Research status and advances in dexmedetomidine for sepsis-induced multiple organ dysfunction syndrome (Review)

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Abstract. Sepsis-induced organ dysfunction syndrome (ODS) arises from a dysregulated response to infection, leading to multiple life-threatening organ dysfunctions, and is a common complication in critically ill patients. Sepsis results in varying degrees of injury to the brain, lungs, kidneys and liver, culminating in immune dysfunction and multiple ODS (MODS). Current evidence indicates a direct correlation between the severity of organ injury and the prognosis of septic patients. Understanding the mechanisms of MODS in sepsis and developing effective management strategies are vital research areas. The protective effects of dexmedetomidine (DEX) on sepsis are well established, demonstrating its capacity to mitigate injuries to the brain, lungs, kidneys, liver and immune system. The present study reviews recent research progress on the role and mechanisms of action of DEX in the treatment of sepsis.

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Contents

1. Introduction

Sepsis-induced multiple organ dysfunction syndrome (MODS) involves dysfunction of two or more organs triggered by a dysregulated response to infection and is characterized by a series of physiological, pathological and biochemical abnormalities caused by infection (1) (Fig. 1). During the early stage of sepsis, inflammation is activated, leading to the release of numerous proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6, and inflammatory mediators, such as high-mobility group protein B1 and prostaglandins, resulting in immune overactivation. Additionally, immune cells, including T lymphocytes, release various cytokines, accompanied by redox imbalance. These mechanisms collectively activate endothelial cells, increasing the release of cytokines, nitric oxide (NO), platelet-activating factor and coagulation factors, thereby exacerbating sepsis and advancing to MODS, ultimately resulting in patient mortality (2) (Fig. 1). Despite extensive research on the pathogenesis and therapeutic targets of MODS, the incidence and mortality rates have improved little.

Dexmedetomidine (DEX), a potent selective α2-adrenergic receptor agonist, functions as a sympathetic blockade within

the nervous system and provides anxiolytic, sedative, analgesic and hemodynamic stabilizing effects (3). It induces sedation without causing respiratory depression, which is significant in clinical treatment. DEX is commonly used for preanesthetic induction and as a sedative in intensive care units (ICUs) (3,4). Previous studies have indicated that DEX has protective effects on various disease models: i) DEX enhances the 2-year survival of elderly patients in ICUs and improves cognitive function and quality of life in 3-year survivors (5); ii) DEX mitigates apoptosis, necrosis and autophagy in the brain and surrounding tissues in both *in vitro* and *in vivo* models (6); iii) DEX promotes cell survival by inhibiting apoptosis and protecting against bilirubin-related lung injury (7); iv) DEX protects against cerebral ischemia-reperfusion injury by inhibiting autophagy (7); and v) DEX shields against sepsis-related organ injury (8-11). The roles of DEX in mitigating lung, kidney, liver, brain and immune dysfunctions by regulating signaling pathways related to inflammation, apoptosis, pyroptosis, autophagy, and ferroptosis in sepsis treatment are summarized in Fig. 2.

2. Epidemiology of sepsis and multiple organ dysfunction

Sepsis, a severe disease that threatens human health, is not only a medical issue but also a public health problem. A search of the World Health Organization website revealed that, according to data released in 2020 (12), there are 48.9 million cases and 11 million sepsis-related deaths globally, accounting for nearly 20% of all global deaths. Of these, nearly half of the sepsis cases occur in children, with an estimated 20 million child cases and 2.9 million deaths among children under the age of 5. The incidence and mortality rates of sepsis vary by region, with ~85% of sepsis cases and sepsis-related deaths occurring in low- and middle-income countries. Sepsis treatment is costly, and in high-income countries, the average hospital cost for sepsis exceeds $32,000 per patient (13). The incidence of sepsis in mainland China is similar to that in developed countries. However, owing to the large population base and relatively low ICU bed-to-population ratio, more patients with sepsis are not admitted to the ICU because of insufficient bed availability. A population-based epidemiological study of hospitalized sepsis patients conducted by Zhou *et al* (14) revealed that only 20% of patients with severe sepsis and 59% of patients with septic shock were admitted to the ICU. The burden of sepsis in mainland China may thus be underestimated. The study also revealed that the standardized incidence rate of sepsis is 461/10 million, with a mortality rate of 79/10 million. The high incidence and mortality of sepsis, as well as the annual medical burden it causes, highlight the need to improve the diagnosis and treatment of sepsis and, at the macrolevel, strengthen the management of sepsis prevention and treatment.

Sepsis-related organ injury or dysfunction is a common complication of sepsis, and in severe cases, it can lead to multiple organ dysfunction or failure, resulting in a poor prognosis (15). According to the American Society of Critical Care Medicine, the incidence of MODS in the United States is ~240-300/100,000 people, with ~54% of ICU-admitted patients developing MODS (16). The pathophysiology of MODS is complex, with an unclear pathogenesis and rapid disease progression, and the mortality rate is as high as ~30-40% (14). Studies have reported that the average mortality rate for individuals with two organ dysfunctions is 59%; for those with three organ dysfunctions, the average mortality rate is 75%; and for those with four or more organ dysfunctions, the average mortality rate is 100% (17). In terms of the frequency of organ dysfunctions occurring in MODS, the highest incidence is respiratory dysfunction, followed by gastrointestinal and renal dysfunction. Among them, renal dysfunction has the highest mortality rate, with an average of 79%, followed by respiratory dysfunction at 68%, gastrointestinal dysfunction at 59%, hepatic dysfunction at 55% and coagulation dysfunction at 44% (18). If severe infection is present, the mortality rate increases significantly. In recent years, the mortality rate of MODS has significantly increased with the number of organ failures and the age of patients, making MODS a major clinical challenge that urgently needs to be addressed in medicine.

3. Pharmacokinetics of DEX

The chemical molecular formula of DEX is C13H16N2, and its chemical name is (+)-4-(2,3-dimethylphenyl)-ethyl-1H-imidazole (19). DEX shares a similar chemical structure with clonidine, including an imidazole ring and a benzene ring, indicating that both can act as agonists on α-adrenergic receptors. As a highly selective α2-adrenergic receptor agonist, DEX has a binding affinity ratio of 1,620:1 for α2-adrenergic receptors compared with α1 receptors. Its affinity for α2-adrenergic receptors is 8-fold greater than that of clonidine. Studies have shown that the pharmacokinetics of DEX are strongly predictable (20). For example, during absorption, owing to the first-pass effect, the oral bioavailability of DEX is extremely low. The bioavailability is only 16% for sublingual administration, whereas intranasal administration achieves a bioavailability of 84%. For intramuscular and subcutaneous injections, the bioavailabilities are 73 and 51%, respectively. Therefore, intranasal, intravenous and intramuscular routes of administration are all applicable. However, considering the storage and usage of DEX, along with its physicochemical property of being fully soluble in water at a pH of 7.4, clinical formulations are commonly provided as colorless, clear liquid hydrochloride injection solutions. Intranasal administration is particularly beneficial for special populations, such as children and elderly individuals (21). DEX is a highly plasma protein-bound drug, with a binding rate of 94% to plasma albumin and α1-glycoprotein. Studies have shown that the plasma protein binding rate of DEX is not significantly influenced by sex or age (22). Additionally, DEX has a shorter half-life than does clonidine. Its distribution half-life is ~6 min, allowing it to be distributed rapidly in the body following intravenous injection. The elimination half-life (t1/2) is ~2 h, with intravenous infusion lasting up to 24 h. The linear pharmacokinetic range of DEX in the body is 0.2-0.7 μg/kg·h. It is metabolized primarily in the liver, with the metabolites being excreted mainly through urine (95%) and feces (5%) (21).

4. Pharmacodynamics of DEX

DEX is a potent and highly selective α2-adrenergic receptor agonist that exerts various effects by stimulating three subtypes

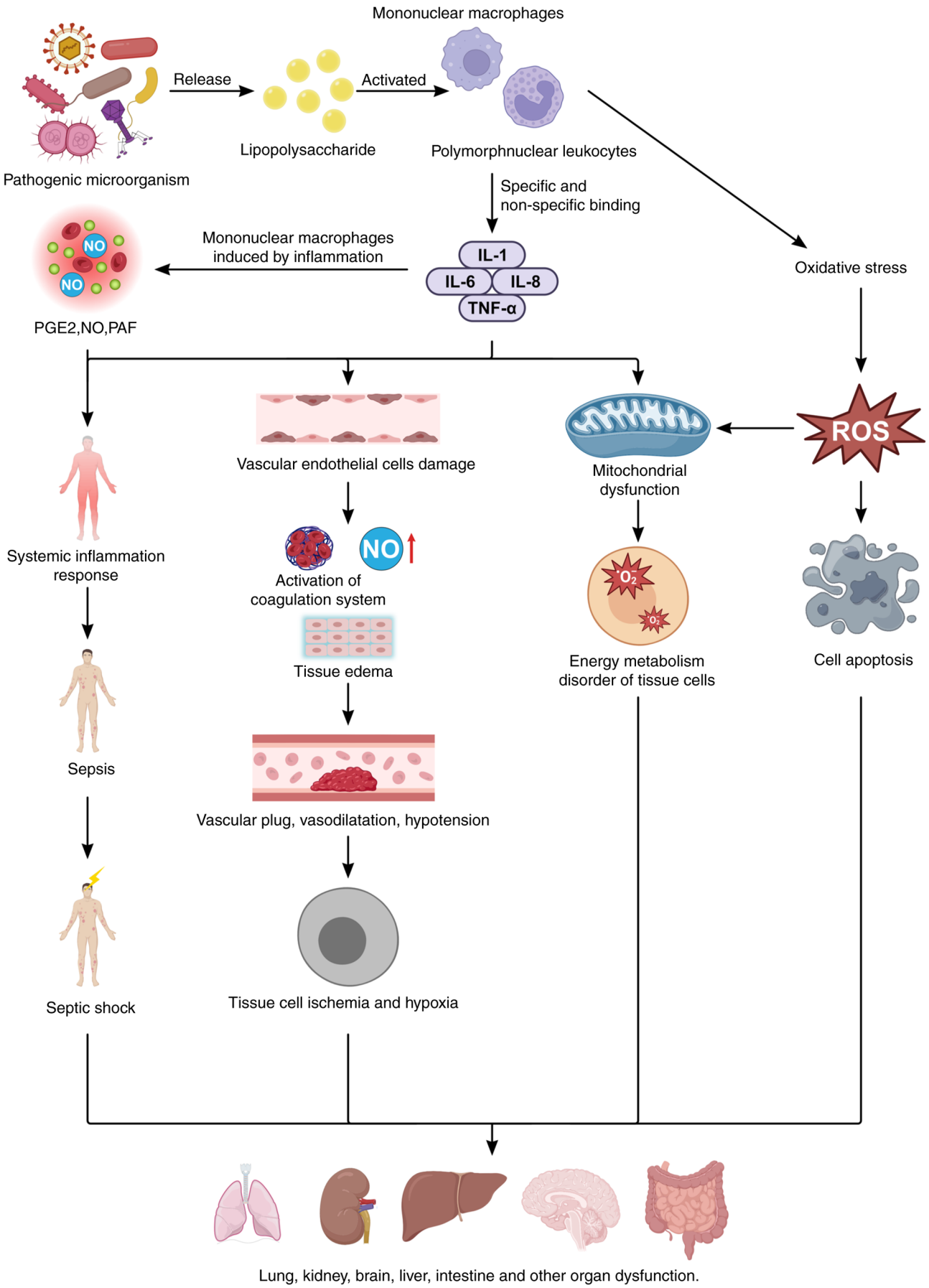

Figure 1. Mechanism of multiple organ dysfunction caused by sepsis. The endotoxins produced by pathogenic microorganisms stimulate inflammatory cells, which produce a large concentration of inflammatory mediators, leading to sepsis, septic shock and multiple organ dysfunction. Moreover, inflammatory mediators can lead to mitochondrial dysfunction, an oxidative stress response, coagulation dysfunction and microvascular blockage and exacerbate damage to multiple organs, such as the liver, brain and lungs. PGE2, prostaglandin E2; NO, nitric oxide; PAF, platelet-activating factor; ROS, reactive oxygen species.

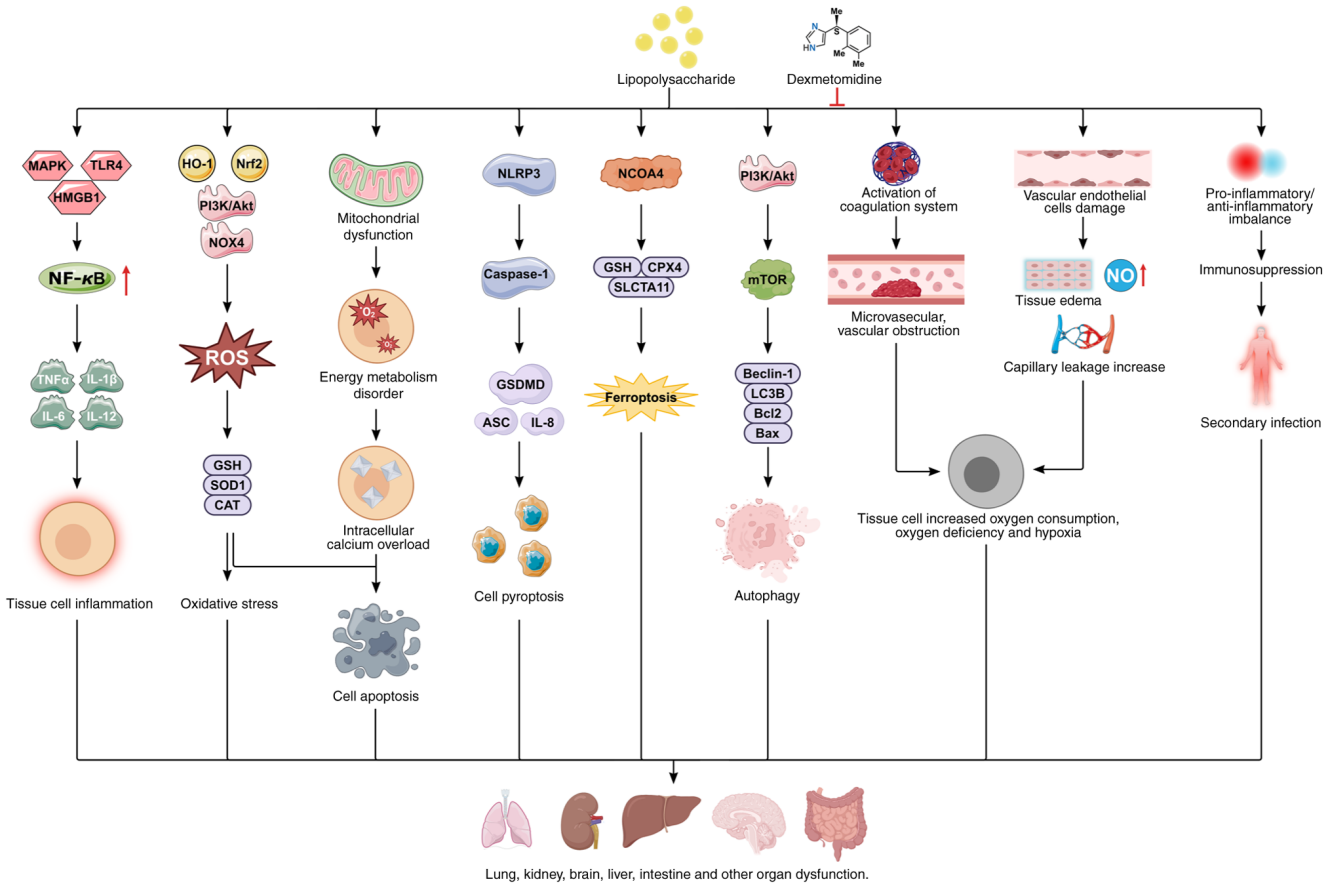

Figure 2. Protective mechanism of dexmedetomidine against multiorgan dysfunction. LPS regulate tissue cell inflammation by modulating the MAPK, TLR4, or HMGB1/NF-κB signaling pathways; regulate tissue cell oxidative stress by modulating Nrf2/HO-1, P13K/Akt and NOX4 signaling pathways; and regulate cellular autophagy by modulating the P13K/Akt/mTOR signaling pathways. In addition, lipolysis can lead to endothelial damage, abnormal coagulation function and immune imbalance. Lipopolysaccharides induce multiple organ dysfunction through these mechanisms; however, dexmedetomidine alleviates lipopolysaccharide-induced multiple organ dysfunction by regulating these pathways. LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; TLR4, Toll-like receptor 4; HMGB1, high mobility group protein box-1; NLRP3, NOD-like receptor family pyrin domain containing 3; NF-κB, Nuclear factor κB; CAT, catalase; HO-1, heme oxygenase 1; ASC, apoptosis-associated speck-like protein; NCOA4, nuclear receptor coactivator 4; GSH, glutathione; GPX4, glutathione peroxidase 4; ROS, reactive oxygen species; SOD, superoxide dismutase; GSDMD, gasdermin D.

of α2 receptors in the body (α2A, α2B and α2C). For example, the activation of α2A receptors, which are located primarily in the locus coeruleus of the brain, can produce effects such as sedation, analgesia, hypnosis and neuroprotection; the activation of α2B receptors, which are distributed mainly in the thalamus, heart, liver, spleen and aorta, can lead to analgesia, peripheral arterial vasoconstriction, and the suppression of centrally mediated shivering; and the activation of α2C receptors, which are found in the heart, spleen and aorta, can result in cognitive and emotional changes (3). Therefore, by stimulating α2 receptors in these organs and tissues, DEX can exert multiple biological effects, including sedation, analgesia, hypnosis, maintenance of normal respiration, and a reduction in organ damage.

DEX induces a unique sedative response characterized by a smooth transition from sleep to wakefulness, allowing patients to communicate and interact when stimulated by external factors. It mimics the effects of 'natural sleep', enabling patients to remain in a sleep-like state during surgery while being easily arousable. DEX has minimal toxic side effects on the body and, regardless of the dosage, does not cause respiratory depression (23). Sleigh *et al* (24) suggested that the sedative and hypnotic effects of DEX are mediated by the activation of pre- and postsynaptic α2 receptors in the central nucleus of the brainstem locus coeruleus, which function through endogenous physiological sleep pathways to exert sedative and hypnotic effects. Clinical studies have shown that DEX has dose-dependent sedative effects, with doses of 0.2-0.6 μg/kg·h inducing significant yet easily reversible sedation. At sufficiently high doses, DEX can produce deep sedation and even general anesthesia, indicating its potential role as part of total intravenous anesthesia. Although the U.S. Food and Drug Administration has approved DEX for short-term sedation (<24 h), multiple clinical studies have confirmed that continuous use of DEX for several days can mitigate adverse effects in patients with ICU (3,23). Ding *et al* (25) reported that, compared with traditional sedatives, long-term ICU sedation with DEX reduced mechanical ventilation time of patients by 22%, shortened hospital stays by 14%, and did not significantly affect mortality. When the sedative effects of midazolam, propofol and DEX in mechanically ventilated ICU sepsis patients were compared, DEX demonstrated comparable sedation efficacy while better stabilizing blood pressure and cardiac function. Kawazoe *et al* (26), in a study of 201 mechanically-ventilated patients with sepsis, reported that the sedation control rate

during mechanical ventilation was significantly greater in the DEX group than in the non-DEX group. Furthermore, DEX significantly reduced the levels of inflammatory markers such as C-reactive protein and procalcitonin, alleviating systemic inflammatory responses.

5. Pharmacokinetic study of DEX in special populations

Inside the child's body. DEX can be administered via intramuscular injection, intravenous injection, nasal drops, or oral administration inside the child's body. The use of nasal drops or oral administration can prevent high peak plasma levels that may cause respiratory and circulatory depression after intravenous injection. It also helps avoid the irritation caused by intravenous administration, rendering it more suitable for children. The nasal mucosa has a rich distribution of aqueous channels, providing high drug permeability and rapid absorption. It also bypasses the hepatic first-pass effect. Research by Miller *et al* (27) indicates that nasal administration of DEX for pediatric sedation can provide adequate blood drug concentrations, with a bioavailability >80%, whereas oral administration has a bioavailability of only 16% owing to the first-pass effect (20). Yadav and Ramdas (28) conducted a randomized controlled trial of intranasal DEX for preoperative pediatric anesthesia. The results showed that, compared with midazolam, it offered more stable hemodynamics, a shorter time to achieve sedation, and lower anxiety scores. It is an excellent sedative and anxiolytic and can be safely used in children. DEX is a drug with a strong binding ability to proteins, with a protein binding rate of 94%. It is distributed quickly and extensively in the human body and is also a highly lipophilic drug that easily crosses the blood-brain barrier (29). Non-compartmental analysis has shown that the distribution half-life in healthy volunteers is ~6 min (30). Studies have indicated that in critically ill patients with hypoalbuminemia, long-term administration of DEX significantly increases its apparent Vd (31). In pediatric pharmacokinetics for children <11 years old, the results revealed that the steady-state Vd (Vss) is negatively correlated with the age of the subjects (32), indicating that younger children require a larger initial dose of DEX to reach a certain blood concentration. DEX is metabolized primarily in the liver, with most of its metabolites excreted through the kidneys and a small portion through feces (33,34). Research on the pharmacokinetics of DEX in neonates and infants shows that the drug clearance (CL) rate increases with age, particularly within the first 2 weeks after birth, whereas after 1 month of age, the impact of age on the CL rate is minimal (33). The metabolic enzyme system of newborns and infants is not fully mature, resulting in low CL rates. Research has shown that the expression and activity of cytochrome P450 enzymes approach adult levels by the age of 1 (35). The CL rate of full-term newborns is ~42.2% of that of adults, reaching 84.5% at 1 year of age (29). Premature infants have even lower CL rates [0.3 l/(h x kg) than 0.9 l/(h x kg)] and longer elimination half-lives (7.6 compared with 3.2 h) (33). The CL rate of DEX is only mildly affected by hypoproteinemia, but since the liver is the primary metabolic organ, the CL rate decreases as the severity of liver damage increases (32).

Among the elderly group. With increasing age, the body fat content also increases in the elderly group (36). For males, from the ages of 20 to 30, the fat content increases from 8% to 20%, whereas for females, it increases from 30 to 50% (37). First, lipophilic drugs (such as DEX) have a relatively large volume of distribution (Vd) (38). Second, the plasma protein concentration decreases with age, which in turn increases the free fraction of drugs with a high protein binding rate (39), thus increasing the Vd of DEX. Changes in liver and kidney function in elderly individuals can affect plasma protein binding rates. Additionally, an increase in fat content affects organ blood flow and the activity of mixed-function oxidases (40). Studies on the population pharmacokinetics of ICU patients receiving long-term DEX infusion have revealed that age and plasma protein concentration can influence the pharmacokinetic characteristics of DEX. In the elderly population, CL decreases, and the t1/2 increases. Moreover, patients with low plasma ALB concentrations have an increased Vd and a prolonged t1/2. The CL of the elderly population, with an average age of 80 years, is 25% lower than that of those aged 60 years (41). This finding is consistent with the report by Venn *et al* (42). CL is related primarily to liver blood flow and is less affected by the protein binding rate (43). As various bodily functions decline in elderly individuals, the CL of DEX decreases, leading to an extended t1/2. Lin *et al* (44) conducted a population pharmacokinetic study on post-operative ICU patients, and the results revealed that factors such as age and sex had no impact on their pharmacokinetics. This may be due to the small sample size and the high variability in the pharmacokinetic parameters of DEX (45). Moreover, the aforementioned study did not provide standard errors or confidence intervals, indicating insufficient model stability and reliability.

In individuals with liver dysfunction. Individuals with liver dysfunction, the CL of DEX decreases, with significant individual variability (46). According to the Child-Pugh classification, liver dysfunction patients are divided into three groups: mild (n=5), moderate (n=6), and severe (n=5). Compared with those in the three control groups, the average CL rates of DEX were 41, 49 and 68% lower in patients with mild, moderate and severe liver dysfunction, respectively. Compared with those in both the mild group and the control group, the Vss and t1/2 were significantly greater in severe liver dysfunction patients ($P<0.05$) (47), indicating that when DEX is used in patients with liver dysfunction, dose adjustments should be considered.

In individuals with renal insufficiency. There was no statistically significant difference in the pharmacokinetic parameters of DEX in patients with renal insufficiency compared with healthy subjects. A comparative study was conducted between 6 patients with renal insufficiency (creatinine CL <30 ml/min) and 6 healthy volunteers, and the results revealed that there were no statistically significant differences in maximal plasma/serum concentration, time to maximal plasma/serum concentration, area-under-the-curve plasma/serum concentrations, CL, or Vss (48). However, in patients with renal insufficiency, the elimination-phase concentration was lower, and elimination was faster, with a 17% decrease at t1/2 ($P<0.05$). In patients with renal insufficiency, the protein binding rate

of alfentanil, which has a high plasma protein binding rate, decreases from 19 to 11% (49). Therefore, the decrease in the t1/2 of DEX may also be due to the reduced plasma protein binding rate in patients with renal insufficiency, leading to an increase in the amount of drug entering the elimination phase.

Others. There have been few studies on the pharmacokinetics of DEX in other special populations (including pregnant women, parturient women and lactating patients). In one case, a pregnant woman with spinal muscular atrophy who underwent routine cesarean section had DEX infusion stopped, and 68 min later, the fetus was delivered. DEX was detected in the umbilical blood, suggesting that DEX can cross the placental barrier (50). DEX can cause a significant increase in blood glucose levels in both the mother and the fetus (51).

6. Organ protection mechanisms of DEX

In recent years, an increasing number of basic and clinical studies have shown that DEX may exert organ-protective effects through anti-inflammatory, antiapoptotic, antioxidative stress, and autophagy-regulating mechanisms involving the heart, brain, lungs, kidneys, liver and gastrointestinal tract. Despite its common effects, the biological mechanisms of DEX vary across different organs. Studies have shown that perioperative infusion of DEX can reduce the levels of inflammatory factors such as interleukin-6 (IL-6), IL-8, and TNF-α, with the effect being more significant during continuous intraoperative infusion than during single-dose administration (52). The anti-inflammatory mechanism of DEX is closely related to the inhibition of the nuclear factor κB (NF-κB) pathway and Toll-like receptors via α2 receptors (53). The vagus nerve and nicotinic acetylcholine receptors are key components of the cholinergic anti-inflammatory pathway. In addition to acting directly on α2 receptors, DEX can activate the cholinergic anti-inflammatory pathway to exert its anti-inflammatory effects (54,55). DEX also has antiapoptotic effects on various cell types, potentially through activation of the α2AR/PI3K/Akt and p38MAPK/ERK signaling pathways (56-58). Additionally, DEX may inhibit mitochondrial apoptosis by activating the JAK2/STAT3 signaling pathway via the long non-coding RNA HCP5 (59). However, some studies have shown that high concentrations of DEX can induce hippocampal neuronal apoptosis. *In vitro* experiments suggest that DEX concentrations ≥100 μmol/l significantly reduce cell viability and induce neuronal apoptosis (60). In different cell injury models, such as vascular smooth muscle cells, renal tubular epithelial cells and hepatocytes, DEX can alleviate oxidative stress by inhibiting the production of malondialdehyde (MDA) and reactive oxygen species (ROS) and increasing the activity of superoxide dismutase (SOD) (61-63). DEX also inhibits the decrease in the mitochondrial membrane potential and reduces respiratory chain enzyme complex damage, thereby suppressing the mitochondrial oxidative stress induced by general anesthesia (64). Autophagy is an adaptive catabolic process that maintains intracellular homeostasis by engulfing intracellular substances, including damaged organelles, unfolded proteins and pathogens. In cases of damage to critical organs such as the heart, lungs, brain and kidneys, DEX treatment can increase autophagy levels (65,66). However, studies have also shown that DEX can suppress excessive autophagy in cardiomyocytes and neurons to protect organs (67,68). Therefore, under different pathological conditions in various organs, DEX has distinct regulatory effects on autophagy.

7. Mechanism of MODS induced by sepsis

Currently, MODS caused by sepsis is considered to be associated with factors such as uncontrollable infection, the systemic inflammatory response, immune paralysis, coagulation activation, microcirculatory failure and hypoxia (69). Studies have shown that immune-metabolic reprogramming occurs at various stages of sepsis, making it a key regulatory factor in the pathogenesis of this disease (70). Polymorphonuclear neutrophils (PMNs) are innate immune cells that respond first to infectious pathogens and play a crucial role in host defense. During infection, the body reacts rapidly to local inflammatory stimuli, recruiting numerous PMNs efficiently from the bloodstream to the site of inflammation. PMNs eliminate pathogens through phagocytosis, degranulation, respiratory bursts, the generation and release of neutrophil extracellular traps (NETs), and the production of inflammatory factors such as TNF-α, IL-1β, IL-6 and IL-8, thus controlling infection (71). Under normal conditions, inflammatory responses are tightly regulated and confined to the infection site. After infection is resolved, inflammation subsides, and PMNs undergo apoptosis and are cleared. However, during sepsis, systemic inflammation causes PMN polarization. The chemotaxis and migration functions of PMNs are impaired, leading to a reduced number of PMNs at the infection site (source site) and increased PMN infiltration in distant vital organs (72). Activated PMNs in organs release proinflammatory cytokines, ROS, lysosomal enzymes, NETs and other active substances, resulting in cell, tissue and organ damage and ultimately leading to MODS (73). A previous study has reported that ROS produced by polarized PMNs during sepsis can damage various organs, including the heart, kidneys, liver and lungs, through multiple mechanisms, contributing to the development of MODS (74). Moreover, activated PMNs are significant sources of matrix metalloproteinases (MMPs), particularly MMP-9, which can degrade extracellular matrix proteins such as elastin and collagen. This degradation can stimulate the immune system and create a positive feedback loop of tissue degradation and immune cell infiltration, further exacerbating organ damage at infiltration sites (75). Substances released by PMNs also stimulate the production of NO by various cells, leading to blood pressure reduction and the generation of peroxynitrite, which causes cellular damage. In sepsis-induced myocardial injury, peroxynitrite can alter protein structure and function, causing PMNs to adhere to and accumulate in the endothelium and myocardium, ultimately resulting in cardiovascular dysfunction (76). Additionally, ROS, NETs and lysosomal enzymes released by polarized PMNs can act as damage-associated molecular patterns (DAMPs), causing endothelial injury and increased vascular permeability. DAMPs can also activate immune cells, including macrophages, triggering uncontrolled inflammatory responses. The release of inflammatory factors results in the recruitment of more PMNs, further stimulating the excessive production of NETs and ROS and creating a

positive feedback loop that exacerbates organ damage. These harmful substances contribute to vascular injury and death in organs, eventually leading to organ failure. During the development of sepsis-induced lung injury, increased PMN infiltration promotes bacterial translocation in the lungs, exacerbating ROS production and worsening lung damage (77). The progression of MODS in sepsis significantly increases patient mortality, making the protection of organ function a critical strategy for improving sepsis outcomes, with the regulation of immune cell function being a key factor.

8. Protective mechanism of DEX on important organs

Current research indicates that DEX has a protective effect on sepsis-induced multiorgan dysfunction, as follows:

Lung injury. Sepsis often leads to multiple organ injuries, with lung injury being particularly prevalent, occurring in 83-100% of cases (78). The lipopolysaccharide (LPS)-induced inflammatory response and oxidative stress through the regulation of inflammatory pathways such as MAPK and TLR4, as well as the oxidative stress pathway Nrf2/heme oxygenase-1 (HO-1), are the primary causes of lung injury, and sepsis-induced alveolar cell pyroptosis and ferroptosis through the regulation of pyroptosis pathways such as the NLRP3 pathway, as well as the ferroptosis pathway SLC7A11/glutathione peroxidase 4 (GPX4), are also involved in acute lung injury (Fig. 3) (78). Research has shown that inhibiting the high mobility group protein box-1 (HMGB1)/myeloid differentiation factor-88 (MyD88)/NF-κB pathway and NLRP inflammasome activation induced by cecal ligation and puncture (CLP) can reduce CLP-induced lung inflammation and alveolar cell pyroptosis and ameliorate sepsis-induced acute lung injury (79), and increasing the activity of the Nrf2/HO-1 pathway can reduce LPS-induced oxidative stress and inflammation in alveolar cells and ameliorate sepsis-induced acute lung injury (80,81). Therefore, inhibitors of sepsis-induced alveolar cell inflammation, oxidative stress, pyroptosis and ferroptosis may help improve sepsis-induced lung injury. Wu *et al* (82) demonstrated that DEX inhibits the expression of Toll-like receptor 4 (TLR4), a molecule associated with endotoxin recognition, and the activation of the nuclear transcription factor NF-κB. This inhibition reduces TNF-α and IL-6 levels in alveolar lavage fluid and plasma, significantly decreasing the fatality rate in CLP-induced septic rats within 24 h. Additionally, DEX attenuates LPS-induced acute lung injury in rats by inhibiting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/forkhead box O1 (FoxO1) signaling pathway and mitigating oxidative stress, mitochondrial dysfunction and apoptosis (83). DEX also reduces oxidative stress and inflammation in alveolar cells and maintains the balance of mitochondrial dynamics through the HIF-1α/HO-1 signaling pathway, thereby ameliorating endotoxin-induced acute lung injury both *in vivo* and *in vitro* (84). Furthermore, DEX inhibits the secretion of inflammatory mediators such as TNF-α, IL-6, IL-1β and NO by alveolar cells via the HMGB1-mediated TLR4/NF-κB and PI3K/Akt/mammalian target of rapamycin (mTOR) pathways, increases the production of the antioxidant stress markers SOD and glutathione peroxidase, and alleviates LPS-induced lung injury by reducing inflammation and oxidative stress (85). A previous study indicated that DEX maintains endothelial barrier integrity by reducing angiopoietin 2 (ANG2) levels and increasing endothelial VE-cadherin in rats with CLP-induced sepsis, thereby mitigating lung inflammation (86,87). The Ang-tyrosine kinase receptor 2 (Tie2) axis is a well-studied pathway that regulates endothelial barrier function. Ang1 binds to and activates angiopoietin Tie2 receptors, upregulating VE-cadherin to stabilize the cell barrier. Conversely, ANG2 competes with Tie2 receptors, antagonizing the anti-inflammatory effects of Ang1, leading to barrier damage and endothelial cell activation, which induces inflammation (87). DEX reduces the wet/dry weight ratio of lung tissue, leukocyte infiltration, plasma ANG2 levels and ANG2/ANG1 ratios and decreases VE-cadherin phosphorylation through the ANG1-Tie2-VE-cadherin signaling pathway, thereby alleviating endothelial barrier damage and lung injury in septic rats (87). Additionally, DEX ameliorates sepsis-induced acute lung injury by modulating the adenosine monophosphate-activated protein kinase (AMPK)/silent information regulator 1 (SIRT1) pathway (88). These data suggest that DEX improves sepsis-induced lung injury by inhibiting multiple proinflammatory and oxidative stress pathways. However, these studies remain in the animal experimentation stage, and further research is needed to explore their clinical applications.

Kidney injury. The kidney is a primary target organ in sepsis (89). Acute kidney injury (AKI) manifests as progressively worsening renal function, severe oliguria and fluid overload, often necessitating renal replacement therapy. This condition not only increases hospitalization and treatment costs but also severely impacts patient prognosis. The pathophysiological process of sepsis-induced AKI remains poorly understood, and effective prevention and treatment measures are lacking in clinical settings. Studies have revealed that the pathogenic mechanisms of sepsis-induced AKI are complex, involving LPS-induced inflammation, microcirculatory disorders and oxidative stress by regulating inflammatory pathways, such as TLR4 and MAPK, as well as oxidative stress-related pathways, such as Nrf2, NADPH oxidase 4 (NOX4) and P13k/Akt, with inflammation being a pivotal factor (Fig. 4) (89,90). Research has shown that inhibiting the activity of the TLR4/MyD88/NF-κB signaling pathway can inhibit LPS-induced kidney inflammation and improve sepsis-induced AKI in mice (91) and that decreasing NLRP3 inflammasome activation can alleviate LPS-induced tubular cell inflammation and pyroptosis and ameliorate LPS-induced kidney injury (92). The inhibition of NOX4 protects against sepsis-induced AKI by reducing the generation of ROS and the activation of NF-κB signaling, which suppresses mitochondrial dysfunction, oxidative stress, inflammation and apoptosis (93). Therefore, inhibiting inflammation and oxidative stress and improving renal microcirculation may help alleviate sepsis-induced AKI. Liu *et al* (94) investigated the immunomodulatory effects of DEX on sepsis-related AKI induced by tail vein injection of LPS in rats at doses of 3, 5, 10 and 20 μg/kg iv. DEX was found to reduce inflammatory cytokine levels in a dose-dependent manner. The addition of the α2 adrenergic receptor antagonist yohimbine negated the regulatory effect of DEX on cytokine production, confirming its anti-inflammatory role as an

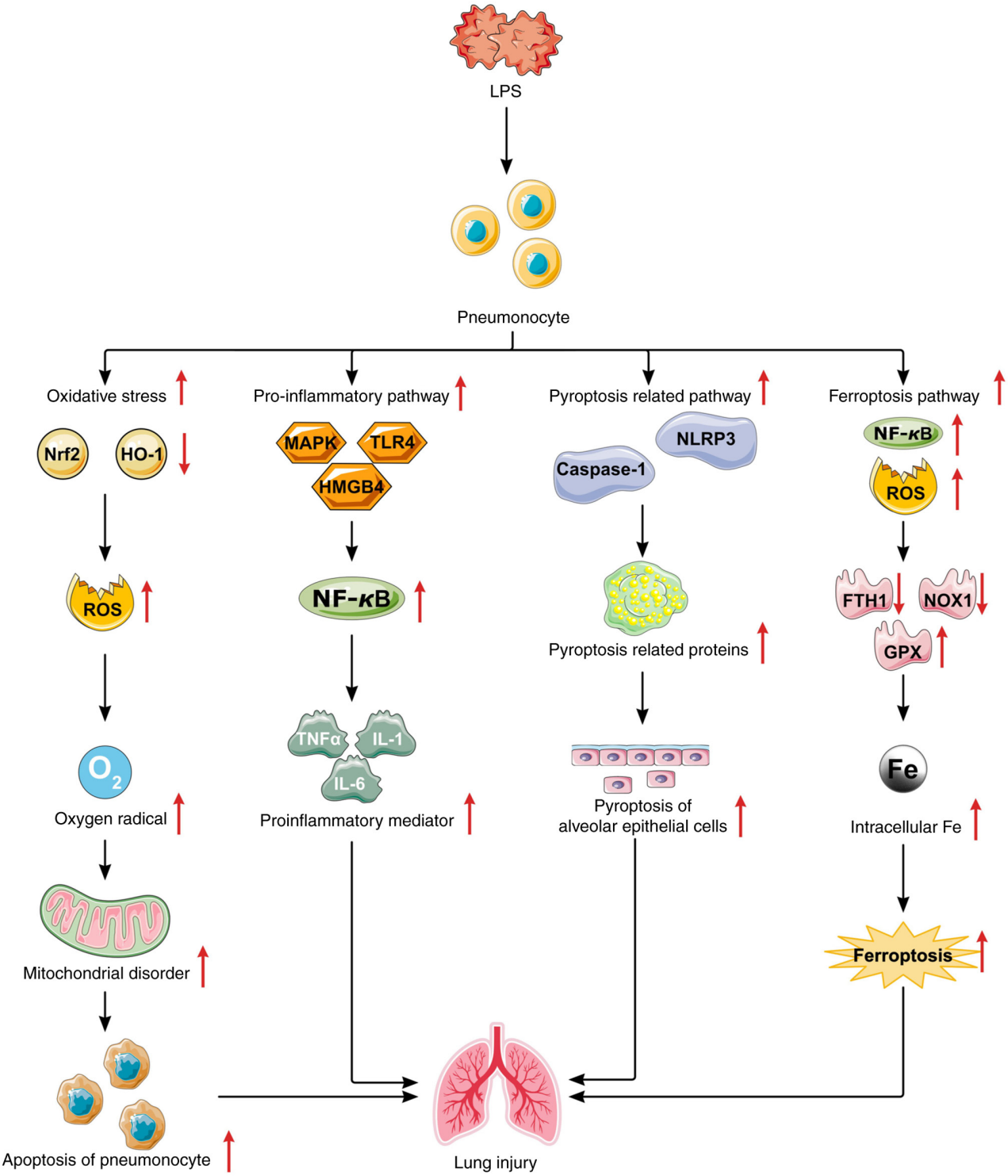

Figure 3. Mechanisms of sepsis-induced lung injury. LPS regulates oxidative stress and mitochondrial dysfunction by modulating the Nrf2/HO-1 signaling pathways; regulates lung inflammation by modulating the MAPK, TLR4 or HMGB1/NF-κB signaling pathways; regulates lung inflammation by modulating the MAPK or TLR4 or HMGB1/NF-κB signaling pathways; and regulates alveolar cell pyroptosis by modulating the NLRP3/caspase-1 signaling pathway and regulates alveolar cell ferroptosis by modulating the NF-κB/ROS/GPX4 signaling pathway. LPS, lipopolysaccharide; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; TLR4, Toll-like receptor 4; HMGB1, high mobility group protein box-1; NLRP3, NOD-like receptor family pyrin domain containing 3; NF-κB, nuclear factor κB.

α2 adrenergic receptor agonist. Jin *et al* (95) established a sepsis-related AKI model in rats via LPS induction. The DEX group received 80 mg/kg DEX daily starting 4 days before modeling. The results indicated that DEX downregulates TLR4 protein expression, inhibits MyD88 and NF-κB activation, and causes expression of inducible NO synthase (iNOS), thereby suppressing inflammatory factor production. These findings indicate that DEX may reduce inflammation by inhibiting the TLR4/MyD88/NF-κB/iNOS signaling pathway and attenuating LPS-induced NLRP3 inflammasome activation through

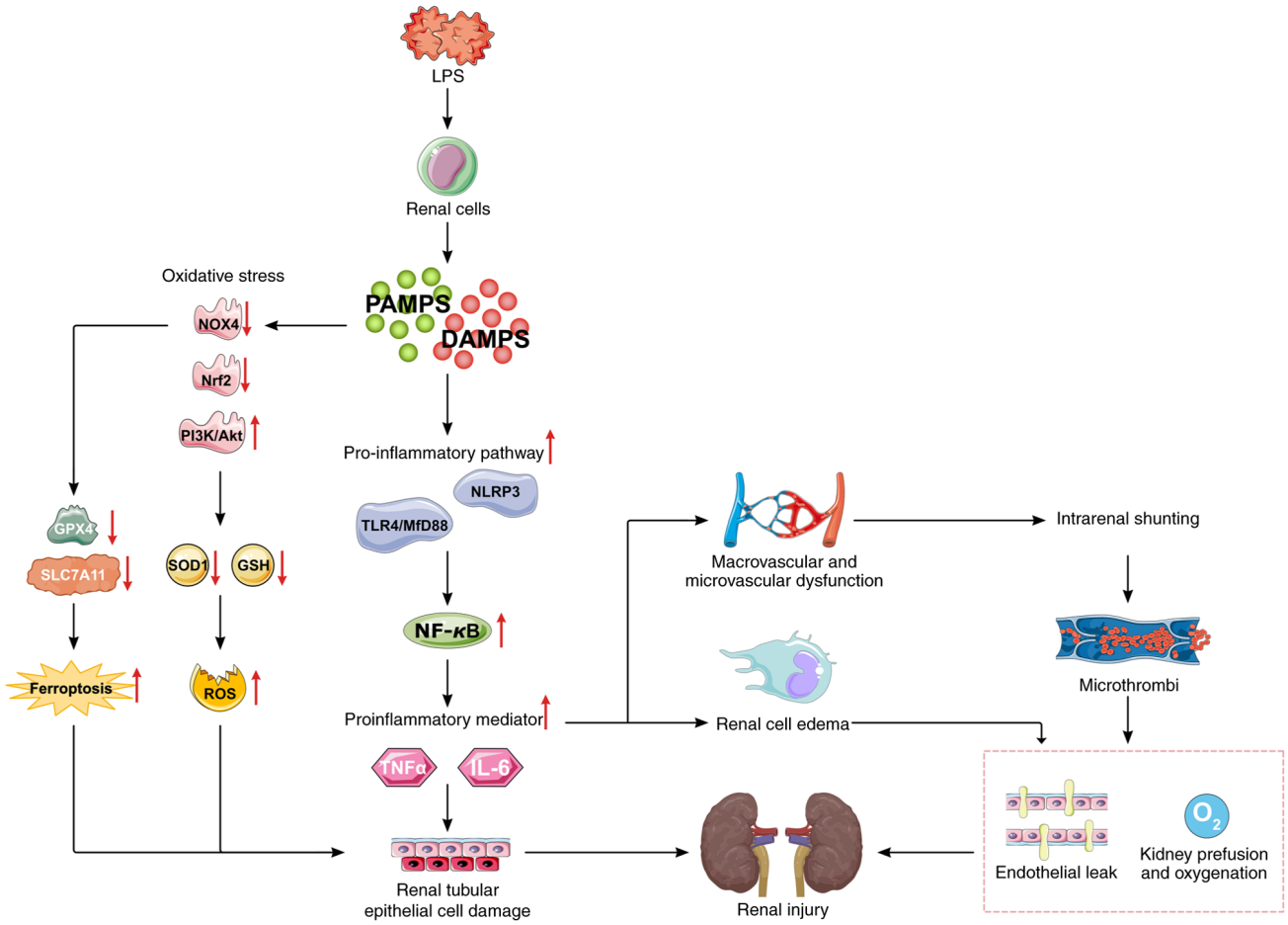

Figure 4. Mechanisms of sepsis-induced kidney injury. LPS regulate kidney inflammation by modulating the NLRP3/NF-κB or TLR4/Myd88/NF-κB signaling pathways; regulate oxidative stress and ferroptosis by modulating the NOX4, Nrf2 or PI3K/Akt signaling pathways; and LPS-induced inflammatory mediators can lead to renal microcirculation disorders, renal hypoperfusion, ischemia and hypoxia and exacerbate sepsis-induced kidney injury. LPS, lipopolysaccharide; PAMPS, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; NLRP3, NOD-like receptor family pyrin domain containing 3; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation factor 88; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; NOX4, NADPH oxidase 4; ROS, reactive oxygen species; SOD, superoxide dismutase; GSH, glutathione; GPX4, glutathione peroxidase 4.

the TLR4/NOX4/NF-κB pathway, thereby mitigating oxidative stress (96). Wang *et al* (97) investigated an inflammatory proximal tubular epithelial cell model and an LPS-induced sepsis-related AKI model in mice. The results revealed that DEX significantly increased SOD activity in renal tissue, decreased the production of the lipid peroxidation product MDA, inhibited ROS production in renal tubular epithelial cells, and ameliorated sepsis-induced AKI. Zhao *et al* (98) pretreated an LPS-induced sepsis-related AKI model in rats with ip DEX at 30 μg/kg and discovered that DEX enhanced autophagy through α2 adrenergic receptors and inhibited the PI3K/Akt/mTOR pathway, leading to the CL of damaged mitochondria and a reduction in oxidative stress and apoptosis in LPS-induced AKI. The use of autophagy inhibitors, such as AT2 receptor-interacting proteins and 3-methyladenine, blocked the reno-protective effect of DEX, suggesting that regulating autophagy is crucial in the pathogenesis of LPS-induced AKI. By modulating renal autophagy, DEX improved oxidative stress and cell apoptosis. These studies demonstrate the protective effects of DEX on the kidney through various signaling pathways. However, since most experiments are based on animal models and the mechanisms of action have not yet been fully elucidated, further research is necessary.

Liver injury. Endotoxin-induced liver failure is the second leading cause of multiple organ failure (99). Sepsis-induced hepatic injury resulting from endotoxin induces inflammation, hepatic blood flow alterations, microcirculatory disturbances and mitochondrial dysfunction by regulating inflammatory pathways, such as the MAPK and TLR4 pathways, and oxidative stress- and ferroptosis-related pathways, such as the Nrf2/HO-1 pathways (Fig. 5) (99,100). Hepatic sinusoidal cells are the initial sites of liver injury. The macrophages (KCs) within these sinusoids are pivotal in the inflammatory process and endotoxin-mediated hepatic injury (101). High doses of LPS provoked KC overactivation and reduced phagocytic capacity while increasing CD14 expression on KC surfaces. The LPS receptor/signaling complex, which is composed of TLR4, CD14 and MD2, further activates KCs, releasing a cascade of proinflammatory mediators that exacerbate endotoxin-induced hepatic damage (102). Thus, inflammation is central to sepsis-induced liver injury. Suppressing this inflammation may mitigate acute hepatic injury in sepsis. Studies on septic murine liver tissue revealed that DEX mitigates portal venous and sinusoidal congestion, reduces hepatic sinusoidal swelling, and decreases lymphocyte and neutrophil infiltration in the liver hilum, effectively curbing

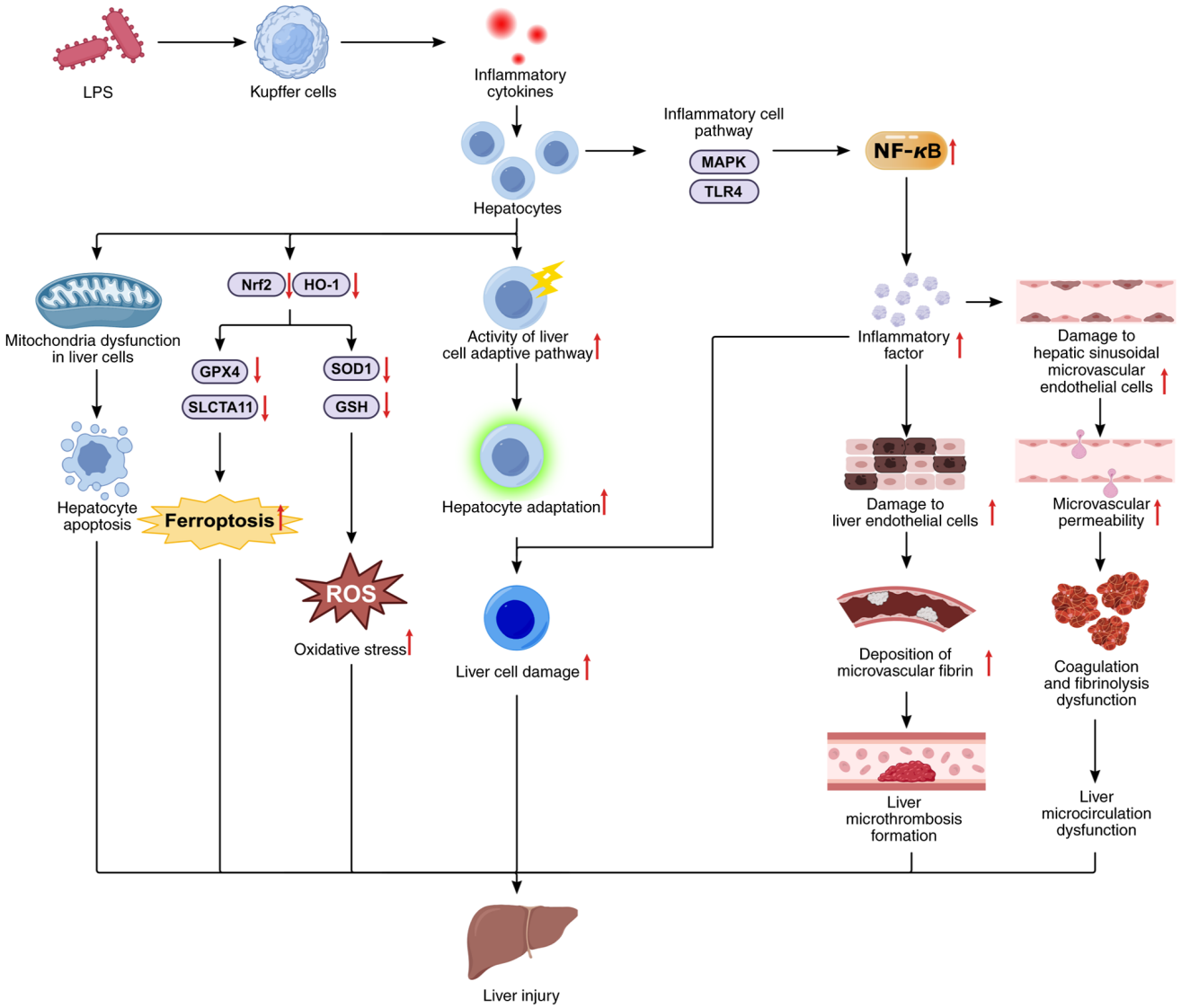

Figure 5. Mechanism of sepsis-induced liver injury. LPS regulate liver cell inflammation by modulating the MAPK/NF-κB and TLR4/NF-κB signaling pathways; regulate liver cell oxidative stress and ferroptosis by modulating the Nrf2/HO-1 signaling pathways; and LPS-induced inflammatory mediators can lead to endothelial cell damage, microcirculation disorders, adaptive pathway activity in liver cells, and exacerbated sepsis-induced liver injury. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation factor 88; NLRP3, NOD-like receptor family pyrin domain containing 3; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; NOX4, NADPH oxidase 4; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; SOD, superoxide dismutase; GSH, glutathione; GPX4, glutathione peroxidase 4; NF-κB, nuclear factor-kappa B.

hepatic inflammation (103). DEX has been demonstrated to prevent acute hepatic injury in LPS-induced septic rats by inhibiting the TLR4/MyD88/NF-KB pathway. Additionally, DEX modulates caveolin-1, inhibits the TLR4/NLRP3 pathway, and curtails proinflammatory cytokine release, thus alleviating sepsis-induced hepatic injury (104,105). Furthermore, autophagy in the liver is crucial for maintaining cellular energy and nutrient balance, clearing damaged hepatic proteins, and counteracting oxidative stress (106). Research conducted by Yu *et al* (106) indicated that DEX potentially enhances autophagy via the SIRT1/AMPK pathway, mitigating inflammation in CLP-induced liver injury and increasing the survival rate of model mice by 20% within 24 h. LPS induces liver damage through apoptosis mediated by ROS. DEX activates the GSK-3β/MKP-1/Nrf2 pathway via the α2-adrenergic receptor, diminishing LPS-induced oxidative stress and apoptosis in the rat liver and thereby ameliorating sepsis-induced liver injury (107). DEX pretreatment facilitates M2 macrophage activation through PPARγ/STAT3 signaling, reducing liver inflammation and alleviating ischemia-reperfusion injury in mice (108). This evidence indicates that DEX confers protection against sepsis-induced liver injury by modulating inflammation, apoptosis, autophagy, and ferroptosis-related pathways and proteins. However, these findings are confined to animal research, and clinical validation is needed.

Myocardial injury. Epidemiological studies indicate that the global mortality rate of sepsis remains high and is gradually increasing (109). The heart is the organ most frequently affected during sepsis. It has been revealed that 40-60% of septic patients suffer from myocardial injury, with a fatality rate of 70-90%, which correlates positively with the severity of the injury (110). The extensive inflammation and 'cytokine storm' associated with sepsis lead to ischemia, oxidative stress,

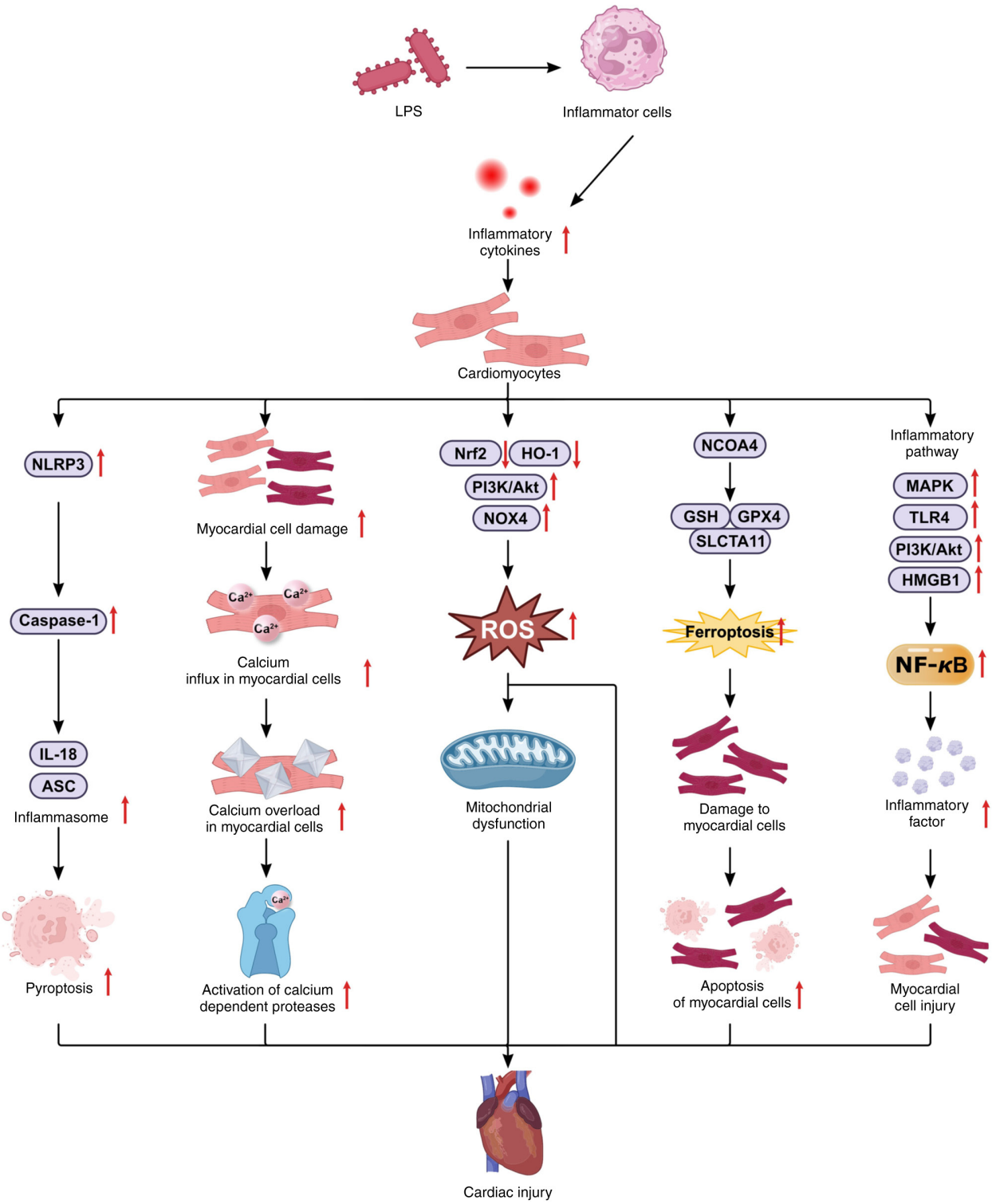

Figure 6. Mechanisms of sepsis-induced myocardial injury. LPS regulate cardiomyocyte inflammation by modulating the MAPK/NF-κB, MGB1/TLR4/NF-κB, and P13K/Akt/NF-κB signaling pathways; regulate liver cell oxidative stress and ferroptosis by modulating the Nrf2/HO-1 signaling pathways; regulate cardiomyocyte pyroptosis by modulating the NLRP3/caspase-1 signaling pathways; and regulate cardiomyocyte oxidative stress by modulating the Nrf2/HO-1, P13K/Akt, and NOX4 signaling pathways. In addition, LPS-induced inflammatory mediators can lead to calcium influx, and calcium overload in myocardial cells exacerbates sepsis-induced cardiac injury. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; MyD88, Myeloid differentiation factor 88; NLRP3, NOD-like receptor family pyrin domain containing 3; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; NOX4, NADPH oxidase 4; HO-1, heme oxygenase 1; ASC, apoptosis-associated speck-like protein; NCOA4, nuclear receptor coactivator 4; GSH, glutathione; GPX4, glutathione peroxidase 4; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species.

pyroptosis, ferroptosis, and hypoxic damage to myocardial cells by regulating pathways related to pyroptosis and inflammation, such as NLRP3 and MAPK, as well as pathways related to oxidative stress and iron death, such as Nrf2/HO-1 and NCOA4/GPX4 (Fig. 6), resulting in a significantly higher mortality rate than that in septic patients without myocardial

injury. Long-term prognosis studies have also shown that survivors of sepsis-induced myocardial injury experience markedly reduced quality of life (111). Previous studies have identified that the activation of Nrf2/HO-1 and the inhibition of the NLRP3 signaling pathway can inhibit LPS-induced inflammation and oxidative stress; protect cardiomyocytes against LPS-induced injury (112); suppress NLRP3-mediated pyroptosis via the upregulation of the Nrf2/HO-1 signaling pathway *in vivo* and *in vitro*; decrease oxidative stress, inflammatory responses and NLRP3-mediated pyroptosis; and reduce LPS-induced myocardial injury (113,114). Thus, mitigating sepsis-related inflammation may alleviate myocardial injury and reduce mortality (115). In experimental mice treated with DEX, the incidence of septic shock was lower, and the plasma levels of the inflammatory factors TNF-a, IL-1β and IL-6 were significantly lower. Additionally, NF-κB binding activity was downregulated, increasing survival rates (116,117). In LPS-induced septic heart injury in rats, DEX appears to confer cardioprotective effects by diminishing the expression of NF-κB p65 and phosphorylated STAT3, thereby inhibiting the expression of the apoptotic proteins Caspase-3, Caspase-8, Bax and p53 and the inflammatory factors IL-6, IL-1β and TNF-α (118). DEX also inhibits GPX4 expression, upregulates HO-1, and reduces sepsis-induced cardiomyocyte ferroptosis and myocardial injury in mice (119). Compared with pre-surgery, the administration of varying doses of DEX to septic patients significantly decreased the levels of inflammatory factors such as IL-1, IL-6 and TNF-α within 24 h post-surgery. Moreover, high, medium, and low doses of DEX maintain and enhance cardiac function, significantly mitigating the adverse effects of inflammatory mediators on the heart (120). Despite substantial progress in understanding the myocardial protective effects of DEX, the underlying mechanisms remain incompletely elucidated, necessitating further research.

Gastrointestinal injury. Late-stage sepsis often progresses to MODS, a primary cause of mortality in ICU patients (121). As the body's largest 'bacteria reservoir' and 'endotoxin reservoir', the gastrointestinal tract is among the first and most severely impacted organs in the pathophysiological progression of sepsis (122). Sepsis results in the generation of substantial amounts of endotoxins and inflammatory mediators that compromise the gastrointestinal mucosal barrier, increase mucosal permeability, and promote intestinal bacterial translocation. Consequently, numerous bacteria and endotoxins infiltrate the bloodstream via lymphatic and capillary pathways, instigating a 'secondary infection' and triggering entheogenic endotoxemia. This can elicit unrestrained inflammatory responses, exacerbate intestinal damage, create a vicious cycle, and potentially advance to MODS, resulting in fatality (122,123). Hence, prompt evaluation of gastrointestinal function and early intervention in sepsis patients are essential to mitigate damage and improve patient prognosis. As shown in Table I (124-131), DEX ameliorates ischemia/reperfusion, LPS and CLP-induced intestinal injury in rats by suppressing TLR4, p38 MAPK/NF-κB SIRT3-dependent PINK1/HDAC3/p53, and alpha2AR/caveolin-1/p38MAPK/NF-κB signaling pathways in intestinal tissue; increasing ZO-1 and occludin expression; decreasing inflammatory cytokine levels and MLCK protein expression; and increasing intestinal permeability resulting from burns with concurrent histological damage. However, deep sedation with DEX, unlike propofol, significantly suppresses gastrointestinal motility in endotoxemic mice, an effect that dissipates after 24 h of sedation (131). These results indicate that while DEX has protective effects against intestinal barrier dysfunction, its administration in sepsis and intestinal paralysis requires careful consideration.

Brain injury. During sepsis, various inflammatory mediators and endotoxins damage capillary endothelial cells, resulting in leakage, inflammatory damage and tight junction dysfunction. This compromises the blood-brain barrier, permitting systemic inflammation and neurotoxic mediators to infiltrate the brain, leading to sepsis-associated brain injury (Fig. 7) (132). Following central nervous system damage, microglia are activated, proliferate rapidly, polarize, migrate to the injury site, and secrete proinflammatory factors such as IL-1β and TNF-α (133), which further degrade the blood-brain barrier, perpetuating microglial activation in a vicious cycle that exacerbates neuronal damage (Fig. 7). Mitigation of microglial activation is crucial for ameliorating sepsis-induced brain injury. Research indicates that DEX attenuates neuroinflammation in LPS-stimulated BV2 microglia by upregulating miR-340 (134) and modulates neuroinflammation and microglial activation through the circ-Shank3/miR-140-3p/TLR4 axis (135). Additionally, DEX inhibits the TLR4/MyD88/NF-κB signaling pathway, reducing the expression of inflammatory factors, such as TNF-α, thereby protecting against ischemia-reperfusion injury (126). By inhibiting MAPK and NF-κB activation, DEX decreases TNF-α and IL-1β levels, shielding brain tissue from inflammatory damage (136). It also enhances microglial M2 polarization by inhibiting ERK1/2 phosphorylation, exerting anti-inflammatory effects in BV2 cells (137). Consequently, DEX mitigates sepsis-induced brain injury through multiple mechanisms. Current research on the protective mechanisms of DEX against sepsis-induced injury has focused primarily on animal and cell studies. Extensive clinical research is necessary to validate these findings and establish a theoretical foundation for the clinical treatment of sepsis-induced injury.

Modulating the proinflammatory/anti-inflammatory imbalance. Sepsis involves hyperinflammation and acquired immunosuppression (Fig. 8). Multiple studies (138-140) have indicated immune dysregulation during sepsis. Initially, infection triggers an immune response, leading to the extensive production of inflammatory factors and consequent immune stress, exacerbating organ injury. As sepsis progresses, there is a decline in lymphocyte subsets, further intensifying inflammation. This period is characterized by concurrent immunosuppression and inflammation, which mutually exacerbate sepsis. Thus, immune regulation is pivotal in sepsis treatment. Research on DEX, a novel sedative in sepsis, is expanding, although studies on its impact on immune dysfunction are limited. Wang *et al*'s meta-analysis (52) demonstrated that intraoperative DEX infusion is correlated with i) reduced plasma levels of epinephrine, norepinephrine and cortisol; ii) increased NK cells, B cells and CD4 cells; decreased $CD8^+$ T cells; iii) elevated $CD4^+CD8^+$ and Th1:Th2

Table I. Study on the protective mechanism of DEX against intestinal injury caused by sepsis.

First author, year	Object of study	Dosage of DEX	Effect	Regulatory mechanism of the intestine injury	(Refs.)
Chen *et al*, 2015	CLP-ICLP-induced intestinal injury	5 μg x kg^{-1} x h^{-1}	Reducing systemic inflammation and alleviating CLP- induced intestinal tissue damage	Suppressing TLR4 expression in intestinal tissue, curtailing inflammatory mediators	(124)
Qin *et al*, 2021	Burn-induced intestinal barrier damage	5 μg x kg^{-1} x h^{-1}	Decrease in intestinal permeability and histological damage to the intestine	Anti-inflammatory effect and protected tight junction complexes by inhibiting the MLCK/ p-MLC signaling pathways	(125)
Yang *et al*, 2021	Intestinal ischemia/ reperfusion injury	5 μg x kg^{-1} x h^{-1}	Reduce intestinal I/R injury in rats and OGD/R damage in Caco-2 cells	Attributed to anti-inflammatory effects and inhibition of the TLR4/MyD88/NF-κB signaling pathway	(126)
Ye *et al*, 2022	DSS-induced colitis mice	5 μg x kg^{-1} x h^{-1}	Improve weight loss, shortening of the colon, increased DAI score, histological abnormalities	Reduces colonic inflammation and intestinal epithelial cell apoptosis by inhibiting the p38 MAPK/NF- κB signaling pathway	(127)
Zhang *et al*, 2021	Rat model of intestinal I/R injury	2.5 μg x kg^{-1} x h^{-1} and 5 μg x kg^{-1} x h^{-1}	Protection against experimentally induced intestinal I/R injury	Suppresses apoptosis of EGCs through SIRT3-mediated PINK1/HDAC3/p53 pathway	(128)
Dong *et al*, 2022	Mice model of intestinal I/R injury	5 μg·kg^{-1} x h^{-1}	Alleviate intestinal I/R injury	Reverses I/R-induced bacterial abnormalities	(129)
Xu *et al*, 2021	Rat model of intestinal I/R injury	5 μg x kg^{-1} x h^{-1}	Protection against lung injury following intestinal ischemia-reperfusion	Ca^{2+}-regulating alpha 2AR/Caveolin-1/ p38MAPK/NF-kappa-B axis	(130)
Chang *et al*, 2020	LPS-induced intestinal injury in mice	80 μg x kg^{-1}	Inhibits gastrointestinal motility disorder	Markedly inhibits gastric emptying, small intestinal transit, colonic transit, gastrointestinal transit and the whole gut transit	(131)

DEX, dexmedetomidine; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; CLP, cecal ligation and puncture; OGD/R, oxygen-glucose deprivation/reoxygenation; DAI, disease activity index; p38MAPK, p38 mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; EGCs, enteric glial cells; MLCK, Myosin light chain kinase; p-MLC, phosphorylated myosin light chain; MyD88, myeloid differentiation factor-88; SIRT3, Sirtuin-3; PINK1, PTEN-induced putative kinase 1; HDAC3, histone deacetylase 3.

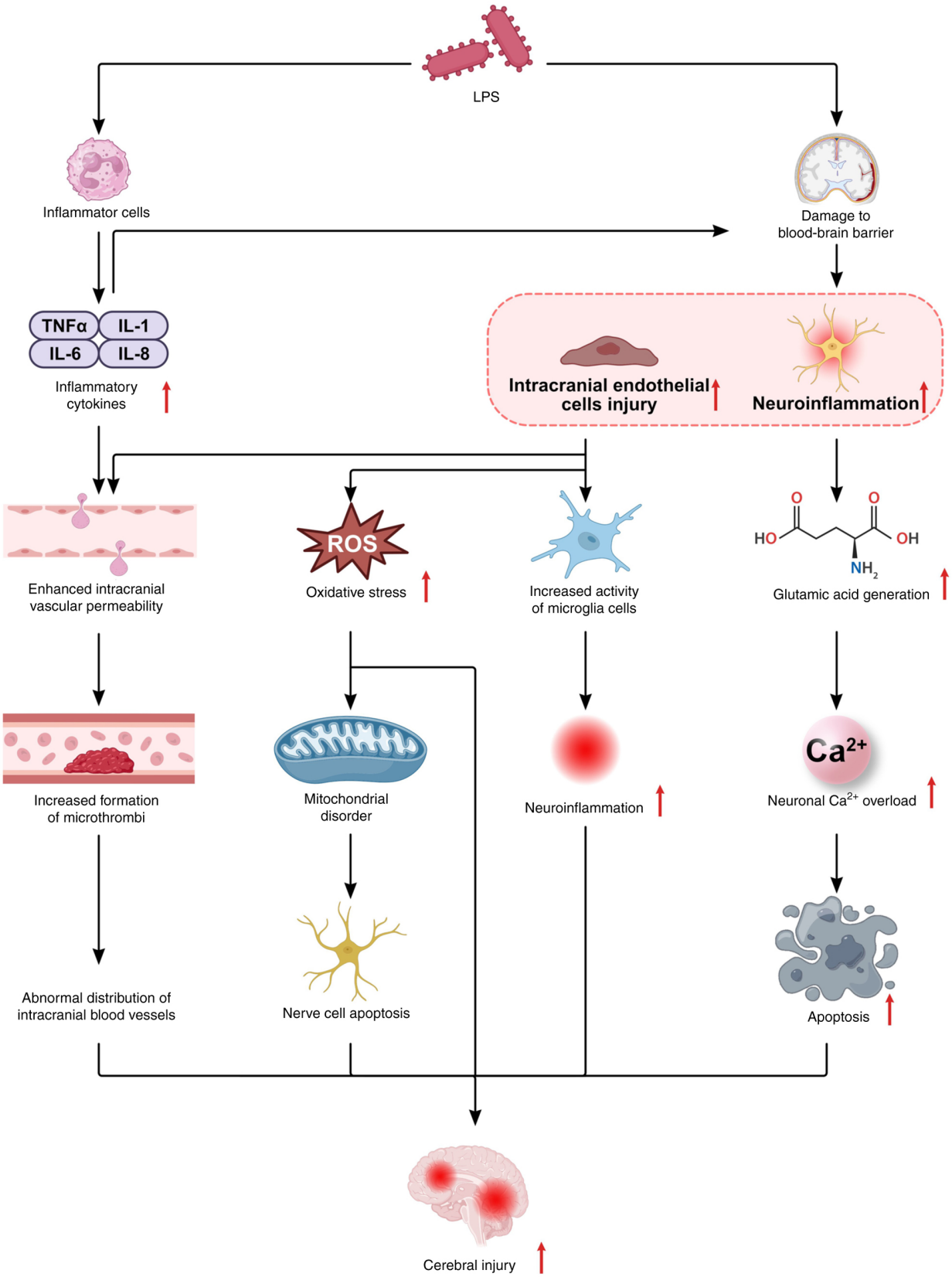

Figure 7. Mechanisms of sepsis-induced brain injury. Endotoxins enter the brain by damaging the blood-brain barrier, activating microglia and leading to neuroinflammation. During sepsis, various inflammatory mediators and endotoxins damage capillary endothelial cells, resulting in leakage and inflammatory damage. Neuroinflammation can lead to oxidative stress in nerve cells, mitochondrial dysfunction, and neuronal apoptosis. Neuroinflammation can increase glutamate production and increase calcium influx into nerve cells, leading to mitochondrial dysfunction and neuronal apoptosis. LPS, lipopolysaccharide; ROS, reactive oxygen species.

ratios; iv) reduced TNF-α and IL-6; and increased IL-10. The Th1/Th2 helper T-cell 2 (Th2) and helper T-cell 17 Th17/regulatory T-cell (Treg) ratios reflect immune response dynamics. In patients under surgical and anesthesia stress,

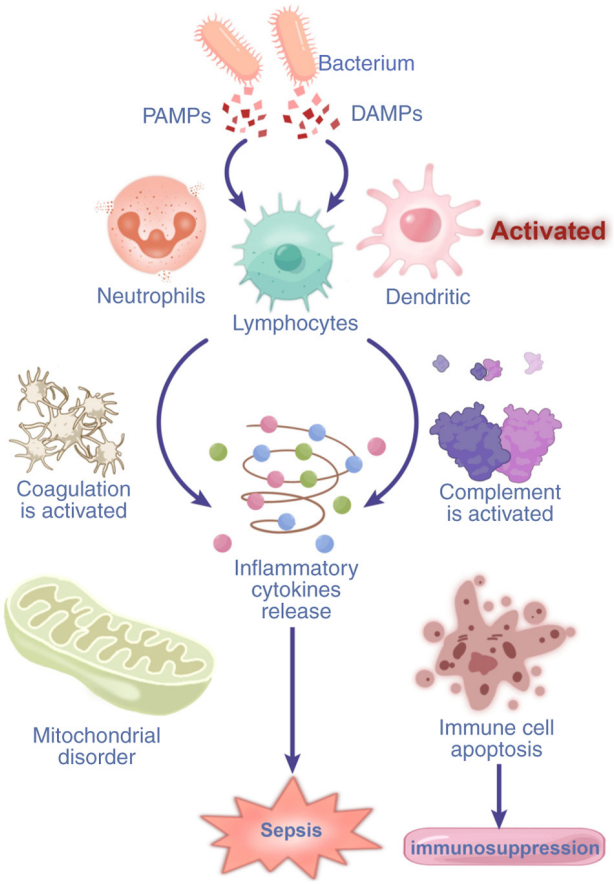

Figure 8. Impact of pathogenic microorganisms on inflammation and immune suppression. During sepsis, endotoxins produced by pathogenic microorganisms stimulate neutrophils, dendritic cells and lymphocytes, producing large amounts of inflammatory cytokines and complement, leading to sepsis, mitochondrial dysfunction and activation of the coagulation system. Moreover, inflammatory cytokines can induce the apoptosis of immune cells, leading to immune suppression. PAMPS, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns.

DEX elevates the IFN-γ to IL-4 and IL-17 to IL-10 ratios, shifting the Th1/Th2 and Th17/Treg cytokine balance toward Th1 and Th17 in an alcohol-dependent manner and resulting in immunomodulatory effects (141). DEX effectively increases $CD3^+$, $CD4^+$ and NK cells and $CD4^+/CD8^+$ levels in patients undergoing radical mastectomy for breast cancer, maintaining cellular immune function homeostasis (142). These studies reveal that DEX possesses anti-inflammatory properties and enhances cellular immunity, making it suitable for septic patients with immunosuppression.

Maintaining hemodynamics. DEX inhibits norepinephrine neuron activity in the locus coeruleus through negative feedback, suppresses sympathetic nerve excitation, and lowers blood catecholamine levels. This stabilizes the intraoperative circulatory status and minimizes the hemodynamic fluctuations induced by surgical trauma and painful stimulation (143,144). Norepinephrine is the preferred vasopressor for restoring mean arterial pressure in septic patients. Refractory septic shock often necessitates higher doses of norepinephrine to maintain blood pressure. However, in sepsis-related AKI, norepinephrine-induced blood pressure restoration exacerbates renal medullary hypoperfusion and hypoxia (145). DEX enhances responsiveness to exogenous vasopressors (146). The results of the present study are shown in Table II (11,117,147-151). DEX significantly reduced catecholamine requirements, halved the required norepinephrine dose, prevented further renal medullary hypoperfusion and hypoxia, and progressively improved creatinine CL, potentially through an enhanced vascular response to catecholamines and angiotensin II. Thus, DEX reduces the norepinephrine dosage in septic patients and is suitable for anesthesia and sedation in severe sepsis and septic shock patients. Nonetheless, large, randomized trials are needed to confirm whether DEX consistently reduces the norepinephrine dosage in septic patients.

Regulating endothelial cells. During sepsis, the activation and dysfunction of vascular endothelial cells result in leukocyte chemotaxis, inflammatory outbreaks, microcirculatory disturbances and altered vascular permeability (Fig. 9) (152). Endothelial cell damage leads to intermittent or complete cessation of capillary blood flow, reducing capillary density and causing nonuniform organ perfusion (153). This endothelial damage-induced microcirculatory disorder results in tissue hypoxia and abnormal cellular oxygenation despite adequate organ blood supply, precipitating organ dysfunction (154). The results of the present study are shown in Table III (87,155-160). Dex pretreatment effectively decreased EC inflammation, apoptosis and hypoxia/reoxygenation injury by inhibiting the DUSP1/MAPK/NF-κB, HMGB1/TLR4/NF-κB, MAPK and angiopoietin II signaling pathways. These studies indicate that DEX protects endothelial barrier function; mitigates sepsis-induced inflammation, microcirculatory disturbances and vascular permeability; and exerts protective effects on vital organs such as the brain, lungs, heart and kidneys during sepsis.

Reducing postoperative arrhythmias. DEX mitigates postoperative arrhythmias through its antisympathetic effects. Perioperative administration of DEX [with or without a loading dose of 0.2-1.5 μg/kg or an intraoperative maintenance dose of 0.2-1.5 μg/(kg x h)] has been shown to decrease the incidence of atrial fibrillation following cardiac surgery (161), although it may increase the risk of bradycardia (162). A previous large multicenter randomized controlled trial indicated that a lower dose of DEX [0.1-0.4 μg/(kg x h)] as a continuous infusion for 24 h from the induction of anesthesia did not reduce atrial arrhythmias post-cardiac surgery (163). The efficacy of DEX in managing postoperative atrial arrhythmias in septic patients remains controversial and warrants further investigation.

Alleviating brain injury related to general anesthetics. Neurotoxicity associated with general anesthetic drugs is a significant concern. Animal studies have demonstrated that exposure to general anesthetics can induce structural and functional changes in the developing brain, leading to the apoptosis of neurons and glial cells (164,165). The results of the present study are shown in Table IV (166-176). DEX reduced the serum levels of IL-6, TNF-α, MDA and S100β neuron-specific enolase, whereas SOD levels significantly increased 24 h post-surgery, decreased the incidence of postoperative delirium from 23-9%, reduced postoperative agitation within 3 days, inhibited caspase-3 expression in certain cortical and

Table II. Studies on the effects of DEX on sepsis-induced hemodynamics.

First author, year	Object of study	Dosage of DEX	Effect	Regulatory mechanism of the hemodynamics	(Refs.)
Morelli *et al*, 2019	Patients with septic shock	0.7 μg/kg x h	Significantly reducing catecholamine. requirements	Inhibits norepinephrine neuron activity in the locus coeruleus.	(147)
Lankadeva *et al*, 2019	Sheep model of sepsis-related acute kidney injury	0.5 μg/kg x h	Restore mean arterial pressure to pre-illness levels, halved the required norepinephrine dose.	Enhanced vascular response to catecholamines and angiotensin II.	(148)
Taniguchi *et al*, 2004	Endotoxemic rats	0.5 μg/kg x h	Improving endotoxin induced. hypotension	Inhibitory effect on inflammatory response during endotoxemia.	(117)
Yao *et al*, 2021	Patients with septic shock	0.7 μg/kg x h	Has a smaller effect on hemodynamics in patients with septic shock than midazolam.	Reduce plasma catecholamine levels in patients with septic shock.	(149)
Carnicelli *et al*, 2022	Model of septic shock pigs	0.5 μg/kg x h	Maintain hemodynamic stability.	Not affecting the early metabolic, and inflammatory disorders induced by septic shock.	(11)
Moore *et al*, 2022	Patients who underwent rhytidectomy	0.7 μg/kg x h	Resulted in a significant reduction and maintenance of blood pressure from onset of anesthesia.	Suppresses sympathetic nerve excitation and lowers blood catecholamine levels.	(150)
Hazrati *et al*, 2022	Patients with hip fracture surgery.	0.7 μg/kg x h	Maintain hemodynamic stability.	Reduces the amount of intraoperative bleeding without causing any significant hemodynamic disturbances.	(151)

DEX, dexmedetomidine.

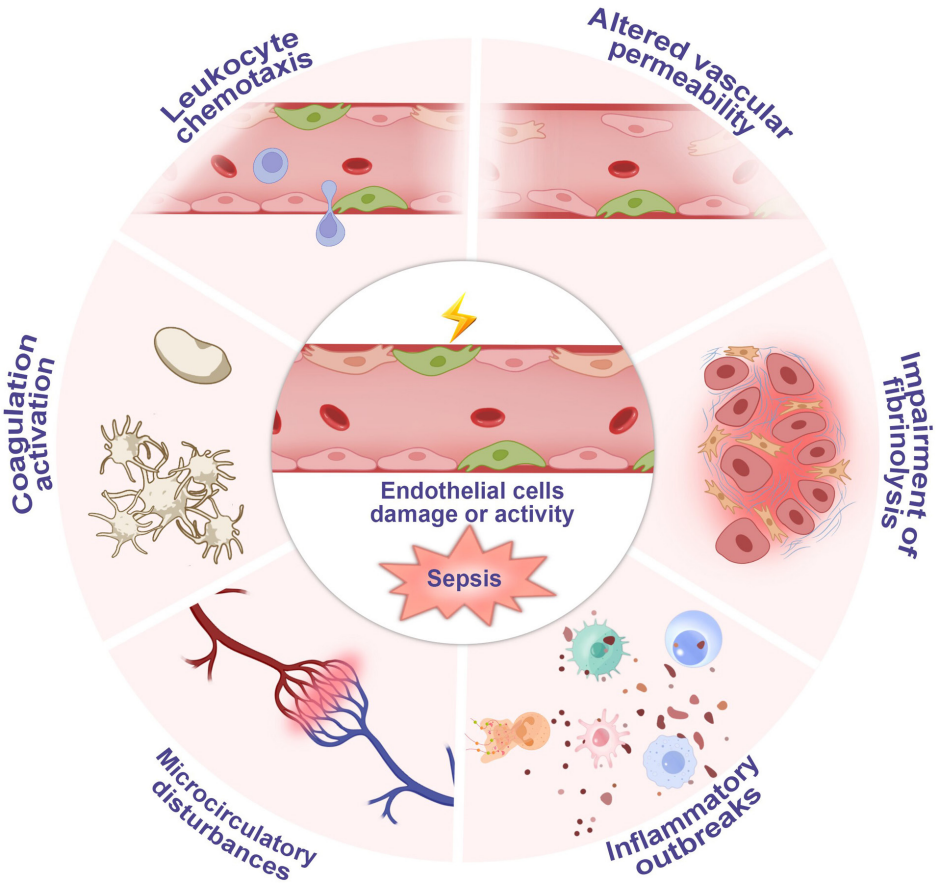

Figure 9. Mechanism by which sepsis induces endothelial cell dysfunction in multiorgan dysfunction. Sepsis can induce the activation and dysfunction of vascular endothelial cells, resulting in leukocyte chemotaxis, inflammatory outbreaks, microcirculatory disturbances and altered vascular permeability.

subcortical regions, and exhibited notable neuroprotective effects. However, higher doses of DEX (5 μg/kg) increased mortality rates in rats. Thus, the use of DEX during anesthesia in septic patients may mitigate brain injury caused by sepsis and anesthetic drugs.

Improving coagulation disorders. Pathogenic microorganisms invade the body, triggering immune cells to release proinflammatory mediators that induce tissue factor expression (177). Concurrently, activated coagulation factors engage protein-activated receptors on cell membranes, activating NF-κB and exacerbating inflammation, leading to systemic inflammatory response syndrome, organ damage and potentially MODS (178). The antisympathetic effects of DEX mitigate inflammation, alleviating the hypercoagulable state. Additionally, DEX promotes vasodilation, accelerates blood circulation, reduces red blood cell aggregation, reverses thrombosis, and mitigates organ damage caused by coagulation. Thus, DEX diminishes sepsis-induced inflammation, enhances coagulation function in septic patients, dilates blood vessels, and inhibits the progression of multiple organ failure induced by sepsis.

9. Future expectations

Although DEX shows promise in reducing organ damage, randomized controlled trials on its efficacy and safety in sepsis are limited. Future research should further assess the therapeutic potential of DEX in sepsis. At present, the protective mechanism of DEX against sepsis-induced damage to organs such as the brain, lungs, liver and heart remains unclear and requires further research. With further research, new targets and clear mechanisms of DEX in the treatment of sepsis may be discovered, expanding its clinical indications beyond perioperative sedatives and providing evidence-based support for promoting patient recovery and improving prognosis. Although numerous studies have reported the organ-protective effects of DEX, numerous aspects of this effect remain controversial. For example, the clinical evidence on whether DEX can reduce postoperative atrial fibrillation and long-term postoperative neurocognitive disorders is not yet unified and still needs to be validated through multicenter large-scale randomized controlled trials.

10. Conclusions

Sepsis-induced MODS is a leading cause of mortality among critically ill patients and those outside ICUs, with infections primarily originating from the respiratory, digestive and urinary systems. Respiratory infections constitute ~50% of these cases. Sepsis impairs the respiratory and circulatory systems to varying extents, initially presenting as decreased systemic vascular resistance and increased cardiac workload. The severity of sepsis progression is correlated with the characteristics of the infecting bacteria and the patient's immune status. Effective treatment of sepsis-induced MODS hinges on early administration of broad-spectrum antibiotics,

Table III. Study of the protective mechanism of DEX against sepsis-induced injury to endothelial cells.

First author, year	Object of study	Dosage of Dex	Effect	Regulatory mechanism of the alleviating endothelial cells injury	(Refs.)
Dai *et al*, 2023	Angiotensin II-induced endothelial cell	100 ng/ml	Attenuates Ang II-induced EC dysfunction	Inactivating HMGB1/TLR4/NF-κB signaling. pathway	(155)
Newton *et al*, 2002	Statin-statin-induced apoptosis of vascular endothelial cells	1 μM	Blocks apoptosis of vascular endothelial cells	Inhibit serum deprivation, tumor necrosis factor-alpha, oxidants, DNA damage and mitochondrial disruption.	(156)
Chai *et al*, 2020	Monocyte-vascular endothelial cells	0.1 and 1 nM	Reduce monocyte-endothelial adherence	Inhibit Cx43 alternation regulating the activation of MAPK signaling pathways.	(157)
Dong *et al*, 2020	H/R induced mouse pulmonary vascular endothelial cells	0.1 nM	Reduce mouse pulmonary vascular endothelial cells apoptosis	Increased cell viability, reduced apoptotic ratio and downregulated expression levels of Cleaved Caspase-3 and Cleaved Caspase-9 in H/R induced MPVECs	(158)
Han *et al*, 2022	LPS induced MPMVECs	0.1 nM	Alleviate LPS-induced MPMVECs injury	Regulate DUSP1/MAPK/NF-κB axis by inhibiting miR-152-3p	(159)
Zhao *et al*, 2021	Hypoxia/reoxygenation-induced brain endothelial cells	0.1 nM	Alleviated hypoxia/reoxygenation-induced brain endothelial cells injury	OGD/alleviated Hypoxia/reoxygenation-induced inflammatory injury and permeability in brain endothelial cells mediated by sigma-1 receptor	(160)
Zhang *et al*, 2021	CLP-induced rat model of sepsis	10 μg/kg	Protective effect against CLP-induced endothelial injury	Decreasing angiopoietin 2 and increasing vascular endothelial cadherin levels	(87)

DEX, dexmedetomidine; CLP, cecal ligation and puncture; EC, endothelial cell; HMGB1, high mobility group box-1 protein; TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharide; MPVECs, pulmonary microvascular endothelial cells; MAPK, mitogen-activated protein kinase; DUSP1, dual-specificity phosphatase 1.

Table IV. Study on the protective mechanism of DEX against brain injury related to general anesthetics.

First author, year	Object of study	Dosage of DEX	Brain protective effect	Regulatory mechanism of the alleviating brain injury	(Refs.)
Luo *et al*, 2016	Patients undergoing craniotomy	1 μg/kg before anesthesia induction, maintenance dose of 0.4 μg/kg x h	Alleviating brain injury by inhibiting inflammation	Reduces serum levels of IL-6, TNF-α, malondialdehyde, and S100β neuron-specific enolase, while superoxide dismutase levels significantly increased	(166)
Sanches *et al*, 2022	Cats subjected to ovariohysterectomy	1-5 μg/kg x h	Alleviating brain injury by reducing propofol consumption and quicker recovery from anesthesia	Reduces propofol consumption and improves cardiorespiratory stability and intraoperative analgesia, while promoting a improved and quicker recovery from anesthesia	(167)
Liu *et al*, 2022	Mice undergoing Intracerebral hemorrhage	25-100 μg/kg	Alleviating brain injury by reducing the neurological damage, brain edema, the lesion volume and pathological damage	Reducing damage induced by ferroptosis after ICH by regulating iron metabolism, amino acid metabolism and lipid peroxidation processes	(168)
Perez-Zoghbi *et al*, 2017	sevoflurane-induced neonatal rats	1-50 μg/kg	Affording the highest protection in the thalamus (84% reduction) and lowest in the hippocampus and cortical areas (50% reduction)	Decreases sevoflurane anesthesia-induced widespread apoptosis	(169)
Goyagi, 2019	Sevoflurane-induced neonatal rats	6.6-50 μg/kg	Improving long-term cognitive function and ameliorate the neuronal degeneration	Suppresses neuronal apoptosis	(170)
Sun *et al*, 2021	Sevoflurane-induced mice	10 μg/kg	Improved sevoflurane-induced cognitive impairment	Inhibits the sevoflurane-induced Tau phosphorylation via activation of alpha-2 adrenergic receptor	(171)
Chai *et al*, 2024	Ketamine-induced mice	0.1 μM	Improved ketamine-anesthesia-induced the neurotoxicity (reduced motor coordination in mice)	Mitigated ketamine-induced apoptosis in hippocampal neurons.	(172)
Lv *et al*, 2020	Ethanol-neonatal mice		Protects against EtOH-mediated inhibition of hippocampal neurogenesis	Reverses EtOH-induced neuroinflammation via repressing microglia activation and the expression of inflammatory cytokines	(173)
Lee *et al*, 2021	Sevoflurane-induced neonatal rats	2.5-50 μg/kg/h	Reduce the anesthetic dosage of Sevofluran and improve the neurotoxicity induced by Sevofluran.	Inhibit programmed cell death in several developing brain regions.	(174)
Fu *et al*, 2024	Patients undergoing craniocerebral surgery	0.5 μg/kg/h	enhance postoperative cognitive function	Mitigates oxidative stress	(175)
Shan *et al*, 2018	Sevoflurane-induced rats	20 μg/kg	Improved sevoflurane- anesthesia-induced the neurotoxicity (including apoptosis and axonal injury, long-term learning and memory dysfunction in the offspring rats)	Inhibits neuronal apoptosis by activating the BMP/SMAD signaling pathway	(176)

DEX, dexmedetomidine; ICH, intracerebral hemorrhage; EtOH, ethanol; BMPs, bone morphogenetic proteins; Smads, small mothers against decapentaplegic; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α.

stabilization of blood pressure and organ perfusion, timely surgical intervention at the primary infection site and restoration of organ function. Despite these measures, the incidence and mortality rates of sepsis-related MODS remain high (179).

DEX, a highly selective α2-adrenergic receptor agonist initially used for surgical sedation in intensive care units, exhibits anti-inflammatory, antioxidant and antiapoptotic properties both *in vivo* and *in vitro*. Research indicates that DEX modulates immune dysfunction, enhances the immune response, lowers cytokine levels, and mitigates organ inflammation during sepsis. It protects against lung and kidney injury, reduces astrocyte inflammatory necrosis in the nervous system, decreases hepatocyte oxidative stress, and inhibits apoptosis pathways, thereby improving circulatory function and reducing mortality in septic rats.

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Availability of data and materials

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Authors' contributions

MWL conceptualized the study, acquired funding, and wrote, reviewed and edited the manuscript. SXD curated data. XYZ conducted investigation and design. QFW provided resources, analyzed and interpretated the data. SLY performed software analysis and validation. XL supervised the study and interpretation of data. NM performed visualization and interpretation of data. All authors read and approved the final the version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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