesis and progression of OSA. OSA has a high global prevalence. It is estimated that approximately 936 million adults aged 30–69 is affected by mild to severe OSA, among whom 425 million have moderate to severe conditions. China has the largest number of OSA patients, followed by the United States, Brazil, and India [2]. OSA is widely recognized as a major public health concern, significantly elevating the risk of various complications such as hypertension, diabetes, cardiovascular diseases, dementia, cerebrovascular diseases, and metabolic syndrome [3-5]. This imposes a substantial burden on global healthcare systems. Therefore, a deeper understanding of its pathogenesis is crucial for developing effective diagnostic and therapeutic strategies. SIRT1 is involved in regulating multiple pathophysiological processes, including cellular senescence and apoptosis, DNA repair, glucose and lipid metabolism, oxidative stress, inflammatory responses, and tumorigenesis. In recent years, growing attention has been paid to the relationship between SIRT1 and obstructive sleep apnea (OSA). Changes in SIRT1 expression levels, its gene polymorphisms, and its interactions with other signaling

pathways may play significant roles in the pathogenesis of OSA and the development of its complications. This review systematically summarizes the association between SIRT1 and its gene polymorphisms with the occurrence and progression of OSA and its complications. It elaborates on the characteristics of SIRT1 expression changes in both OSA animal models and patients, and evaluates the progress in clinical research regarding targeting SIRT1 activation as a potential therapeutic strategy for OSA, aiming to provide a theoretical basis and new insights for future in-depth research and clinical practice.

2. The Biological Functions of SIRT1 Protein

SIRT1 is a nicotinamide adenine dinucleotide (NAD⁺)-dependent class III histone deacetylase that is widely expressed in various tissues and cells. Its protein structure consists of a large domain primarily composed of a Rossmann fold and a small domain containing a zinc-binding motif (Cys-X-X-Cys-(X)_{15–20}-Cys-X-X-Cys). Through its deacetylation activity, SIRT1 regulates a diverse array of substrates, including histone residues and key non-histone transcription factors such as p53, forkhead box protein O1/O3 (FOXO1/FOXO3), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), and nuclear factor-kappa B (NF- κ B). These regulatory functions profoundly influence critical biological processes, including glucose and lipid metabolism [6], cell cycle progression, oxidative stress and inflammatory responses [7], DNA repair, as well as cellular senescence and apoptosis [8].

In regulating glucose and lipid metabolism, SIRT1 activates PGC-1 α through deacetylation, modulates the transcription of genes involved in gluconeogenesis, and enhances hepatic glucose production [9]. Regarding cell cycle control, SIRT1 inhibits p53 activity via deacetylation, thereby reducing the expression of p53-induced pro-apoptotic

proteins, which suppresses apoptosis and influences the cell cycle [10]. Concurrently, SIRT1 deacetylates FOXO proteins, shifting FOXO-dependent cellular responses from apoptosis towards stress resistance, thereby further impacting cell cycle progression [11]. In the realm of inflammatory regulation, SIRT1 suppresses key inflammatory pathway factors such as NF- κ B, hypoxia-inducible factor 1 α (HIF-1 α) [12], tumor necrosis factor- α (TNF- α) [13], and interleukin-6 (IL-6) [14, 15] through histone deacetylation, leading to reduced release of inflammatory cytokines. Concerning anti-aging, SIRT1 modulates senescence-associated proteins including NF- κ B, AMP-activated protein kinase (AMPK), p53, PGC-1 α , and FOXO via deacetylation, thereby promoting DNA repair and delaying cellular senescence. Given that telomere shortening is a hallmark of aging, SIRT1 helps prevent telomere attrition and vascular aging by enhancing endothelial nitric oxide (NO) production [16].

3. Expression Changes of SIRT1 Protein in OSA

The core feature of OSA is chronic intermittent hypoxia (CIH). CIH activates pro-inflammatory factors, increases downstream inflammatory mediators, and triggers a series of pathophysiological changes including oxidative stress, cytokine dysregulation, systemic inflammation, activation of thrombotic factors, hypercoagulability, sympathetic nervous system dysfunction, reduced nitric oxide (NO) production, and endothelial dysfunction [17,18].

In animal model studies, after exposure to an intermittent hypoxia environment simulating OSA, the expression of SIRT1 in multiple tissues of mice tends to be downregulated. This downregulation may be related to CIH-induced oxidative stress and inflammatory responses suppressing SIRT1 expression. A study investigating the correlation between brainstem SIRT1 expression and the sleep apnea index in rats found that brainstem SIRT1 levels were negatively correlated with the frequency of spontaneous apnea during the rapid eye movement (REM) sleep phase, but positively correlated with the frequency of post-sigh apnea during REM sleep. When rats were divided into normal control, sustained hypoxia, intermittent hypoxia, and intermittent hypoxia with hypercapnia groups, significant differences in brainstem SIRT1 protein expression were observed among the groups. This study suggested that low SIRT1 levels might weaken antioxidant capacity, leading to an increased frequency of spontaneous apnea, while increased SIRT1 expression during hypoxia could be a compensatory protective response [19]. Another recent study using a CIH mouse model also confirmed that SIRT1 plays a protective role in CIH-induced neural injury [20].

In clinical studies, serum SIRT1 concentration and activity in OSA patients are lower than those in healthy populations. Notably, SIRT1 expression levels are negatively correlated with the severity of OSA, suggesting that SIRT1 downregulation may be involved in OSA progression [21]. Studies have also found that untreated OSA patients exhibit reduced SIRT1 activity and decreased levels of serum nitric oxide metabolites (NOx). SIRT1 protein levels were positively correlated with the minimum arterial oxygen saturation (SaO₂) and negatively correlated with the apnea-hypopnea index (AHI). The decrease in SIRT1 leads to reduced NO bioavailability, inhibiting vasodilation and promoting vascular aging and cardiovascular diseases. The

reduction of SIRT1 is associated with minimum SaO₂, AHI, and potentially existing oxidative stress [22]. Similarly, Khalyfa et al., through investigating the relationship between OSA patients and the risk of end-organ morbidity, found significantly reduced SIRT1 expression in untreated OSA patients, which induced vascular aging and exacerbated the risk of end-organ morbidity in OSA patients [23]. Furthermore, a prospective study involving 40 patients with moderately severe to severe OSA requiring mandibular advancement device (MAD) therapy and 20 healthy controls found that OSA patients had shortened leukocyte telomere length (LTL) and reduced SIRT1 protein levels before MAD treatment. After 3 months of MAD therapy, SIRT1 levels could return to normal [24].

4. SIRT1 Gene Polymorphisms and OSA

The SIRT1 gene has various single nucleotide polymorphism (SNP) sites, among which rs7895833 is a frequently studied locus. Research indicates that this polymorphism may be associated with OSA susceptibility and severity. Individuals carrying specific alleles (such as the G allele) may have a higher risk of developing OSA or more severe conditions [21]. A study on adult Turkish OSA patients using opposing twin-color primer PCR technology found that the rs7895833 G allele had the highest frequency in female patients with severe OSA, indicating a gender-dependent effect on OSA severity. The study also found that plasma SIRT1 levels were negatively correlated with age in the total sample and in males, and positively correlated with body mass index (BMI) in females, suggesting that SIRT1 might indirectly influence OSA occurrence through pathways related to aging and BMI [21].

5. Research on SIRT1 in OSA-Related Complications

5.1. OSA and Metabolic Syndrome

OSA patients often exhibit manifestations of metabolic syndrome such as insulin resistance, hyperglycemia, dyslipidemia, and obesity. SIRT1 plays a key role in regulating glucose and lipid metabolism. Wang et al. [25] studied the effect of resveratrol (RSV) on CIH-induced insulin resistance in rats. The results showed that RSV inhibited weight gain in a dose-dependent manner, improved liver morphology, and significantly reduced insulin resistance. Upper airway muscle dysfunction in obese OSA patients is closely related to nicotinamide phosphoribosyltransferase (NAMPT)-mediated imbalance in nicotinamide adenine dinucleotide (NAD⁺) metabolism. Clinical studies showed that the lean mass percentage of upper airway muscles in patients with moderate-to-severe OSA significantly decreased, accompanied by elevated NAMPT levels. A diet-induced obesity (DIO) mouse model further revealed that NAMPT overexpression led to dysregulation of the NAD⁺/NADH ratio and inhibited SIRT1 activity via acetylation modification, triggering mitochondrial dysfunction, myofiber structural damage, and decreased muscle contractility. Targeted inhibition of NAMPT acetylation could restore SIRT1 function and reverse muscle damage [26].

5.2. OSA and Cardiovascular Diseases

OSA is closely associated with cardiovascular diseases

such as hypertension, coronary heart disease, heart failure, and atrial fibrillation. Animal experiments have shown that in atrial tissue of chronic OSA canines, the activities of SIRT1 and AMPK were decreased, accompanied by the occurrence of atrial fibrillation[27]. In another study, a chronic hypoxic OSA rat model showed decreased cardiac SIRT1 levels and increased angiotensin II (Ang II) levels. The signaling mediated by Ang II might be one of the pathways inhibiting SIRT1 expression[28]. Wei et al.[29] investigated the age-dependent effects of CIH on cardiac function and its mechanisms. They found that after 8 weeks of severe CIH exposure, young mice only exhibited mild physiological hypertrophy, decreased diastolic function, and type I collagen accumulation, with no significant change in systolic function. In contrast, aged mice showed a significant decrease in cardiac systolic function. CIH promoted mitochondrial fragmentation and decreased membrane potential in the hearts of aged mice, significantly reducing their basal respiration, maximum respiration, and ATP production capacity.

5.3. OSA and Cognitive Dysfunction

Downregulation of SIRT1 exacerbates oxidative stress and neuroinflammation, which can impair neuronal integrity and cognitive function. One study divided C57BL/6J mice into control, mild CIH, and severe CIH groups. It was found that as the severity of CIH increased, the learning and memory abilities of mice progressively declined, accompanied by a reduction in the number of hippocampal neurons and morphological abnormalities. RNA sequencing and Western blot analysis revealed that downregulation of leptin receptor (LepR), SIRT1, and Nrf2 genes exacerbated oxidative stress and neuroinflammation, damaging neurons and cognitive function. This indicates that SIRT1 is a key target in CIH-induced cognitive impairment[30].

5.4. OSA and Renal Injury

Besides causing cardio-cerebral and metabolic pathologies, CIH can also lead to subclinical renal injury. Rat models have confirmed that CIH exposure can induce ultrastructural damage such as podocyte foot process fusion and mitochondrial degeneration in renal tubules. The molecular mechanism involves significant downregulation of SIRT1 ($p < 0.05$) and activation of the HMGB1 pathway: hypoxia relieves the negative regulation of HMGB1 by inhibiting SIRT1, promotes HMGB1 nuclear translocation, subsequently upregulates RAGE/TLR4 receptors and the expression of TNF- α and IL-6, forming an HMGB1-RAGE/TLR4-TNF- α inflammatory axis. This pathway provides a new direction for the early diagnosis of OSA-related renal injury and SIRT1-targeted therapy [31].

6. Potential Applications of SIRT1 in OSA Treatment

Continuous Positive Airway Pressure (CPAP) is the current gold standard method for treating moderate to severe OSA [32]. However, CPAP adherence is generally low. Studies have found that the abnormally low expression of SIRT1 in the blood of successfully treated OSA patients can be reversed[22, 24], suggesting that SIRT1 levels could serve as a potential biomarker for assessing the effectiveness of OSA treatment. Given the pivotal role of SIRT1 in counteracting OSA-induced pathological damage and its consistently downregulated expression in patients, targeted

activation or upregulation of SIRT1 has emerged as a highly promising therapeutic strategy.

Resveratrol (RSV), a natural polyphenolic compound, exerts antioxidant, anti-inflammatory, and metabolism-improving effects by activating SIRT1. It also has the potential to improve synaptic dysfunction, contributing to its positive impact on cognitive impairment. For instance, one study simulated the effects of prenatal intermittent hypoxia (PIH) by treating pregnant C57BL/6J mice with intermittent hypoxia during the postpartum period. It was found that PIH led to learning and memory decline in male offspring. Administration of resveratrol (40 mg/kg) from postnatal days 60 to 88 significantly ameliorated these cognitive deficits. The study also found that PIH reduced the expression of key proteins in the hippocampus, such as SIRT1 and HIF-1 α , and resveratrol intervention restored the expression of these proteins to normal levels. This indicates that resveratrol, by modulating the SIRT1/HIF-1 α signaling pathway, effectively alleviates cognitive impairment, inflammatory response, and synaptic plasticity damage caused by maternal intermittent hypoxia [33].

Astragaloside IV (As-IV) is one of the main active components of the traditional Chinese medicine Astragalus membranaceus. It can exert various effects such as antioxidant stress, anti-inflammation, and cardiovascular protection by activating SIRT1. One study established calpain-1 (Calpain-1) knockout and wild-type C57BL/6 mouse models exposed to CIH to investigate the mechanism of As-IV on vascular endothelial dysfunction (VED). The study found that As-IV improved CIH-induced endothelium-dependent vasodilation and increased NO generation, while simultaneously inhibiting inflammatory and oxidative stress responses and mitochondrial dysfunction. Furthermore, As-IV reduced Calpain-1 expression and restored the levels of SIRT1 and the phosphorylation of AMPK and eNOS. These results indicate that As-IV ameliorates VED induced by CIH through the Calpain-1/SIRT1/AMPK signaling pathway [34].

The traditional Chinese medicine compound Danggui Buxue Decoction (DBD) can alleviate CIH-induced vascular dysfunction through synergistic actions on multiple pathways. In a CIH-exposed mouse model, it was found that DBD synergistically activated the Nrf2/HO-1 antioxidant pathway and significantly upregulated SIRT1 expression, inhibiting the inflammatory cascade and oxidative damage, thereby reversing the CIH-driven vascular aging process and reducing the incidence of cardiovascular diseases[35].

SRT1720 is a SIRT1 agonist. In a CIH mouse model, it inhibited myocardial apoptosis and hypertrophy by enhancing SIRT1 expression, leading to the inference that SRT1720 might alleviate systemic complications induced by CIH in OSA patients. Intervening with upstream regulators of SIRT1 is another important approach. For example, inhibiting miR-34c-5p, which is highly expressed under hypoxia. Anti-agomiR-34c-5p, as an inhibitor of miR-34c-5p, binds to miR-34c-5p, preventing its interaction with the Sirt1 mRNA 3' untranslated region, thereby relieving the targeted inhibition of SIRT1 mRNA by miR-34c-5p, increasing Sirt1 protein stability, and consequently enhancing its expression level. One study explored the role of miR-34c-5p as a potential drug target in a CIH-induced myocardial injury mouse model. A myocardial injury model was established by alternating 7% or 21% O₂ for 12 hours per day for 12 weeks. Mice were treated via tail vein injection with anti-agomiR-34c-5p (20 nM/0.1 ml; once per week for 12 weeks) as the miR-34c-5p inhibitor [36].

In another experiment, mice were treated with the SIRT1 agonist SRT1720 via intraperitoneal injection. The results showed that anti-agomiR-34c-5p treatment significantly inhibited CIH-triggered myocardial apoptosis, alleviated myocardial hypertrophy and oxidative stress, and increased SIRT1 expression in CIH-exposed mice. Both anti-agomiR-34c-5p and the SIRT1 agonist SRT1720 exhibited antioxidant activity and cardioprotective effects in CIH-stimulated mice.

It is worth noting that existing drugs also show potential for indirect regulation. Pai et al. [28] constructed a CIH rat model and found that the angiotensin receptor blocker (ARB) irbesartan alleviated CIH-induced SIRT1 degradation by inhibiting Ang II signaling, thereby preventing the enhanced cardiac apoptosis pathway in chronic sleep apnea. Additionally, leptin, a peptide hormone involved in energy metabolism, has shown neuroprotective effects in various neurological diseases. Scholar Zhang et al. [20] found that leptin alleviated CIH-related cognitive dysfunction, neuronal damage, and oxidative stress in mice by upregulating SIRT1.

As a new therapeutic target for OSA, SIRT1 can not only serve as a efficacy biomarker through its restored expression after CPAP/MAD treatment but can also be targeted for activation through various strategies (natural/synthetic agonists, traditional Chinese medicine compounds, miRNA intervention, and drug repurposing), significantly improving multiple systemic complications induced by intermittent hypoxia, such as cognitive impairment, metabolic disorders, vascular endothelial dysfunction, and myocardial injury.

7. Summary and Perspectives

In summary, there is a close relationship between SIRT1 and OSA. The expression level of SIRT1 is decreased in OSA patients. SIRT1 protein gene polymorphisms may influence the susceptibility and severity of OSA. However, studies on polymorphisms have small sample sizes, and the interaction between genes and environmental factors is complex, making the interpretation of results challenging. SIRT1 plays a significant role in the pathogenesis of OSA and the development of its related complications by regulating various cellular processes. As a new therapeutic target for OSA, SIRT1 significantly improves multiple systemic complications induced by intermittent hypoxia in animal models. However, over 90% of the evidence is limited to animal experiments, and the safety in humans and dynamic mechanisms remain unclear. Future research should strengthen the clinical application of SIRT1 in OSA treatment to verify its safety and efficacy in humans, providing new hope for improving the prognosis and quality of life for OSA patients. Simultaneously, exploring the feasibility and application prospects of gene therapy in OSA treatment will provide more evidence for developing novel SIRT1-based therapeutic strategies.

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