

Review

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Posted Date: 2 August 2024

doi: 10.20944/preprints202408.0155.v1

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Review

Research Progress into the Regulatory Mechanism of Silent Information Regulator 1 in Sepsis

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Abstract: Sepsis, characterized by a dysregulated systemic inflammatory response to infection, remains a significant global health burden, despite substantial advancements in its treatment. An understanding of the underlying mechanisms driving sepsis is crucial for the development of targeted therapeutic strategies. Silent information regulator 1 (SIRT1), a member of the class III histone deacetylases, plays a pivotal role in regulating gene expression by catalyzing the deacetylation of lysine residues on non-histone and histone proteins. With the advancement of sepsis research, SIRT1 has been shown to exert significant anti-inflammatory, anti-oxidative, anti-apoptotic, and metabolic regulatory effects, positioning it as a potential therapeutic target for sepsis. This article reviews the latest progress on research into the signaling pathways modulated by SIRT1 in sepsis and its associated regulatory mechanisms to further elucidate the pathogenesis of sepsis and assist in guiding clinical treatment.

Keywords: silent information regulator 1; sepsis; regulatory mechanism; signaling pathway; progression

1. Introduction

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection [1], remains a significant global health burden despite the implementation of evidence-based clinical guidelines and notable advancements in treatment. The high mortality rate, prolonged hospital stay, and substantial medical costs associated with sepsis [2,3] highlight the need for a deeper understanding of its complex and multifaceted pathogenesis. The mechanisms underlying its pathogenesis include immune dysregulation, complement system inactivation, mitochondrial damage, endoplasmic reticulum stress, autophagy, cell death, and endothelial barrier disruption [4].

Among the proteins extensively studied for their role in sepsis is silent information regulator 1 (SIRT1), a member of the sirtuins protein family. SIRT1, a class III histone deacetylase that dependent on nicotinamide adenine dinucleotide (NAD⁺), has been extensively studied for its role in modulating gene expression and cellular processes [5]. The deacetylation activity of SIRT1 on both histone and non-histone proteins influences a wide range of cellular functions, making it a crucial player in the inflammatory and metabolic responses observed in sepsis. Recent studies have shed light on the intricate regulatory mechanisms and signaling pathways modulated by SIRT1, offering new insights into the pathophysiological processes of sepsis [6,7]. Researches have demonstrated that SIRT1 plays a crucial role in the inflammatory response, oxidative damage, apoptosis, and metabolic dysregulation associated with sepsis [8].

This review focuses on elucidating the role of SIRT1 in sepsis pathogenesis. By synthesizing recent advances in the understanding of the potential regulatory mechanisms and associated signaling pathways of SIRT1 in sepsis, the review aims to provide new insights into the pathophysiological processes of sepsis and explore potential novel therapeutic strategies.

2. SIRT1 and Sepsis-Induced Inflammation

2.1. SIRT1 and Inflammatory Cells

Inflammatory cells, including macrophages, dendritic cells, and neutrophils, play a pivotal role in the inflammatory response [9]. As a deacetylase, SIRT1 modulates the secretion of inflammatory mediators, influencing the differentiation, activation, and maturation of these cells [5]. Studies in animal models have shown that SIRT1 can inhibit the activation of nuclear transcription factor- κ B (NF- κ B) by promoting the deacetylation of AKT, a serine/threonine kinase, thereby 'decreasing the production of pro-inflammatory cytokines and alleviating macrophage inflammation. Conversely, the absence of SIRT1 leads to excessive acetylation of AKT, exacerbating the production of inflammatory cytokines by macrophages and promoting the progression of sepsis [10].

Additionally, SIRT1 is involved in the inflammatory signaling of dendritic cells, regulating the balance between type 1 T helper (Th1) cells and regulatory T (Treg) cells [11]. Dendritic cells with SIRT1 knockout inhibit the generation of Tregs while promoting the development of Th1, leading to an enhanced T cell-mediated inflammatory response against pathogens [12]. In SIRT1-deficient murine models, reduced neutrophil infiltration at the infection site, an immature phenotype shift in neutrophils, and a decrease in the number of myeloperoxidase-positive neutrophils have been observed, processes that have been hypothesized to lead to impaired neutrophil function and pathogen clearance [13].

2.2. SIRT1 and Inflammatory Mediators

Inflammatory mediators play a critical role in the development of sepsis, participating in pathogen clearance and potentially causing severe pathological consequences by their overactivation [14]. Recent research indicates that SIRT1 plays a significant role in regulating inflammatory mediators, with activation or increased expression of SIRT1 effectively 'decreasing inflammation and exerting anti-inflammatory effects [15,16]. Tumor necrosis factor- α (TNF- α), a pleiotropic pro-inflammatory cytokine produced by macrophages and monocytes, plays a key role in sepsis by orchestrating a cytokine cascade [17]. SIRT1 reduces the secretion of TNF- α by deacetylating the NF- κ B p65 subunit, inhibiting TNF- α -induced NF- κ B transcriptional activation. Furthermore, overexpression of SIRT1 can also 'decrease the release of interleukin (IL)-1 and IL-6 by inhibiting the protein levels of P-P65 and the activity of high mobility group box 1 (HMGB1), suppressing lipopolysaccharide (LPS)-induced apoptosis [18].

2.3. SIRT1 and Inflammatory Signaling Pathways

NF- κ B is considered a central regulator of inflammation, typically existing in an inactive form in the cytoplasm [19]. Under the influence of various pro-inflammatory factors, including interleukin-1 β (IL-1 β), IL-6, and TNF- α , NF- κ B rapidly translocates to the nucleus, regulating the transcription or expression of a series of inflammation-related genes [20]. Recent studies have shown that SIRT1 inhibits the transcriptional activity of NF- κ B by deacetylating lysine 310, a key site of the NF- κ B p65 subunit, thereby playing an anti-inflammatory role [21]. Specifically, overexpression of SIRT1 promotes the deacetylation of the NF- κ B p65 subunit, significantly 'decreasing levels of the pro-inflammatory cytokines IL-1 β , TNF- α , IL-6, and monocyte chemoattractant protein-1 (MCP-1), alleviating LPS-induced inflammation and organ damage [22].

A decrease in SIRT1 activity or the absence thereof leads to increased NF- κ B activity, further promoting the progression of inflammation [23]. In the context of sepsis, pathogenic microorganisms or endogenous molecules activate NF- κ B, promoting the formation of the NOD-like receptor protein 3 (NLRP3) inflammasome and the expression of pro-IL-1 β [24]. Activation of the NLRP3

inflammasome further leads to the activation of caspase-1, promoting the secretion of the mature pro-inflammatory cytokines IL-1 β , IL-18, TNF- α , and transforming growth factor- β (TGF- β). These factors not only enhance the inflammatory response but also recruit immune cells to the site of infection and modulate the activity of adaptive immune cells [25].

However, excessive activation of the NLRP3 inflammasome can lead to an uncontrolled inflammatory response [26]. In a sepsis murine model, Guo et al. [27] found that upregulating the expression and activity of SIRT1 can achieve the deacetylation of NF- κ B, inhibiting transcription factors associated with the NLRP3 inflammasome and thereby 'decreasing the assembly and activation of the inflammasome. This reduction in inflammasome activity decreases the maturation and secretion of IL-1 β and IL-18, improving myocardial inflammatory status and 'decreasing myocardial cell apoptosis and damage. SIRT1 can also directly affect the activity of activator protein-1 (AP-1), a key transcription factor in the inflammatory response composed of c-Jun and c-Fos proteins, by deacetylating specific lysine residues (e.g., Lys271) of the c-Jun protein, decreasing the transcriptional activity of AP-1 and subsequently inhibiting the expression of inflammatory genes. Additionally, SIRT1 may indirectly regulate the activity of AP-1 by affecting other signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway, further affecting the inflammatory response [28].

3. SIRT1 and Non-Coding RNAs in Sepsis

SIRT1 has been shown in recent studies to regulate various non-coding RNAs, including long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs), thereby affecting the development of sepsis [6]. In patients with sepsis and in corresponding murine models, growth arrest-specific 5 (GAS5), which acts as a sponge for microRNA-155-5p (miR-155-5p), promotes the expression of SIRT1 upon upregulation. By helping to inhibit excessive acetylation and release of HMGB1, GAS5 alleviates cellular inflammatory responses [7]. Zou et al. [29] discovered that under sepsis conditions, increased expression of connexin43 (Cx43) leads to enhanced intercellular transfer of miR-181b, affecting the SIRT1/forkhead box O3a (FOXO3a)-signaling pathway and subsequently causing cell and tissue damage. Conversely, Cx43 inhibitors can decrease the activity of the SIRT1/FOXO3a signaling pathway by regulating the intercellular transfer of miR-181b, thereby mitigating organ damage during sepsis.

Further research has revealed that by targeting miR-212-3p, circRNA vesicle-associated membrane protein-associated protein A (circVAPA) negatively regulates the expression of SIRT1 and cell pyroptosis-related factors, including nuclear erythroid 2-related factor 2 (Nrf2) and NLRP3 and inhibit LPS-induced cell pyroptosis and Th17-related inflammatory responses, which are significant factors in alleviating inflammatory damage in sepsis-induced acute lung injury [30]. Additionally, SIRT1 has shown potential for inhibiting inflammation and the expression of cyclooxygenase-2 and inducible nitric oxide synthase by targeting the p53/miR-22 axis [31].

4. Role of SIRT1 in Metabolism during Sepsis

Metabolism is a fundamental physiological process that sustains growth, reproduction, and normal functions in living organisms [32]. In the context of sepsis, patients often exhibit a series of acute responses, such as tachycardia; fever; rapid breathing; and activation of the immune, coagulation, and complement systems, accompanied by significant energy metabolism imbalances [33]. Specifically, glycolysis enhancement, hepatic glycogen breakdown, and lipolysis, along with accelerated fatty acid oxidation, leads to the breakdown of muscle tissue proteins, promoting a cachectic state [34]. Concurrently, immune cells must compete with pathogens for glucose resources during their function execution, and the disruption of glycolysis can impair the phagocytic and bactericidal capabilities of immune cells [35].

Through interactions with various sensing proteins, such as AMP-activated protein kinase (AMPK), FOXO1, and peroxisome proliferator-activated receptor gamma coactivator (PGC-1 α), SIRT1 forms a complex sensing network that affects glucose metabolism, lipid metabolism, and mitochondrial quality control [36]. During sepsis, SIRT1 promotes a transition from a high-

inflammatory stage characterized by glycolysis to a low-inflammatory stage characterized by fatty acid oxidation, and promotes this transition by regulating metabolic pathways to meet the energy demands of immune cells and maintaining the balance between immune function and immune metabolism [37]. However, persistent overexpression of SIRT1 may also lead to immune function suppression, hinder the clearance of infection foci, and ultimately result in energy exhaustion and organ dysfunction [38]. Ryan et al. [39] found that SIRT1 regulates the glycolysis process in endothelial cells by directly acting on key rate-limiting enzymes in glycolysis, including hexokinase 2, platelet-type phosphofructokinase, and M2-type pyruvate kinase. This mechanism may be a critical regulatory factor in the host's effective defense against pathogens during sepsis. Despite knowledge of this mechanism, much remains unknown, as current research on the impact of SIRT1 on energy metabolism and its potential regulatory mechanisms during sepsis remains limited. Further progress requires broader and more in-depth exploration in this area.

5. Role of SIRT1 in Oxidative Stress during Sepsis

Oxidative stress is a key factor in cellular damage resulting from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense system [40]. Numerous studies have indicated that SIRT1 is involved in the management of oxidative stress processes during sepsis by its regulation of various signaling pathways and gene expressions [41]. A study of the role of quercetin showed that through SIRT1, quercetin can elevate intracellular NAD⁺ levels and activate antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), which help to clear intracellular ROS and alleviate oxidative stress. SIRT1 can also directly improve mitochondrial function by deacetylating and activating AMPK, decreasing ROS production, and promoting mitochondrial biogenesis, thus maintaining mitochondrial integrity and function. Furthermore, activated AMPK enhances fatty acid oxidation and increases intracellular adenosine triphosphate (ATP) production, improving cell resistance to oxidative stress [42]. The multifaceted mechanisms underlying the SIRT1/AMPK signaling pathway are involved in directly combating oxidative stress, protecting mitochondrial function, and enhancing cellular resistance to oxidative stress [42].

Nrf2 is a leucine zipper transcription factor that directly regulates the expression levels of antioxidant genes [43]. The deacetylation of Nrf2 by SIRT1 promotes its binding to antioxidant response elements, enhancing the expression of downstream antioxidant proteins, such as quinone oxidoreductase and heme oxygenase-1, effectively clearing excess ROS and alleviating damage caused by oxidative stress [44]. Additionally, SIRT1 regulates members of the FOX family, including FOXO1, to upregulate the expression of the antioxidant enzymes SOD and CAT, decreasing oxidative stress-induced cellular damage [45]. Zhu et al. [46] found that through the SIRT1/FOXO1 pathway, SIRT1 reduces malondialdehyde concentrations and increases the activities of the antioxidant enzymes SOD and CAT, which can alleviate oxidative stress and protect against sepsis-related brain cell damage.

Similarly, regulation of FOXO3 and FOXO4 by SIRT1 helps mitigate oxidative stress responses [47,48]. In sepsis models, SIRT1 increases the acetylation of PGC-1 α to enhance its activity, thereby strengthening mitochondrial function, decreasing oxidative stress, and protecting neurons from damage [49]. SIRT1 activates antioxidant enzyme-related genes encoded by p53, such as SOD and GPx, to neutralize or clear ROS, protecting cells from oxidative stress injury. At the same time, SIRT1 inhibits p53 activity by deacetylation, decreasing the expression of oxidative factors and enhancing cell resistance to oxidative stress [50]. In the NF- κ B signaling pathway, activation of SIRT1 can inhibit the activity of NF- κ B factors, alleviating oxidative stress injury in sepsis hepatocytes [51]. One study showed that by regulating the SIRT1/NF- κ B signaling pathway, the oxidative stress response induced by LPS in mice can be improved, mitigating renal damage [52].

6. SIRT1 and Endoplasmic Reticulum Stress in Sepsis

SIRT1 plays a significant role in endoplasmic reticulum stress (ERS), a critical component of the pathophysiological process of sepsis closely related to several important processes, including

inflammatory responses, immune cell dysfunction, and apoptosis [53]. In the regulation of ERS. Studies have shown that increased expression of SIRT1 can significantly suppress ERS responses in lung tissue and macrophages through the protein kinase R-like ER kinase (PERK)/eukaryotic initiation factor 2 alpha (eIF2 α)/activating transcription factor 4 (4ATF4)/C/EBP homologous protein (CHOP) signaling pathway, thereby improving sepsis-related lung injury and alleviating pulmonary inflammation [54]. Moreover, quercetin can inhibit oxidative stress-mediated ERS by activating the SIRT1/AMPK signaling pathway, decreasing acute lung injury caused by sepsis [42].

7. SIRT1 and Autophagy in Sepsis

Autophagy is a process by which intracellular materials or pathogens are engulfed by autophagosomes and degraded upon fusion with lysosomes [55]. In sepsis, autophagy plays a protective role by clearing pathogens, neutralizing microbial toxins, regulating cytokine release, decreasing target cell apoptosis, and promoting antigen presentation [56]. SIRT1 also exerts a multifaceted influence on the regulation of autophagy in sepsis. In a murine model of LPS-induced sepsis, Sun et al. [57] demonstrated that SIRT1 enhances autophagy in renal tubular epithelial cells through the deacetylation of p53, thereby mitigating acute kidney injury. Furthermore, it was observed that acetylated p53 was more prone to bind with Beclin1, accelerating its ubiquitination-mediated degradation and inhibiting autophagy. In another LPS-induced sepsis experiment, recombinant human erythropoietin altered the expression levels of autophagy-related proteins, including microtubule-associated protein 1A/1B-light chain 3 I (LC3-I)/LC3-II and P62, through the SIRT1/AMPK pathway, activating autophagy to prevent cell apoptosis [58]. These findings indicate that the use of SIRT1 inhibitors can block autophagy, leading to exacerbated cell apoptosis.

8. SIRT1 and Apoptosis in Sepsis

SIRT1 regulates apoptosis, a critical component in the pathogenesis of sepsis influenced by multiple signaling pathways that exerts effects on various organs, at multiple levels [59]. Particularly during sepsis progression, apoptosis of immune cells plays a significant role in not only disease advancement but also immune suppression. In a study of LPS-induced sepsis, Lin et al. [60] found that upregulation of SIRT1 reduced apoptosis in sepsis-associated target organs through the p53/solute carrier family 7 member 11 (SLC7A11) signaling pathway. Yang et al. [61] observed similar results in a sepsis murine model treated with matrine, confirming the role of the SIRT1/p53 signaling pathway in improving sepsis-associated cell apoptosis. Their study also revealed the anti-apoptotic role of the SIRT1/NF- κ B pathway, in which SIRT1 modulates the NF- κ B pathway to control the secretion of inflammatory cytokines, thereby inhibiting apoptosis. Regulation of FOXO1 by SIRT1 also contributes to alleviating apoptosis caused by oxidative stress and mitochondrial dysfunction [62]. Moreover, SIRT1 inhibits the pro-apoptotic activity of p53 through deacetylation, a mechanism essential for protecting immune cells from apoptotic signals [8]. These findings indicate that SIRT1 plays a vital protective role in the apoptotic process of sepsis.

9. SIRT1 and Pyroptosis in Sepsis

Pyroptosis is a form of programmed cell death activated by inflammasomes primarily through the activation of caspase family proteins, which cleave gasdermin proteins, such as gasdermin D (GSDMD) [63]. By releasing the N-terminal active fragments of gasdermin proteins that form pores on the cell membrane, pyroptosis leads to the release of cellular contents and cell death [64]. SIRT1 has been found to influence the process of pyroptosis by modulating the activity of the NLRP3 inflammasome. In a study of a quercetin-mediated septic murine model, quercetin upregulated the expression of SIRT1 and reduced the activation of the NLRP3 inflammasome, thereby improving pyroptosis in target organs [65]. Jiao et al. [66] showed that by targeting and suppressing SIRT1 expression in macrophages, exosomal miR-30d-5p increased the acetylation level of p65 and activated NF- κ B, leading to macrophage pyroptosis, which is associated with sepsis-related pneumonia. SIRT1 can also activate PGC-1 α through deacetylation, which in turn activates Nrf2, the latter entering the

nucleus to promote the expression of antioxidant genes, thereby decreasing oxidative stress and pyroptosis [67].

10. SIRT1 and Ferroptosis in Sepsis

Ferroptosis is a recently discovered form of cell death dependent on iron-dependent lipid peroxidation [68] with a pathogenesis closely related to that of sepsis [69]. A study has demonstrated that quercetin (a SIRT1 agonist) exerted an anti-ferroptotic effect via activation of the SIRT1/p53/SLC7A11 signaling pathway to alleviate sepsis-induced myocardial injury both in vivo and in vitro [60]. Another study in an LPS-induced mouse model revealed that quercetin inhibits ferroptosis by activating the SIRT1/Nrf2/GPx4 signaling pathway, providing significant protection against LPS-induced lung injury [70]. In another study, irisin suppressed ferroptosis levels in a cecal ligation and puncture murine model through the SIRT1/Nrf2 signaling pathway, reducing the extent of renal damage [53]. This mechanism involves decreasing malondialdehyde levels, increasing glutathione levels to inhibit lipid peroxidation, decreasing iron content in the kidney, increasing GPX4 expression, and decreasing the expression of acetyl-CoA synthetase 4, thereby inhibiting ferroptosis [71].

11. Other Mechanisms of SIRT1 in Sepsis

Damage to the endothelial glycocalyx is an essential component of the sepsis pathological process, exacerbating inflammatory responses and promoting the activation of the coagulation system, leading to vascular dysregulation and inducing endothelial cell apoptosis [72]. A recent study that explored the effects of Interferon-beta (IFN- β) combined with nicotinamide riboside in an LPS-induced sepsis model found that this combination therapy effectively alleviated vascular endothelial injury caused by sepsis. Notably, in a model with specific knock-out of endothelial cell SIRT1, this protective mechanism was significantly weakened, indicating the essential role of SIRT1 in maintaining vascular endothelial integrity. Further mechanistic studies revealed that IFN- β may protect vascular endothelial cells from injury by stabilizing the expression of SIRT1 protein. Additionally, the activation of SIRT1 can regulate the SIRT1/heparanase 1 pathway, contributing to the repair of damaged endothelial glycocalyx [73].

12. Conclusion and Future Perspectives

In this study, it was found that SIRT1 modulated various signaling pathways and mechanisms and regulated inflammation, immune function, cellular metabolism, apoptosis, pyroptosis, ferroptosis, and autophagy in sepsis, as illustrated in Figure 1. With its ability to exert anti-inflammatory, anti-apoptotic, and cytoprotective effects, SIRT1 holds promise as a potential therapeutic target for sepsis. Researchers have developed various agonists and antagonists. Despite progress in cellular and animal model experiments, our understanding of the regulatory mechanisms of SIRT1 in sepsis remains limited. Most studies have focused on the impact of a single target organ, leaving the comprehensive mechanism of action of SIRT1 not fully understood. Additionally, clinical trial data for SIRT1 modulators are extremely scarce, limiting acquisition of a comprehensive understanding of the role of SIRT1 in sepsis [74]. To address these limitations, future research should delve deeper into the regulatory mechanisms of SIRT1 in sepsis using a multidisciplinary approach combining advanced techniques, such as genomics, proteomics, and metabolomics, to fully elucidate these mechanisms. Using the findings of these studies, we can develop more specific and effective SIRT1 modulators, providing new strategies for the prevention and treatment of sepsis.

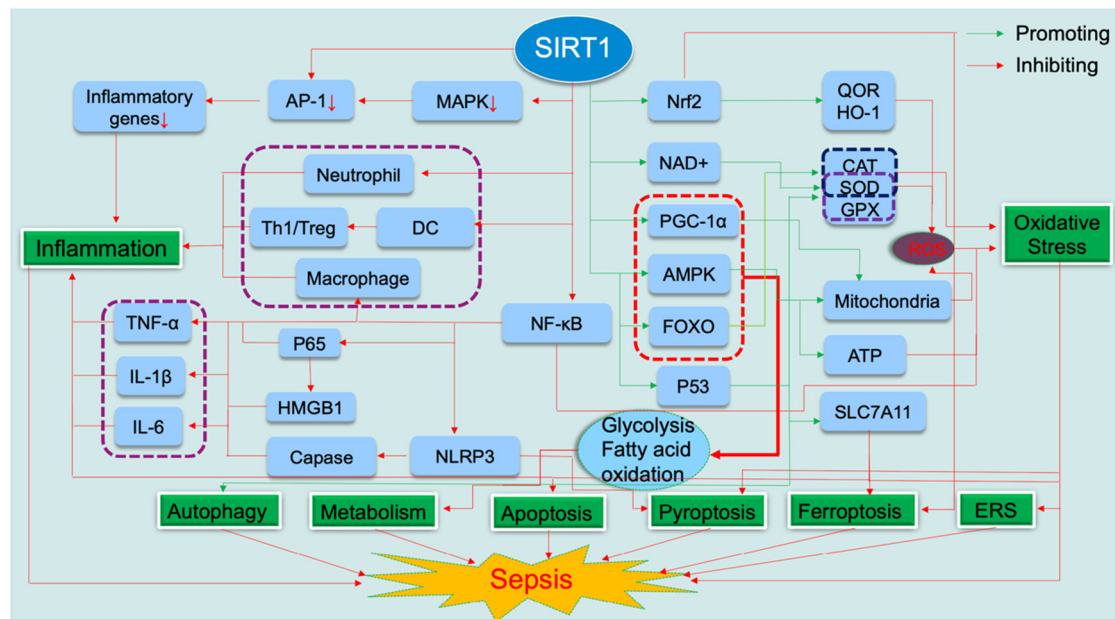


Figure 1. The Central Regulatory Role of SIRT1 in Sepsis Pathophysiology. SIRT1, a NAD⁺-dependent deacetylase, plays a pivotal role in modulating the pathophysiological processes in sepsis. It initiates its anti-inflammatory action by deacetylating key proteins such as AKT and the NF- κ B p65 subunit, which in turn suppresses the activation of inflammatory signaling cascades and diminishes the secretion of pro-inflammatory cytokines, leading to a regulated inflammatory response. Furthermore, SIRT1 contributes to the attenuation of oxidative stress through the upregulation of antioxidant enzymes and the improvement of mitochondrial function, thereby reducing oxidative damage to cellular components. Metabolically, SIRT1 interacts with AMPK and PGC-1 α , orchestrating a metabolic reprogramming that aligns with the energy requirements of immune cells, thus preserving the balance of immune metabolism. SIRT1 also safeguards cells from endoplasmic reticulum stress-induced damage and modulates autophagy, a critical process for cellular homeostasis. In terms of cell death regulation, SIRT1 exerts its influence through pathways involving p53 and SLC7A11, curtailing both apoptosis and pyroptosis, which are significant contributors to tissue damage in sepsis. Abbreviation: AMPK, AMP-activated protein kinase; AP-1, activator protein-1; CAT, catalase; DC, dendritic cell; ERS, endoplasmic reticulum stress; FOXO, forkhead box O; GPX, glutathione peroxidase; HMGB1, high mobility group box 1; HO-1, heme oxygenase-1; IL-1 β , interleukin-1beta; IL-6, interleukin-6; MAPK, mitogen-activated protein kinase; NAD⁺, nicotinamide adenine dinucleotide; NF- κ B, nuclear transcription factor- κ B; NLRP3, NOD-like receptor protein 3; Nrf2, nuclear erythroid 2-related factor 2; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator-1 alpha; QOR, quinone oxidoreductase; ROS, reactive oxygen species; SIRT1, silent information regulator 1; SLC7A11, solute carrier family 7 member 11; SOD, superoxide dismutase; Th1/Treg, type 1 T helper cells/regulatory T cells; TNF- α , tumor necrosis factor- α .

Author Contributions: Q.Z.: writing original draft and editing. W.G.: writing original draft and editing. W.Z.: writing-review and funding acquisition. S.T.: writing original draft. H.F.: editing. P.P.: writing-review and editing and supervision and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by Chongqing Science and Technology Foundation (CSTC2020JCYJ-MSXMX1069), the Chongqing Medical Scientific Research Project (Joint project of Chongqing Health Commission and Science and Technology Bureau) (2024QNXM054), the Joint Medical Scientific Research Project of the Health Commission and Science and Technology Bureau of Wanzhou, Chongqing (wzstc-kw2021001).

Acknowledgments: We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Institutional Review Board Statement: Not applicable. Informed Consent

Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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