Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) 2022 23(6):437-450
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2101075

Roles of neutrophil reactive oxygen species (ROS) generation in organ function impairment in sepsis

Jiaqi LU, Jingyuan LIU, Ang LI✉

Intensive Care Unit, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China

Abstract: Sepsis is a condition of severe organ failure caused by the maladaptive response of the host to an infection. It is a severe complication affecting critically ill patients, which can progress to severe sepsis, septic shock, and ultimately death. As a vital part of the human innate immune system, neutrophils are essential in resisting pathogen invasion, infection, and immune surveillance. Neutrophil-produced reactive oxygen species (ROS) play a pivotal role in organ dysfunction related to sepsis. In recent years, ROS have received a lot of attention as a major cause of sepsis, which can progress to severe sepsis and septic shock. This paper reviews the existing knowledge on the production mechanism of neutrophil ROS in human organ function impairment because of sepsis.

Key words: Sepsis; Neutrophils; Oxidative stress; Reactive oxygen species (ROS); Organ dysfunction

1 Introduction

Sepsis is a serious medical emergency involving severe organ dysfunction induced by host dysregulation in response to infection, in which the organ function of patients is clinically assessed using the Sepsis-related Organ Failure Assessment (SOFA) score (Singer et al., 2016). Estimated 48.9 million patients are affected globally by sepsis, with 30.1 million getting septic shock, resulting in approximately 11 million deaths every year (Rudd et al., 2020). The clinical definition of sepsis is evolving; initially, its primary pathogenesis was believed to involve systemic inflammatory response syndrome (SIRS) mediated by the massive release of inflammatory mediators (Mariampillai et al., 2018). With the partial failure of anti-inflammatory treatment for sepsis, the emergence of the problem of low specificity for sepsis diagnosis based on SIRS criteria, and given the ongoing progress in basic research, it is clear that the key to sepsis development is not only the inflammatory response but also the disturbance of the body's immune function. This entails the over-activation of immune system caused by the initial targeting of pathogenic factors, such as infection, to develop widespread immunosuppression. Furthermore, the state of sepsis-mediated immunosuppression has been demonstrated in both basic experimental (Cohen, 2002) and clinical studies (Bae et al., 2016).

The immune system initiates the innate immune response to fight pathogen invasion during sepsis, leading to a robust systemic inflammatory response. Afterwards, the body upregulates anti-inflammatory and immunosuppressive effects through negative feedback regulation in order to reduce excessive inflammatory reactions (Winterbourn et al., 2016). However, it may also allow the host to enter an immunosuppressive state, subsequently failing to clear existing infections or resulting in increased susceptibility to new infections. Neutrophils, also known as polymorphonuclear leukocytes, are important components of the innate immune system, playing a crucial role in host defense. As the most abundant cells in peripheral blood leukocytes, they are derived from hematopoietic stem cells in the bone marrow where they develop and differentiate to enter the bloodstream or other tissues (Kim and Bae, 2016). During pathogen invasion, neutrophils accumulate at the infection site through chemokine

✉ Ang LI, liang@ccmu.edu.cn
Ang LI, https://orcid.org/0000-0002-1478-3072

Received Dec. 26, 2021; Revision accepted Mar. 1, 2022;
Crosschecked May 31, 2022

signaling to kill the pathogen via phagocytosis, degranulation, and other means (Thieblemont et al., 2016). During this process, a rapid and massive release of reactive oxygen species (ROS) is accompanied by a surge in oxygen consumption, known as respiratory burst, catalyzed by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) (McCracken and Allen, 2014). NOX is an important class of enzymes that generate O_2^- by passing electrons from NADPH to molecular oxygen, producing a range of ROS. ROS are also generated in the mitochondria from the partial oxygen reduction to form superoxide (Li F et al., 2016). In addition, macrophages produce elevated levels of mitochondrial ROS in an NOX-independent fashion (Mills et al., 2016).

Oxidative stress is defined as a state of increased ROS production and/or a decline in the body's ability to scavenge ROS because of alterations in various organic body environments. Numerous studies have established a link between ROS and the occurrence and development of organ function impairment in sepsis (Landskron et al., 2014). Exogenous ROS are primarily produced when cells are stimulated by physical, chemical, or biological stimuli, as opposed to the intracellular source of ROS, which is the regular physiological metabolism of cells (Rea et al., 2018). Under stress conditions during sepsis, the body can immediately mobilize many neutrophils into the bloodstream and migrate to specific infection sites to become the first effector cells to reach these sites. Neutrophils can produce ROS and multiple cytokines during sepsis, which participate in bacterial death and disease progression (Landskron et al., 2014). ROS in turn can oxidize DNA, proteins, lipids, and carbohydrates, among others, thereby regulating multiple redox-mediated pathological processes (Jaganjac et al., 2016).

Given the links between neutrophil activation, ROS generation and the development of organ dysfunction during sepsis, the significance of the mechanism of neutrophil ROS in the innate immune response to sepsis has been increasingly highlighted. This review aims to summarize the appropriate mechanisms of neutrophil ROS in sepsis organ function impairment, and hopefully shed new light on the occurrence and development of disruptive organ dysfunction during sepsis (Fig. 1).

2 Organ function impairment in sepsis

2.1 Role of ROS in brain injury in sepsis

Increasing evidence has recently highlighted that the poor prognosis of sepsis is closely related to ROS released by neutrophils. Sepsis, which results from dysregulated host response to infection, usually causes acute injury to the central nervous system, triggering sepsis-associated encephalopathy. Septic encephalopathy is usually a transient, reversible brain dysfunction

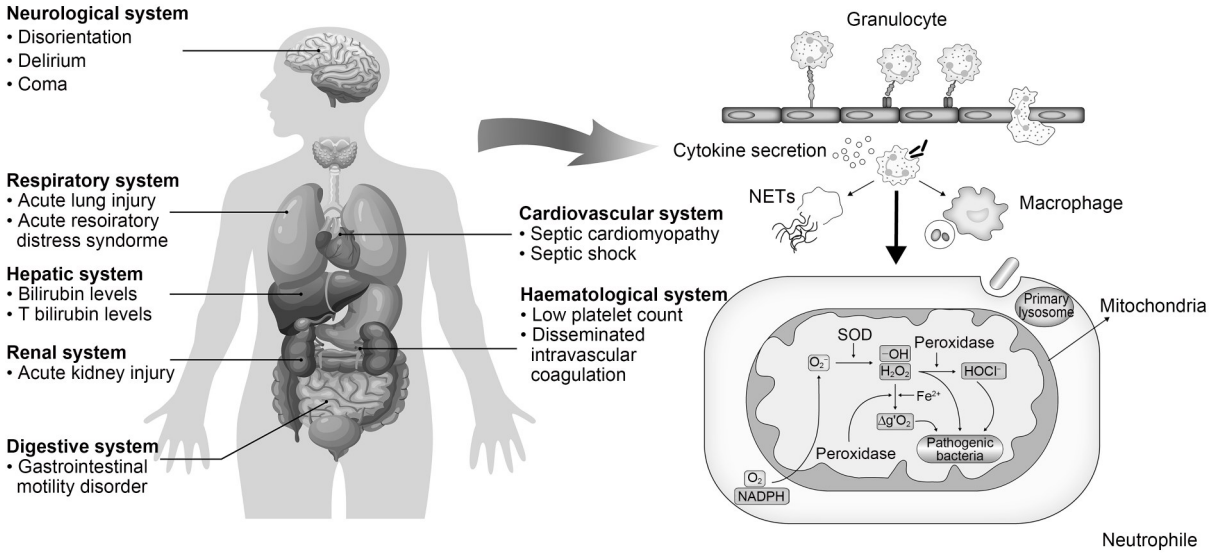

Fig. 1 Roles of ROS in organ dysfunction in sepsis. ROS: reactive oxygen species; NETs: neutrophil extracellular traps; SOD: superoxide dismutase; NADPH: nicotinamide adenine dinucleotide phosphate.

affecting 30% to 70% of sepsis patients (Eidelman et al., 1996). Its clinical manifestations include disorientation, confusion, and coma, while some sepsis survivors develop long-term cognitive impairment and learning disabilities (Catalão et al., 2017; Tang et al., 2017; Gamal et al., 2018; Zarbato et al., 2018). Inflammatory, ischemic, and neurotoxic processes lead to brain dysfunction, with clinical symptoms ranging from delirium to coma. In critically ill patients, delirium is linked to increased risk of death, longer intensive care unit (ICU) and hospital stays, higher medical costs, and higher long-term cognitive damage rates. When present, delirium may be a symptom of prolonged systemic hypoperfusion (Ely et al., 2004).

Both animal models of sepsis and human patients have been found to exhibit a massive production of superoxide anion, nitric oxide (NO), and peroxynitrite anion ($ONOO^-$) at the time of sepsis, and the destruction of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) was shown to lead to their reduced activity (Zarbato et al., 2018). While the oxygen consumption of the brain is high, the brain is exposed to large amounts of active factors during sepsis and is rapidly affected by the disease. According to some studies, ROS can inhibit acetylcholinesterase (AChE) activity in various tissues (Liu et al., 2017). Lipid peroxidation (measured by thiobarbituric acid reactive substance (TBARS)) can also reduce membrane fluidity during sepsis and further diminish AChE activity through lipid–protein interactions. ROS generated within neutrophils can induce the lipid peroxidation of polyunsaturated fatty acids that are chemically active due to multiple double bonds in the cell membrane of nearby cells, producing reactive aldehydes. These include 4-hydroxynonenal (4-HNE), malondialdehyde, and acrolein, which trigger increased membrane permeability and fluidity, cytoplasmic efflux, and loss of membrane protein activity (Jaganjac et al., 2016). In turn, a large amount of generated ROS cannot eradicate the occurring lipid peroxidation, causing damage to the cell membrane and mitochondria and ultimately leading to neuronal apoptosis (Tang et al., 2017).

According to the above findings, sepsis combined with encephalopathy is a common cause of brain cell death in critically ill patients, leading to long-term mental status changes. Furthermore, oxidative stress plays a critical role in sepsis brain injury.

2.2 Role of ROS in lung injury in sepsis

Sepsis can result in various organ injuries, including acute lung injury (ALI), which can progress to acute respiratory distress syndrome (ARDS). ALI is clinically characterized by increased pulmonary vascular permeability, pulmonary interstitial and alveolar edema, resulting in refractory hypoxemia (Gerin et al., 2016). During sepsis, the alveolar space is infiltrated with inflammatory cells, some alveolar structures become damaged, epithelial cells are deformed, lung tissue hemorrhages or develops a hyaline film, its structure is impaired, and lung interstitial edema shows ALI pathological changes (Zeng et al., 2015). In humans, ROS can be generated through various oxidase enzymes (including the mitochondrial respiratory chain, xanthine oxidase, and cyclooxygenases), initiated by a variety of inflammatory mediators in sepsis-induced lung injury (Livaditi et al., 2006).

According to certain studies, activated neutrophils in septic rats produce an excessive amount of ROS, which might be further aggravated by the reciprocal reaction between ROS and peroxynitrite, resulting in cytotoxic effects (Zeng et al., 2015). The opposite reaction may prompt the over-activation of nuclear repair enzyme poly(adenosine diphosphate ribose) polymerase (PARP), resulting in adenosine triphosphate (ATP) depletion and cellular damage. Moreover, over-activated PARP can also stimulate the expression of multiple inflammatory genes, leading to increased inflammation and associated tissue damage, which ultimately triggers respiratory failure and ARDS (Zeng et al., 2015). Because of the highly complex pathogenesis, sepsis and sepsis-induced ALI represent unsolved clinical problems involving an imbalance of pro- and anti-inflammatory systems, complement activation, endothelial activation, neutrophil and macrophage activation, oxidative stress, transcription factor activation, and many other factors (Guo and Ward, 2007). ROS can damage vascular endothelial cells, resulting in increased vascular permeability, tissue hyperemia and edema, as well as oxidative damage (Saffarzadeh et al., 2012). In one study, ROS caused damage to lung epithelial cells, which were unaffected when normal neutrophils were co-cultured with lung epithelial cells. However, after activating neutrophils with H_2O_2, lung epithelial cells were clearly damaged (Caudrillier et al., 2012). In a murine model of septic lung injury, a considerable increase in neutrophil

infiltration was detected in the alveolar lavage fluid of mice in parallel with an increase in the inflammatory cytokines interleukin-1β (IL-1β) and IL-6; tumor necrosis factor-α (TNF-α) was also significantly elevated. In light of this result, sepsis-induced ALI formation is related to the activation of p38 mitogen-activated protein kinase (MAPK) (Gan et al., 2018). The activation of p38 signaling pathway is triggered by the generation of ROS by neutrophils, which results in lung failure.

The above findings imply that ROS play an important role in septic lung injury. Nonetheless, to improve antioxidant intervention, a better understanding of the mechanisms and characteristics of oxidative stress damage in disease-specific settings is required, which could lead to new ideas for the treatment of septic lung injury.

2.3 Role of ROS in cardiovascular injury in sepsis

As the most vital organ in the human body, the heart's primary function is to regulate blood pressure and blood flow to various body parts. ROS generation during sepsis induces cardiomyocyte injury, causing septic cardiomyopathy (Drifte et al., 2013). This leads to hypotension and heart failure, further damaging other organs. To protect against cardiac injury and enhance the prognosis of sepsis, it is of great importance to investigate the role of oxidative stress in cardiac injury during sepsis.

2.3.1 Septic cardiomyopathy

In sepsis, the heart is one of the most vulnerable organs to functional failure. Therefore, heart failure is a common complication in patients with sepsis, also known as septic cardiomyopathy. Over the past 20 years, the pathophysiology of myocardial dysfunction in septic patients has been intensively studied, with investigations initially focusing on global myocardial ischemia as a cause of cardiac cell necrosis. However, a growing body of evidence from both animal and human studies has revealed that this phenomenon is not significant; thus, the initial view was later disproved by scholars and myocardial dysfunction was seen to be reversible (Zanotti-Cavazzoni and Hollenberg, 2009). In this context, several researchers have described the mechanisms of septic cardiomyopathy. Many associated molecular mechanisms have been described, including apoptosis, cytokine activation, immunomodulatory suppression, toxin release, oxidative stress, mitochondrial damage, and energy metabolism disorders, among others (Beesley et al., 2018; Martin et al., 2019). However, the roles of numerous mechanisms in the development and progression of septic cardiomyopathy are yet unknown. In one example, the sepsis-related dysregulation of inflammatory response has been suggested to be directly connected to cardiomyocyte dysfunction. This in turn can lead to a variety of cardiomyopathies, including impaired ventricular systolic or diastolic function and impaired cardiac output, oxygen delivery, and primary cardiomyocyte damage (Li F et al., 2016).

Like other sepsis-related organ dysfunctions, septic cardiomyopathy is caused by an overresponse to infection in the host. In sepsis, a large amount of ROS are produced, resulting in cellular oxidative damage. Mitochondria are responsible for intracellular energy metabolism, ATP synthesis, and respiratory chain transmission. According to some studies, mitochondria are a major site of ROS production during sepsis and a principal target of oxidative stress damage (Haileselassie et al., 2017). NO is formed by all cardiac cells and has a variety of functions in the cardiovascular system in healthy subjects and critically ill patients. The effects of sepsis-induced NO accumulation include vasodilation, the inhibition of mitochondrial respiration, and the release of proinflammatory cytokines. Early myocardial dysfunction in sepsis may be caused by stimuli such as inflammatory factors, and nitric oxide synthase (NOS) activation in cardiomyocytes produces excessive NO, which in turn leads to cyclic guanosine monophosphate (cGMP) generation. The sources of overproduced inducible NOS (iNOS) are dysregulated, and therefore, physiological NO levels are decreased. NOS activation affects the downregulation of β-adrenergic receptors, decreasing myofilament Ca^{2+} responses, and eventually improving NO formation with subsequent cytotoxic effects. The subsequently formed nitrite can hinder myocardial energy production, induce myocardial contractile dysfunction, and ultimately cause septic heart failure (Bateman et al., 2003).

Furthermore, ROS can directly damage the integrity of the mitochondrial membrane and the activity of biological enzymes. Sepsis is featured by mitochondrial swelling and disappearance, vacuolar deformation, and other changes seen under electron microscopy. The resulting mitochondrial dysfunction causes

cellular energy failure, which ultimately leads to cell damage and death. When cardiomyocyte mitochondria are oxidatively damaged during sepsis, cardiomyocytes themselves undergo damage and death, and finally cause weakened cardiac contractility (Brealey et al., 2002). Furthermore, cytokine levels rise due to inflammatory stimuli during sepsis. It was further discovered that TNF-α plays a vital role in the cardiovascular changes associated with septic shock, including myocardial function, probably due to its influence on NO and calcium metabolism, and the effects of β-adrenoceptor downregulation (Zanotti-Cavazzoni and Hollenberg, 2009).

2.3.2 Septic shock

Septic shock is associated with mitochondrial dysfunction and the dysregulation of cell signaling pathways, which results in multiorgan failure and, ultimately, untreated hemodynamic instability and death (Singer, 2014). The pathophysiology of septic shock may be associated with the overproduction of NO and other vasodilatory substances that inhibit the metabolic autoregulation of vascular tone (Bougaki et al., 2010). Furthermore, endogenous vasopressin levels are regularly reduced, which collectively lead to reductions in systemic vascular resistance and systemic blood pressure, consistent with distributive shock (Kumar, 2014). When adequately resuscitated, the patient will experience skin warmth, vigorous pulsation, and widening pulse pressure, leading to an increase in cardiac output if their basic cardiac function is normal (Landry et al., 1997). Both the arterial and venous systems are affected by vasodilation. In the absence of fluid resuscitation, the venous system becomes a large blood reservoir with reduced cardiac preload; vascular endothelial cells suffer damage, and intravascular fluid extravasates out of the vessel, aggravating central hypovolemia, which clinically manifests as tissue edema. It is not exceptional that myocardial contractility is also affected. All of these changes in preload, myocardial contractility, and afterload contribute to the reduction of oxygen delivery to tissues (Brealey et al., 2004).

Septic shock modifies tissue metabolism by disturbing mitochondrial function. Subsequently, an energy metabolism disorder is established as lactic acidosis. The cumulative effects of hypoxia and cellular injury result in severe organ dysfunction, including cardiovascular dysfunction, central nervous dysfunction (delirium), lung injury (ARDS), acute kidney injury (AKI), coagulopathy, intestinal obstruction, and liver dysfunction, followed by a prolonged recovery period lasting for several weeks. The longer the patient is in shock, the more tissue damage occurs.

2.4 Role of ROS in liver injury in sepsis

The liver, which is the largest gland in the human body, is responsible for a variety of biological functions such as detoxification, storage, energy production, nutrient conversion, hormone balancing, and coagulation. It plays a critical role in maintaining drug metabolism and immune homeostasis. In sepsis, associated liver dysfunction and liver failure occur in 34% to 46% and 1.3% to 22% of cases, respectively, with higher rates in patients with preexisting liver dysfunction (Yan et al., 2014). During sepsis, the liver may be impaired by numerous factors, such as pathogens, toxins, and inflammatory mediators. The damage begins with hepatocyte dysfunction and progresses to extensive liver damage, ultimately resulting in liver dysfunction (Guo et al., 2017), which is a predictor of sepsis-associated mortality. Laboratory data may reproduce abnormal hepatic synthetic function (abnormal coagulation and platelet count), impaired clearance (lactic acidemia), deficient gluconeogenesis and glycogenolysis (hypoglycemia), or acute cellular injury (elevated transaminases). Moreover, increased serum bilirubin may be an indicator of liver dysfunction and a key component of ICU prognostic scores, such as SOFA score (Starczewska et al., 2017).

The products of oxidative stress include ROS, which are mainly generated by mitochondria, neutrophils, and endothelial cells (Fink and Evans, 2002). The mechanisms of liver dysfunction by ROS comprise lipid peroxidation, mitochondrial damage, and apoptosis. Since ROS can destroy polyunsaturated fatty acids to cause lipid peroxidation, the hepatocyte membrane's polyunsaturated fatty acid structure makes it particularly sensitive to oxidative damage. ROS can act directly on the mitochondrial membrane of hepatocytes to release cytochrome *c* and other pro-apoptotic substances into the cytoplasm and initiate extensive apoptosis (Larsen, 2019). According to some studies, ROS increase in liver tissue during sepsis and decrease in response to antioxidants. ROS can activate the p38 signal pathway, leading to the activation of the hepatocyte mitochondrial apoptosis pathway

and eventually causing hepatocyte energy failure (Zhong et al., 2016). In addition, ROS can degrade the polysaccharide-coated layer on the surface of endothelial cells, triggering apoptotic signaling pathways in these cells, which in turn leads to the formation of dysfunctional liver sinusoidal endothelial cells (Cogger et al., 2001). According to another study, ROS decrease the endothelial NOS (eNOS) messenger RNA (mRNA) activity, which is beneficial to liver endothelial cells (Hadem et al., 2012).

Furthermore, neutrophils can activate aromatic amines, aflatoxin, estrogen, phenols, and polycyclic aromatic hydrocarbons through ROS-dependent mechanisms to cause DNA damage (Sakaguchi and Furusawa, 2006). Wilson et al. (2015) discovered that neutrophil-generated ROS can damage liver telomere DNA, resulting in liver cancer and liver failure. At the same time, liver ischemia, hypoxia reperfusion, or activated neutrophils create a large amount of ROS, ultimately damaging biological membranes and subcellular organelles through lipid peroxidation. The latter process damages the lysosomal membrane, causing excessive hydrolase leakage and inducing functional and structural damages to hepatocytes and tissues. Meanwhile, the activity of ROS scavengers like SOD and glutathione peroxidase (GSH-PX) considerably decreases in the liver. A large quantity of ROS damage the Ca^{2+} ATPase in the plasma membrane of hepatocytes, leading to a decline in the exclusion of Ca^{2+} from the cytoplasm and causing Ca^{2+} overload in hepatocytes. Subsequently, Ca^{2+} overload induces hepatocyte deformation and the uncoupling of mitochondrial oxidative phosphorylation, causing energy failure and dysfunction in hepatocytes, and eventually triggering septic liver injury (Kurepa and Smalle, 2019).

As oxidative stress causes mitochondrial damage in hepatocytes during sepsis, antioxidant therapy, especially that targeting mitochondria, may be important in sepsis treatment.

2.5 Role of ROS in kidney injury in sepsis

AKI is a frequent complication associated with sepsis, as 23% of patients with severe sepsis and 51% of patients with septic shock will develop acute renal failure (ARF); 70% of mortality from sepsis features the ARF complication, which is strictly related with the progression of chronic kidney disease (CKD) (Peerapornratana et al., 2019). There are distinct pathophysiological differences between sepsis-induced AKI and AKI under nonseptic conditions. Many studies have suggested that inflammatory mediator release (Morrell et al., 2014), oxidative stress (Chelazzi et al., 2015), mitochondrial respiratory chain dysfunction (Guerci et al., 2017), microcirculatory disruption (Post et al., 2017), renal hypoperfusion (Fani et al., 2018), and renal venous congestion (Ostermann et al., 2019) all contribute to AKI during sepsis. Endothelial damage and hemodynamic dysfunction are commonly associated symptoms, and oxidative stress plays a major role in the pathogenesis of endothelial dysfunction (Ge et al., 2017).

Generally, ROS can be created through multiple pathways, with mitochondria being the primary source of ROS production in renal parenchymal cells. Under normal physiological conditions, intracellular ROS levels are low and even contribute to the physiological regulation of tubular function and renal microcirculation. In addition, antioxidants in the body can convert ROS into hydrogen peroxide, reconvert hydrogen peroxide into water, and finally eliminate ROS (Vaisbich et al., 2011). Numerous inflammatory factors are activated during sepsis. Systemic inflammatory response and reduced antioxidant content such as GSH within the tissue increase ROS formation in the kidney and renal vasculature. ROS attack cellular complexes, including proteins, nucleic acids, and plasma membrane components, resulting in renal cell membrane damage and mitochondrial superoxide anion leakage. ROS can also increase vascular permeability and platelet adhesion, cause endothelial dysfunction, and increase renal tubular oxygen consumption (Zhang et al., 2018). Because the straight renal tubules are extremely sensitive to ROS, they cause a reduction in renal medullary oxygenation, resulting in tissue hypoxia. With the onset of shock and tissue hypoxia, the cellular ROS levels rise even higher, and the proline hydroxylase activity that degrades hypoxia-inducible factor (HIF) elevates, leading to HIF destabilization and an insufficient cellular response to hypoxic stress and renal cell injury. This eventually causes kidney injury in sepsis (Chen et al., 2018). ARF in sepsis is caused by the cytokine-mediated induction of NO synthesis and reduced systemic vascular resistance, along with increased plasma concentrations of relevant resistance and endogenous vasoconstrictor hormones (catecholamines, angiotensin II, and endothelins) driven by

the effects of exogenous vasopressors, ultimately resulting in renal vasoconstriction (Wang et al., 2012).

Sepsis-induced AKI has high clinical morbidity and mortality, featured by the accumulation of metabolic waste products, disturbance of water and electrolyte balance, and numerous insidious hazards, such as reduction in the level of immunity and deficiency of other organs (Peerapornratana et al., 2019). At the moment, mitochondrial damage and apoptosis are considered to play a role in pathogenesis. On the other hand, oxidative stress-induced mitochondrial and renal cell membrane damage is not only a significant mechanism of pathogenesis but also a therapeutic target for this disease.

2.6 Role of ROS in gastrointestinal dysmotility in sepsis

With its complex pathogenesis and diverse etiologies, sepsis remains the most common cause of death in ICU patients. The majority of affected patients are elderly, immunodeficient, or critically ill (Singer et al., 2016). The combination of multiorgan dysfunction, hypoperfusion, and hypotension will lead to severe sepsis and septic shock, ultimately causing the death of the patient. The processes behind the development of gastrointestinal dysmotility during sepsis are still being researched. The leading factors contributing to this condition may be the initiation of inflammatory factors, inhibitory transmitters of gastrointestinal motility, and the substantial ROS production by the locally over-activated inflammatory response in the intestine by endotoxins.

Under normal circumstances, ROS are important molecules involved in maintaining organismal homeostasis. Nicotinamide ribonucleoside (NR) is the precursor of nicotinamide adenine dinucleotide (NAD^+). In a mouse model of sepsis, the application of NR increased tissue NAD^+ levels, decreased ROS expression and inflammatory factors in lung and heart tissues, reduced caspase-3 activity, and improved microvascular permeability and gastrointestinal function, which eventually reduced animal mortality in sepsis (Hong et al., 2018). Some investigations have revealed that ROS production increases in small intestinal tissue during sepsis, whereas the levels of antioxidant ROS, GSH, and others dwindle, and a large quantity of ROS are generated, which damages mitochondrial membrane integrity and reduces the activity of various enzymes, leading to cellular energy failure (Zhu et al., 2016). This contributes to gastrointestinal cell function disorders and gastrointestinal motility generation disorders. In general, intestinal microecology is beneficial to the human body. During sepsis, intestinal flora translocation, exacerbation, and even multivisceral failure may occur due to gastrointestinal dysmotility. This could eventually lead to a dysfunctional gut in terms of nutrient absorption or maintenance of water–electrolyte balance.

Hence, ongoing studies on the mechanisms underlying gastrointestinal dysmotility during sepsis are important to improve the relevant disease management. In this regard, inflammatory factor release, oxidative stress injury, microcirculation disruption, and other multifaceted factors are involved in the mechanisms of organ injury caused by sepsis.

2.7 Role of oxidative stress in coagulation dysfunction in sepsis

Among other complications, sepsis may also lead to severe coagulopathy, and finally lead to disseminated intravascular coagulation.

As the body's first line of defense, neutrophils play a vital role in the early stages of infection by killing pathogens by phagocytosis, degranulation, and the formation of neutrophil extracellular traps (NETs) (Brinkmann et al., 2004). Increased intracellular ROS in neutrophils may result in the release of such NETs (Perl et al., 2008). It has been found that the formation of NETs is dependent on ROS, NOX activation, and the upregulation of anti-apoptotic proteins, which are part of the MAPK pathway (Tan et al., 2021). Marin-Esteban et al. (2012) stated that protein kinase C (PKC) activators (phorbol myristate acetate (PMA) or H_2O_2) could generate NETs after stimulation to induce the differentiation of human myeloid leukemia cell line PLB-985 into mature neutrophils in vitro. In contrast, the stimulation of NOX2-deficient X-linked chronic granulomatous myeloid leukemia cell line PLB-985 (X-CGD PLB-985) exhibited no generation of NETs; however, the addition of H_2O_2 could stimulate the generation of few NETs. Accordingly, it was confirmed that the formation of NETs is dependent on NOX2 and ROS (Marin-Esteban et al., 2012). Numerous components of NETs facilitate thrombosis. According to Fuchs et al. (2010), NETs provided a scaffold for the formation of thrombus and even stimulated

it due to their unique network structure. The formation of NETs in blood vessels can make platelets adhere, aggregate, and activate, and also provide a scaffold for the aggregation of erythrocytes, which can recruit more erythrocytes and promote fibrin deposition, resulting in the formation of red thrombus. The net structure of NETs could be damaged after DNase treatment to prevent thrombus formation (Fuchs et al., 2010). Moreover, the constituent components of NETs can also stimulate thrombus formation. For example, platelets can aggregate when stimulated by pure histones. Particularly, the incubation of H3 and H4 histones with platelets stimulated their aggregation, while the incubation of H1, H2A, and H2B histones with platelets failed to stimulate their aggregation (Fuchs et al., 2010). This shows that the interaction between neutrophil ROS signaling and NETs may be crucial in the development of thrombosis in sepsis patients. A study by Caudrillier et al. (2012) indicated that the in vitro co-culture of sepsis neutrophils with PMA produces higher amounts of ROS than the controls. Further investigation revealed that the increased neutrophil activation and ROS secretion were caused by direct contact with PMA. Meanwhile, the upregulated expression of cluster of differentiation 11b (CD11b)/CD18 adhesion factor in neutrophils enhanced their adhesive capacity, which provides strong evidence that neutrophil-produced ROS are involved in promoting inflammation.

2.8 Role of ROS in endothelial cells in sepsis

Endothelial cells lining the lumen of blood vessels and the heart are recognized to be critical for the maintenance of vascular function and homeostasis (Cai and Harrison, 2000). Endothelial damage is secondary to various stimuli, which results in the loss of endothelial integrity and aberrations in the regulation of vasodilation and vasoconstriction, eventually leading to the alteration of vascular environment (Iantorno et al., 2014). Subsequently, this will cause changes in the vascular hemodynamics, affect organ perfusion, and lead to cardiovascular events and high mortality (Wang and Bennett, 2012). Endothelial cell activation refers to a unique and complex change in the phenotype of endothelial cells (Cernuda-Morollón and Ridley, 2006). The most significant aspect of this process is the increase of endothelial cell–leukocyte interaction, which is key to the inflammatory response in both physiological and pathological environments (Hordijk, 2006). When endothelial cells are exposed to ROS, subsequent high endothelial permeability occurs due to ROS-related cascade effects, leading to various diseases, such as acute respiratory syndrome and asthma (Lee et al., 2006).

The primary sources of ROS produced by endothelial cells include the mitochondrial electron transport chain, NADPH oxidase, xanthine oxidase, cytochrome P450, etc. (Yu and Auwerx, 2010; Zheng et al., 2016). Mitochondria are not only the primary source of ROS, but also particularly vulnerable to oxidative damage by ROS. Therefore, mitochondria suffer oxidative damage with age, leading to mitochondrial dysfunction (Zorov et al., 2014). Mitochondria are primary sources of ROS, and have recently come under increased scrutiny as drivers of ROS-induced endothelial cell dysfunction in sepsis (Li XY et al., 2016). Since mitochondria are considered the oxygen receptors of cells, mitochondrial ROS (mtROS) may associate the changes of oxygen concentration with the changes in cell signal and function caused by hypoxia. NADPH oxidase was first identified in phagocytes, and it plays a vital role in the defense of nonspecific hosts against microorganisms (Zeng et al., 2019). It catalyzes the transfer of electrons from NADPH to molecular oxygen through enzymes, resulting in superoxide and protons. Thus far, the existence and function of NADPH oxidase activity have been found in many non-phagocytic cells, and a complete NADPH oxidase family has been gradually discovered. Each family is based on a different gp91phox or NOX subtype. Five NOX subtypes (i.e., NOX1–NOX5) have been identified to date, and each subtype is encoded by other genes (Lambeth, 2004). Both NOX2 and NOX4 oxidase subtypes are expressed in endothelial cells (Griendling et al., 2000; Li and Shah, 2004). When NOX2 and NOX4 subtypes are co-expressed in endothelial cells, they may have other functions; it is becoming clear that they may be expressed in different subcellular locations and have different regulations (Cave et al., 2006). Partly due to the limitations of ROS measurement methods, the difficulty of mitochondrial O_2 measurement in vivo, and the evaluation of various effects of superoxide dismutation, the exact relationship between hypoxia and mtROS is still an active research field (Dunham-Snary et al., 2016). Although the role of ROS in vascular

functional changes in sepsis is unclear, recent reports indicated that the induction of ROS promotes the migration and proliferation of arterial endothelial cells in the process involving p38 MAPK (Wang et al., 2011; Li Q et al., 2016). The mtROS produced by mitochondria are key components of downstream signaling pathways, including those regulating immune response and autophagy (Morgan and Liu, 2011; Zhang et al., 2016).

The proinflammatory and procoagulant states of activated endothelial cells are related to many pathological conditions, including atherosclerosis (Yin et al., 2022), sepsis (Cao et al., 2022), diabetes (Avagimyan et al., 2022), pulmonary hypertension (Suresh and Shimoda, 2017), tumor (Li et al., 2022), etc. Growing evidence shows that the ROS-mediated signal transduction pathway plays an essential role in many processes involving endothelial activation. Therefore, particular attention should be paid to the protection of microvascular endothelial cell structure and function in sepsis, to improve ROS-dependent endothelial dysfunction and further delay the development of related diseases.

3 Treatments and their limitations

The uncontrolled activation of neutrophils in sepsis leads to various inflammatory reactions. The treatment option of oxidative stress control has remained in the research stage. Endothelial cell-targeting and ROS-supersensitive nanocomposites have been developed, which are composed of polyethylene glycol-modified polylactic acid glycolic acid copolymer nanoparticles to mediate the efficient co-delivery of vascular cell adhesion molecule-1 (VCAM-1) small interfering RNA (siRNA) (siVCAM-1) and dexamethasone. These two drugs have complementary functions, which can inhibit the migration and adhesion of neutrophils and effectively disrupt the inflammatory cascade of injured neutrophil recruitment and self-amplification (Hou et al., 2022). In addition, the importance of biopolymer matrix nanocomposites with the ability to scavenge ROS is increasing. A nanoscale matrix has extremely beneficial effects on cell adhesion, proliferation, and migration (Smith et al., 2009; Zhu et al., 2020). Another study designed a nano-sized matrix, on which the fate of cells was greatly affected by many factors (hydrophilicity, hardness, porosity, roughness, and ROS responsiveness) defined by the surface modification. For example, in a gelatin methacryloyl (GelMA) hybrid matrix modified with uniform nanoceria (NCE), prepared as nanoceria (nCe)-decorated GelMA (Ce@GelMA) scaffolds, ROS were clearly evaluated by NCE, and the developed scaffold could also be used as an antioxidant matrix (Kurian et al., 2022). ROS play a role throughout sepsis and are involved in the function of each affected organ. However, at present, the specific mechanism of action of ROS in each organ is still in the research stage, and studies on treatments to address the excessive ROS in sepsis are relatively limited. In the future, more research is needed to clearly explain the relevant mechanisms, and also to determine the performance of such treatments in in vivo models.

4 Summary

As a common clinical syndrome in critical care medicine, sepsis has complicated etiology, diverse population characteristics, and severe diagnostic difficulties. Although the case fatality rate of sepsis has dropped in recent years due to the improvement of diagnosis and treatment options, the number of deaths is still accumulating with the number of clinical incidences. During the clinical diagnosis and treatment of sepsis, it is crucial to figure out how to enhance patient outcomes. In this regard, the present review discusses the impairment of organ function due to ROS production by neutrophils in sepsis.

Our literature review shows that neutrophils, as an essential constituent of the innate immune system, are inherently capable of inflammatory immune surveillance. Accordingly, compared with other sources of ROS, neutrophil-generated ROS should have better research and application prospects in sepsis prevention and treatment. Although treatments aimed at oxidative stress injury in sepsis have shown adequate success, we should also note that, due to the causes of systemic hemodynamics and organ specificity, the processes of production and alterations of neutrophil-generated ROS in numerous organs are extremely complex and have not yet been well investigated. Moreover, the mechanism of sepsis occurrence is also complex, and relieving oxidative stress alone is

unlikely to be effective in preventing sepsis-associated organ damage. As a result, further comprehensive investigations are necessary to unravel the mechanism of ROS in the dysfunction of various organs in sepsis, which can be the key to directing the intracellular ROS of neutrophils to participate in the prevention and treatment of immune inflammation.

Acknowledgments

We would like to thank the medical and nursing staff from the Department of Critical Care Medicine, Beijing Ditan Hospital, Beijing, China, for their valuable comments during the course of this study.

Author contributions

Jiaqi LU designed and wrote the manuscript. Jingyuan LIU participated in searching and summarizing the relevant literature. Ang LI provided the theme and design, and edited the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Jiaqi LU, Jingyuan LIU, and Ang LI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by the authors.

References

Avagimyan A, Popov S, Shalnova S, 2022. The pathophysiological basis of diabetic cardiomyopathy development. *Curr Probl Cardiol*, in press. https://doi.org/10.1016/j.cpcardiol.2022.101156

Bae MH, Park SH, Park CJ, et al., 2016. Flow cytometric measurement of respiratory burst activity and surface expression of neutrophils for septic patient prognosis. *Cytom B Clin Cytom*, 90(4):368-375. https://doi.org/10.1002/cyto.b.21274

Bateman RM, Sharpe MD, Ellis CG, 2003. Bench-to-bedside review: microvascular dysfunction in sepsis—hemodynamics, oxygen transport, and nitric oxide. *Crit Care*, 7(5):359. https://doi.org/10.1186/cc2353

Beesley SJ, Weber G, Sarge T, et al., 2018. Septic cardiomyopathy. *Crit Care Med*, 46(4):625-634. https://doi.org/10.1097/ccm.0000000000002851

Bougaki M, Searles RJ, Kida K, et al., 2010. NOS3 protects against systemic inflammation and myocardial dysfunction in murine polymicrobial sepsis. *Shock*, 34(3):281-290. https://doi.org/10.1097/SHK.0b013e3181cdc327

Brealey D, Brand M, Hargreaves I, et al., 2002. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*, 360(9328):219-223. https://doi.org/10.1016/s0140-6736(02)09459-x

Brealey D, Karyampudi S, Jacques TS, et al., 2004. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. *Am J Physiol Regul Integr Comp Physiol*, 286(3):R491-R497. https://doi.org/10.1152/ajpregu.00432.2003

Brinkmann V, Reichard U, Goosmann C, et al., 2004. Neutrophil extracellular traps kill bacteria. *Science*, 303(5663):1532-1535. https://doi.org/10.1126/science.1092385

Cai H, Harrison DG, 2000. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res*, 87(10):840-844. https://doi.org/10.1161/01.RES.87.10.840

Cao ZZ, Qin HQ, Huang YH, et al., 2022. Crosstalk of pyroptosis, ferroptosis, and mitochondrial aldehyde dehydrogenase 2-related mechanisms in sepsis-induced lung injury in a mouse model. *Bioengineered*, 13(3):4810-4820. https://doi.org/10.1080/21655979.2022.2033381

Catalão CHR, Santos-Júnior NN, da Costa LHA, et al., 2017. Brain oxidative stress during experimental sepsis is attenuated by simvastatin administration. *Mol Neurobiol*, 54(9):7008-7018. https://doi.org/10.1007/s12035-016-0218-3

Caudrillier A, Kessenbrock K, Gilliss BM, et al., 2012. Platelets induce neutrophil extracellular traps in transfusion-related acute lung injury. *J Clin Invest*, 122(7):2661-2671. https://doi.org/10.1172/jci61303

Cave AC, Brewer AC, Narayanapanicker A, et al., 2006. NADPH oxidases in cardiovascular health and disease. *Antioxid Redox Signal*, 8(5-6):691-728. https://doi.org/10.1089/ars.2006.8.691

Cernuda-Morollón E, Ridley AJ, 2006. Rho GTPases and leukocyte adhesion receptor expression and function in endothelial cells. *Circ Res*, 98(6):757-767. https://doi.org/10.1161/01.RES.0000210579.35304.d3

Chelazzi C, Villa G, Mancinelli P, et al., 2015. Glycocalyx and sepsis-induced alterations in vascular permeability. *Crit Care*, 19:26. https://doi.org/10.1186/s13054-015-0741-z

Chen YH, Jin S, Teng X, et al., 2018. Hydrogen sulfide attenuates LPS-induced acute kidney injury by inhibiting inflammation and oxidative stress. *Oxid Med Cell Longev*, 2018:6717212. https://doi.org/10.1155/2018/6717212

Cogger VC, Mross PE, Hosie MJ, et al., 2001. The effect of acute oxidative stress on the ultrastructure of the perfused rat liver. *Pharmacol Toxicol*, 89(6):306-311. https://doi.org/10.1034/j.1600-0773.2001.d01-165.x

Cohen J, 2002. The immunopathogenesis of sepsis. *Nature*, 420(6917):885-891. https://doi.org/10.1038/nature01326

Drifte G, Dunn-Siegrist I, Tissières P, et al., 2013. Innate immune functions of immature neutrophils in patients with sepsis and severe systemic inflammatory response syndrome. *Crit Care Med*, 41(3):820-832.

https://doi.org/10.1097/CCM.0b013e318274647d

Dunham-Snary KJ, Hong ZG, Xiong PY, et al., 2016. A mitochondrial redox oxygen sensor in the pulmonary vasculature and ductus arteriosus. *Pflugers Arch*, 468(1):43-58. https://doi.org/10.1007/s00424-015-1736-y

Eidelman LA, Putterman D, Putterman C, et al., 1996. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. *JAMA*, 275(6):470-473. https://doi.org/10.1001/jama.1996.03530300054040

Ely EW, Shintani A, Truman B, et al., 2004. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*, 291(14):1753-1762. https://doi.org/10.1001/jama.291.14.1753

Fani F, Regolisti G, Delsante M, et al., 2018. Recent advances in the pathogenetic mechanisms of sepsis-associated acute kidney injury. *J Nephrol*, 31(3):351-359. https://doi.org/10.1007/s40620-017-0452-4

Fink MP, Evans TW, 2002. Mechanisms of organ dysfunction in critical illness: report from a Round Table Conference held in Brussels. *Intensive Care Med*, 28(3):369-375. https://doi.org/10.1007/s00134-001-1205-2

Fuchs TA, Brill A, Duerschmied D, et al., 2010. Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci USA*, 107(36):15880-15885. https://doi.org/10.1073/pnas.1005743107

Gamal M, Moawad J, Rashed L, et al., 2018. Possible involvement of tetrahydrobiopterin in the disturbance of redox homeostasis in sepsis-induced brain dysfunction. *Brain Res*, 1685:19-28. https://doi.org/10.1016/j.brainres.2018.02.008

Gan TT, Yang YL, Hu F, et al., 2018. TLR3 regulated poly I: C-induced neutrophil extracellular traps and acute lung injury partly through p38 MAP kinase. *Front Microbiol*, 9:3174. https://doi.org/10.3389/fmicb.2018.03174

Ge QM, Huang CM, Zhu XY, et al., 2017. Differentially expressed miRNAs in sepsis-induced acute kidney injury target oxidative stress and mitochondrial dysfunction pathways. *PLoS ONE*, 12(3):e0173292. https://doi.org/10.1371/journal.pone.0173292

Gerin F, Sener U, Erman H, et al., 2016. The effects of quercetin on acute lung injury and biomarkers of inflammation and oxidative stress in the rat model of sepsis. *Inflammation*, 39(2):700-705. https://doi.org/10.1007/s10753-015-0296-9

Griendling KK, Sorescu D, Ushio-Fukai M, 2000. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res*, 86(5):494-501. https://doi.org/10.1161/01.res.86.5.494

Guerci P, Ergin B, Ince C, 2017. The macro- and microcirculation of the kidney. *Best Pract Res Clin Anaesthesiol*, 31(3):315-329. https://doi.org/10.1016/j.bpa.2017.10.002

Guo RF, Ward PA, 2007. Role of oxidants in lung injury during sepsis. *Antioxid Redox Signal*, 9(11):1991-2002. https://doi.org/10.1089/ars.2007.1785

Guo SQ, Zhang Y, Wang ZF, et al., 2017. Intraperitoneal gardiquimod protects against hepatotoxicity through inhibition of oxidative stress and inflammation in mice with sepsis. *J Biochem Mol Toxicol*, 31(8):e21923. https://doi.org/10.1002/jbt.21923

Hadem J, Bockmeyer CL, Lukasz A, et al., 2012. Angiopoietin-2 in acute liver failure. *Crit Care Med*, 40(5):1499-1505. https://doi.org/10.1097/CCM.0b013e318241e34e

Haileselassie B, Su E, Pozios I, et al., 2017. Myocardial oxidative stress correlates with left ventricular dysfunction on strain echocardiography in a rodent model of sepsis. *Intensive Care Med Exp*, 5:21. https://doi.org/10.1186/s40635-017-0134-5

Hong GL, Zheng D, Zhang LL, et al., 2018. Administration of nicotinamide riboside prevents oxidative stress and organ injury in sepsis. *Free Radic Biol Med*, 123:125-137. https://doi.org/10.1016/j.freeradbiomed.2018.05.073

Hordijk PL, 2006. Endothelial signalling events during leukocyte transmigration. *FEBS J*, 273(19):4408-4415. https://doi.org/10.1111/j.1742-4658.2006.05440.x

Hou MY, Wu XJ, Zhao ZY, et al., 2022. Endothelial cell-targeting, ROS-ultrasensitive drug/siRNA co-delivery nanocomplexes mitigate early-stage neutrophil recruitment for the anti-inflammatory treatment of myocardial ischemia reperfusion injury. *Acta Biomater*, 143:344-355. https://doi.org/10.1016/j.actbio.2022.02.018

Iantorno M, Campia U, di Daniele N, et al., 2014. Obesity, inflammation and endothelial dysfunction. *J Biol Regul Homeost Agents*, 28(2):169-176.

Jaganjac M, Cipak A, Schaur RJ, et al., 2016. Pathophysiology of neutrophil-mediated extracellular redox reactions. *Front Biosci (Landmark Ed)*, 21(4):839-855. https://doi.org/10.2741/4423

Kim J, Bae JS, 2016. Tumor-associated macrophages and neutrophils in tumor microenvironment. *Mediators Inflamm*, 2016:6058147. https://doi.org/10.1155/2016/6058147

Kumar A, 2014. An alternate pathophysiologic paradigm of sepsis and septic shock: implications for optimizing antimicrobial therapy. *Virulence*, 5(1):80-97. https://doi.org/10.4161/viru.26913

Kurepa J, Smalle JA, 2019. Oxidative stress-induced formation of covalently linked ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit dimer in tobacco plants. *BMC Res Notes*, 12:112. https://doi.org/10.1186/s13104-019-4153-z

Kurian AG, Singh RK, Lee JH, et al., 2022. Surface-engineered hybrid gelatin methacryloyl with nanoceria as reactive oxygen species responsive matrixes for bone therapeutics. *ACS Appl Bio Mater*, 5(3):1130-1138. https://doi.org/10.1021/acsabm.1c01189

Lambeth JD, 2004. NOX enzymes and the biology of reactive oxygen. *Nat Rev Immunol*, 4(3):181-189. https://doi.org/10.1038/nri1312

Landry DW, Levin HR, Gallant EM, et al., 1997. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation*, 95(5):1122-1125. https://doi.org/10.1161/01.cir.95.5.1122

Landskron G, de la Fuente M, Thuwajit P, et al., 2014. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res*, 2014:149185. https://doi.org/10.1155/2014/149185

Larsen FS, 2019. Artificial liver support in acute and acute-on-chronic liver failure. *Curr Opin Crit Care*, 25(2): 187-191. https://doi.org/10.1097/mcc.0000000000000584

Lee KS, Kim SR, Park SJ, et al., 2006. Hydrogen peroxide induces vascular permeability via regulation of vascular endothelial growth factor. *Am J Respir Cell Mol Biol*, 35(2):190-197. https://doi.org/10.1165/rcmb.2005-0482OC

Li F, Lang FF, Zhang HL, et al., 2016. Role of TFEB mediated autophagy, oxidative stress, inflammation, and cell death in endotoxin induced myocardial toxicity of young and aged mice. *Oxid Med Cell Longev*, 2016: 5380319. https://doi.org/10.1155/2016/5380319

Li JM, Shah AM, 2004. Endothelial cell superoxide generation: regulation and relevance for cardiovascular pathophysiology. *Am J Physiol Regul Integr Comp Physiol*, 287(5):R1014-R1030. https://doi.org/10.1152/ajpregu.00124.2004

Li Q, Mao M, Qiu YL, et al., 2016. Key role of ROS in the process of 15-lipoxygenase/15-hydroxyeicosatetraenoiccid-induced pulmonary vascular remodeling in hypoxia pulmonary hypertension. *PLoS ONE*, 11(2):e0149164. https://doi.org/10.1371/journal.pone.0149164

Li Q, Zhong XF, Yao WC, et al., 2022. Inhibitor of glutamine metabolism V9302 promotes ROS-induced autophagic degradation of B7H3 to enhance antitumor immunity. *J Biol Chem*, 298(4):101753. https://doi.org/10.1016/j.jbc.2022.101753

Li XY, Fang P, Li YF, et al., 2016. Mitochondrial reactive oxygen species mediate lysophosphatidylcholine-induced endothelial cell activation. *Arterioscler Thromb Vasc Biol*, 36(6):1090-1100. https://doi.org/10.1161/atvbaha.115.306964

Liu H, Wu J, Yao JY, et al., 2017. The role of oxidative stress in decreased acetylcholinesterase activity at the neuromuscular junction of the diaphragm during sepsis. *Oxid Med Cell Longev*, 2017:9718615. https://doi.org/10.1155/2017/9718615

Livaditi O, Kotanidou A, Psarra A, et al., 2006. Neutrophil CD64 expression and serum IL-8: sensitive early markers of severity and outcome in sepsis. *Cytokine*, 36(5-6): 283-290. https://doi.org/10.1016/j.cyto.2007.02.007

Mariampillai K, Granger B, Amelin D, et al., 2018. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. *JAMA Neurol*, 75(12):1528-1537. https://doi.org/10.1001/jamaneurol.2018.2598

Marin-Esteban V, Turbica I, Dufour G, et al., 2012. Afa/Dr diffusely adhering *Escherichia coli* strain C1845 induces neutrophil extracellular traps that kill bacteria and damage human enterocyte-like cells. *Infect Immun*, 80(5):1891-1899. https://doi.org/10.1128/iai.00050-12

Martin L, Derwall M, Al Zoubi S, et al., 2019. The septic heart: current understanding of molecular mechanisms and clinical implications. *Chest*, 155(2):427-437. https://doi.org/10.1016/j.chest.2018.08.1037

McCracken JM, Allen LAH, 2014. Regulation of human neutrophil apoptosis and lifespan in health and disease. *J Cell Death*, 7:15-23. https://doi.org/10.4137/jcd.S11038

Mills EL, Kelly B, Logan A, et al., 2016. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. *Cell*, 167(2):457-470.e13. https://doi.org/10.1016/j.cell.2016.08.064

Morgan MJ, Liu ZG, 2011. Crosstalk of reactive oxygen species and NF-κB signaling. *Cell Res*, 21(1):103-115. https://doi.org/10.1038/cr.2010.178

Morrell ED, Kellum JA, Pastor-Soler NM, et al., 2014. Septic acute kidney injury: molecular mechanisms and the importance of stratification and targeting therapy. *Crit Care*, 18(5):501. https://doi.org/10.1186/s13054-014-0501-5

Ostermann M, Liu K, Kashani K, 2019. Fluid management in acute kidney injury. *Chest*, 156(3):594-603. https://doi.org/10.1016/j.chest.2019.04.004

Peerapornratana S, Manrique-Caballero CL, Gómez H, et al., 2019. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int*, 96(5):1083-1099. https://doi.org/10.1016/j.kint.2019.05.026

Perl M, Lomas-Neira J, Chung CS, et al., 2008. Epithelial cell apoptosis and neutrophil recruitment in acute lung injury—a unifying hypothesis? What we have learned from small interfering RNAs. *Mol Med*, 14(7-8):465-475. https://doi.org/10.2119/2008-00011.Perl

Post EH, Kellum JA, Bellomo R, et al., 2017. Renal perfusion in sepsis: from macro- to microcirculation. *Kidney Int*, 91(1):45-60. https://doi.org/10.1016/j.kint.2016.07.032

Rea IM, Gibson DS, McGilligan V, et al., 2018. Age and age-related diseases: role of inflammation triggers and cytokines. *Front Immunol*, 9:586. https://doi.org/10.3389/fimmu.2018.00586

Rudd KE, Johnson SC, Agesa KM, et al., 2020. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. *Lancet*, 395(10219):200-211.

https://doi.org/10.1016/s0140-6736(19)32989-7

Saffarzadeh M, Juenemann C, Queisser MA, et al., 2012. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. *PLoS ONE*, 7(2):e32366. https://doi.org/10.1371/journal.pone.0032366

Sakaguchi S, Furusawa S, 2006. Oxidative stress and septic shock: metabolic aspects of oxygen-derived free radicals generated in the liver during endotoxemia. *FEMS Immunol Med Microbiol*, 47(2):167-177. https://doi.org/10.1111/j.1574-695X.2006.00072.x

Singer M, 2014. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence*, 5(1):66-72. https://doi.org/10.4161/viru.26907

Singer M, Deutschman CS, Seymour CW, et al., 2016. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*, 315(8):801-810. https://doi.org/10.1001/jama.2016.0287

Smith IO, Liu XH, Smith LA, et al., 2009. Nanostructured polymer scaffolds for tissue engineering and regenerative medicine. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*, 1(2):226-236. https://doi.org/10.1002/wnan.26

Starczewska MH, Mon W, Shirley P, 2017. Anaesthesia in patients with liver disease. *Curr Opin Anaesthesiol*, 30(3): 392-398. https://doi.org/10.1097/aco.0000000000000470

Suresh K, Shimoda LA, 2017. Endothelial cell reactive oxygen species and Ca^{2+} signaling in pulmonary hypertension. *In:* Wang YX (Ed.), Pulmonary Vasculature Redox Signaling in Health and Disease. Springer, Cham, p.299-314. https://doi.org/10.1007/978-3-319-63245-2_18

Tan CY, Aziz M, Wang P, 2021. The vitals of nets. *J Leukoc Biol*, 110(4):797-808. https://doi.org/10.1002/JLB.3RU0620-375R

Tang GM, Yang HY, Chen J, et al., 2017. Metformin ameliorates sepsis-induced brain injury by inhibiting apoptosis, oxidative stress and neuroinflammation via the PI3K/Akt signaling pathway. *Oncotarget*, 8(58):97977-97989. https://doi.org/10.18632/oncotarget.20105

Thieblemont N, Wright HL, Edwards SW, et al., 2016. Human neutrophils in auto-immunity. *Semin Immunol*, 28(2): 159-173. https://doi.org/10.1016/j.smim.2016.03.004

Vaisbich MH, Pache de Faria Guimaraes L, Shimizu MHM, et al., 2011. Oxidative stress in cystinosis patients. *Nephron Extra*, 1(1):73-77. https://doi.org/10.1159/000331445

Wang JC, Bennett M, 2012. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res*, 111(2):245-259. https://doi.org/10.1161/circresaha.111.261388

Wang YX, Zang QS, Liu ZJ, et al., 2011. Regulation of VEGF-induced endothelial cell migration by mitochondrial reactive oxygen species. *Am J Physiol Cell Physiol*, 301(3): C695-C704. https://doi.org/10.1152/ajpcell.00322.2010

Wang Z, Holthoff JH, Seely KA, et al., 2012. Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. *Am J Pathol*, 180(2): 505-516. https://doi.org/10.1016/j.ajpath.2011.10.011

Wilson CL, Jurk D, Fullard N, et al., 2015. *NFκB1* is a suppressor of neutrophil-driven hepatocellular carcinoma. *Nat Commun*, 6:6818. https://doi.org/10.1038/ncomms7818

Winterbourn CC, Kettle AJ, Hampton MB, 2016. Reactive oxygen species and neutrophil function. *Annu Rev Biochem*, 85:765-792. https://doi.org/10.1146/annurev-biochem-060815-014442

Yan J, Li S, Li SL, 2014. The role of the liver in sepsis. *Int Rev Immunol*, 33(6):498-510. https://doi.org/10.3109/08830185.2014.889129

Yin R, Wang H, Li C, et al., 2022. Induction of apoptosis and autosis in cardiomyocytes by the combination of homocysteine and copper via NOX-mediated p62 expression. *Cell Death Discov*, 8:75. https://doi.org/10.1038/s41420-022-00870-4

Yu JJ, Auwerx J, 2010. Protein deacetylation by SIRT1: an emerging key post-translational modification in metabolic regulation. *Pharmacol Res*, 62(1):35-41. https://doi.org/10.1016/j.phrs.2009.12.006

Zanotti-Cavazzoni SL, Hollenberg SM, 2009. Cardiac dysfunction in severe sepsis and septic shock. *Curr Opin Crit Care*, 15(5):392-397. https://doi.org/10.1097/MCC.0b013e3283307a4e

Zarbato GF, de Souza Goldim MP, Giustina AD, et al., 2018. Dimethyl fumarate limits neuroinflammation and oxidative stress and improves cognitive impairment after polymicrobial sepsis. *Neurotox Res*, 34(3):418-430. https://doi.org/10.1007/s12640-018-9900-8

Zeng M, He WM, Li LJ, et al., 2015. Ghrelin attenuates sepsis-associated acute lung injury oxidative stress in rats. *Inflammation*, 38(2):683-690. https://doi.org/10.1007/s10753-014-9977-z

Zeng MY, Miralda I, Armstrong CL, et al., 2019. The roles of NADPH oxidase in modulating neutrophil effector responses. *Mol Oral Microbiol*, 34(2):27-38. https://doi.org/10.1111/omi.12252

Zhang XL, Yu L, Xu HX, 2016. Lysosome calcium in ROS regulation of autophagy. *Autophagy*, 12(10):1954-1955. https://doi.org/10.1080/15548627.2016.1212787

Zhang ZY, Zhang H, Chen R, et al., 2018. Oral supplementation with ursolic acid ameliorates sepsis-induced acute kidney injury in a mouse model by inhibiting oxidative stress and inflammatory responses. *Mol Med Rep*, 17(5): 7142-7148. https://doi.org/10.3892/mmr.2018.8767

Zheng JL, Yuan SS, Wu CW, et al., 2016. Acute exposure to

waterborne cadmium induced oxidative stress and immunotoxicity in the brain, ovary and liver of zebrafish (*Danio rerio*). *Aquat Toxicol*, 180:36-44. https://doi.org/10.1016/j.aquatox.2016.09.012

Zhong WH, Qian KJ, Xiong JB, et al., 2016. Curcumin alleviates lipopolysaccharide induced sepsis and liver failure by suppression of oxidative stress-related inflammation via PI3K/AKT and NF-κB related signaling. *Biomed Pharmacother*, 83:302-313. https://doi.org/10.1016/j.biopha.2016.06.036

Zhu LS, Luo D, Liu Y, 2020. Effect of the nano/microscale structure of biomaterial scaffolds on bone regeneration. *Int J Oral Sci*, 12:6. https://doi.org/10.1038/s41368-020-0073-y

Zhu W, Lu Q, Wan L, et al., 2016. Sodium tanshinone II A sulfonate ameliorates microcirculatory disturbance of small intestine by attenuating the production of reactie oxygen species in rats with sepsis. *Chin J Integr Med*, 22(10):745-751. https://doi.org/10.1007/s11655-015-2083-8

Zorov DB, Juhaszova M, Sollott SJ, 2014. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol Rev*, 94(3):909-950. https://doi.org/10.1152/physrev.00026.2013