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Review

Regulation of Sirtuins in Sepsis-Induced Myocardial Damage: The Underlying Mechanisms for Cardioprotection

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Abstract

Sepsis is defined as "a life-threatening organ dysfunction caused by a dysregulated host response to infection". Although the treatment of sepsis has evolved rapidly in the last few years, the morbidity and mortality of sepsis in clinical treatment are still climbing. Sirtuins (SIRTs) are a highly conserved family of histone deacetylation involved in energy metabolism. There are many mechanisms of sepsis-induced myocardial damage, and more and more evidence show that SIRTs play a vital role in the occurrence and development of sepsis-induced myocardial damage, including the regulation of sepsis inflammation, oxidative stress and metabolic signals. This review describes our understanding of the molecular mechanisms and pathophysiology of sepsis-induced myocardial damage, with a focus on disrupted SIRTs regulation. In addition, this review also describes the research status of related therapeutic drugs, so as to provide reference for the treatment of sepsis.

Keywords: sirtuins; sepsis; myocardial damage; mitochondria; inflammation

1. Introduction

Sepsis is a life-threatening disease that involves multiple organs of the human body. It is an important cause of global health burden due to its high mortality, long hospital stays and high cost. In recent years, many people have explored the pathophysiology and mechanism of sepsis, involved the interaction of multiple factors, such as the immune system, coagulation cascade, gut microbiota, neuroendocrine system, energy metabolism, and so on, which has led to different degrees of understanding of sepsis [1,2]. However, the overall situation of sepsis is still uncontrollable. In addition, sepsis survivors have an increased risk of death or decreased health-related quality of life even after hospital discharge [3]. Therefore, sepsis is still one of the most important problems we need to solve. Studies have shown that sepsis inhibits energy metabolism of the cardiac, reduces ATP production, and causes myocardial damage [4]. Myocardial damage is one of the main complications of sepsis, and cardiac dysfunction can predict a poor clinical prognosis.

Sirtuins (SIRTs) are histone deacetylases III, divided into groups I to IV (SIRT1-3, SIRT4, SIRT5, and SIRT6/7). SIRTs regulates a variety of physiological functions ranging from energy metabolism to stress response and also exhibits significant antioxidant activity, mainly due to its deacetylation and activation of antioxidant enzymes [5]. A growing number of evidences support the critical role of the highly conserved nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases of SIRTs in directing the sepsis process [6,7]. Thus, this review primarily focuses on the progress of potential molecular mechanism, pathophysiology underlying myocardial dysfunction, and therapeutic targets for SIRTs in sepsis.

2. The Molecular Mechanism of Sepsis-Induced Myocardial Damage

2.1 Extramitochondrial Mechanisms

Inflammation, oxidative stress, autophagy, and cardiomyocyte apoptosis ultimately contribute to cardiac dysfunction in sepsis [8,9]. Large amounts of reactive oxygen species (ROS) and reactive nitrogen species are accumulated. When the oxidation/antioxidation becomes unbalanced, excessive ROS production can cause damage to the cardiac, as well as damage the structure of cardiomyocytes and promote apoptosis directly [10]. In addition, excessive ROS production during sepsis can exacerbate myocardial inflammation, attenuates the endothelium-dependent vasodilatory response and exacerbates microcirculatory disturbances [11].

During the acute infection stage of sepsis, some monocytes are activated and produce a variety of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These cytokines trigger an inflammatory cascade, which in turn leads to apoptosis and cytotoxicity of cardiomyocytes and endothelial cells [12]. Sepsis-induced myocardial damage occurs when macrophages infiltrate the

heart. Nucleotide-binding and oligomerization domain-like receptor protein 3 (*NLRP3*)-mediated inflammatory responses occur in macrophages, releasing multiple pro-inflammatory factors and causing accumulation of ROS in cardiomyocytes, leading to cardiac dysfunction. The *NLRP3* inflammasome activates *caspase-1*, produce IL-18, and IL-1β, and triggers inflammation and focal death [13,14]. Recent studies have provided intriguing evidence suggesting that *SIRTs* may indeed influence *NLRP3* activation. These studies have shown that *SIRT3*, in particular, can deacetylate and inhibit the activity of the nuclear factor kappa-B (NF-κB) pathway, a major regulator of *NLRP3* gene expression [15,16]. By suppressing NF-κB signaling, SIRT3 may indirectly downregulate *NLRP3* inflammasome activation, potentially mitigating the excessive inflammation observed in sepsis.

Several studies have reported that aberrant host responses mediated by Toll-like receptors (TLR) contribute to the pathogenesis of sepsis [17–19]. TLR is expressed in immune and other cells, including cardiomyocytes, and interacts with different pathogen-associated molecular patterns (PAMPs), leading to activation of NF-κB and subsequent formation of pro-inflammatory cytokines [20]. TNF-α is a cause of cardiovascular changes associated with infectious shock, including myocardial dysfunction [21]. TLR7 as pattern recognition receptors were found in the intranuclear soma membrane [22]. The expression of TLR7 is upregulated in cardiomyocytes in response to sepsis, and TLR7 activation further activates the Cyclic Adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway in the sarcoplasmic reticulum [19,22]. Activated TLR7 narrow moves into the Golgi apparatus and endosomes, and enhances the myeloid differentiation primary response 88 (MyD88)/interleukin-1 receptor associated kinase1 (IRAK)/NF-κB cascade, ultimately leading to inflammation [23]. Furthermore, TLR7 regulates Ca^{2+} release through activation of the adenosine (cAMP)-protein kinase A (PKA)-phospholamban (PLN) pathway and protects against sepsis-induced myocardial damage [19].

Activation of the TLR4 signaling pathway may directly contribute to cardiomyocyte dysfunction. Besides, sepsis directly impairs cardiac function by binding to its receptor TLR4 through its binding protein CD14, which produces inflammatory factors such as TNF-α, IL-1β, and IL-18 [24]. Invasive bacteria or other external stimuli first trigger innate immunity, which then induces TLR4 expression through activation of NF-κB transcription, leading to the production of various inflammatory mediators such as cytokines, chemokines, and antimicrobial peptides [25]. Other cell wall components of pathogenic microorganisms (e.g., lipoproteins) are released and recognized by pattern recognition receptors (e.g., 2, 5, 9), leading to inflammation and dysfunction of cardiomyocytes [26,27]. Sepsis activates Janus Kinase 2 (JAK2)/transcription 6 (STAT6) phosphorylation, which is accompanied by increased levels of oxidative stress, apoptosis and inflammatory responses in cardiomyocytes thereby causing cardiomyocyte damage [12].

MiR-146a is typically considered a negative regulator of the TLR4 and NF-κB signaling pathways. It acts to inhibit the expression and activity of TLR4 and NF-κB, thus exerting an anti-inflammatory effect [28]. NF-κB rapidly translocate from the cytoplasm to the nucleus, initiating transcription of target genes and releasing downstream inflammatory factors, including TNF-α and IL-6. Then TNF-α and IL-6 contribute to the myocardial dysfunction observed in sepsis by inhibiting Ca^{2+} transport, regulating nitric oxide pathways, degrading key contractile proteins, affecting mitochondrial function, and activating intracellular signaling to inhibit the myocardium [29–33].

Sepsis triggers endoplasmic reticulum stress, leading to activation of calmodulin-dependent protein kinase kinase beta (CaMKKβ) and adenosine 5′-monophosphate-activated protein kinase (AMPK), inhibiting the mTOR signaling pathway and ultimately leading to excessive autophagy. Meanwhile, sepsis promoted early endosome formation to favor autophagosome formation, while inhibiting late endosome formation to delay autophagic lysosome formation [34].

2.2 Mitochondrial Mechanisms

Mitochondria, as energy suppliers to cardiomyocytes, contribute to the pathophysiology of myocardial dysfunction in sepsis [35]. Mitochondrial dysfunction associated with septic cardiomyopathy consists of the following: changes in mitochondrial structure (swelling, internal vesicle formation, and cristae abnormalities), mitochondrial DNA damage, elevated mitochondrial permeability transition, and inhibition of cytochrome C oxidase activity [36–39]. Sepsis causes mitochondrial damage through multiple mechanisms [40,41]. Damaged mitochondria promote cardiomyocyte apoptosis, which in turn exacerbates sepsis-induced myocardial damage. Biogenesis of damaged or defective mitochondria is associated with accumulation of useless or dysfunctional mitochondria with reduced mitochondrial potential or increased ROS [42]. These damaged mitochondria subsequently interfere with cardiomyocyte metabolism and induce mitochondrial apoptosis or necrosis via activation of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (mPTP) [43,44].

Mitochondrial damage and dysfunction are highly associated with sepsis-induced myocardial damage [45,46]. Mitochondria are the main source of intracellular ROS in the myocardium during sepsis. Sepsis damages myocardial mitochondria by disrupting membrane integrity, which in turn increases ROS production and oxidative stress [47]. Increased ROS production leads to oxidative stress that impairs mitochondrial biosynthesis, division/fusion homeostasis, and mitochondrial autophagy, thereby promoting apoptosis, hypertrophy, and remodeling, which have been

widely reported in sepsis-induced cardiac, renal, and pulmonary damage [48]. The expression of Gasdermin D (GSDMD) functional fragment is up-regulated in the heart tissue of septic WT mice, accompanied by reduced cardiac function and myocardial injury. GSDMD leads to mitochondrial dysfunction and ROS overproduction by enriching mitochondria, which in turn regulates the activation of *NLRP3* inflammasome, leading to myocardial injury, pyroptosis, and cell death in sepsis. GSDMD enrichment in the mitochondrial membrane triggers ROS production and may be partially involved in *NLRP3* activation [49,50]. *NLPR3*-deficient mice show improved cardiac systolic and diastolic function and increased survival from sepsis [51]. GSDMD plays a role in sepsis plays an important role in the pathophysiology of sepsis-induced myocardial damage [50].

In addition, inhibition of the NLRP3/IL-1β axis prevents systolic and diastolic dysfunction in sepsis [51]. Because IL-1β activates NF-κB through its receptor, this leads to decrease deformability, and decreased cardiomyocyte contraction and diastole. In turn, it leads to septic cardiomyopathy with myocardial atrophy, cardiac systolic and diastolic dysfunction and increased expression of pro-inflammatory cytokines of the cardiac [51]. Overall, inhibitors of NLRP3 inflammasomes, IL-1β, interleukin- 1 receptor antagonist (IL-1RA), and NF-κB are used to prevent sepsis-induced myocardial damage.

We summarized the current mechanism of myocardial damage caused by sepsis, and then we started from the damage mechanism to explore whether SIRTs can inhibit these damages and thus achieve protective effects. The molecular mechanisms of mitochondria associated with myocardial damage caused by sepsis are summarized in Fig. 1.

3. The Relationship Between Sirtuins and Sepsis

3.1 SIRT1

SIRT1 is a conserved NAD^+-dependent protein deacetylase that exerts anti-inflammatory, antioxidant, and anti-aging effects by regulating gene transcription, chromosome stability, and target protein activity through deacetylation [52], which is reported to be involved in sepsis-induced myocardial damage.

Clinical studies have found that SIRT1 can still be clinically relevant as a rapid measurable prognostic biomarker for patients with sepsis in the clinical setting [53]. SIRT1 expression is downregulated in the hyperinflammatory response to sepsis, and SIRT1 activation counteracts sepsis-induced myocardial damage [54–56]. Besides, SIRT1 played a negative role in regulating the activation of *NLRP3* inflammasome [57,58]. *NLRP3* interacts with apoptosis-associated speckle-like protein (ASC) and promotes its own cleavage and activation through ASC recruitment of caspase1 precursor monomers. Thus, activated caspase 1 stimulates the cleavage of pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, which triggers an inflammatory response [59,60]. Resveratrol (RESV), plant antioxidant, has been shown to reduce myocardial damage in sepsis by activating SIRT1 signaling to reduce neutrophil accumulation, TNF-α expression, and cardiomyocyte apoptosis [61]. In studies of acute renal damage caused by sepsis, SIRT1 mitigates acute renal damage by promoting autophagy mediated by deacetylation of Beclin1. However, this mechanism has not been validated in the cardiac and therefore needs to be further explored [7].

Besides, injection of a cell-permeable Tat-Beclin-1 peptide to activate autophagy improved cardiac function, attenuated inflammation, and rescued the phenotypes caused by *Beclin-1* deficiency in sepsis-challenged mice, this suggests that *Beclin-1* protects against cardiac damage during sepsis [62]. *miR-181a* is one of the MicroRNAs that represses gene expression at the post-transcriptional level by binding to target mRNAs [63]. *MiR-181* levels were significantly increased in the presence of enhanced inflammatory response and apoptosis. *MiR-181* binds directly to its target genes and inhibits SIRT1 expression. *MiR-181a* inhibition leads to upregulation of SIRT1 expression and downregulation of pro-inflammatory cytokines and apoptosis. Inhibition of *miR-181a* attenuates sepsis-induced inflammation and apoptosis by activating the Nuclear factor erythroid2-related factor 2 (Nrf2) pathway while inhibiting the NF-κB pathway, achieved through the targeting of SIRT1 [63]. Thus, *miR-181* plays a key role in inflammation during sepsis and could be a potential therapeutic target for patients with sepsis. Serum lactate has been recognized as a biomarker of sepsis prognosis, and elevated serum lactate levels are positively correlated with sepsis mortality [64]. Clinical studies have shown that circulating high mobility group box-1 (HMGB1) levels are significantly elevated and positively correlate with the severity of sepsis and mortality [65,66]. Lactate can strongly inhibit the gene expression of *SIRT1* [67]. SIRT1 acetylation promotes HMGB1 release and is essential for sepsis pathogenesis [68]. This process is closely linked to the pathogenic role of lactate in sepsis, as lactate can inhibit SIRT1's nuclear translocation and its function in deacetylation [7].

Restoring mitochondrial quality control mechanisms by activating mitochondrial biosynthesis or reducing mitochondrial division is a promising approach to improve organ dysfunction in sepsis [69,70]. SIRT1/peroxisome proliferator-activated receptor-gamma co-activator-1alpha (PGC-1α) network enhances the regulation of cardiac mitochondrial activity and plays a protective role in sepsis-induced myocardial injury [71,72]. Melatonin upregulates SIRT1 and autophagy, protecting from sepsis in relation to mitochondrial mechanism [73].

3.2 SIRT2

SIRT2, far less studied than SIRT1, is mainly located in the cytoplasm, but under certain conditions, it also enters

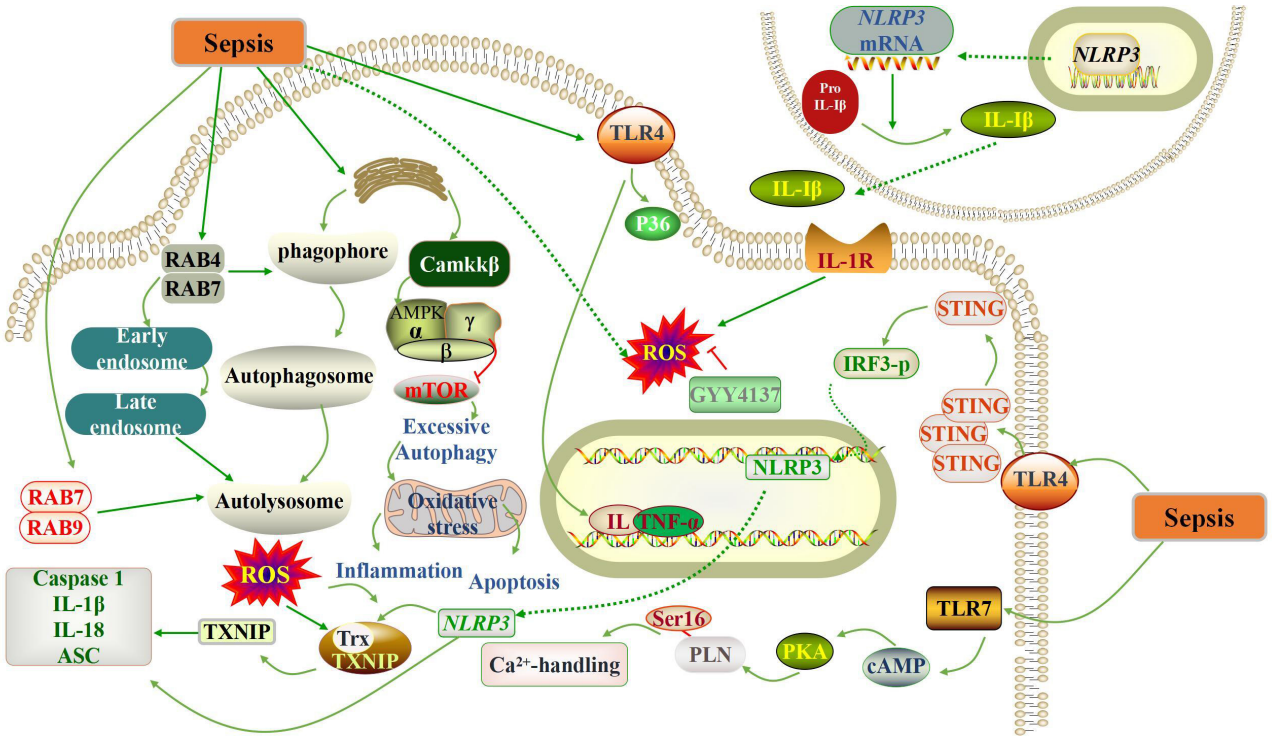

Fig. 1. Schematic representation of the pathogenesis of sepsis-induced myocardial damage. Sepsis triggers a complex cascade of reactions, including the activation of oxidative stress, the occurrence of autophagy, apoptosis and systemic inflammatory response. IL, interleukin; AMPK, adenosine 5′-monophosphate-activated protein kinase; ROS, reactive oxygen species; NLRP3, Nucleotide-binding and oligomerization domainlike receptor protein 3; TLR, Toll-like receptors; TNF-α, tumor necrosis factor-α; PLN, phospholamban; PKA, protein kinase A; cAMP, Cyclic Adenosine monophosphate; IRF3-p, Type-I interferons regulatory factor 3- Phosphorylated; Trx, thioredoxin; TXNIP, Thioredoxin-interacting protein; mTOR, mammalian target of rapamycin; ASC, apoptosis-associated speckle-like protein; RAB, Ras-related proteins in brain; GYY4137, hydrogen sulfide donor.

the nucleus and performs the corresponding functions [74]. SIRT2 is a nutrient sensor in adipose and immune cells, like SIRT1, increased caloric restriction lead to a high nutrient and high fat diet decreases SIRT2 expression in white adipose tissue of mice [75,76]. In obese mice with sepsis, elevated levels of SIRT2 protein instead prolonged low inflammation; SIRT2 is the most abundant SIRTs in adipose tissue [77]. Specifically, there are some studies found that through direct deacetylation of NF-κB and p65. SIRT2 expression in obesity with sepsis was reduced in the high inflammatory phase and increased in the low inflammatory phase [78].

3.3 SIRT3

SIRT3 is an NAD^+-dependent histone deacetylase with functions in the regulation of mitochondrial oxidative stress, bioenergetics, anti-senescence, anti-fibrosis, and anti-inflammation [79–82]. In the cardiac, SIRT3 is highly expressed and is required for the maintenance of cardiomyocyte energy and cardiac contractility [83]. SIRT3 located mainly in mitochondria, represents the major protein deacetylase in mitochondria and detoxifies ROS and increases mitochondrial ATP regeneration by activating manganese superoxide dismutase (MnSOD) and various energy metabolizing enzymes [83–86]. The activation of SIRT3 is currently considered as a potential therapeutic strategy for the treatment of septic cardiomyopathy [87]. It was demonstrated that SIRT3 expression was significantly reduced in myocardial tissue from mice with sepsis-induced cardiac damage, and that restoration of SIRT3 expression prevented sepsis-induced cardiac damage [88]. Antioxidant and anti-inflammatory effects on the SIRT3 have also been demonstrated in sepsis-induced cardiac damage [89].

Mitochondrial dysfunction impairs the contractility of cardiomyocytes and even triggers cardiomyocyte death [90]. Annexin A1 (ANXA1), a glucocorticoid-regulated protein that is widely expressed in human tissues and cells [91]. ANXA1 promotes p53 deacetylation in sepsis-treated H9C2 cells by enhancing SIRT3 expression thereby reducing cardiomyocyte death [92]. Impaired SIRT3 activity may mediate cardiac dysfunction in endotoxemia by promoting calpain-mediated disruption of ATP synthesis, suggesting SIRT3 activation as a potential therapeutic strategy for the treatment of septic cardiomyopathy [87]. Tubeimoside I (TBM) prevents sepsis-induced endothelial dysfunction by reducing oxidative stress and apoptosis through SIRT3. TBM is a promising new therapeutic agent for

sepsis-induced endothelial dysfunction [89]. Polydatin-mediated SIRT3 activation preserves mitochondrial function through mitochondrial superoxide dismutase 2 (SOD2) and Cyclophilin D (CypD) deacetylation, thereby reversing sepsis-induced endothelial hyperpermeability [93]. In addition, the role of SIRT3-CypD signaling in barrier protection was identified. SIRT 3-mediated deacetylation inhibited CypD activity, thereby inhibiting mPTP opening and $\Delta\Psi$m reduction [94]. It was shown that reduced CypD hyperacetylation and interaction with SIRT3 in response to sepsis attack resulted in a reduction in mPTP opening and subsequent $\Delta\Psi$m [93]. Estrogen related receptors (ERRs) can bind to the SIRT3 promoter and induce transcription of SIRT3 [95]. Tubeimoside I may protect against sepsisinduced cardiac dysfunction (SICD) by binding to and activating ERRα, thereby activating ERRα to promote SIRT3 transcription to reduce inflammation, oxidative stress and apoptosis [89].

SIRT3 deficiency leads to hyperacetylation of key enzymes in the cardiac trichloroacetic acid (TCA) cycle, which subsequently shifts myocardial metabolism to anaerobic glycolysis and subsequently promotes lactate and nicotinamide adenine dinucleotide (NADH) production, ultimately exacerbating cardiac function after sepsis [88]. SIRT3 overexpression increases AMPK activity and improves mitochondrial biosynthesis, which maintains mitochondrial function and reduces sepsis-associated cardiomyocyte damage [90]. These studies suggest that targeting SIRT3 may provide a potential new target to maintain normal cardiac performance after sepsis. However, the precise mechanisms of protection still need further investigation.

3.4 SIRT5

Unlike SIRT1 and SIRT3 deacetylases, SIRT5 has relatively weak deacetylation, but shows stronger desuccinylation activity, mainly removing succinyl, malonyl and glutaryl groups from lysine residues of mitochondria and peroxisome metabolic enzymes [96]. For example, SIRT5 has been reported to be able to descuccinylate pyruvate dehydrogenase 1 (PDHA1) and succinate dehydrogenase (SHDB), and play a role in regulating the activity of these protein [97]. As a member of SIRTs, SIRT5 has been proved to be located in mitochondria and cytosol [98]. As far as its cell biological function is concerned, SIRT5 can promote ammonia detoxification, regulate glycolysis, TCA cycle and electron transfer chain. In addition, SIRT5 can also promote fatty acid β oxidation and ketone body production [99]. Studies have shown that SIRT5 deficiency can promote enteritis, acute lung damage and ischemia-reperfusion damage [96].

In sepsis, SIRT5 has also attracted great attention. Studies have shown that in sepsis, SIRT5 can enhance the innate inflammatory response of macrophages or endotoxin-tolerant macrophages by promoting the acetylation of p65 and activating NF-κB pathway. This process is completed by competing with SIRT2 and blocking the deacetylation of SIRT 2 to p65 [100]. In an experimental study on burn sepsis model in mice, the inhibition of SIRT5 expression reduced the deacetylation of PDHA1, restored the activity of pyruvate dehydrogenase, promoted the polarization of macrophage M2, and alleviated burn sepsis in mice [101]. Another study using renal tubular cells (RTSCs) showed that in sepsis, the expression level of phosphorylation-AMPK (p-AMPK) decreased, the structure of mitochondria was destroyed, and the content of ATP decreased, while AMPK agonists could alleviate septic acute renal damage (SAKI), and this process was mediated by SIRT5. Knockout of SIRT5 will significantly aggravate SAKI. On the contrary, up-regulation of SIRT5 expression can reduce mitochondrial dysfunction of renal tubular epithelial cells (RTECs) and reduce SAKI by enhancing AMPK phosphorylation [102]. In a word, SIRT5 may play a regulatory role in the pathogenesis of sepsis by regulating cell metabolism, apoptosis and oxidative stress.

3.5 SIRT6

SIRT6 is another protein that depends on NAD^+ for its deacetylation activity. It regulates gene expression by removing acetyl groups from histones and transcription factors. Its biological functions include deacetylation, defatty-acylation, and ADP-ribosylation, which are involved in DNA repair, gene expression, and telomere maintenance, ultimately regulating lifespan and controlling aging [103]. In addition, SIRT6 is also related to energy metabolism, aging, obesity, inflammation, cancer and so on [104].

As far as sepsis is concerned, SIRT6 can reduce the inflammatory reaction of human venous endothelial cells (HUVECs) induced by sepsis by positively regulating the expression of Nrf2 and activating anti-inflammatory and antioxidant enzymes regulated by Nrf2, which suggests that SIRT6 is a possible target for preventing lung damage induced by sepsis [105]. Further research shows that the overexpression of SIRT6 in renal proximal convoluted tubule epithelial cells will alleviate SAKI by activating autophagy, which promotes AMPK activation, inhibits mTOR signaling pathway, promotes the polarization of macrophage M2 in autophagy-dependent and non-autophagy-dependent ways, and then plays a role in alleviating SAKI [104]. In another experiment of damage and apoptosis of renal tubular epithelial cells induced by sepsis, it was found that SIRT6 can activate nuclear factor erythroid-2-related factor 2-antioxidant response element (Nrf2)/ARE signal, alleviate renal dysfunction induced by sepsis, and reduce apoptosis and oxidative stress of renal tubular epithelial cells [106].

Because SIRT6 can promote autophagy, studies show that the overexpression of SIRT6 can alleviate sepsis-induced apoptosis, and further induce autophagy to play a protective role in renal epithelial cell damage caused by sepsis [107]. On the one hand, the up-regulated expres-

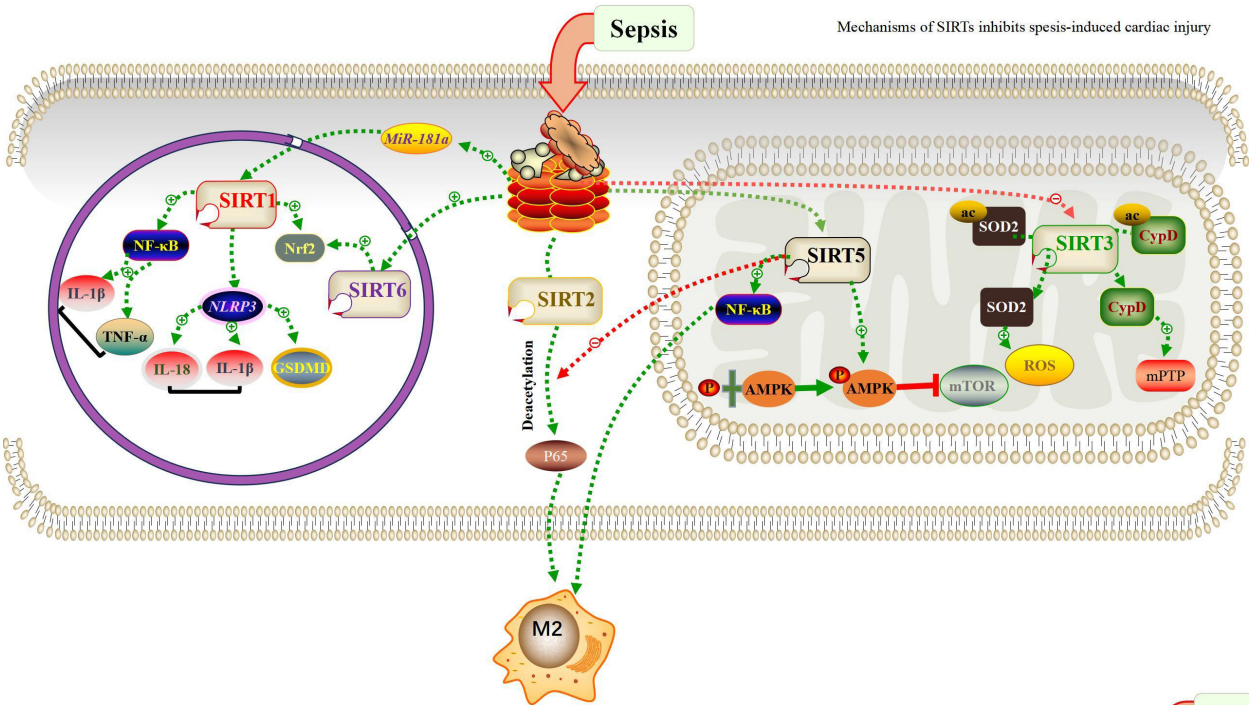

Fig. 2. Schematic representation of SIRTs modulates the inhibition of sepsis through intracellular mechanisms. SIRTs is dispersed in subcellular compartments of cells. Each SIRTs has its own unique targets that define its biological activity, as described in the review. SIRT, Sirtuin; NF-κB, nuclear factor kappa-B; GSDMD, Gasdermin D; Nrf2, Nuclear factor erythroid2-related factor 2; SOD2, superoxide dismutase 2; mPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; CypD, Cyclophilin D; ac, acetylation; M2, Macrophages 2; MiR-181a, miRNAs-181a; p65, reLA.

sion of SIRT6 can promote autophagy, on the other hand, it can protect renal tubular epithelial cells from oxidative stress, inflammatory reaction and apoptosis, and then play a protective role in sepsis-induced renal damage [108]. Another study on the treatment of sepsis shows that the activation of SIRT6 can inhibit the apoptosis of myocardial cells and the expression of inflammatory factors by promoting autophagy, and then inhibit the myocardial dysfunction induced by sepsis [109]. Besides promoting autophagy, SIRT6 plays an important role in regulating glucose metabolism *in vivo*, and the decrease of SIRT6 activity will reverse glycolysis block related to monocytes caused by endotoxin, which is a process that leads to immune metabolism paralysis of monocytes in human and mice sepsis [110]. This shows that SIRT6 mainly promotes autophagy, reduces oxidative stress and alleviates sepsis mediated by inflammatory factors.

3.6 SIRT7

SIRT7 is also a deacetylase belonging to SIRT family. Many studies have shown that SIRT7 can regulate protein deposition, endoplasmic reticulum stress, mitochondrial protein folding and mitochondrial metabolism [111]. SIRT7 is mainly located in nucleoli [112], which combines with ribosomal RNA gene and participates in the transcription process of ribosomal DNA during mitosis. One of its important functions is to regulate chromatin remodeling [113]. SIRT7 can exert deacetylation activity at DNA damage sites, and show other catalytic activities for protein involved in DNA damage and repair [111,112]. Although there are few studies on the role of SIRT7 in sepsis at present, a study on the mechanism of resveratrol found that the activation of SIRT7 can reduce inflammatory factors and play a positive role in the treatment and protection of sepsis and its cardiac damage [114]. Another study shows that liver damage will be caused during the pathogenesis of sepsis, and the activation of endoplasmic reticulum stress (ERS) pathway will cause apoptosis of hepatocytes. SIRT7 can inhibit glucose-r\regulated protein 78 (GRP78) in ERS pathway to inhibit apoptosis of hepatocytes, which provides clues for the treatment of liver damage caused by sepsis in the future [115]. Due to its unique biological function, SIRTs reduces sepsis by deacetylating several histone and non-histone proteins. Fig. 2 summarizes the role of these SIRTs in cells and their mechanisms of action in sepsis.

4. Application of Therapeutic Targets of SIRTs in Sepsis

As mentioned above, SIRTs play an important role in the development of sepsis. Therefore, it is extremely important to find a cure for sepsis with SIRTs as the tar-

get. On the one hand, the up-regulation of SIRT1 induces deacetylation of NF-κB, and then reduces inflammatory cytokines. On the other hand, it upregulates the deacetylation of SOD2 induced by SIRT3, reduces oxidative stress, improves autophagy and protects mitochondrial function [116]. Syringaresinol is a natural extract with anti-inflammatory properties, which improves sepsis-induced myocardial damage through SIRT1/NLRP3/GSDMD pathway [117]. Resveratrol alleviates sepsis-induced myocardial damage by inhibiting ferroptosis through up-regulation of SIRT1/Nrf2 signaling pathway [118]. Melatonin, an important hormone that regulates sleep, regulates apoptosis and autophagy by activating SIRT1 in mice, and protects mice from septicaemia induced cardiac dysfunction [73]. Ganoderma lucidum polysaccharides regulates inflammation, apoptosis and proliferation by activating SIRT1 [119]. Rosmarinic acid alleviates sepsis-induced cardiac damage by activating SIRT1, thereby alleviating mitochondrial damage [120]. Ttrimetazidine has a protective effect on sepsis-induced myocardial damage and apoptosis, and is associated with inhibition of macrophage proinflammatory through normalizing the SIRT1/AMP signal pathway [121]. A study using renal tubular epithelial cells showed that SIRT3 was activated and p-AMPK was also activated after 2-deoxy-D-glucose (2-DG) treatment, thus promoting autophagy and reducing cell apoptosis [122]. Tubeimoside I supplementation can significantly relieve sepsis by reversing SIRT3 expression [89]. Dietary eicosapentaenoic acid protects mitochondrial integrity and protects sepsis-induced cardiac damage through increased expression of SIRT3 [123]. Experiments have proved that after SIRT1 is activated by resveratrol, Beclin1 is induced to deacetylate, and then autophagy is promoted and it plays a protective role in sepsis-induced acute renal damage [7]. By detecting the expression level of *SIRT2* mRNA in patients with sepsis and septic shock, it was found that the expression level of *SIRT2* mRNA in patients with sepsis and septic shock decreased, which indicated that SIRT2 could be used as a potential biomarker for diagnosis on the one hand and a therapeutic target on the other [124]. Other studies have shown that SIRT2 is a potential therapeutic target for ethanol-induced sepsis [125]. It is further found that obesity will increase the incidence of sepsis patients, and the treatment with SIRT2 inhibitor adenylate kinase (AK7) can reverse autophagy disorder and improve the autophagy clearance rate of free fatty acid tolerant cells in endotoxin tolerance period [126,127], which indicates that SIRT2 is a potential target in the treatment of sepsis. In acute renal damage induced by sepsis, SIRT5 knockout significantly aggravated acute renal damage, indicating that SIRT5 plays an important role in the treatment of sepsis [102]. The activation of SIRT6 can inhibit the apoptosis of myocardial cells and the expression of inflammatory factors by promoting autophagy, and then inhibit the myocardial dysfunction induced by sepsis, which shows that SIRT6 also plays an important role in alleviating the damage of sepsis [109]. Different from other SIRTs, SIRT7 has advantages in the treatment of liver damage caused by sepsis. SIRT7 can inhibit GRP78 in ERS pathway to inhibit hepatocyte apoptosis [115]. Generally, SIRTs play a role by inhibiting the production of inflammatory mediators and regulating the function of immune cells, so SIRTs will be a promising target in the treatment of sepsis.

5. Conclusion and Prospect

In summary, SIRTs are involved in important metabolic reactions and play an important role in the development of sepsis. We have witnessed great advances in our understanding of sepsis in the SIRTs involved. However, our exploration of the upstream and downstream pathways of SIRTs is very limited, we will also focus on the SIRTs up-down pathway. We believe that it is feasible to regulate the occurrence and development of sepsis by regulating the level of SIRTs, and the subsequent research on its mechanism and the development of new drugs will open up new avenues for the treatment of sepsis.

Author Contributions

ZP and WY: contributing to conceptualization ideas; formulation and evolution of review aims; contributing to management and coordination responsibility for the research activity planning and execution; revise the draft. SW and YW: contributing to the visualization preparation, creation and presentation of the published work; contributing to write the initial draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest. Zuowei Pei is serving as one of the Guest editors of this journal. Zuowei Pei had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec.

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