Histol Histopathol (2019) 34: 1205-1215

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

Research progress on SIRT1 and sepsis

Lincheng Li[1]*, Mingchuan Liu[1]*, Mengyuan Cao[2], Ting He[3] and Xiaozhi Bai[3]

[1]Brigade 4, College of Basic Medicine, the Fourth Military Medical University, [2]Emergency Department, Xijing Hospital, the Fourth Military Medical University and [3]Department of Burns and Cutaneous surgery, Xijing Hospital, the Fourth Military Medical University, Xi'an, Shaanxi, China

*Lincheng Li and Mingchuan Liu contributed equally to this review

Summary. SIRT1, a member of the sirtuin family, belongs to the NAD^+-dependent class III histone deacetylase. SIRT1 can regulate gene expression by catalyzing non-histone and histone lysine residues deacetylation. SIRT1 also plays important roles in glucose and lipid metabolism, cell aging, tumorigenesis and inflammation. Recent studies indicate that SIRT1 can inhibit the inflammatory responses *via* regulating several inflammatory signaling pathways. It is closely related to the occurrence and development of sepsis and other inflammatory diseases. Research has been done on relevant signaling pathways of SIRT1 as well as its target genes during inflammation. SIRT1 is a hot spot in uncontrolled inflammatory response research. This article focuses on the role of SIRT1 in inflammation, especially its targets and involved signaling pathways in sepsis, and tries to provide more convincing evidence for the clinical treatment of sepsis and other inflammatory diseases.

Key words: SIRT1, Deacetylase, Sepsis; NF-κB, MAPK

Offprint requests to: Xiaozhi Bai and Ting He, Department of Burns and Cutaneous Surgery, Xijing Hospital, the Fourth Military Medical University, Xi'an, 710032 Shaanxi, China. e-mail: baixiaozhi006@126.com and heting17@163.com

DOI: 10.14670/HH-18-146

Introduction

Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, which is a severe complication of burns, trauma, and other critical injuries. The new definition pays more attention to a series of pathophysiological responses of the body's response to infection, not just infection itself (Singer et al., 2016). The mortality of sepsis is about 20% (Jones and Puskarich, 2014).

SIRT1 is a member of the Sirtuin family, and its functions are complex and diverse. More and more studies indicate that SIRT1 may be involved in the process of sepsis, inflammation, oxidative damage, cell apoptosis and metabolic disorders. Additionally, it regulates multiple signaling pathways in sepsis. Therefore, SIRT1 is seen as a promising candidate molecule in the treatment of sepsis.

Introduction of SIRT1

In 1986, Ivy et al. (1986) discovered a gene that prolonged cell life in lower organisms such as yeast, nematodes, and fruit flies, and named it Silence Information Regulator 2 (Sir2). In 1999, Frye found five genes highly homologous to yeast Sir2 in human belonging to the Sirtuin family, named Sirt1 to Sirt5. Later, Sirt6 and Sirt7 were discovered. The members of the Sirtuin family have different locations in cells and perform different biological functions in life. SIRT1, 6 and 7 mainly function in the nucleus, while SIRT3, 4 and

5 are localized in mitochondria. SIRT2 is mainly located in cytoplasm (Houtkooper et al., 2012). The members of the Sirtuin family play an important role in sepsis (Table 1). The Sirtuin family may be homeostasis protectors that coordinate immunometabolism. SIRT1 is widely studied. It is a star molecular in various fields. SIRT1, a NAD^+-dependent protein deacetylase with a highly conserved amino region, performs different functions mainly by catalyzing the deacetylation of histones or non-histones. SIRT1 removes the acetyl moieties from the ε-acetamido groups of lysine residues of histones and other signaling proteins, thus promoting chromatin condensation and suppressing gene transcription (Rahman et al., 2012). A number of studies have shown that SIRT1 is involved in the regulation of metabolism, cellular senescence, inflammatory response and oxidative stress, which is associated with the development of metabolic syndrome, and tumorigenesis, as well as neurodegenerative diseases (Martin et al., 2015). SIRT1 participates in the deacetylation of FOXO1, NF-ϰB, and p53, which makes it a key factor in sepsis.

Recent research on sepsis and SIRT1

With the improvement of intensive care systems and the standardization of sepsis treatment (Rhodes et al., 2017), sepsis mortality rate has decreased significantly, but it is still reported as a leading cause of death in critically ill patients (Xavier et al., 2017). The mechanism of sepsis is complex. During sepsis, the early hyperinflammatory state evolves to a subsequent hypoinflammatory state with significant immunosuppression characterized by loss of immune cells but no enduring cell-autonomous defects in T-cell function (Markwart et al., 2014). A few exemplary cytokines which could be regarded as biomarkers change at different stages of sepsis (Faix, 2013) (Table 2). A clear difference in cellular metabolism can be observed between the hyperinflammatory and the immunotolerant state (Fig. 1) (Table 3) Glycolysis and pentose phosphate pathway are up-regulated but oxidative phosphorylation is suppressed in the hyperinflammatory state (Wang et al., 2018a,b). While during immune tolerance, ATP generation is dependent on fatty acid β-oxidation, glycolysis is often down-regulated (Cheng et al., 2016). Compared with TCA cycle and oxidative phosphorylation, glycolysis can become highly up-regulated following stimulation with rapid ATP generation, which is more favorable in acute inflammation (Arts et al., 2017). Nicotinamide adenine dinucleotide (NAD+) is an important hydrogen carrier in glycolysis and TCA cycle, which is an indispensable cofactor for SIRT1 in regulating the inflammatory response. Interestingly, NAD+ concentrations highly differ between hyperinflammatory and immunotolerant state. Therefore, SIRT1 has different roles at different stages of sepsis.

Signaling pathways that involve in SIRT1 and sepsis

Multiple signaling pathways such as NF-ϰB, MAPK, JAK/STAT, and PI3K/Akt are involved in the development of sepsis (Zhang et al., 2016a,b). Several processes, including uncontrolled inflammatory response, immune dysfunction, coagulopathy, mitochondria injury, autophagy and gene polymorphism,

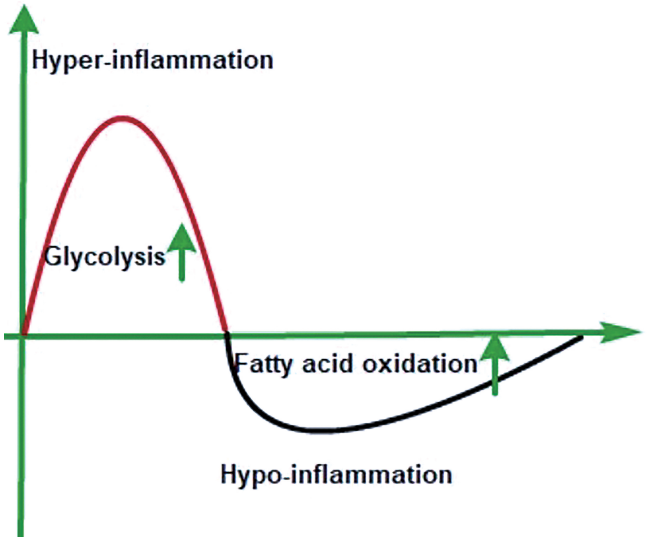

Fig. 1. Metabolic changes in sepsis. There is increased glycolysis in the hyper-inflammatory phase, while the hypo-inflammatory phase is associated with increased fatty acid oxidation.

Table 1. The role of different sirtuins during sepsis.

Sirtuin	Biological Function
SIRT1	Decreases pro-inflammatory cytokine/chemokine and adhesion molecule expression (Wang et al., 2015a,b)
SIRT2	Represses adipocyte differentiation (Lin et al., 2013)
SIRT3	Represses mitochondrial OXPHOS and reduces mitochondrial biogenesis (Liu et al., 2015)
SIRT4	Increases glycolysis and glucose oxidation (Mathias et al., 2014)
SIRT5	Decreases interaction between SIRT2 and NF-κB p65; Enhances the pro-inflammatory response (Qin et al., 2017)
SIRT6	Modulates glucose and fatty acid homeostat (Long et al., 2017)
SIRT7	Regulates genomic stability and metabolic response of cells (Li et al., 2016)

are related in this process (Rizzo and Dudek, 2017). During these, uncontrolled inflammatory response is thought to be one of the most important factors. The therapy of sepsis is still a tough problem. Among all these studies, SIRT1 is one of the most promising molecules for the alleviation of sepsis. SIRT1 can suppress inflammation and oxidative stress as well as change metabolism by regulating NF-κB, MAPK, JAK/STAT and PI3K/Akt signaling pathways during sepsis. And finally it could alleviate organ damage in sepsis.

SIRT1 and NF-κB signaling pathway

NF-κB is a nuclear transcription factor that mediates intracellular signaling transduction. NF-κB, a heterodimer composed of p50 and p65, usually binds to the IκB subunit and stays in an inactive state. During sepsis, IκB kinase (IKK) catalyzes the phosphorylation of IκB subunit and leads to the degradation of it. Then NF-κB complex is released to enter the nucleus and regulates inflammation related gene transcription (Shih et al., 2015). NF-κB signaling pathway can be activated by the acetylation of multiple lysine sites of p65 subunit (eg, Lys218, Lys221, Lys310) to increase the transcription of inflammatory factors (Greene and Chen, 2004). Recent studies have confirmed that SIRT1 can alleviate NF-κB-mediated inflammation and metabolic disorders (Xie et al., 2013; Edwards et al., 2013; Chen et al., 2018). SIRT1 is able to bind to RelA/p65 (Lys310) to deacetylate p65 subunit and to inhibit the activity of NF-κB pathway, which finally reduces inflammatory damage and apoptosis (Zhou et al., 2014). With the deacetylation of RelA/p65 (Lys310), other lysine sites (eg, Lys314, Lys315) of p65 are exposed and methylated, which enhances the ubiquitination and degradation of p65 (Yang et al., 2010) (Fig. 2). In addition, the inhibitory RelB protein could suppress the transcriptional expression of TNF-α by replacing the deacetylated RelA/p65 protein, and SIRT1 could recruit RelB protein (Liu et al., 2011). A number of studies have shown that in SIRT1 knockout mice, cecal ligation and puncture (CLP) induces phosphorylation and degradation of IκBα and activation of NF-κB pathway in lung. Then it increases precursor and mature forms of IL-1 and finally aggravates inflammation (Gao et al., 2015; Lan et al., 2017). Vice versa, NF-κB signaling pathway can inhibit the expression of SIRT1 (Zhang et al., 2010; Kauppinen et al., 2013). The promoter region of SIRT1 gene contains multiple binding sites for NF-κB transcription factors (Voelter-Mahlknecht and Mahlknecht, 2006). Li et al. (2012a,b) have discovered that NF-κB can increase the expression of miR-34a,

Table 2. Major cytokines at different stages of sepsis.

hyperinflammatory phase	immunosuppressive phase
TNF-α	IL-10
IL-1β	TGF-β
IL-6	CTLA-4
IL-8	PD-1
MCP-1	

Table 3. Metabolic changes in sepsis.

State/Metabolic	Glycolysis	PPP	TCA Cycle	OxPhos	fatty acid oxidation
Hyperinflammatory	up-regulated	up-regulated	down-regulated	down-regulated	up-regulated
Immunosuppressive	down-regulated	unknown or unchanged	unknown or unchanged	up-regulated	up-regulated

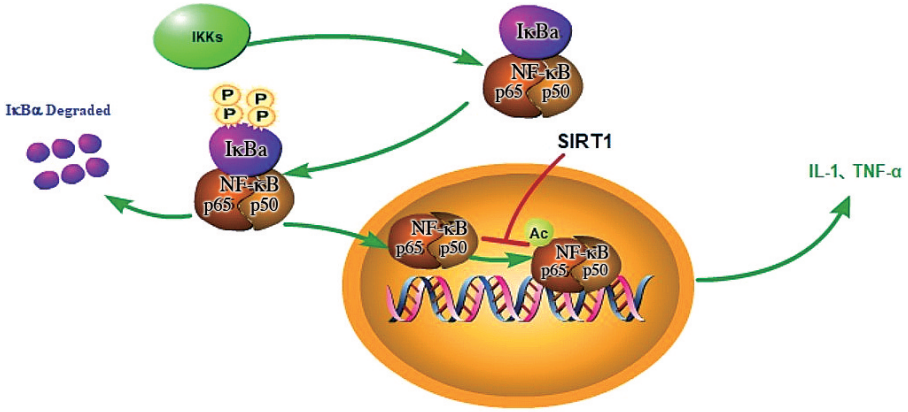

Fig. 2. IκB kinase (IKK) catalyzes the phosphorylation of IκBα subunit and leads to the degradation of it. Then NF-κB complex is released to enter the nucleus and regulates inflammation related gene transcription. However, SIRT1 is able to deacetylate RelA/p65 and inhibit the activity of NF-κB pathway and finally reduces the release of inflammatory factors (eg, IL-1, TNF-α).

which depends on the presence of p53. And miR-34a can inhibit SIRT1 expression by targeting the 3 'UTR region of SIRT1 (Yamakuchi et al., 2008). Research has shown that NF-κB signaling pathway can increase the expression of IFN-γ (Sica et al., 1997; Kang et al., 2014), CIITA and HIC1, and thus inhibit the expression of SIRT1 (Li et al., 2012b).

SIRT1 and MAPK signaling pathway

Mitogen-activated protein kinase (MAPK) is a group of highly conserved serine-threonine protein kinase expressed by eukaryotic cells that mediates signaling transfer from cell surface to the nucleus (Lee et al., 2016). Each of the MAPK signaling pathways consists of three tiers of protein kinases termed MAP3K, MAPKK and MAPK. It also has two additional tiers, the upstream MAP4K and the downstream MAPKAPK (Keshet and Seger, 2010). The five protein kinase cascades are sequentially activated by phosphorylation, and then activate downstream targets (such as transcription factors, protein kinases, etc.). The signaling pathway of MAPK family includes ERK, p38, JNK and BMK-1 pathway (Cossa et al., 2013). MAPK signaling pathway is involved in the release of inflammatory cytokines, oxidative stress, cell apoptosis and calcium overload (Koffel et al., 2014; de Oliveira et al., 2015), which are important mechanisms of organ damage in sepsis. Several studies have shown that SIRT1 can regulate MAPK pathway *via* Akt/ASK1 signaling by reducing p38 and JNK phosphorylation and increasing ERK phosphorylation (Becatti et al., 2012, 2014), improving organ functions in sepsis (Yang et al., 2018). Studies have shown that in mice, macrophage specific SIRT1 knockout can broadly activate the JNK pathway, increasing JNK phosphorylation and LPS-stimulated TNF-α secretion (Yoshizaki et al., 2009, 2010). It is also reported that SIRT1 can inhibit the activity of MKK3, which is an upstream kinase of p38, and then increase the mitochondrial biogenesis in tissue and cell, reducing the production of reactive oxygen species (ROS), and inhibiting inflammation and lung injury in septic mice (Mannam et al., 2014). Bai et al. (2015) has reported that SIRT1 activation may attenuate the apoptosis of pulmonary microvascular endothelial cells (PMVEC) through p38 MAPK pathway. SIRT1 also has protective and anti-apoptotic effects on severe burn induced acute lung injury mice, suggesting that SIRT1 activation may be a potential strategy for organ protection after severe burns.

SIRT1 and JAK/STAT signaling pathway

JAK/STAT signaling pathway can be activated by various cytokines and growth factors. It is involved in processes such as cell proliferation, differentiation, inflammation and immune response (Ladyman and Grattan, 2013; Palanivel et al., 2014; Arumuggam et al., 2015; Villarino et al., 2017). The JAK/STAT signaling pathway is mainly composed of three parts: tyrosine kinase-related receptor, tyrosine kinase JAK and transcription factor STAT. JAK is a family of non-receptor tyrosine kinases, including four tyrosine kinases named JAK1, JAK2, JAK3 and TYK2. The STAT family, a signaling transduction and transcriptional activator, is a substrate of JAK, including seven transcription factors (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6) (Villarino et al., 2015). Dimerization of receptors occurs after ligand binding, which activates JAK through phosphorylation of tyrosine residues. Then JAK selectively phosphorylates STAT, and dimeric STAT translocates to nucleus to regulate gene transcription (Nicolas et al., 2013; Jang and Baik, 2013). Studies have shown that JAK/STAT

Table 4. Signaling pathways involved in SIRT1 and sepsis.

Signaling Pathway	Interactions with SIRT1
NF-κB	SIRT1 binds to RelA/p65 (Lys310) to deacetylate p65 subunit (Zhou et al., 2014) SIRT1 recruits RelB protein to silence proinflammatory genes (Liu et al., 2011) NF-κB inhibits SIRT1 by increasing the expression of miR-34a (Yamakuchi et al., 2008)
MAPK	SIRT1 reduces p38 and JNK phosphorylation and increase ERK phosphorylation (Becatti et al., 2012; Becatti et al., 2014) SIRT1 reduces the production of ROS by inhibiting MKK3 (Mannam et al., 2014)
JAK/STAT	SIRT1 inhibits phosphorylation of JAK2/STAT3 pathway and then inhibits pro-inflammatory (Park et al., 2016) JAK1 catalyzes the phosphorylation of tyrosine residues in SIRT1 (eg, Tyr280, Tyr301) (Gao et al., 2011)
PI3K/Akt	SIRT1 promotes the inactivation of p300 acetyltransferase and inhibits PI3K acetylation (Shakibaei et al., 2011)
FoxO	SIRT1 deacetylates FOXO3a, enhances the expression of SOD2 and reduces the expression of NOX4 (Shimada et al., 2014; Zhang et al., 2017)
Notch	SIRT1 inhibits Notch signaling through NICD deacetylation and interactions with LSD1 (Mulligan et al., 2011)
PGC-1α	SIRT1 deacetylates PGC-1α and regulates the translocation of NFE2L2 into the nucleus and binds to the ARE (Zschoernigand Mahlknecht, 2008) SIRT1 activates GABPA to promote translocation of transcription factors in mitochondria (McCreath et al., 2016).
HMGB1	SIRT1 deacetylates HMGB1 and negatively regulates the nuclear export of HMGB1 (Hwang et al., 2015)
Other	SIRT1 down-regulates lncRNA-CCL2 and then reduces the expression of inflammatory cytokines (Jia et al., 2018) SIRT1 inhibits the NLRP3/IL-1β axis in the hippocampus of septic mice (Sui et al., 2016)

pathway is related to many important cytokines involved in sepsis (Cai et al., 2015; Lv et al., 2015). The interaction between SIRT1 and JAK2/STAT3 pathway cannot be ignored. A study indicates that SIRT1/JAK/STAT3 signaling pathway is an important target for the inhibition of tumorigenesis of various drugs (Xu et al., 2018a). Park et al. (2016) has reported that activation of SIRT1 can inhibit phosphorylation of JAK2/STAT3 pathway and then inhibit pro-inflammatory responses and increase cell viability. Recent research has shown that activation of JAK/STAT signaling pathway in mice macrophages can increase SIRT1 expression (Yoo et al., 2014). Further studies reveal that JAK1 is a tyrosine kinase which catalyzes the phosphorylation of tyrosine residues in SIRT1 (eg, Tyr280, Tyr301), and thereby to promote the interaction of SIRT1 and STAT3. It finally inhibits STAT3 transcription. JAK1 may feedback to regulate JAK1/STAT3 signaling pathway by mediating the phosphorylation of SIRT1 (Gao et al., 2011; Wang et al., 2018a,b).

SIRT1 and PI3K/Akt signaling pathway

Phosphatidylinositol 3 kinase (PI3K) is a class of kinases that specifically catalyzes the phosphorylation of phosphatidylinositol at position 3 (Kong and Yamori, 2009). PI3K can be divided into three categories, in which class I PI3K is most widely studied. Class I PI3K is a heterodimer, composed of a catalytic subunit p110 and a regulatory subunit p85. In mammal, there are seven kinds of regulatory subunits (p85α, p85β, p55α, p55γ, p50α, p101 and p87) and four kinds of catalytic subunits (p110α, p110β, p110γ and p110δ) (Vanhaesebroeck et al., 2010). Various stimulus can activate PI3K, including cytokines, growth factors, and hormones (Guo et al., 2015). In addition, PI3K also possesses serine/threonine (Ser/Thr) kinase activity. The serine/threonine kinase Akt (also known as PKB) is a serine/threonine-specific protein kinase comprising three subtypes (AKT1, AKT2 and AKT3) (Jha et al., 2015). Akt and its upstream kinase PDK1 interact with the PI3K-producing phosphatidylinositol triphosphate (PIP3) and form a complex. The complex enters cell membrane *via* PH domain. PDK1 catalyzes phosphorylation of Akt at Thr308 to partially activate the Akt pathway. Phosphorylation of Akt at Ser473 by the mammalian target of rapamycin (mTOR) stimulates full Akt activity (Hemmings and Restuccia, 2012). Studies have shown that PI3K/AKT signaling pathway can improve LPS-induced acute lung injury by regulating IκBα/NF-κB pathway (Kim et al., 2012). Narsa et al. (Reddy et al., 2015) have found that the PI3K/AKT signaling pathway may improve inflammation by regulating the Nrf2-ARE signaling pathway and thus protect hyperoxia-induced ALI. Multiple studies have indicated that PI3K/AKT is involved in pathological changes such as insulin resistance and tumorigenesis. And the mechanism of improving these diseases by SIRT1 is closely related to PI3K/AKT pathway (Carnero et al., 2008; Frojdo et al., 2011; Sarma et al., 2015; Wang et al., 2015a,b). In addition, SIRT1 is reported to inhibit the PI3K/AKT pathway and mediate the deacetylation of PI3K and NF-κB to inhibit inflammation (Busch et al., 2012; Liu et al., 2016). Shakibaei et al. (2011) found that SIRT1 can promote the formation of SIRT1-p300 complex, leading to the inactivation of p300 acetyltransferase and inhibition of IL-1β-induced PI3K acetylation, and finally improve inflammation such as rheumatoid arthritis.

SIRT1 and FoxO signaling pathway

The FoxO family is a subclass of the forkhead transcription factor (Kousteni, 2011). The "forkhead domain" of FoxO protein has three alpha helices (helix 1, 2, 3) and two winged structures formed by two large loops (Maiese et al., 2008). Both nematodes and drosophila have a homologous gene of FoxO (Webb and Brunet, 2014). In human, there are four major FoxO proteins (FoxO1a, FoxO3a, FoxO4 and FoxO6), which are widely expressed in different tissues and participate in oxidative stress response, antioxidant defense, metabolism, cell death and proliferation (Monsalve and Olmos, 2011). Studies have shown that FoxO transcription factors play a role in anti-oxidative stress by regulating the expression of genes encoding antioxidant proteins (such as SOD, CAT, etc.) intracellularly and extracellularly (Klotz et al., 2015). It has been reported that SIRT1 can deacetylate and activate FoxO, and then synthesize SOD and catalase (CAT) (Daitoku et al., 2004). It could enhance the antioxidant activity, and reduce LPS-induced oxidative stress damage. Other studies have shown that SIRT1 can reduce the oxidative damage of ROS and protect the endothelial barrier. The mechanism is related to deacetylating FOXO3a, enhancing the expression of SOD2 and reducing the expression of NOX4 (Shimada et al., 2014; Zhang et al., 2017). It is suggested that SIRT1/FoxO/SOD pathway plays an important role in the improvement of sepsis.

SIRT1 and Notch signaling pathway

Mammals have four Notch receptors (Notch 1-4) and five ligands. Receptor-ligand interaction initiates three times cleavage in the Notch receptor protein extracellular domains and transmembrane domains, and then releases Notch receptor intracellular domain (NICD). NICD enters the nucleus and binds to transcription factor (RBP)-Jκ and activates the transcription of Notch target genes (Geisler and Strazzabosco, 2015), including HES and HEY family. Studies have shown that Notch signaling is closely related to innate immunity and inflammation (Shang et al., 2016). It has been reported that in the early stage of sepsis, Notch signaling is activated and then participates in the regulation of PD-1 expression. Conversely,

inhibition of Notch signaling reduces PD-1 expression and alleviates sepsis (Pan et al., 2015). Bai et al. (2018) has also reported that SIRT1 knockout significantly aggravates LPS-induced inflammation and organ damage, since SIRT1 inhibits Notch signaling through NICD deacetylation and ultimately alleviates sepsis. It has also been reported that SIRT1 interacts with lysine specific demethylase 1 (LSD1) directly, and then affects histone deacetylation and inhibits the regulation of Notch signaling pathway (Mulligan et al., 2011).

SIRT1 and PGC-1α pathway

PGC-1α is a transcriptional coactivator of peroxisome proliferator-activated receptor (PPARγ) and is a major regulator of mitochondrial biogenesis (Valero, 2014). PGC-1α interacts with different transcription factors, such as nuclear receptor PPAR-γ, cAMP response element binding protein (CREB) and nuclear respiratory factor (NRFs), to regulate mitochondrial biogenesis and fatty acid oxidation (Sweeney and Song, 2016). In addition, PGC-1α can increase the expression of SOD and exert its anti-oxidative effect (Lu et al., 2010). Mitochondrial destruction caused by oxidative stress and dysregulated energy metabolism is a prominent feature of sepsis (Larche et al., 2006). It leads to multiple organ failures and is life threatening (Singer, 2008; Duran-Bedolla et al., 2014). SIRT1 plays an important role in improving energy metabolism disorders and releasing oxidative stress (Li et al., 2013b; Xu et al., 2018b). It has been reported that NAD+/SIRT1 signaling can effectively alleviate oxidative stress in sepsis, reduce myocardial dysfunction, and increase the survival rate of sepsis (Hong et al., 2018). PGC-1α is important for SIRT1 to improve sepsis (Lagouge et al., 2006). Zschoernig and Mahlknecht (2008) have reported that SIRT1 can catalyze the deacetylation of PGC-1α and regulate the translocation of NFE2L2 into the nucleus and bind to the antioxidant element (ARE) to induce the up-regulation of key antioxidant enzymes. It has also been reported that SIRT1 can catalyze the deacetylation of PGC-1α and then activate GA-binding protein transcription factor alpha (GABPA). It promotes translocation of transcription factors in mitochondria and ultimately leads to mitochondrial biogenesis and improves energy metabolism disorders in sepsis (McCreath et al., 2016).

SIRT1 and HMGB1-dependent signaling pathways

Many studies have shown that high mobility group box-1 protein (HMGB1) is involved in immune response in sepsis. It is an important late mediator in infection. The mechanism of HMGB1-mediated signal transduction is still unclear. However, receptors for advanced glycation end products (RAGE) and toll-like receptors 2/4 have been identified as important functional receptors for HMGB (van Beijnum et al., 2008). HMGB1 promotes the secretion of pro-inflammatory cytokines from mononuclear-macrophages *via* RAGE and TLRs receptor pathways and induces inflammatory responses by activating NF-κB (Zurolo et al., 2011). When inflammatory signals such as LPS and TNF-α activate monocytes, the two major lysine residues of HMGB1 are highly acetylated. Then HMGB1 is transferred from nucleus to cytoplasm (Bonaldi et al., 2003), and then released to extracellular as a pro-inflammatory cytokine. Acetylation is a key determinant of HMGB1 migration, while SIRT1 is capable of deacetylating HMGB1 and negatively regulates the nuclear export of HMGB1, and then inhibits the extracellular releasing of HMGB1 and improves inflammation (Hwang et al., 2015). Lan et al. (2017) shows that the enhancement of SIRT1 significantly inhibits HMGB1-mediated inflammatory pathway and alleviates lung injury in CLP mice. In contrast, inhibition of SIRT1 leads to hyperacetylation of HMGB1 and promotes its extracellular release (Hong et al., 2018; Kim et al., 2018), suggesting that inhibition of HMGB1-mediated inflammatory pathway may be an important mechanism for SIRT1 to improve sepsis.

SIRT1 and other signaling molecules

Several studies have shown that miRNAs and lncRNAs are involved in both proinflammatory and anti-inflammatory responses in sepsis (Zhou et al., 2015; Mao et al., 2015). It is reported that SIRT1 can regulate miR-92 through the modulation of their upstream TFs under oxidative stress (Chen et al., 2013). Other studies have shown that SIRT1 can regulate memory and plasticity *via* its suppression of miR-134 by cooperating with YY1 (Gao et al., 2010). Besides, miR-132 can increase the acetylation levels of a SIRT1 target gene to regulate chemokine production (Strum et al., 2009). In addition to alleviating sepsis through the above pathways, SIRT1 has also been reported to inhibit the expression of lncRNA-CCL2 *via* sustaining a repressive chromatin state in the lncRNA-CCL2 locus, and down-regulating lncRNA-CCL2 and then reducing the expression of inflammatory cytokines (Jia et al., 2018). Sui et al. (2016) showed that SIRT1 can inhibit the NLRP3/IL-1β axis in the hippocampus of septic mice, and suppress the development of brain diseases associated with sepsis. Other studies have shown that SIRT1 significantly promotes the deacetylation of p53, heat shock protein 1 (HSF1) and H4K16, and reduces inflammation (Chen et al., 2016; Wang et al., 2017a).

The application prospect of SIRT1 in the treatment of sepsis

SIRT1 activators and inhibitors have been discovered and been used in molecular biological research, which may become a promising drug for the treatment of sepsis. At present, SIRT1 activators include paclitaxel, resveratrol, SRT1720, etc. SIRT1 inhibitors

include Ex-527, AGK2, etc. (Dai et al., 2018). Resveratrol is a potential SIRT1 activator with anti-inflammatory effect. Studies have shown that resveratrol can reduce the expression of VCAM-1, ICAM-1, CRP and other molecules by inhibiting the activity of purified human proteasome (X, Y, Z) and immune proteasome (LMP7, LMP2, LMP10), and then decreasing organ damage during sepsis (Silswal et al., 2017). Moreover, changes of vascular permeability induced by LPS can be relieved by RhoA-ROCK-MLCP pathway (Wang et al., 2017a,b), and alleviates microcirculation disorders and multiple organ damage. Li et al. (2013a,b) also reports that resveratrol can reduce pulmonary edema in LPS-induced septic mice and improve lung function as well as reduce pathological changes of lung. SRT1720 reduces ROS production by activating SIRT1. It reverses hemodynamic changes and microvascular barrier dysfunction in sepsis. It then reduces the production of pro-inflammatory cytokines and reduces the activation of inflammasome, which finally reduces multiple organ damage in septic mice (Khader et al., 2017; Zhang et al., 2017). In addition, some medicines can suppress inflammation and oxidative stress to effectively improve sepsis and to decrease mortality by increasing the activity of SIRT1. Qi et al. (2017) find that salidroside can reduce the release of HMGB1 through activating AMPK-SIRT1 signaling pathway. It inhibits HMGB1 acetylation and nuclear cytoplasmic metastasis, ultimately reducing lung injury in septic rats. Cudratricusxanthone A (CTXA) reduces the acetylation of FoxO1, p53 and NF-κB/p65 by activating SIRT1 signaling, and finally suppresses inflammation and sepsis-induced liver damage (Lee et al., 2018). However, with one study of sepsis, it is found that most people who survived early sepsis are often susceptible to opportunistic pathogens and new serious infections (Boomer et al., 2011). But this is highly controversial. In spite of this, it would be better if patients could receive stage-specific treatment. The role of SIRT1 in sepsis also depends on the stage of sepsis. Unlike in the early stage, SIRT1 may be harmful during the adaptation stage. It has been reported that the inhibition of SIRT1, but not activation, may be a new method for the treatment of sepsis. Inhibition of SIRT1 can enhance immunity and improve prognosis (Vachharajani et al., 2014a). Liu et al. (2015) used TLR4 to stimulate human THP1 cells to simulate the adaptation stage of sepsis, and found that inhibition of SIRT1 by SIRT1 blocker Ex-527 in the sepsis adaptation stage can reverse energy metabolism changes caused by sepsis, increase the mitochondrial biogenesis, improve the development of sepsis, and prolong survival time. Other studies have shown that after sepsis mice go from high inflammation to low inflammation and immunosuppression, blocking SIRT1 can save almost all mice and reverse the abnormal adhesion of MVI leukocyte (Vachharajani et al., 2014b). This kind of difference may indicate that the treatment of sepsis should be based on the stage of sepsis, which means stage-specific treatment is necessary.

Conclusion

Sepsis is a major problem in critical care medicine, which seriously endangers human life and health. Till now, the prevention and treatment of sepsis is not very effective. SIRT1 could be a breakthrough to understand the pathogenesis and referred signaling pathways of sepsis. With the deepening of research, the role of SIRT1 in acute inflammation and sepsis is becoming more and more prominent. Recent studies indicate that SIRT1 can improve sepsis and survival by regulating multiple signaling pathways such as NF-κB, MAPK, JAK/STAT and PI3K/Akt. However, SIRT1 may be harmful during the adaptation stage. The mechanism of SIRT1 in sepsis is complex and still needs further understanding. Nevertheless, with the continuous understanding of it, SIRT1 may become a promising factor in the treatment of sepsis.

Acknowledgements. This work was supported by grants from the National Natural Sciences Foundation of China (No. 81601689, No. 81501663).

References

Arts R.J., Gresnigt M.S., Joosten L.A. and Netea M.G. (2017). Cellular metabolism of myeloid cells in sepsis. J. Leukoc. Biol. 101, 151-164.

Arumuggam N., Bhowmick N.A. and Rupasinghe H.P. (2015). A review: Phytochemicals targeting JAK/STAT signaling and IDO expression in cancer. Phytother. Res. 29, 805-817.

Bai X., Fan L., He T., Jia W., Yang L., Zhang J., Liu Y., Shi J., Su L. and Hu D. (2015). SIRT1 protects rat lung tissue against severe burn-induced remote ALI by attenuating the apoptosis of PMVECs *via* p38 MAPK signaling. Sci. Rep. 5, 10277.

Bai X., He T., Liu Y., Zhang J., Li X., Shi J., Wang K., Han F., Zhang W., Zhang Y., Cai W. and Hu D. (2018). Acetylation-dependent regulation of notch signaling in macrophages by SIRT1 affects sepsis development. Front. Immunol. 9, 762.

Becatti M., Fiorillo C., Barygina V., Cecchi C., Lotti T., Prignano F., Silvestro A., Nassi P. and Taddei N. (2014). SIRT1 regulates MAPK pathways in vitiligo skin: insight into the molecular pathways of cell survival. J. Cell. Mol. Med. 18, 514-529.

Becatti M., Taddei N., Cecchi C., Nassi N., Nassi P. A. and Fiorillo C. (2012). SIRT1 modulates MAPK pathways in ischemic-reperfused cardiomyocytes. Cell. Mol. Life Sci. 69, 2245-2260.

Bonaldi T., Talamo F., Scaffidi P., Ferrera D., Porto A., Bachi A., Rubartelli A., Agresti A. and Bianchi M. E. (2003). Monocytic cells hyperacetylate chromatin protein HMGB1 to redirect it towards secretion. EMBO J. 22, 5551-5560.

Boomer J.S., To K., Chang K.C., Takasu O., Osborne D.F., Walton A.H., Bricker T.L., Jarman S.N., Kreisel D., Krupnick A.S., Srivastava A., Swanson P.E., Green J.M. and Hotchkiss R.S. (2011). Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA 306, 2594-2605.

Busch F., Mobasheri A., Shayan P., Lueders C., Stahlmann R. and Shakibaei M. (2012). Resveratrol modulates interleukin-1beta-induced phosphatidylinositol 3-kinase and nuclear factor kappaB signaling pathways in human tenocytes. J. Biol. Chem. 287, 38050-

38063.

Cai B., Cai J.P., Luo Y.L., Chen C. and Zhang S. (2015). The specific roles of JAK/STAT signaling pathway in sepsis. Inflammation 38, 1599-1608.

Carnero A., Blanco-Aparicio C., Renner O., Link W. and Leal J.F. (2008). The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. Curr. Cancer Drug Targets 8, 187-198.

Chen Z., Shentu T.P., Wen L., Johnson D.A. and Shyy J.Y. (2013). Regulation of SIRT1 by oxidative stress-responsive miRNAs and a systematic approach to identify its role in the endothelium. Antioxid. Redox Signal. 19, 1522-1538.

Chen G.D., Yu W.D. and Chen X.P. (2016). SirT1 activator represses the transcription of TNFalpha in THP1 cells of a sepsis model *via* deacetylation of H4K16. Mol. Med. Rep. 14, 5544-5550.

Chen X., Chen C., Fan S., Wu S., Yang F., Fang Z., Fu H. and Li Y. (2018). Omega-3 polyunsaturated fatty acid attenuates the inflammatory response by modulating microglia polarization through SIRT1-mediated deacetylation of the HMGB1/NF-kappaB pathway following experimental traumatic brain injury. J. Neuroinflammation 15, 116.

Cheng S.C., Scicluna B.P., Arts R.J., Gresnigt M.S., Lachmandas E., Giamarellos-Bourboulis E.J., Kox M., Manjeri G.R., Wagenaars J.A., Cremer O.L., Leentjens J., van der Meer A.J., van de Veerdonk F.L., Bonten M.J., Schultz M.J., Willems P.H., Pickkers P., Joosten L.A., van der Poll T. and Netea M.G. (2016). Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. Nat. Immunol. 17, 406-413.

Cossa G., Gatti L., Cassinelli G., Lanzi C., Zaffaroni N. and Perego P. (2013). Modulation of sensitivity to antitumor agents by targeting the MAPK survival pathway. Curr. Pharm. Des. 19, 883-894.

Dai H., Sinclair D.A., Ellis J.L. and Steegborn C. (2018). Sirtuin activators and inhibitors: Promises, achievements, and challenges. Pharmacol Ther. 188, 140-154.

Daitoku H., Hatta M., Matsuzaki H., Aratani S., Ohshima T., Miyagishi M., Nakajima T. and Fukamizu A. (2004). Silent information regulator 2 potentiates Foxo1-mediated transcription through its deacetylase activity. Proc. Natl. Acad. Sci. USA 101, 10042-10047.

de Oliveira L.R., Mombach J.C. and Castellani G. (2015). A simple stochastic model for the feedback circuit between p16INK4a and p53 mediated by p38MAPK: implications for senescence and apoptosis. Mol. Biosyst. 11, 2955-2963.

Duran-Bedolla J., Montes D.O.M., Saldana-Navor V., Villalobos-Silva J.A., Rodriguez M.C. and Rivas-Arancibia S. (2014). Sepsis, mitochondrial failure and multiple organ dysfunction. Clin. Invest. Med. 37, E58-E69.

Edwards J.R., Perrien D.S., Fleming N., Nyman J.S., Ono K., Connelly L., Moore M.M., Lwin S.T., Yull F.E., Mundy G.R. and Elefteriou F. (2013). Silent information regulator (Sir)T1 inhibits NF-kappaB signaling to maintain normal skeletal remodeling. J. Bone Miner. Res. 28, 960-969.

Faix J.D. (2013). Biomarkers of sepsis. Crit. Rev. Clin Lab. Sci. 50, 23-36.

Frojdo S., Durand C., Molin L., Carey A.L., El-Osta A., Kingwell B.A., Febbraio M.A., Solari F., Vidal H. and Pirola L. (2011). Phosphoinositide 3-kinase as a novel functional target for the regulation of the insulin signaling pathway by SIRT1. Mol. Cell. Endocrinol. 335, 166-176.

Frye R.A. (1999). Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. Biochem. Biophys. Res. Commun. 260, 273-279.

Gao J., Wang W.Y., Mao Y.W., Graff J., Guan J.S., Pan L., Mak G., Kim D., Su S.C. and Tsai L.H. (2010). A novel pathway regulates memory and plasticity *via* SIRT1 and miR-134. Nature 466, 1105-1109.

Gao Z., Zhang J., Kheterpal I., Kennedy N., Davis R.J. and Ye J. (2011). Sirtuin 1 (SIRT1) protein degradation in response to persistent c-Jun N-terminal kinase 1 (JNK1) activation contributes to hepatic steatosis in obesity. J. Biol. Chem. 286, 22227-22234.

Gao R., Ma Z., Hu Y., Chen J., Shetty S. and Fu J. (2015). Sirt1 restrains lung inflammasome activation in a murine model of sepsis. Am. J. Physiol. Lung Cell Mol. Physiol. 308, L847-L853.

Geisler F. and Strazzabosco M. (2015). Emerging roles of Notch signaling in liver disease. Hepatology 61, 382-392.

Greene W.C. and Chen L.F. (2004). Regulation of NF-kappaB action by reversible acetylation. Novartis Found Symp. 259, 208-217.

Guo H., German P., Bai S., Barnes S., Guo W., Qi X., Lou H., Liang J., Jonasch E., Mills G.B. and Ding Z. (2015). The PI3K/AKT pathway and renal cell carcinoma. J. Genet. Genomics. 42, 343-353.

Hemmings B.A. and Restuccia D.F. (2012). PI3K-PKB/Akt pathway. Cold Spring Harb. Perspect. Biol. 4, a11189.

Hong G., Zheng D., Zhang L., Ni R., Wang G., Fan G.C., Lu Z. and Peng T. (2018). Administration of nicotinamide riboside prevents oxidative stress and organ injury in sepsis. Free Radic. Biol. Med. 123, 125-137.

Houtkooper R.H., Pirinen E. and Auwerx J. (2012). Sirtuins as regulators of metabolism and healthspan. Nat. Rev. Mol. Cell Biol. 13, 225-238.

Hwang J.S., Choi H.S., Ham S.A., Yoo T., Lee W.J., Paek K.S. and Seo H.G. (2015). Deacetylation-mediated interaction of SIRT1-HMGB1 improves survival in a mouse model of endotoxemia. Sci. Rep. 5, 15971.

Ivy J.M., Klar A.J. and Hicks J.B. (1986). Cloning and characterization of four SIR genes of Saccharomyces cerevisiae. Mol. Cell. Biol. 6, 688-702.

Jang Y.N. and Baik E.J. (2013). JAK-STAT pathway and myogenic differentiation. JAKSTAT 2, e23282.

Jha S.K., Jha N.K., Kar R., Ambasta R.K. and Kumar P. (2015). p38 MAPK and PI3K/AKT signalling cascades in Parkinson's disease. Int. J. Mol. Cell Med. 4, 67-86.

Jia Y., Li Z., Cai W., Xiao D., Han S., Han F., Bai X., Wang K., Liu Y., Li X., Guan H. and Hu D. (2018). SIRT1 regulates inflammation response of macrophages in sepsis mediated by long noncoding RNA. Biochim. Biophys Acta 1864, 784-792.

Jones A.E. and Puskarich M.A. (2014). The surviving sepsis campaign guidelines 2012: update for emergency physicians. Ann. Emerg. Med. 63, 35-47.

Kang H.B., Ahn K.S., Oh S.R. and Kim J.W. (2014). Genkwadaphnin induces IFN-gamma *via* PKD1/NF-kappaB/STAT1 dependent pathway in NK-92 cells. PLoS One 9, e115146.

Kauppinen A., Suuronen T., Ojala J., Kaarniranta K. and Salminen A. (2013). Antagonistic crosstalk between NF-kappaB and SIRT1 in the regulation of inflammation and metabolic disorders. Cell. Signal. 25, 1939-1948.

Keshet Y. and Seger R. (2010). The MAP kinase signaling cascades: a system of hundreds of components regulates a diverse array of physiological functions. Methods Mol. Biol. 661, 3-38.

Khader A., Yang W.L., Hansen L.W., Rajayer S.R., Prince J.M., Nicastro

J.M., Coppa G.F. and Wang P. (2017). SRT1720, a sirtuin 1 activator, attenuates organ injury and inflammation in sepsis. J. Surg. Res. 219, 288-295.

Kim D.I., Kim S.R., Kim H.J., Lee S.J., Lee H.B., Park S.J., Im M.J. and Lee Y.C. (2012). PI3K-gamma inhibition ameliorates acute lung injury through regulation of IkappaBalpha/NF-kappaB pathway and innate immune responses. J. Clin. Immunol. 32, 340-351.

Kim Y.M., Park E.J., Kim H.J. and Chang K.C. (2018). Sirt1 S-nitrosylation induces acetylation of HMGB1 in LPS-activated RAW264.7 cells and endotoxemic mice. Biochem. Biophys. Res. Commun. 501, 73-79.

Klotz L.O., Sanchez-Ramos C., Prieto-Arroyo I., Urbanek P., Steinbrenner H. and Monsalve M. (2015). Redox regulation of FoxO transcription factors. Redox Biol. 6, 51-72.

Koffel R., Meshcheryakova A., Warszawska J., Hennig A., Wagner K., Jorgl A., Gubi D., Moser D., Hladik A., Hoffmann U., Fischer M.B., van den Berg W., Koenders M., Scheinecker C., Gesslbauer B., Knapp S. and Strobl H. (2014). Monocytic cell differentiation from band-stage neutrophils under inflammatory conditions *via* MKK6 activation. Blood 124, 2713-2724.

Kong D. and Yamori T. (2009). Advances in development of phosphatidylinositol 3-kinase inhibitors. Curr. Med. Chem. 16, 2839-2854.

Kousteni S. (2011). FoxO1: a molecule for all seasons. J. Bone Miner. Res. 26, 912-917.

Ladyman S.R. and Grattan D.R. (2013). JAK-STAT and feeding. JAKSTAT 2, e23675.

Lagouge M., Argmann C., Gerhart-Hines Z., Meziane H., Lerin C., Daussin F., Messadeq N., Milne J., Lambert P., Elliott P., Geny B., Laakso M., Puigserver P. and Auwerx J. (2006). Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 127, 1109-1122.

Lan K.C., Chao S.C., Wu H.Y., Chiang C.L., Wang C.C., Liu S.H. and Weng T.I. (2017). Salidroside ameliorates sepsis-induced acute lung injury and mortality *via* downregulating NF-kappaB and HMGB1 pathways through the upregulation of SIRT1. Sci. Rep. 7, 12026.

Larche J., Lancel S., Hassoun S.M., Favory R., Decoster B., Marchetti P., Chopin C. and Neviere R. (2006). Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality. J. Am. Coll. Cardiol. 48, 377-385.

Lee Y., Kim Y.J., Kim M.H. and Kwak J.M. (2016). MAPK cascades in guard cell signal transduction. Front. Plant Sci. 7, 80.

Lee Y., Jeong G.S., Kim K.M., Lee W. and Bae J.S. (2018). Cudratricusxanthone A attenuates sepsis-induced liver injury *via* SIRT1 signaling. J. Cell. Physiol. 233, 5441-5446.

Li J., Wang K., Chen X., Meng H., Song M., Wang Y., Xu X. and Bai Y. (2012a). Transcriptional activation of microRNA-34a by NF-kappa B in human esophageal cancer cells. BMC Mol. Biol. 13, 4.

Li P., Zhao Y., Wu X., Xia M., Fang M., Iwasaki Y., Sha J., Chen Q., Xu Y. and Shen A. (2012b). Interferon gamma (IFN-gamma) disrupts energy expenditure and metabolic homeostasis by suppressing SIRT1 transcription. Nucleic Acids Res. 40, 1609-1620.

Li T., Zhang J., Feng J., Li Q., Wu L., Ye Q., Sun J., Lin Y., Zhang M., Huang R., Cheng J., Cao Y., Xiang G., Zhang J. and Wu Q. (2013a). Resveratrol reduces acute lung injury in a LPS induced sepsis mouse model *via* activation of Sirt1. Mol. Med. Rep. 7, 1889-1895.

Li Y.G., Zhu W., Tao J.P., Xin P., Liu M.Y., Li J.B. and Wei M. (2013b). Resveratrol protects cardiomyocytes from oxidative stress through SIRT1 and mitochondrial biogenesis signaling pathways. Biochem. Biophys Res. Commun. 438, 270-276.

Li L., Shi L., Yang S., Yan R., Zhang D., Yang J., He L., Li W., Yi X., Sun L., Liang J., Cheng Z., Shi L., Shang Y. and Yu W. (2016). SIRT7 is a histone desuccinylase that functionally links to chromatin compaction and genome stability. Nat. Commun. 7, 12235.

Lin R., Tao R., Gao X., Li T., Zhou X., Guan K.L., Xiong Y. and Lei Q.Y. (2013). Acetylation stabilizes ATP-citrate lyase to promote lipid biosynthesis and tumor growth. Mol. Cell 51, 506-518.

Liu T.F., Yoza B.K., El G.M., Vachharajani V.T. and McCall C.E. (2011). NAD+-dependent SIRT1 deacetylase participates in epigenetic reprogramming during endotoxin tolerance. J. Biol. Chem. 286, 9856-9864.

Liu T.F., Vachharajani V., Millet P., Bharadwaj M.S., Molina A.J. and McCall C.E. (2015). Sequential actions of SIRT1-RELB-SIRT3 coordinate nuclear-mitochondrial communication during immunometabolic adaptation to acute inflammation and sepsis. J. Biol. Chem. 290, 396-408.

Liu J., Han W., Chen L. and Tang K. (2016). Mechanism of osteogenic and adipogenic differentiation of tendon stem cells induced by sirtuin 1. Mol. Med. Rep. 14, 1643-1648.

Long D., Wu H., Tsang A.W., Poole L.B., Yoza B.K., Wang X., Vachharajani V., Furdui C.M. and McCall C.E. (2017). The oxidative state of cysteine thiol 144 regulates the SIRT6 glucose homeostat. Sci. Rep. 7, 11005.

Lu Z., Xu X., Hu X., Fassett J., Zhu G., Tao Y., Li J., Huang Y., Zhang P., Zhao B. and Chen Y. (2010). PGC-1 alpha regulates expression of myocardial mitochondrial antioxidants and myocardial oxidative stress after chronic systolic overload. Antioxid. Redox Signal. 13, 1011-1022.

Lv X., Zhang Y., Cui Y., Ren Y., Li R. and Rong Q. (2015). Inhibition of microRNA155 relieves sepsisinduced liver injury through inactivating the JAK/STAT pathway. Mol. Med. Rep. 12, 6013-6018.

Maiese K., Chong Z.Z. and Shang Y.C. (2008). OutFOXOing disease and disability: the therapeutic potential of targeting FoxO proteins. Trends Mol. Med. 14, 219-227.

Mannam P., Shinn A.S., Srivastava A., Neamu R.F., Walker W.E., Bohanon M., Merkel J., Kang M.J., Dela C.C., Ahasic A.M., Pisani M.A., Trentalange M., West A.P., Shadel G.S., Elias J.A. and Lee P.J. (2014). MKK3 regulates mitochondrial biogenesis and mitophagy in sepsis-induced lung injury. Am. J. Physiol. Lung Cell Mol. Physiol. 306, L604-L619.

Mao A.P., Shen J. and Zuo Z. (2015). Expression and regulation of long noncoding RNAs in TLR4 signaling in mouse macrophages. BMC Genomics 16, 45.

Markwart R., Condotta S.A., Requardt R.P., Borken F., Schubert K., Weigel C., Bauer M., Griffith T.S., Forster M., Brunkhorst F.M., Badovinac V.P. and Rubio I. (2014). Immunosuppression after sepsis: systemic inflammation and sepsis induce a loss of naive T-cells but no enduring cell-autonomous defects in T-cell function. PLoS One 9, e115094.

Martin A., Tegla C.A., Cudrici C.D., Kruszewski A.M., Azimzadeh P., Boodhoo D., Mekala A.P., Rus V. and Rus H. (2015). Role of SIRT1 in autoimmune demyelination and neurodegeneration. Immunol. Res. 61, 187-197.

Mathias R.A., Greco T.M., Oberstein A., Budayeva H.G., Chakrabarti R., Rowland E.A., Kang Y., Shenk T. and Cristea I.M. (2014). Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity. Cell 159, 1615-1625.

McCreath G., Scullion M.M., Lowes D.A., Webster N.R. and Galley H.F.

(2016). Pharmacological activation of endogenous protective pathways against oxidative stress under conditions of sepsis. Br. J. Anaesth. 116, 131-139.

Monsalve M. and Olmos Y. (2011). The complex biology of FOXO. Curr. Drug Targets. 12, 1322-1350.

Mulligan P., Yang F., Di Stefano L., Ji J.Y., Ouyang J., Nishikawa J.L., Toiber D., Kulkarni M., Wang Q., Najafi-Shoushtari S.H., Mostoslavsky R., Gygi S.P., Gill G., Dyson N.J. and Naar A.M. (2011). A SIRT1-LSD1 corepressor complex regulates Notch target gene expression and development. Mol. Cell 42, 689-699.

Nicolas C.S., Amici M., Bortolotto Z.A., Doherty A., Csaba Z., Fafouri A., Dournaud P., Gressens P., Collingridge G.L. and Peineau S. (2013). The role of JAK-STAT signaling within the CNS. JAKSTAT 2, e22925.

Palanivel J.A., Macbeth A.E., Chetty N.C. and Levell N.J. (2014). An insight into JAK-STAT signalling in dermatology. Clin. Exp. Dermatol. 39, 513-518.

Pan T., Liu Z., Yin J., Zhou T., Liu J. and Qu H. (2015). Notch signaling pathway was involved in regulating programmed cell death 1 expression during sepsis-induced immunosuppression. Mediators Inflamm. 2015, 539841.

Park S.Y., Kim H.Y., Park H.J., Shin H.K., Hong K.W. and Kim C.D. (2016). Concurrent treatment with taxifolin and cilostazol on the lowering of beta-amyloid accumulation and neurotoxicity via the suppression of P-JAK2/P-STAT3/NF-kappaB/BACE1 signaling pathways. PLoS One 11, e168286.

Qi Z., Zhang Y., Qi S., Ling L., Gui L., Yan L., Lv J. and Li Q. (2017). Salidroside inhibits HMGB1 acetylation and release through upregulation of SirT1 during inflammation. Oxid. Med. Cell. Longev. 2017, 9821543.

Qin K., Han C., Zhang H., Li T., Li N. and Cao X. (2017). NAD(+) dependent deacetylase Sirtuin 5 rescues the innate inflammatory response of endotoxin tolerant macrophages by promoting acetylation of p65. J. Autoimmun. 81, 120-129.

Rahman I., Kinnula V.L., Gorbunova V. and Yao H. (2012). SIRT1 as a therapeutic target in inflammaging of the pulmonary disease. Prev. Med. 54 (Suppl), S20-S28.

Reddy N.M., Potteti H.R., Vegiraju S., Chen H.J., Tamatam C.M. and Reddy S.P. (2015). PI3K-AKT signaling *via* Nrf2 protects against hyperoxia-induced acute lung injury, but promotes inflammation post-injury independent of Nrf2 in mice. PLoS One. 10, e129676.

Rhodes A., Evans L.E., Alhazzani W., Levy M.M., Antonelli M., Ferrer R., Kumar A., Sevransky J.E., Sprung C.L., Nunnally M.E., Rochwerg B., Rubenfeld G.D., Angus D.C., Annane D., Beale R.J., Bellinghan G.J., Bernard G.R., Chiche J.D., Coopersmith C., De Backer D.P., French C.J., Fujishima S., Gerlach H., Hidalgo J.L., Hollenberg S.M., Jones A.E., Karnad D.R., Kleinpell R.M., Koh Y., Lisboa T.C., Machado F.R., Marini J.J., Marshall J.C., Mazuski J.E., McIntyre L.A., McLean A.S., Mehta S., Moreno R.P., Myburgh J., Navalesi P., Nishida O., Osborn T.M., Perner A., Plunkett C.M., Ranieri M., Schorr C.A., Seckel M.A., Seymour C.W., Shieh L., Shukri K.A., Simpson S.Q., Singer M., Thompson B.T., Townsend S.R., Van der Poll T., Vincent J.L., Wiersinga W.J., Zimmerman J.L. and Dellinger R.P. (2017). Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 43, 304-377.

Rizzo A.N. and Dudek S.M. (2017). Endothelial glycocalyx repair: Building a wall to protect the lung during sepsis. Am. J. Respir. Cell Mol. Biol. 56, 687-688.

Sarma P., Bag I., Ramaiah M.J., Kamal A., Bhadra U. and Pal B.M. (2015). Bisindole-PBD regulates breast cancer cell proliferation *via* SIRT-p53 axis. Cancer Biol. Ther. 16, 1486-1501.

Shakibaei M., Buhrmann C. and Mobasheri A. (2011). Resveratrol-mediated SIRT-1 interactions with p300 modulate receptor activator of NF-kappaB ligand (RANKL) activation of NF-kappaB signaling and inhibit osteoclastogenesis in bone-derived cells. J. Biol. Chem. 286, 11492-11505.

Shang Y., Smith S. and Hu X. (2016). Role of Notch signaling in regulating innate immunity and inflammation in health and disease. Protein Cell 7, 159-174.

Shih R.H., Wang C.Y. and Yang C.M. (2015). NF-kappaB signaling pathways in neurological inflammation: A mini review. Front Mol. Neurosci. 8, 77.

Shimada T., Furuta H., Doi A., Ariyasu H., Kawashima H., Wakasaki H., Nishi M., Sasaki H. and Akamizu T. (2014). Des-acyl ghrelin protects microvascular endothelial cells from oxidative stress-induced apoptosis through sirtuin 1 signaling pathway. Metabolism 63, 469-474.

Sica A., Dorman L., Viggiano V., Cippitelli M., Ghosh P., Rice N. and Young H.A. (1997). Interaction of NF-kappaB and NFAT with the interferon-gamma promoter. J. Biol. Chem. 272, 30412-30420.

Silswal N., Reddy N.S., Qureshi A.A. and Qureshi N. (2017). Resveratrol downregulates biomarkers of sepsis *via* inhibition of proteasome's proteases. Shock 50, 579-588.

Singer M. (2008). Cellular dysfunction in sepsis. Clin. Chest Med. 29, 655-660.

Singer M., Deutschman C.S., Seymour C.W., Shankar-Hari M., Annane D., Bauer M., Bellomo R., Bernard G.R., Chiche J.D., Coopersmith C.M., Hotchkiss R.S., Levy M.M., Marshall J.C., Martin G.S., Opal S.M., Rubenfeld G.D., van der Poll T., Vincent J.L. and Angus D.C. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315, 801-810.

Strum J.C., Johnson J.H., Ward J., Xie H., Feild J., Hester A., Alford A. and Waters K.M. (2009). MicroRNA 132 regulates nutritional stress-induced chemokine production through repression of SirT1. Mol. Endocrinol. 23, 1876-1884.

Sui D.M., Xie Q., Yi W.J., Gupta S., Yu X.Y., Li J.B., Wang J., Wang J.F. and Deng X.M. (2016). Resveratrol protects against sepsis-associated encephalopathy and inhibits the NLRP3/IL-1beta axis in microglia. Mediators Inflamm. 2016, 1045657.

Sweeney G. and Song J. (2016). The association between PGC-1alpha and Alzheimer's disease. Anat. Cell Biol. 49, 1-6.

Vachharajani V.T., Liu T., Brown C.M., Wang X., Buechler N.L., Wells J.D., Yoza B.K. and McCall C.E. (2014a). SIRT1 inhibition during the hypoinflammatory phenotype of sepsis enhances immunity and improves outcome. J. Leukoc. Biol. 96, 785-796.

Vachharajani V., Liu T. and McCall C.E. (2014b). Epigenetic coordination of acute systemic inflammation: potential therapeutic targets. Expert Rev. Clin. Immunol. 10, 1141-1150.

Valero T. (2014). Mitochondrial biogenesis: pharmacological approaches. Curr Pharm. Des. 20, 5507-5509.

van Beijnum J.R., Buurman W.A. and Griffioen A.W. (2008). Convergence and amplification of toll-like receptor (TLR) and receptor for advanced glycation end products (RAGE) signaling pathways *via* high mobility group B1 (HMGB1). Angiogenesis 11, 91-99.

Vanhaesebroeck B., Guillermet-Guibert J., Graupera M. and Bilanges B. (2010). The emerging mechanisms of isoform-specific PI3K

signalling. Nat. Rev. Mol. Cell Biol. 11, 329-341.

Villarino A.V., Kanno Y., Ferdinand J.R. and O'Shea J.J. (2015). Mechanisms of Jak/STAT signaling in immunity and disease. J. Immunol. 194, 21-27.

Villarino A.V., Kanno Y. and O'Shea J.J. (2017). Mechanisms and consequences of Jak-STAT signaling in the immune system. Nat. Immunol. 18, 374-384.

Voelter-Mahlknecht S. and Mahlknecht U. (2006). Cloning, chromosomal characterization and mapping of the NAD-dependent histone deacetylases gene sirtuin 1. Int. J. Mol. Med. 17, 59-67.

Wang Q., Sun X., Li X., Dong X., Li P. and Zhao L. (2015a). Resveratrol attenuates intermittent hypoxia-induced insulin resistance in rats: involvement of Sirtuin 1 and the phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT pathway. Mol. Med. Rep. 11, 151-158.

Wang X., Buechler N.L., Yoza B.K., McCall C.E. and Vachharajani V.T. (2015b). Resveratrol attenuates microvascular inflammation in sepsis *via* SIRT-1-Induced modulation of adhesion molecules in ob/ob mice. Obesity (Silver Spring) 23, 1209-1217.

Wang N., Zhang F., Yang L., Zou J., Wang H., Liu K., Liu M., Zhang H., Xiao X. and Wang K. (2017a). Resveratrol protects against L-arginine-induced acute necrotizing pancreatitis in mice by enhancing SIRT1-mediated deacetylation of p53 and heat shock factor 1. Int. J. Mol. Med. 40, 427-437.

Wang X.Q., Zhang Y.P., Zhang L.M., Feng N.N., Zhang M.Z., Zhao Z.G. and Niu C.Y. (2017b). Resveratrol enhances vascular reactivity in mice following lipopolysaccharide challenge *via* the RhoA-ROCK-MLCP pathway. Exp. Ther. Med. 14, 308-316.

Wang W., Li F., Xu Y., Wei J., Zhang Y., Yang H., Gao B., Yu G. and Fang D. (2018a). JAK1-mediated Sirt1 phosphorylation functions as a negative feedback of the JAK1-STAT3 pathway. J. Biol. Chem. 293, 11067-11075.

Wang X., Buechler N.L., Woodruff A.G., Long D.L., Zabalawi M., Yoza B.K., McCall C.E. and Vachharajani V. (2018b). Sirtuins and Immuno-Metabolism of Sepsis. Int. J. Mol. Sci. 19,

Webb A.E. and Brunet A. (2014). FOXO transcription factors: key regulators of cellular quality control. Trends Biochem. Sci. 39, 159-169.

Xavier M.J., Donnelly J.P., Griffin R., Safford M.M., Howard G., Baddley J. and Wang H.E. (2017). Community characteristics and regional variations in sepsis. Int. J. Epidemiol. 46, 1607-1617.

Xie J., Zhang X. and Zhang L. (2013). Negative regulation of inflammation by SIRT1. Pharmacol. Res. 67, 60-67.

Xu G., Cai J., Wang L., Jiang L., Huang J., Hu R. and Ding F. (2018a). MicroRNA-30e-5p suppresses non-small cell lung cancer tumorigenesis by regulating USP22-mediated Sirt1/JAK/STAT3 signaling. Exp. Cell Res. 362, 268-278.

Xu Y., Qin Q., Chen R., Wei C. and Mo Q. (2018b). SIRT1 promotes proliferation, migration, and invasion of breast cancer cell line MCF-7 by upregulating DNA polymerase delta1 (POLD1). Biochem. Biophys Res. Commun. 502, 351-357.

Yamakuchi M., Ferlito M. and Lowenstein C.J. (2008). miR-34a repression of SIRT1 regulates apoptosis. Proc. Natl. Acad. Sci. USA 105, 13421-13426.

Yang X.D., Tajkhorshid E. and Chen L. F. (2010). Functional interplay between acetylation and methylation of the RelA subunit of NF-kappaB. Mol. Cell. Biol. 30, 2170-2180.

Yang B., Xu B., Zhao H., Wang Y.B., Zhang J., Li C. W., Wu Q., Cao Y.K., Li Y. and Cao F. (2018). Dioscin protects against coronary heart disease by reducing oxidative stress and inflammation *via* Sirt1/Nrf2 and p38 MAPK pathways. Mol. Med. Rep. 18, 973-980.

Yoo C.H., Yeom J.H., Heo J.J., Song E.K., Lee S.I. and Han M.K. (2014). Interferon beta protects against lethal endotoxic and septic shock through SIRT1 upregulation. Sci. Rep. 4, 4220.

Yoshizaki T., Milne J.C., Imamura T., Schenk S., Sonoda N., Babendure J.L., Lu J.C., Smith J.J., Jirousek M.R. and Olefsky J.M. (2009). SIRT1 exerts anti-inflammatory effects and improves insulin sensitivity in adipocytes. Mol. Cell. Biol. 29, 1363-1374.

Yoshizaki T., Schenk S., Imamura T., Babendure J.L., Sonoda N., Bae E.J., Oh D.Y., Lu M., Milne J.C., Westphal C., Bandyopadhyay G. and Olefsky J.M. (2010). SIRT1 inhibits inflammatory pathways in macrophages and modulates insulin sensitivity. Am. J. Physiol. Endocrinol. Metab. 298, E419-E428.

Zhang H.N., Li L., Gao P., Chen H.Z., Zhang R., Wei Y.S., Liu D.P. and Liang C.C. (2010). Involvement of the p65/RelA subunit of NF-kappaB in TNF-alpha-induced SIRT1 expression in vascular smooth muscle cells. Biochem. Biophys Res. Commun. 397, 569-575.

Zhang M., Wang X., Bai B., Zhang R., Li Y. and Wang Y. (2016a). Oxymatrine protects against sepsis-induced myocardial injury *via* inhibition of the TNF-alpha/p38-MAPK/caspase-3 signaling pathway. Mol. Med. Rep. 14, 551-559.

Zhang X., Li N., Shao H., Meng Y., Wang L., Wu Q., Yao Y., Li J., Bian J., Zhang Y. and Deng X. (2016b). Methane limit LPS-induced NF-kappaB/MAPKs signal in macrophages and suppress immune response in mice by enhancing PI3K/AKT/GSK-3beta-mediated IL-10 expression. Sci Rep. 6, 29359.

Zhang W., Zhang Y., Guo X., Zeng Z., Wu J., Liu Y., He J., Wang R., Huang Q. and Chen Z. (2017). Sirt1 protects endothelial cells against LPS-induced barrier dysfunction. Oxid. Med. Cell. Longev. 2017, 4082102.

Zhou X.L., Xu J.J., Ni Y.H., Chen X.C., Zhang H.X., Zhang X.M., Liu W.J., Luo L.L. and Fu Y.C. (2014). SIRT1 activator (SRT1720) improves the follicle reserve and prolongs the ovarian lifespan of diet-induced obesity in female mice *via* activating SIRT1 and suppressing mTOR signaling. J. Ovarian Res. 7, 97.

Zhou J., Chaudhry H., Zhong Y., Ali M.M., Perkins L.A., Owens W.B., Morales J.E., McGuire F.R., Zumbrun E.E., Zhang J., Nagarkatti P.S. and Nagarkatti M. (2015). Dysregulation in microRNA expression in peripheral blood mononuclear cells of sepsis patients is associated with immunopathology. Cytokine 71, 89-100.

Zschoernig B. and Mahlknecht U. (2008). SIRTUIN 1: regulating the regulator. Biochem. Biophys. Res. Commun. 376, 251-255.

Zurolo E., Iyer A., Maroso M., Carbonell C., Anink J.J., Ravizza T., Fluiter K., Spliet W.G., van Rijen P.C., Vezzani A. and Aronica E. (2011). Activation of Toll-like receptor, RAGE and HMGB1 signalling in malformations of cortical development. Brain 134, 1015-1032.

Accepted July 8, 2019