

## Review Article



# As a Modulator, Multitasking Roles of SIRT1 in Respiratory Diseases

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## OPEN ACCESS

Received: Mar 25, 2022

Revised: May 5, 2022

Accepted: May 8, 2022

Published online: Jun 20, 2022

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### Conflict of Interest

The authors declare no potential conflicts of interest.

## ABSTRACT

As far the current severe coronavirus disease 2019 (COVID-19), respiratory disease is still the biggest threat to human health. In addition, infectious respiratory diseases are particularly prominent. In addition to killing and clearing the infection pathogen directly, regulating the immune responses against the pathogens is also an important therapeutic modality. Sirtuins belong to NAD<sup>+</sup>-dependent class III histone deacetylases. Among 7 types of sirtuins, silent information regulator type-1 (SIRT1) played a multitasking role in modulating a wide range of physiological processes, including oxidative stress, inflammation, cell apoptosis, autophagy, antibacterial and antiviral functions. It showed a critical effect in regulating immune responses by deacetylation modification, especially through high-mobility group box 1 (HMGB1), a core molecule regulating the immune system. SIRT1 was associated with many respiratory diseases, including COVID-19 infection, bacterial pneumonia, tuberculosis, and so on. Here, we reviewed the latest research progress regarding the effects of SIRT1 on immune system in respiratory diseases. First, the structure and catalytic characteristics of SIRT1 were introduced. Next, the roles of SIRT1, and the mechanisms underlying the immune regulatory effect through HMGB1, as well as the specific activators/inhibitors of SIRT1, were elaborated. Finally, the multitasking roles of SIRT1 in several respiratory diseases were discussed separately. Taken together, this review implied that SIRT1 could serve as a promising specific therapeutic target for the treatment of respiratory diseases.

**Keywords:** Silent information regulator type-1 (SIRT1); Deacetylation; Respiratory diseases; Modulate; Promising target

## INTRODUCTION

At present, respiratory diseases, especially infectious respiratory diseases, are still the biggest threat to human health. Infection-induced inflammation is a physiological response of the immune system to harmful infectious stimuli. In response to such stimuli, immune cells, such as macrophages and neutrophils cells take concerted actions to recover and maintain immune homeostasis. Immune imbalance has been implicated to be the pathogenesis of various respiratory diseases, including coronavirus disease 2019 (COVID-19), bacterial pneumonia,

### Abbreviations

COVID-19, coronavirus disease 2019; HMGB1, high-mobility group box 1; SIRT1, silent information regulator type-1; NAM, nicotinamide; Lys, lysine; OAADPr, O-acetylated ADP-ribose; PPAR- $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$ ; Bax, B-cell lymphoma 2-associated X protein; miR, microRNA; NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; MyD88, medullary differentiation factor 88; HDAC, histone deacetylase; FoxOs, forkhead box Os; ER, endoplasmic reticulum; I/R, ischemia/reperfusion; UUO, unilateral ureteral obstruction; siRNA, small interfering RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; hBD-2, human  $\beta$ -defensin-2; Mtb, Mycobacterium tuberculosis; ARDS, acute respiratory distress syndrome.

### Author Contributions

Conceptualization: Ding J; Formal analysis: Zhang F; Writing - original draft: Zhou Y, Zhang F; Writing - review & editing: Ding J.

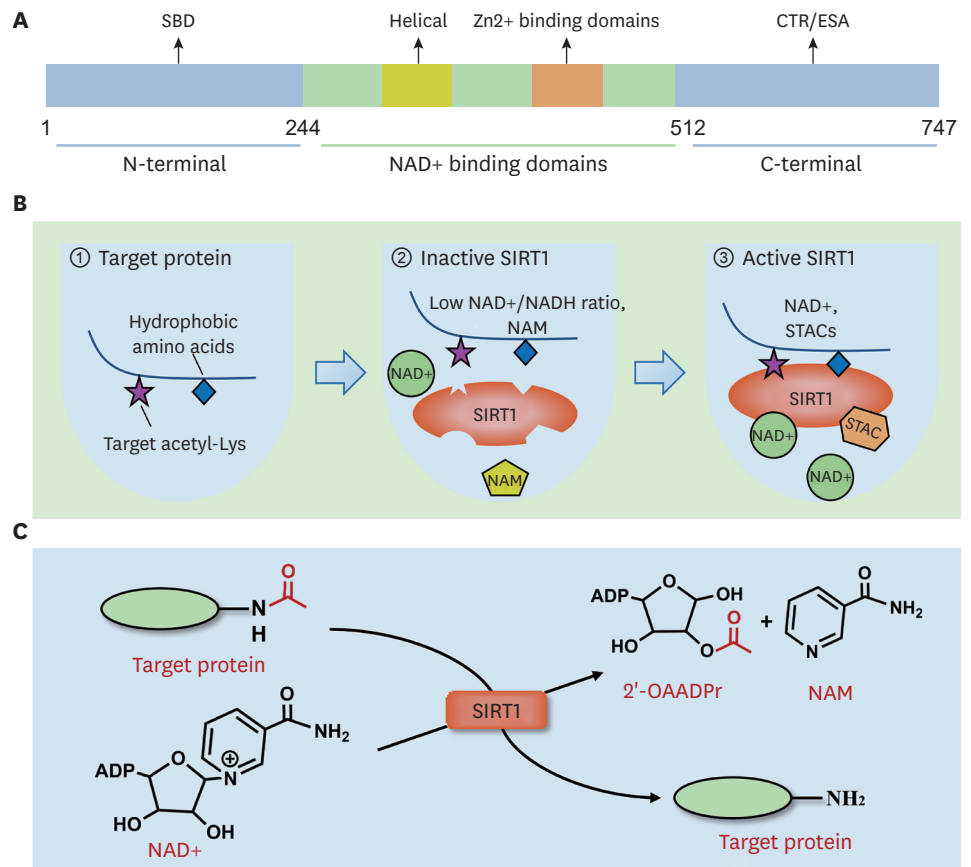
tuberculosis, and so on (1-3). Actively restoring the balance of the immune system will be an effective treatment strategy. High-mobility group box 1 (HMGB1) as the core molecule of the immune regulatory network has become a research hotspot. Silent information regulator type-1 (SIRT1) has received particular attention based on its specific modulatory role on HMGB1.

SIRT1 can regulate the immune system and restore immune homeostasis through its NAD<sup>+</sup> dependent histone deacetylase (HDAC) activity. It shares a generic catalytic core domain with other sirtuins family members, but it has its unique N-terminal and C-terminal sequences. Substrate and catalytic core domain binding plays an essential role in the deacetylation activity of SIRT1. Based on the structure characteristics, SIRT1 was originally identified as a critical enzyme to increase life expectancy in yeast, worm, fly and mice (4). More importantly, it also has other vital functions such as anti-apoptosis, anti-oxidation, anti-inflammation, and regulating autophagy and mitochondrial biogenesis (5). At present, the mechanisms by which SIRT1 and HMGB1 participate in inflammation are still not fully defined. However, there is no doubt that SIRT1 is involved in a variety of respiratory diseases, including COVID-19, bacterial pneumonia, tuberculosis, etc., bringing a heavy burden to patients and society. It is of great significance to validate SIRT1 as a promising therapeutic target. Hence, the focus of this review is to summarize the latest advances regarding the potential beneficial roles of SIRT1 in regulating respiratory inflammation.

## MOLECULE STRUCTURE AND NAD<sup>+</sup> DEPENDENT CATALYTIC CHARACTERISTICS OF SIRT1

Sirtuins belong to the NAD<sup>+</sup> dependent class III HDAC family, and are highly conserved during the process of evolution (6,7). Currently, 7 Sirtuin members including SIRT1-7 have been identified. SIRT1, SIRT6, and SIRT7 are mainly localized in the nucleus, while most SIRT3, SIRT4, and SIRT5 are localized in mitochondria (8). Residues 41-46 of SIRT1 protein constitute a nuclear localization signal (KRKKRK). Moreover, SIRT1 is also expressed in the cytoplasm, and the nuclear import and export sequences on N-terminal region are responsible for nucleocytoplasmic shuttling of SIRT1 (9). SIRT1 gene is located on human chromosome 10q22.1, containing 9 exons and 8 introns. Its exons encode 747 amino acids, including about 270 deacetylated amino acids in the core domain (10). The gene sequence is about 33kb in length, and consists of an untranslated region of 53 bp and 1,793 bp at the 5' and 3' ends, respectively (11).

All sirtuins share an evolutionarily conserved NAD<sup>+</sup>-dependent catalytic core domain. Moreover, each of them has a unique N-terminal and C-terminal sequence that is related to its specific cellular localization and function (12,13). The generic catalytic core domain of about 270 amino acids (spanning residues 244-512) folds into 2 subdomains. The larger subdomain adopts a Rossmann fold conformation that is typical for NAD<sup>+</sup> binding proteins, comprising 6 parallel  $\beta$ -strands forming a central  $\beta$ -sheet surrounded by  $\alpha$ -helices. The small subdomain forms a Zn<sup>2+</sup> binding module in which 4 cysteine residues serve as Zn<sup>2+</sup> binding ligands (13). A groove is shaped between the large and small subdomains, which can bind the substrate. Among SIRT1-7, SIRT1 has the largest terminal region extensions. Its unique N-terminal (the NH<sub>2</sub>-terminal region) contains 513-747 residues, and its unique C-terminal (the COOH-terminal region) includes 1-180 residues. SIRT1 protein is characterized by a N-terminal triple-helix bundle representing the sirtuins-activating compounds binding domain, and a C-terminal regulatory segment (9,12,14) (Fig. 1).



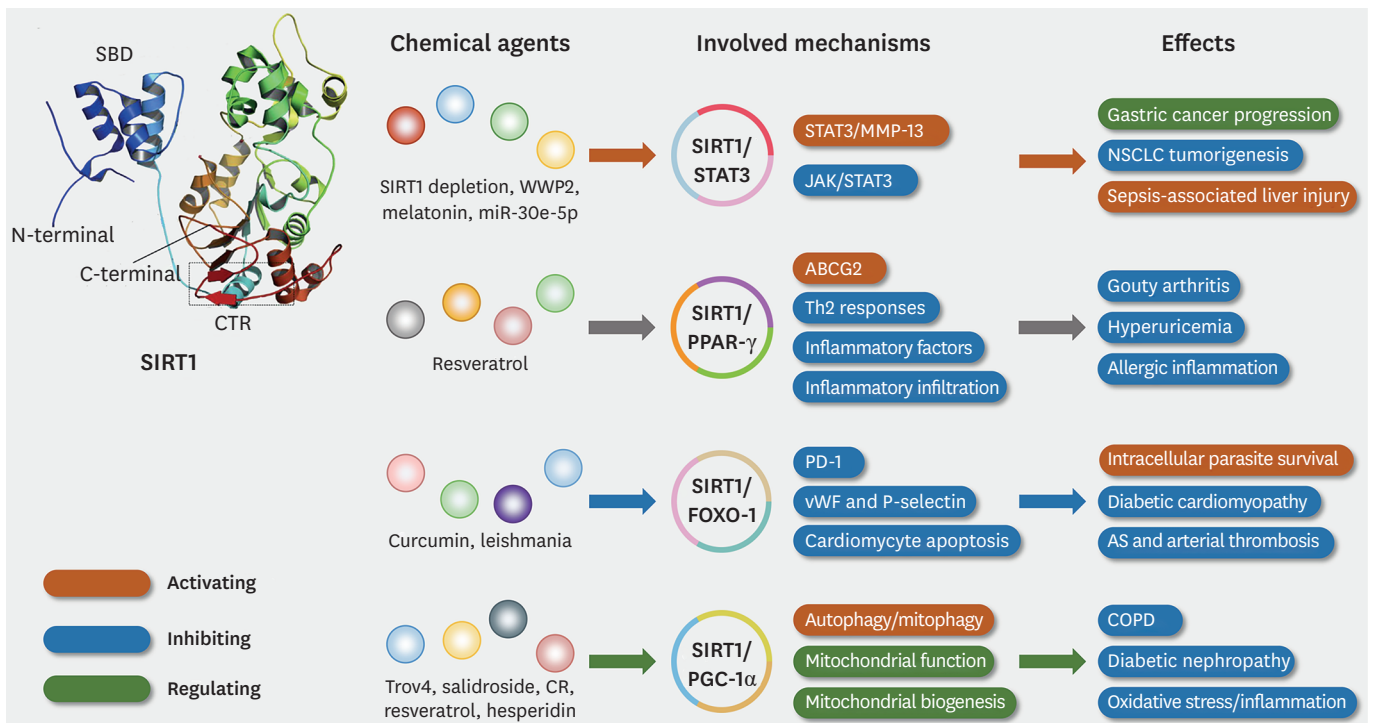
**Figure 1.** Molecular structure and biological functional characteristics of SIRT1. (A) SIRT1 has an evolutionarily conserved NAD<sup>+</sup>-dependent catalytic core domain (244–512 residues), unique N-terminal (513–747 residues), and C-terminal (1–180 residues) sequences. SBD locates on N-terminal, and CTR/ESA locates on C-terminal. (B) SIRT1 prefers specific hydrophobic amino acids near the target Lys residue for substrate recognition (panel 1). Low NAD<sup>+</sup>/NADH ratio and NAM weaken the activity of SIRT1 (panel 2). STACs activate SIRT1 by combining with the SBD, increasing the catalytic activity of SIRT1 (panel 3). (C) The deacetylation mechanism is mediated by SIRT1. The acetyl group of the substrate is transferred to the ADP ribosyl part of NAD<sup>+</sup>, while a NAD<sup>+</sup> molecule is split into 1 NAM and 1 2'-O-AADPr. SBD, sirtuins-activating compounds binding domain; STAC, sirtuins-activating compound; CTR, C-terminal regulatory segment.

In Sirtuin-mediated deacetylation reaction, the acetyl group of the substrate is transferred to the ADP ribosyl moiety of NAD<sup>+</sup>. At the same time, 1 NAD<sup>+</sup> molecule splits into 1 nicotinamide (NAM) and 1 2'-O-acetylated ADP-ribose (15) (Fig. 1). NAD<sup>+</sup> participates in the deacetylation of target proteins, and a low NAD<sup>+</sup>/NADH ratio will weaken SIRT1 activity. Meanwhile, as a product of the deacetylation process, NAM can suppress the activity of SIRT1 through a negative feedback mechanism (16) (Fig. 1). SIRT1 recognizes NAD<sup>+</sup> through the active sites located on the Rossmann fold. One study showed that SIRT1 first approached specific hydrophobic amino acids near target lysine (Lys) residue for substrate recognition (17). Once recognized, SIRT1 deacetylates the substrate using the same catalytic mechanism as other members of the Sirtuin family. When the acetylated substrate binds to the enzyme, the conformation of NAD<sup>+</sup> changes, which allows the NAM group to be easily cleaved. Through the active site on the Rossmann fold of SIRT1, the carbonyl oxygen group of the acetylated Lys residue in the substrate contacts the anomeric carbon of the NAD<sup>+</sup> NAM nucleoside. This combination promotes cleavage of the NAD<sup>+</sup> NAM moiety and transfer of ADP-ribose, resulting in deacetylation of the substrate (18). The process

of deacetylation of acetylated substrates catalyzed by SIRT1 is as follows: Step one, SIRT1 deacetylase recognizes NAD<sup>+</sup> and acetylated substrate to form a ternary complex. Then, NAD<sup>+</sup> is hydrolyzed, releasing NAM from the 1'-ribose carbon of NAD<sup>+</sup>, which concomitantly forms a new covalent bond through binding with the acyl oxygen of the acylated Lys residue on the substrate. Step 2, the resulting 1'-O-alkylimidate intermediate is converted to a second bicyclic 1'-2'-acetal intermediate. The last step, in the presence of water molecules, the bicyclic intermediate is hydrolyzed to yield the deacetylated substrate and 2'-O-acetylated ADP-ribose (2-OAADPr). Under physiological conditions, 2-OAADPr can be reversibly transformed to 3-OAADPr (13).

## DEACETYLATION EFFECTS AND MOMENTOUS SUBSTRATES

Truly, as a HDAC, SIRT1 has been reported to indeed catalyze the deacetylation of histone H1 at Lys 26 (K26), histone H3 at Lys 9 (K9), and histone H4 at Lys 16 (K16) (19). However, it also plays an important role in regulating the deacetylation of non-histone proteins, including p53, HMGB1, forkhead box Os (FoxOs), STAT3, peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), NF- $\kappa$ B, peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), B-cell lymphoma 2-associated X protein (Bax), etc. (8,20). Recently, many studies have reported the emerging roles of SIRT1 in many diseases, especially in the occurrence, development, and prognosis of respiratory diseases (Fig. 2).



**Figure 2.** Three-dimensional structure, effects of SIRT1 and the underlying mechanism. SIRT1 has obvious effects in regulating a variety of respiratory diseases by acting on different momentous substrates. SIRT1 can regulate gastric cancer, NSCLC, and sepsis-associated liver injury by activating the STAT3/MMP-13 pathway or inhibiting the JAK/STAT3 pathway, especially via STAT3. SIRT1 affects gouty arthritis, hyperuricemia, and allergic inflammation by activating ABCG2, inhibiting Th2 response and inflammatory cell infiltration, especially through binding with PPAR- $\gamma$ . SIRT1 can modulate diabetic cardiomyopathy, atherosclerosis, and arterial thrombosis through inhibiting PD-1, cardiomyocyte apoptosis, vWF, and P-selectin, especially acting on FOXO-1. SIRT1 can control COPD, diabetic nephropathy, oxidative stress, and inflammation by activating autophagy, mitophagy, or regulating mitochondrial function, mitochondrial biogenesis, especially via PGC-1 $\alpha$ . vWF, von Willebrand factor; CTR, C-terminal regulatory segment; CR, caloric restriction.

STAT3 is a member of the STATs, and is described as a cytoplasmic transcription factor. It participates in regulating many biological events, including cell proliferation, differentiation, apoptosis, angiogenesis, inflammation, and immune responses (21,22). STAT3 has been reported as a downstream target of SIRT1, which catalyzes the deacetylation of STAT3 Lys residue to control its function (23). Recently, some posttranslational modifications related to the transcriptional function of STAT3 have been mentioned, such as acetylation and methylation (24). Some studies have shown that SIRT1/STAT3 plays an important role in the development of some diseases, including influencing the expression of IL-4 in T-lymphocytes, inhibiting T-cell differentiation into Th7 and Th17 cells, suppressing the proliferation and metastasis of gastric cancer cells, and preventing hyperglycemia in sepsis, etc. (23,25). Moreover, the role of SIRT1 in regulating respiratory diseases has also been revealed. For example, a recent study has found that microRNA (miR)-30e-5p can inhibit the development of non-small cell lung cancer (NSCLC) through downregulating ubiquitin-specific peptidase 22-mediated SIRT1/JAK/STAT3 signaling (26).

Transcriptional coactivator PGC-1 $\alpha$  is regarded as a main regulator of oxidative phosphorylation and ROS detoxification, and it is also described as an essential factor in tying metabolic regulation, redox control, and inflammatory pathways (27). The post-transcriptional activity of PGC-1 $\alpha$  was modulated by several post-translational modifications in cells, including phosphorylation, acetylation, and ubiquitination (28). PGC-1 $\alpha$  is considered as a substrate of SIRT1, which means that the transcriptional activity of PGC-1 $\alpha$  is influenced by SIRT1-mediated deacetylation (29). A number of studies have suggested the protective role of SIRT1/PGC-1 $\alpha$  against some diseases, including protecting the intestinal mucosal barrier from free oxygen radical damage, coping with oxidative stress caused by hyperglycemia, and protecting the diabetic heart (30,31). Specifically, one study indicated that resveratrol could exert a therapeutic effect on the rat chronic obstructive pulmonary disease (COPD) model. This study also pointed out that the efficacy of resveratrol was interrelated to the inhibition of oxidative stress and inflammatory responses, and the possible underlying mechanism might involve the activation and upgrading of the SIRT1/PGC-1 $\alpha$  pathway (32). Another strong evidence showed that hesperidin mitigated inflammatory responses and oxidative stress in cigarette smoke extract-induced COPD mice, which was reported to be associated with the SIRT1/PGC-1 $\alpha$ /NF- $\kappa$ B signaling axis (33). These findings demonstrate that SIRT1 may have a therapeutic effect for some diseases, including respiratory diseases, through targeting its specific substrates, such as PGC-1 $\alpha$ .

FoxOs are a subgroup family of forkhead box transcription factors and play a crucial role in cell proliferation, differentiation, and apoptosis. In mammals, this family consisted of 4 members, including FOXO1 (also named FKHR), FOXO3 (also named FKHL1), FOXO4 (also named AFX1), and FOXO6 (34,35). The activity of FoxOs is dependent on its phosphorylation modification and nuclear localization. In addition, the transcriptional activity of FOXOs can be regulated by other post-translational modifications, such as acetylation and deacetylation (36). FOXO1 is one target of SIRT1. Some studies have reported the role of SIRT1/FOXO1 in some diseases, such as decreasing osteoclast and increasing osteoblast number in bone, preventing the progression of atherosclerosis and arterial thrombosis, and inhibiting oxidative stress and apoptosis in cardiomyocytes (37,38). In a recent study, SIRT1 has been demonstrated to be a major factor to mediate the deacetylation of FOXO1, thus inhibiting apoptosis. This view was further confirmed by the fact that knockdown and inhibition of SIRT1 could maintain the acetylated state of FOXO1. Moreover, this study also showed that *Leishmania* negatively regulated the production of inflammatory TNF $\alpha$ , ROS, and nitric oxide



via the SIRT1/FOXO1 axis (39). A recent study has shown that the expression levels of SIRT1 and FOXO1 in PBMCs of COPD outpatients are positively correlated with the duration of physical activity (40). Although the longitudinal relationship among physical activity, SIRT1, and FOXO1 in COPD is unclear, the results may provide a novel strategy in controlling COPD. According to these evidences, we can infer that SIRT1/FOXO1 may be a potential therapeutic target for the treatment of respiratory diseases, although there are no definite reports on the mechanism underlying the action of SIRT1/FOXO1 in respiratory diseases.

PPAR- $\gamma$  is a member of the PPAR family, which includes 3 members, PPAR- $\alpha$ , PPAR- $\beta/\delta$ , and PPAR- $\gamma$  (41). Recent studies have shown that PPAR- $\gamma$  mediates part of the SIRT1 reactions, and the SIRT1/PPAR- $\gamma$  signaling plays a crucial role in anti-hyperuricemia and anti-inflammatory function (42,43). On one hand, a recent study demonstrated that SIRT1 and RSV (the activator of SIRT1) inhibited inflammatory cell infiltration and secretion of inflammatory factors through mediating PPAR- $\gamma$ , which could control the acute onset of gouty arthritis (43). On the other hand, another study showed that SIRT1 inhibited the activity of PPAR- $\gamma$  in dendritic cells, thus facilitating a Th2 response (44). Based on the substrate profile of SIRT1, it can be indicated that PPAR- $\gamma$  is an emerging target of SIRT1 in controlling some diseases, including respiratory diseases.

## DOWNSTREAM PATHWAYS AND MECHANISMS THROUGH HMGB1

HMGB1 is a nuclear protein that is considered a key component involved in the late inflammatory responses (45). The functions of HMGB1 rely on its localization and post-translational modifications. In addition, translocation and secretion of HMGB1 are important processes influencing inflammation (46). Recently, TLRs have been demonstrated to be of great significance in the innate immune system, and HMGB1 could control the inflammatory responses through binding with other cellular receptors such as TLR2 and TLR4 (47). NF- $\kappa$ B refers to a family of transcription factors that exist in numerous cell types (48). Many studies have shown the key effect of NF- $\kappa$ B on regulating immunity and inflammatory responses. In the process of inflammation, extracellular HMGB1 activates some receptors such as advanced glycation end products and TLRs via medullary differentiation factor 88 (MyD88)-dependent signaling and non-MyD88-dependent signaling pathways (49). These pathways contribute to the activation of NF- $\kappa$ B. Phosphorylation of NF- $\kappa$ B can promote the release of a large number of inflammatory cytokines to initiate inflammation (50). The activation of HMGB1/NF- $\kappa$ B pathway is regulated by post-translational modifications, among which acetylation catalyzed by HDACs and histone acetyltransferases is a common post-translational modification form. Translocation and secretion of HMGB1 are also regulated by these enzymes, including SIRT1 (51).

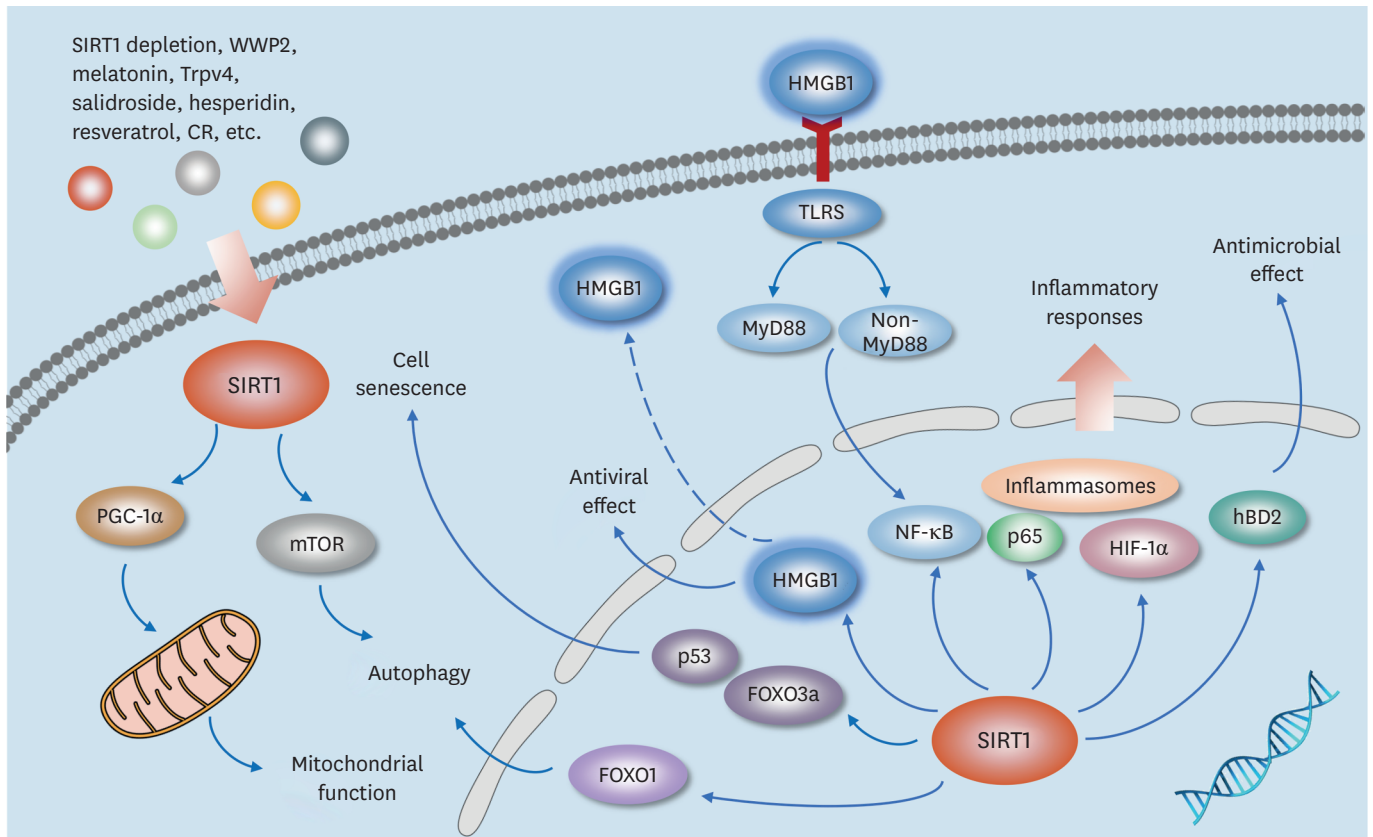
HMGB1/TLR4/NF- $\kappa$ B pathway plays a critical role in regulating the occurrence, development, and prognosis of many diseases, such as the diseases of the digestive system, respiratory system, and nervous system, through acting on NLRP3 and absent in melanoma 2 inflammasomes in macrophages (52). *In vivo* mouse neonatal hypoxic-ischaemic brain injury model and *in vitro* experiments have shown that HMGB1 released from microglia can activate the TLR4/MyD88/NF- $\kappa$ B signaling in microglia, which contributes to high expression of neuroinflammatory mediators, leading to neuroinflammation (53,54). Moreover, another study also reported that  $\omega$ -3 PUFA enhanced the SIRT1 activity to inhibit acetylation of HMGB1, leading to direct interactions between SIRT1 and HMGB1. This kind of interaction

can inhibit the translocation and secretion of HMGB1, and hold back the activation of the NF- $\kappa$ B pathway mediated by HMGB1 after TBI-induced microglia activation, thus controlling the subsequent inflammatory responses (49). In summary, SIRT1 can modulate the development of some diseases via the HMGB1/TLR4/NF- $\kappa$ B pathway.

Other SIRT1-related pathways also play an important role in regulating respiratory diseases, and the mechanisms may involve influencing autophagy, anti-inflammation, anti-apoptosis, and so on (55-59). Recent reports have shown that regulating SIRT1/NF- $\kappa$ B pathway can inhibit TNF- $\alpha$ -induced pro-inflammatory responses (60). SIRT1/GATA-3 signaling could decrease the expression of IL-4 in patients with severe asthma (61). SIRT1/Akt/NF- $\kappa$ B signaling can play an anti-inflammatory role in asthma, while SIRT1/HIF-1 $\alpha$  signaling exhibits a pro-inflammatory effect (62). In addition, SIRT1/TAK1 and SIRT1/Bax pathways are implicated in tuberculosis (63), SIRT1/COX-2 signaling is involved in the development of bacterial pneumonia (64), and SIRT1/MAPK signaling is important in regulating lung cancer progression (65) (Fig. 3).

### ACTIVATORS AND INHIBITORS OF SIRT1

SIRT1 regulates its downstream targets through deacetylation, influencing the occurrence, development, and prognosis of various diseases (63,66-68). Therefore, SIRT1 may become



**Figure 3.** Multitasking roles of SIRT1 through the downstream signaling pathways mediated by HMGB1. The multitasking roles of SIRT1 are shown in regulating antimicrobial effect, inflammatory responses, antiviral effect, autophagy, and mitochondrial function through the downstream signaling pathways mediated by HMGB1. CR, caloric restriction.

a novel therapeutic target in treating many diseases, especially respiratory diseases. In addition, more efforts have been put into developing the modulators of the emerging attractive therapeutic target. The modulators of SIRT1 included 2 forms, the activators and inhibitors (Table 1). The former contained resveratrol, berberine, quercetin, metformin, SRT1720, SRT1460, SRT2183, and so on (69-76). The later comprised EX-527, tenovin-1, tenovin-6, cambinol, sirtinol, salermide, splitomicin, and NAM (77-84). These extensively investigated activators and inhibitors can modulate SIRT1 in cardiovascular diseases, inflammatory diseases, diabetes, and obesity (Fig. 4).

**Activators**

Resveratrol is a natural polyphenol with anti-inflammatory properties that has been deeply studied and can activate sirtuins (85). One study demonstrated that resveratrol could protect osteoblasts in osteoporosis rats by promoting mitophagy, and this effect was realized by mediating SIRT1 and PI3K/AKT/mTOR signaling pathways (69). Another study showed that resveratrol inhibited oxidative stress and apoptosis through SIRT1/FOXO3a and PI3K/AKT signaling pathways, which alleviated radiation-induced intestinal injury (86). Similarly, resveratrol exhibited a protective role against respiratory diseases. For example, resveratrol can inhibit oxidative stress and inflammatory responses on a rat COPD model, probably through activating the SIRT1/PGC-1α signaling (32).

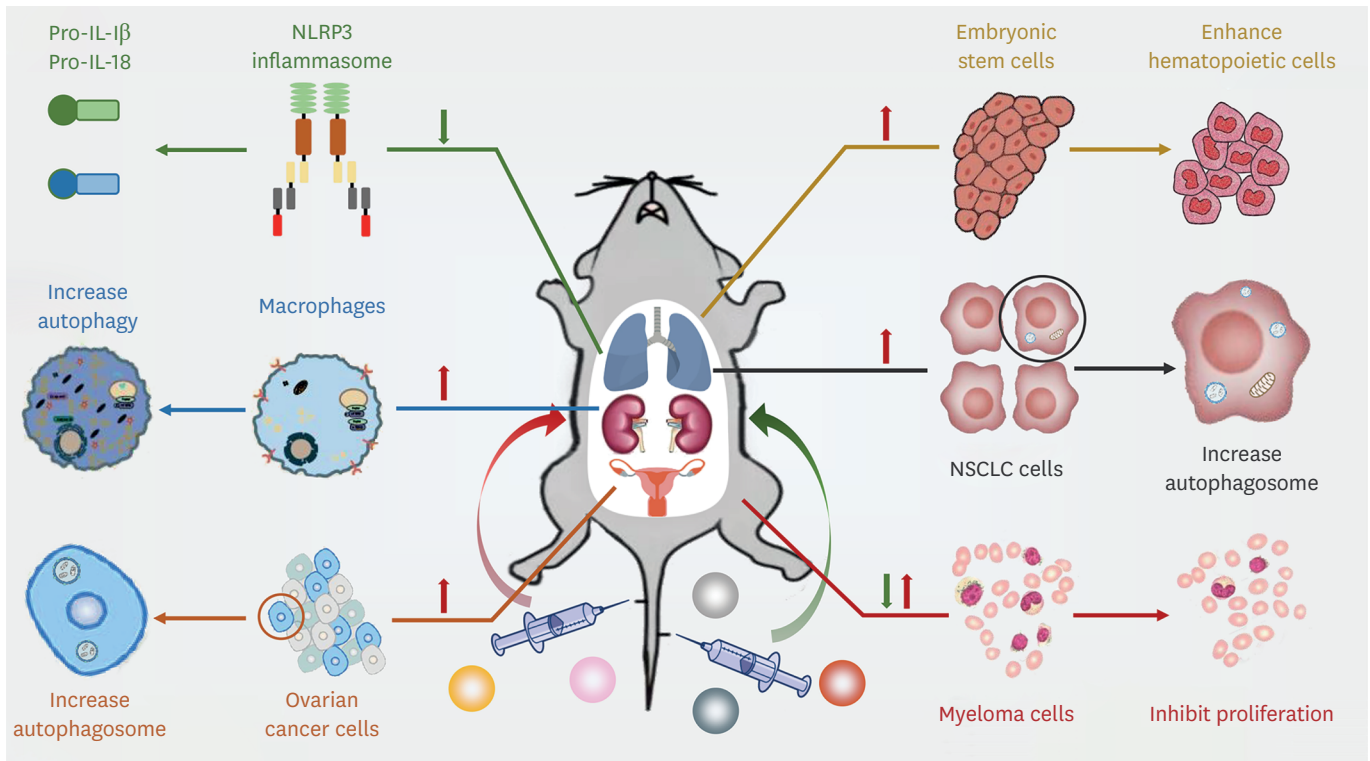
Quercetin is a kind of abundant flavonoid compound present in plants and shows a variety of biological activities. It is reported that quercetin has powerful antioxidant, anti-inflammatory, and anti-tumor effects, offering significant prospects in the clinical application (87). In a study on diabetic encephalopathy, quercetin up-regulated the expression of SIRT1 protein and inhibited the expression of endoplasmic reticulum (ER)-associated proteins, which meant that quercetin may participate in diabetic encephalopathy through the SIRT1/ER pathway (88). In addition, quercetin could increase the expression of SIRT1 and suppress the content of NLRP3 inflammasome in COVID-19 patients, showing therapeutic potential to treat COVID-19 (70).

SRT1720 and SRT1460 are structurally diverse synthetic compounds and are also used as small molecular modulators of SIRT1. It was found that SRT1460 could activate SIRT1, which played a protective role in myocardial ischemia/reperfusion (I/R) injury (71). This finding may

**Table 1.** List of activators and inhibitors of SIRT1

Type	Modulator	Function	Model	Reference
Activator	Resveratrol	Increase mitophagy	Osteoporosis rats	(69)
	Quercetin	Suppress NLRP3 inflammasome	COVID-19	(70)
	Berberine	Promote autophagy of peritoneal macrophages	Atherosclerosis	(73)
	Metformin	Activate autophagy, mitigates cartilage degradation	Mouse osteoarthritis	(74)
	Melatonin	Regulate apoptosis and autophagy	Sepsis-induced cardiac dysfunction	(75)
	SRT1720	Partially attenuate fibrosis and apoptosis	Fibrotic kidney disease	(72)
	SRT1460	Weaken oxidative stress	Myocardial ischemia/reperfusion injury	(71)
	SRT2183	Induce autophagy	Ovarian cancer cells	(76)
Inhibitor	EX-527	Induced cell apoptosis	Glioma	(77)
	Tenovin-1	Induce a nonlinear apoptosis-inducing factor-dependent cell death	p53 null Ewing's sarcoma cell line	(78)
	Tenovin-6	Induced apoptosis and cell cycle arrest	Primary effusion lymphoma	(79)
	Cambinol	Inhibit proliferation and induce apoptosis	Myeloma cell lines	(80)
	Sirtinol	Protect the allograft from inflammatory cell infiltration	Mouse cervical heterotopic heart transplantation	(81)
	Salermide	Induce autophagy in human NSCLC cells	NSCLC	(82)
	Splitomicin	Enhance the yield of specific hematopoietic lineage cells from embryonic stem cells	Hematopoietic differentiation of embryonic stem cells	(83)
	NAM	Increase the sensitivity of chronic myeloid leukemia to doxorubicin	Chronic myeloid leukemia	(84)





**Figure 4.** Regulatory effects verification of SIRT1 by activators or inhibitors injection. The regulatory effects of several SIRT1 activators and inhibitors are shown. Quercetin (an activator of SIRT1) suppresses NLRP3 inflammasome in COVID-19. Berberine (an activator of SIRT1) promotes the autophagy of peritoneal macrophages. SRT2183 (an activator of SIRT1) induces autophagy in ovarian cancer cells. SRT1720 (an activator of SIRT1) notably decreases collagen deposition in the mice kidneys. Salermide (an inhibitor of SIRT1) induces autophagy in human NSCLC cells. EX-527 (an inhibitor of SIRT1) suppresses the proliferation and colony formation ability of human glioma cells.

provide a new treatment strategy for myocardial I/R injury. Moreover, another study showed that SRT1720 improved the level of SIRT1 and partly alleviated unilateral ureteral obstruction (UUO)-induced renal fibrosis and apoptosis (72). This study concluded that SRT1720 as a SIRT1 activator had clinical significance in treating UUO-induced tubulointerstitial fibrosis.

### Inhibitors

EX-527 is a SIRT1 inhibitor with great effectiveness and selectivity compared with other SIRT1 inhibitors (89). A recent study has shown that SIRT1 promotes tumorigenesis in glioma, and EX-527 induces cell apoptosis through activating p53, suggesting that EX-527 might be a potential target in the treatment of glioma (77). Moreover, it was reported that small interfering RNA (siRNA) or EX-527 could inhibit SIRT1 activity, which notably strengthened MK-1775-induced apoptosis and growth inhibition in human lung cancer cells (90).

Tenovin-6 is a potent class III-specific HDAC inhibitor and is also known as a p53 activator (91). It was confirmed in NSCLC cell lines with different liver kinase B1 status that the combination of metformin and tenovin-6 was more effectual in inhibiting cell growth compared with either drug alone (92). In addition, it was demonstrated that knockdown of SIRT1 by specific short hairpin RNAs or using SIRT1 inhibitor tenovin-6 induced apoptosis and cell cycle arrest in primary effusion lymphoma cells (79).

Sirtinol is another SIRT1 inhibitor discovered among more than 1,000 compounds through a high throughput cell-based screen (93). Some data from a recent study revealed the

oncogenic role of SIRT1. In this study, it was also found that sirtinol could reduce cell proliferation of adrenocortical cancer and formation of colony and spheroids, as well as activate the intrinsic apoptotic pathway (94). Another evidence showed that SIRT1 played a key role in the immune responses after organ transplantation. However, inhibiting SIRT1 through sirtinol could protect the allograft from inflammatory cell infiltration then lengthen allograft survival time (81).

Salermide is a reverse amide with a strong inhibitory effect on SIRT1 (95). Some results have shown that SIRT1 inhibitors (such as salermide, NAM, sirtinol, and EX-527) significantly increase the survival rate of taste bud organoids after irradiation (96). Moreover, Mu et al. (82) found that the expression of SIRT1/2 was blocked by salermide or siRNAs, which could induce autophagy in human NSCLC cells.

## MULTITASKING ROLES IN RESPIRATORY DISEASES

The COVID-19 broke out in December 2019. It is a kind of respiratory disease with a highly destructive effect, which has brought a heavy burden to patients, medical systems, and societies worldwide (97). According to recent data, including those on COVID-19, respiratory diseases seriously affected physical and mental health, as well as social development. Among respiratory diseases, infectious diseases account for a large proportion. In addition to acting directly on viruses and bacteria, regulating immunity is also an important therapeutic strategy in the treatment of infectious respiratory diseases and other respiratory diseases. When targeting different substrates, SIRT1 may show different effects in regulating the immunity. Thus, SIRT1 can exhibit multitasking roles in the development and treatment of respiratory diseases (Table 2).

**Table 2.** Summary of the related mechanism of SIRT1 in regulating several respiratory diseases

Disease	Receptor/Pathway	Activation	Inhibition	Function	Reference
COPD	FOXO3a/p53	+		Protect against ACEII senescence in rats	(127)
	PGC-1 $\alpha$ /NF- $\kappa$ B	+		Alleviate inflammation and oxidative stress responses	(33)
	NF- $\kappa$ B/p65		+	Suppress COPD inflammation	(66)
	PGC-1 $\alpha$	+		Inhibit oxidative stress and inflammatory response	(32)
Asthma	IL-6		+	Affect pulmonary function	(56)
	mTOR	+		Inhibit allergic airway inflammation by suppressing autophagy	(57)
	Akt/NF- $\kappa$ B		+	Inhibit the development of airway inflammation	(62)
	HIF-1 $\alpha$ /VEGF	+		Increase the secretion of proinflammatory cytokines	(62)
	PPAR- $\gamma$		+	Inhibit anti-inflammatory actions	(62)
Tuberculosis	TAK1/p65/p38/JNK/ERK		+	Enhance the secretion of IL-6 and TNF- $\alpha$	(63)
	RelA/p65		+	Dampen Mtb-mediated persistent inflammatory responses	(114)
	GSK3 $\beta$	+		Inhibit <i>M. tuberculosis</i> -induced apoptosis in macrophage	(58)
Bacterial pneumonia	hBD-2	+		Antimicrobial effect	(110)
	IL-8		+	Reduce inflammatory response	(110)
	COX-2		+	Reduce the bacterial load in different organs	(64)
Lung cancer	NF- $\kappa$ B/Smac		+	Reduce radiosensitivity	(59)
	NF- $\kappa$ B		+	Attenuate cell proliferation, migration and invasion	(67)
	ATF4 and DDIT4	+		Induce pro-survival autophagy in NSCLC cells	(82)
COVID-19	NLRP3		+	Inhibit inflammation	(70)
	K63	+		Boost virally mediated induction of type 1 interferons	(102)
	HMGB1		+	Enhance the antiviral efficacy of type 1 interferons	(102)
ARDS	p65		+	Ameliorate inflammatory response and oxidative stress	(58)
	MAPK		+	Alleviate ARDS	(132)

### COVID-19

The COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) erupted in December 2019 and was declared a pandemic by the World Health Organization (WHO) (98). COVID-19 infections are related to respiratory dysfunctions that can cause substantial alterations in clinical manifestation and have become a significant public health concern (99). COVID-19 may have 3 clinical phases, including the incipient upper respiratory tract infection phase, the pneumonia phase, and the hyperinflammatory phase that can lead to death (100). It has also been reported that imbalance of inflammatory responses, defectiveness in immune responses, and lymphopenia are annotated as critical factors of the pathogenesis of SARS-CoV-2 infection (100). In addition, high expression of p53 is associated with significantly decreased expression of SIRT1 and is related to higher expression of p21 in COVID-19 patients (101). A study showed that SIRT1 might improve the antiviral efficacy of type 1 interferons by preventing hyperacetylation of HMGB1 (102). Moreover, the inhibition of SIRT1 can reduce cytotoxicity of CD8 T cells in patients with systemic erythematosus lupus who were susceptible to SARS-CoV-2 infections (103). Given the above findings, SIRT1 may be an important factor regulating inflammatory responses, which may be necessary for the fight against COVID-19.

### Bacterial pneumonia

Pneumonia can be caused by bacteria infection, such as *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (104), which is also named bacterial pneumonia. The common complications of bacterial pneumonia include respiratory failure, sepsis, multiorgan failure, coagulopathy, etc. Many studies have shown that drug resistance of bacteria is increasing for some reasons, for example, the abuse of antibiotics (105). Because of the diversity of pathogenic bacteria, the severity of complications, and increased drug resistance, it is critical to develop a better treatment strategy for bacterial pneumonia. *Streptococcus pneumoniae* is a Gram-positive bacterium, and pneumococcal infection is a pathogenic factor for some diseases, including pneumonia, meningitis, and bacteremia/sepsis (106). Recent studies have shown that SIRT1 plays an important role in infection and inflammation (107,108). Previous *in vivo* and *in vitro* studies have demonstrated that celecoxib, a non-antibiotic agent, induced SIRT1 expression, which controlled the expressions of COX-2 and NF- $\kappa$ B, thus causing decreased expressions of pro-inflammatory cytokines (64). Similar effects were shown in a study on the effect of the SRT3025 compound (a SIRT1 activator) in treating pneumococcal pneumonia. The results showed that SRT3025 promoted the elimination of bacteria and reduced inflammatory cytokines in tissues of animals infected with *Streptococcus pneumoniae*, and this effect was most pronounced in the lung (109). Moreover, another study showed similar findings and reported that recombinant human  $\beta$ -defensin-2 (hBD-2) had an antimicrobial effect on *Streptococcus pneumoniae* in human pulmonary epithelial cells. IL-8 is a kind of CXC chemokine that can promote the recruitment of neutrophils and maintain inflammatory responses in the airway. It was found that enhancing expression of SIRT1 through activators could increase mRNA expression of hBD-2 but decrease IL-8 mRNA expression, and this effect could be reversed by SIRT1 inhibitors (110). Furthermore, chlorogenic acid could alleviate *Klebsiella pneumoniae*-induced pneumonia via SIRT1, concretely, chlorogenic acid inhibited the acetylation level and nuclear translocation of HMGB1 by activating SIRT1, thereby promoting M2 polarization and alleviating *Klebsiella pneumoniae*-induced pneumonia (111). Thus, we can deduce that SIRT1 plays an important role in bacteria pneumonia, especially *Streptococcus pneumoniae*.

### Tuberculosis

Tuberculosis, a special kind of bacterial infectious disease caused by *Mycobacterium tuberculosis* (Mtb), is one of the deadliest infectious diseases around the world and has become a global health issue (112). A study reported that the increase in autophagy could promote innate host defense against multiple intracellular pathogens, especially Mtb (113). Thus, regulating autophagy is of great significance in controlling tuberculosis. In addition, it was found that post-translational activation of autophagy was realized by deacetylating autophagy-related genes ATG5, BECN1, and ATG7 through activating SIRT1 (114). In another study on SIRT1 and its activators in cells and animals infected by Mtb, some data such as bacillary loads and SIRT1 mRNA expression indicated that the activation of SIRT1 could inhibit the growth of Mtb and increase the clearance rate of Mtb with anti-tuberculosis drugs (115). Resveratrol can activate SIRT1, and in Mtb-infected macrophages, it can inhibit the activation of MAPK, TAK1, and NF- $\kappa$ B signaling pathways, as well as the levels of inflammatory cytokines, indicating that resveratrol may be used to treat tuberculosis through targeting SIRT1 (63). Therefore, we reasonably speculate that SIRT1 may become a potential target for the treatment of tuberculosis.

### COPD and asthma

COPD is a prevalent and severe disease with high health and social care costs (116). Because of its complicated pathogenesis, there is no curative treatment currently. It has been reported that more than 3 million people die of COPD worldwide, accounting for 6% of all deaths (55). Moreover, COPD can further develop into pulmonary heart disease and respiratory failure (117), so it is of great significance to find a better treatment strategy for COPD. Zhou et al. (118) reported that oxidative stress, inflammation, and apoptosis were considered the most important influential factors for COPD occurrence. It was found that SIRT1 exerted anti-inflammatory, anti-apoptotic, and antioxidant roles in the pathogenesis of COPD (119). A recent study has demonstrated that LINC00987 regulates LPS-induced oxidative stress, cell apoptosis, inflammation, and autophagy through promoting the binding of let-7b-5p with SIRT1, which ameliorated COPD. Moreover, this regulation could be reduced by the knockdown of SIRT1 gene (120). A similar protective role of SIRT1 against COPD was also shown in another study. The results showed that melatonin could alleviate apoptosis and ER stress by upregulating the expression of SIRT1 in rats, which played a positive role in controlling COPD. However, this positive role would be abolished by the addition of EX-527 (an inhibitor of SIRT1) (121). There is also much other evidence showing that SIRT1 plays an important role in regulating COPD (66,122,123), which indicates that SIRT1 might be a key target in the treatment of COPD.

Asthma is a chronic airway inflammatory disease, featured as aberrant immune-inflammatory responses and increased mucus exudation and airway remodeling (124). Epidemiological statistics have shown the increased prevalence of asthma during the past few decades, meaning that asthma poses a great threat to human health (125). There are about 235 million asthma patients, and more than 20 million people in China are suffering from asthma, with an incidence rate of 1.24% (56). Many recent studies have reported that the activity and expression level of SIRT1 are related to asthma conditions (126,127). However, it seems that SIRT1 has dual roles in asthma development, including pro-inflammatory and anti-inflammatory effects. It was reported that increased SIRT1 activity contributed to the suppression of NF- $\kappa$ B p65 acetylation and inhibited the production of IL-6 and IL-8, which could reduce the inflammatory responses in asthma (60). However, the proinflammatory function of SIRT1 may be related to repressed PPAR- $\gamma$  activity (62). It was found that the expression of SIRT1 inhibited the activity of PPAR- $\gamma$  in dendritic cells (44). Meanwhile, in mice dendritic cells with a shortage of SIRT1, the development of airway inflammation was notably reduced with the increased activity of PPAR- $\gamma$

(62). Other evidences also demonstrated that SIRT1 exhibited a vital role in regulating asthma (128-130). Thus, the inhibition of PPAR- $\gamma$  activity by SIRT1 may exert a pro-inflammatory effect in the pathological process of asthma. Since SIRT1 exhibits dual roles in asthma development, it is important to explore the precise effect of SIRT1 in asthma progression, which has a great significance for the treatment of asthma.

### Acute respiratory distress syndrome (ARDS)

ARDS, a syndrome of acute respiratory failure, is mainly caused by direct lung injuries and indirect systemic diseases, such as sepsis and severe trauma. It is featured as a systemic inflammatory response to infection, which can cause multiple-organ dysfunction and death (131,132). The high incidence rate, mortality, and medical costs of ARDS have brought a heavy burden to patients and society. Although some measures have been taken, such as lung-protective ventilation and the establishment of an overall intensive care unit, the fatality rate of ARDS patients is still high (133). Recently, some studies have indicated that SIRT1 may become a novel target in regulating ARDS. It was reported that in alveolar macrophages, SIRT1 was a direct target of miR-199a, and the level of SIRT1 was negatively related to miR-199a. The results also suggested that downregulating miR-199a could suppress excessive inflammatory responses and cellular apoptosis through upregulating SIRT1, which prevented lung tissue from sepsis-induced ARDS (134). Moreover, another study showed that the pretreatment with SRT1720 (the SIRT1 activator) decreased the levels of IL-6, TNF- $\alpha$ , and IFN- $\gamma$ , while increasing the level of IL-10 and attenuating lung injury. It also exhibited that activation of SIRT1 alleviated inflammatory reaction and oxidative stress in ARDS induced by LPS (68). In addition, a present study has illustrated that 3,5,4'-tri-O-acetylresveratrol (AC-Rsv) plays a protective role against LPS exposure-induced ARDS in mice by regulating the expression of SIRT1 (135). Another study showed that low expression of mir-138-5p induced by metformin might increase the expression of SIRT1 and inhibit MAPK signaling, which alleviated ARDS (136). According to these reports, it is indicated that regulating SIRT1 may be a promising treatment strategy for ARDS.

## CONCLUSIONS AND PERSPECTIVES

In this review, we summarize the latest evidence on the multitasking roles of SIRT1 in regulating respiratory diseases. As one of the most well-studied sirtuins, SIRT1 can modulate multiple biological functions, including oxidative stress, inflammation, cell apoptosis, autophagy, antibacterial and antiviral effects, through its NAD<sup>+</sup>-dependent deacetylation enzymatic activity.

The immune-balance regulatory effects of SIRT1 have been stated *in vivo* and *in vitro* models of infectious respiratory disease. Previous research has indicated that SIRT1 can modulate reactions in respiratory disease via many different signaling pathways and molecules. Here some potential modulatory pathways are summarized, especially the downstream signalings mediated by HMGB1. Moreover, specific SIRT1 activators and inhibitors are reviewed respectively, and the molecular functions of SIRT1 are inversely verified by relevant experiments. Some regulatory details of SIRT1 in the process of different respiratory diseases, including COVID-19 infection, bacterial pneumonia, tuberculosis, are further described.

Although numerous mechanisms underlying the action of SIRT1 have been elaborated, some questions still need to be answered. For example, due to the diversity and abundance of substrates, the intricacy of the regulatory mechanisms, and the involvement of



multiple regulating pathways, it is complicated to determine the roles of SIRT1 during the pathogenesis and prognosis of different respiratory diseases. Therefore, further investigations on SIRT1 are still needed to estimate the promising targets for the treatment of respiratory diseases, especially the signaling pathways mediated by HMGB1, which is the core immunomodulatory molecule.

## ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (grant numbers 81503399), Beijing Natural Science Foundation (grant numbers 7182071) and Beijing Construction Program for High-level Public Health of Technical Talents (grant numbers 2022-3-009). This work would not have been possible without the enormous efforts of our collaborators and scientific friends from over the years. We thank Beijing Institute of Chinese Medicine for support in the process.

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