Stem Cell Research & Therapy

REVIEW

Open Access

Harnessing stem cell therapeutics in LPS-induced animal models: mechanisms, efficacies, and future directions

Chengran Wang[1†], Fanghong Ge[1†], Fangjun Ge[2], Zhonghang Xu[3*] and Jinlan Jiang[1*]

Abstract

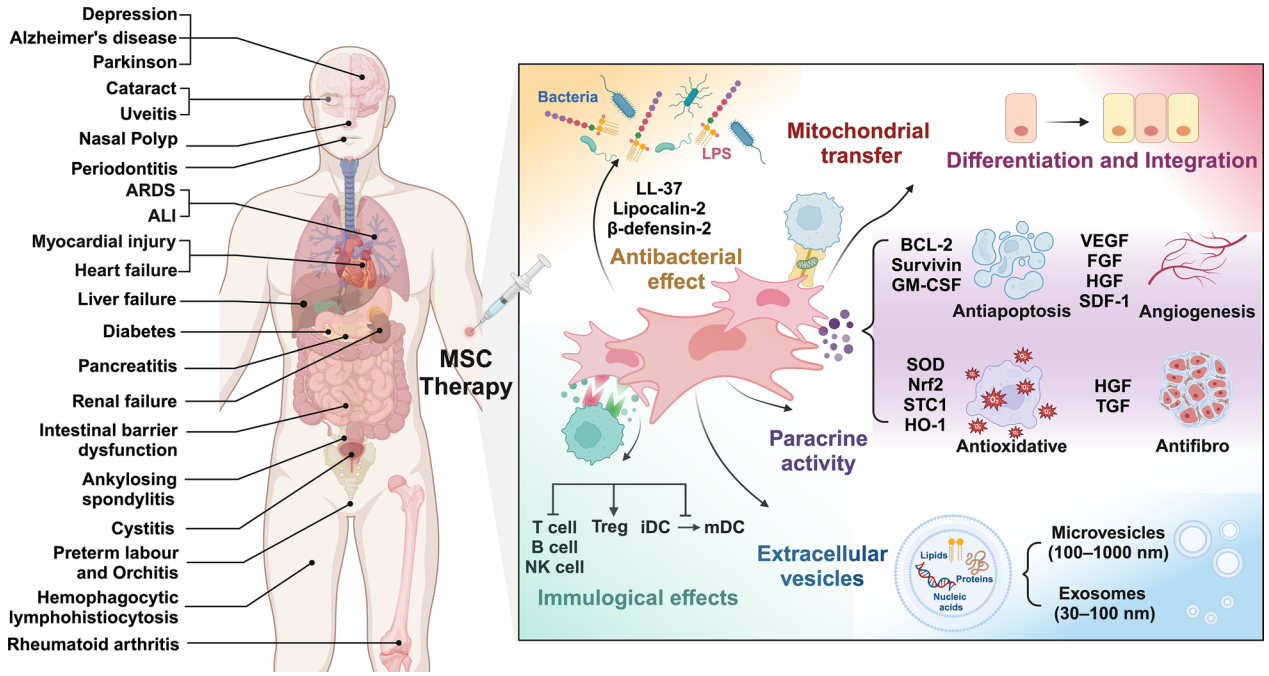
The severity and threat posed by inflammation are well documented, and lipopolysaccharides (LPS), as important inducers of inflammatory responses, are widely recognized for studying host immunity and the resulting tissue and organ damage. The LPS-induced disease model, triggers a remarkable release of inflammatory factors, immune and coagulation dysfunction, and damage to vital organs such as the brain, lungs, heart, liver, and kidneys. Recently, the role of mesenchymal stem cells (MSCs) in various clinical diseases has garnered significant attention due to their immunomodulatory, anti-inflammatory, tissue healing, anti-apoptotic, and antibacterial properties. Despite the common use of LPS models to induce disease models and simulate acute inflammation, the integration of stem cell therapy within these models remains underexplored. This article integrates the LPS induced animal model and reviews the current evidence regarding the therapeutic mechanisms of stem cells in LPS-induced disease models across various human body systems. Furthermore, this review predicts and hypothesizes the feasibility and potential of using stem cells in disease models that have not yet been extensively studied, based on existing animal inflammation models.

Keywords LPS-induced animal models, Stem cell, Therapeutic intervention, Inflammation, Mechanisms

[†]Chengran Wang and Fanghong Ge have contributed equally to this work.

*Correspondence:
Zhonghang Xu
xzh0226@jlu.edu.cn
Jinlan Jiang
jiangjinlan@jlu.edu.cn
Full list of author information is available at the end of the article

Graphic abstract



Introduction

Inflammation is a local pathological process characterized by a defensive response to damage caused by inflammatory factors. Owing to their high mortality rates, inflammation-related diseases have become a global medical challenge [1]. Lipopolysaccharide (LPS), known as an inflammatory inducer, can trigger responses in monocytes, macrophages, endothelial cells, and epithelial cells, activating cellular signaling pathways that result in a surge of cytokines and other inflammatory mediators [2]. Injection of bacterial LPS into the human body results in increased plasma pro-inflammatory cytokines and disease onset. Therefore, inflammation-related animal models are usually induced by administering LPS to study the mechanisms of diseases associated with inflammation and to assess the efficacy of pharmaceutical interventions. However, no effective treatment methods currently exist to improve inflammation-related diseases such as sepsis and multi-organ dysfunction.

Mesenchymal stem cells (MSCs) are multipotent stem cells, having the potential for multidirectional differentiation and migration. MSCs originate from various organs and tissues, such as the muscle, umbilical cord, fat, bone marrow, and placental tissue [3, 4], and are widely used in the field of tissue regeneration. Recently, numerous studies have shown that MSCs can enhance survival by regulating the immune status, balancing inflammatory responses [5–7], reducing bacterial load [8, 9], improving organ function [10–12], repairing tissue damage, and promoting tissue regeneration. MSCs hold promise as a new therapeutic strategy in clinical trials for cardiovascular, neurological, lung, and cerebrovascular diseases, making them a focus of interest for researchers in life sciences and medicine.

Therefore, understanding the research progress in the field related to LPS can help deepen the comprehension and exploration of the pathogenesis and therapeutic approaches of inflammation. This article provides a review of the achievements and advancements in LPS-based inflammation model construction in recent years and comprehensively discusses the potential of stem cell therapy in LPS-induced disease models. We attempt to make reasonable predictions about the potential therapeutic effects of stem cells in disease models that have not yet been extensively studied using existing animal models, with the goal of providing new perspectives and ideas for future research.

LPS-induced animal models

Overview of LPS

The inflammatory response is an interaction between the immune system and damaged tissues in the body.

Various stimuli, such as infections or injuries, can cause tissue damage and trigger an inflammatory response. Gram-negative bacteria such as *Escherichia coli* cause infections in humans and animals. The main component responsible for the infectivity of gram-negative bacteria is LPS, which is a key component of their cell wall and can cause significant pathological damage, making it an important inflammation inducer.

The two most common methods for creating inflammatory models in animal models are the CLP- and LPS-induced methods. The CLP-induced method, also known as the cecal ligation and puncture method, involves surgically exposing the animal's cecum, allowing intestinal contents containing multiple bacteria to flow into the abdominal cavity through a puncture hole [13]. The experimental animals developed polymicrobial peritonitis because of surgical trauma, necrosis of the ligated intestine, and the presence of feces containing multiple bacteria, subsequently showing the classical clinical symptoms of sepsis. The CLP model can simulate the disease process caused by endogenous bacterial translocation and infection, which is similar to clinical disease progression. In contrast, LPS or bacterial suspensions induce more reproducible sepsis with a single bacterial etiology. The LPS-induced method involves injecting endotoxins into the body of an animal, which is a simple and sterile method for inducing disease. This model is reproducible, and its systemic effects are easy to recognize and measure. Compared to CLP, LPS can be qualitatively and quantitatively standardized, with induced signaling pathways depending on Toll-like receptors (TLRs) and cytokines and hemodynamic changes occurring much more rapidly than in human disease processes [14]. As LPS-induced in vivo experimental models closely resemble clinical diseases, LPS is commonly used to induce sepsis and the associated organ failure. LPS can also induce rare diseases, such as intrauterine infection, preterm birth [15], preeclampsia [16], and mouse nasal polyp models [17]. Therefore, LPS is considered the gold standard for establishing acute inflammation models and can induce nearly all inflammation-related diseases. Figure 1 illustrates the application of LPS in constructing animal injury models.

Molecular and cellular mechanisms of LPS action

When bacteria invade the human body, they release LPS, which first binds to LPS-binding protein (LBP). LBP then transports LPS to the membrane surface of immune cells such as monocytes/macrophages and neutrophils, where it binds to the membrane protein CD14. CD14 subsequently transfers LPS to Toll-like receptor 4 (TLR4) and medullary differentiation protein 2 (MD2) to form a protein complex [18, 19]. This complex activates signaling molecules such as myeloid differentiation factor 88 (MyD88), IL-1R-associated kinase (IRAK) and IRAK2, and TNF receptor-associated factor 6 (TRAF6). Through a series of biochemical processes, these molecules phosphorylate the IκB kinase complex (IKK), leading to IκB degradation and the eventual activation of the transcription factor nuclear factor kappa B (NF-κB). NF-κB can bind to specific regions on the chromosome by crossing the nuclear membrane, enabling the expression of certain latent genes that produce various cytokines and other soluble mediators. Additionally, downstream of TRAF6 and TAK1, mitogen-activated protein kinase is phosphorylated to activate the transcription factors AP-1 and CREB [20]. Overall, the MyD88-dependent signaling pathway induces the expression of genes that can encode pro-inflammatory mediators, such as tumor necrosis factor (TNF-α), IL-1β, IL-6, IL-8, high mobility group protein B1 (HMGB1), macrophage inflammatory protein-1β (MIP-1β), and anti-inflammatory cytokines such as IL-10. Pro-inflammatory cytokines such as TNF-α and IL-1 can further upregulate the expression of pro-inflammatory mediators through their respective receptors and downstream signaling pathways. Moreover, TLR4 stimulation activates TRIF, which, along with non-classical TBK1 and IKKi, activates Interferon Regulatory Factor 3 (IRF3) to induce inflammatory cytokines [21, 22], leading to IFN-α/β expression. Figure 2 illustrates the LPS signaling pathway. These activated transcription factors upregulate pro-inflammatory cytokines, leukocyte chemokines, adhesion molecules involved in leukocyte homing and migration, prostaglandins, and inducible nitric oxide synthase (iNOS). Early pro-inflammatory factors are in dynamic balance with anti-inflammatory factors. However, once the body's immune-inflammatory response becomes uncontrolled, a cascade of cytokine and inflammatory mediator activation occurs, along with simultaneous activation of the complement system. These substances collectively lead to an inflammatory cytokine storm, causing endothelial cell damage and resulting in clinical syndromes, such as fever, disseminated intravascular coagulation, multiple organ dysfunction, and shock, eventually leading to organ failure.

Stem cells: types, sources, and therapeutic potential

Stem cells have the ability to self-renew and undergo pluripotent differentiation. Based on their differentiation potential, they can be classified as pluripotent, totipotent, and unipotent stem cells. Among them, adult stem cells, embryonic stem cells, and induced pluripotent stem cells (iPSCs) are the main categories. However, embryonic stem cells pose risks of immune rejection and ethical concerns, while iPSCs may exhibit genetic instability.

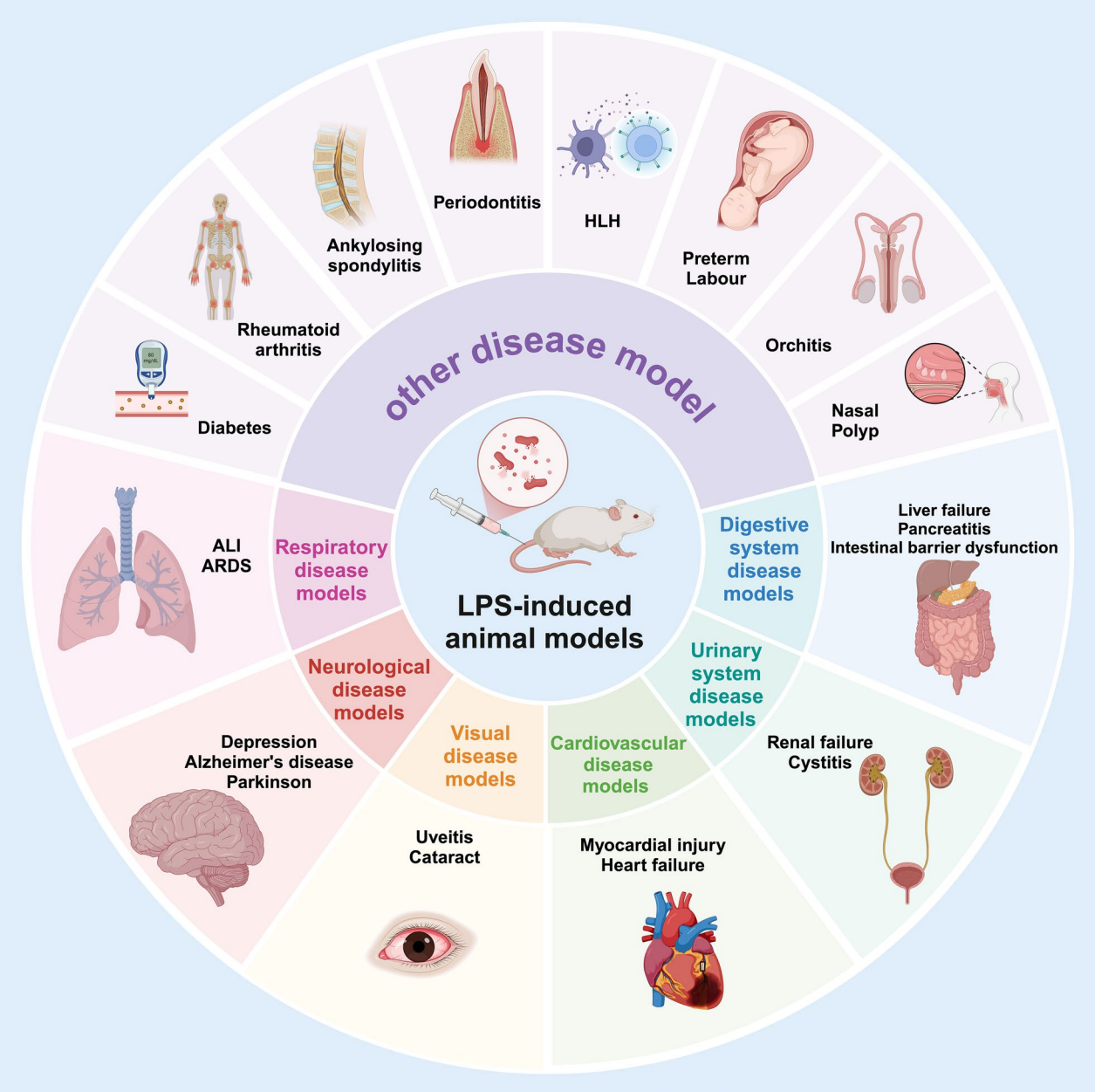


Fig. 1 Application of LPS in constructing animal injury models. LPS is an extract from the cell wall of Gram-negative bacteria, capable of effectively stimulating cells and the body to trigger corresponding inflammatory responses. As a potent inflammation inducer, LPS is widely used to establish models of acute inflammation and various diseases. Currently, commonly studied disease models are typically induced through intravenous or intraperitoneal injection, allowing for the induction of inflammatory disease such as preterm labour [111, 112], hemophagocytic lymphohistiocytosis [113], orchitis [114, 115], nasal polyp [17], rheumatoid arthritis [93, 94], periodontitis [105], diabetes [90], liver failure [66], acute pancreatitis [68], intestinal barrier dysfunction [70], lung injury [60, 62], uveitis [102], cataract, myocardial injury [83], renal failure [75], cystitis [71], neurological disease [80, 81]. LPS, Lipopolysaccharide. ALI, Acute Lung Injury; ARDS, Acute Respiratory Distress Syndrom; HLH, Hemophagocytic Lymphohistiocytosis. The image was created using BioRender (https://biorender.com/) with publication and licensing rights (Agreement number: DO27WBND6R)

Additionally, although adult stem cells have promising applications, their natural abundance in tissues is often low, making extraction more challenging.

Mesenchymal stem cells (MSCs), a type of adult stem cell, were first discovered by Friedenstein et al. in the 1970s [23]. Due to their diverse tissue sources, including bone marrow, umbilical cord blood, placenta,

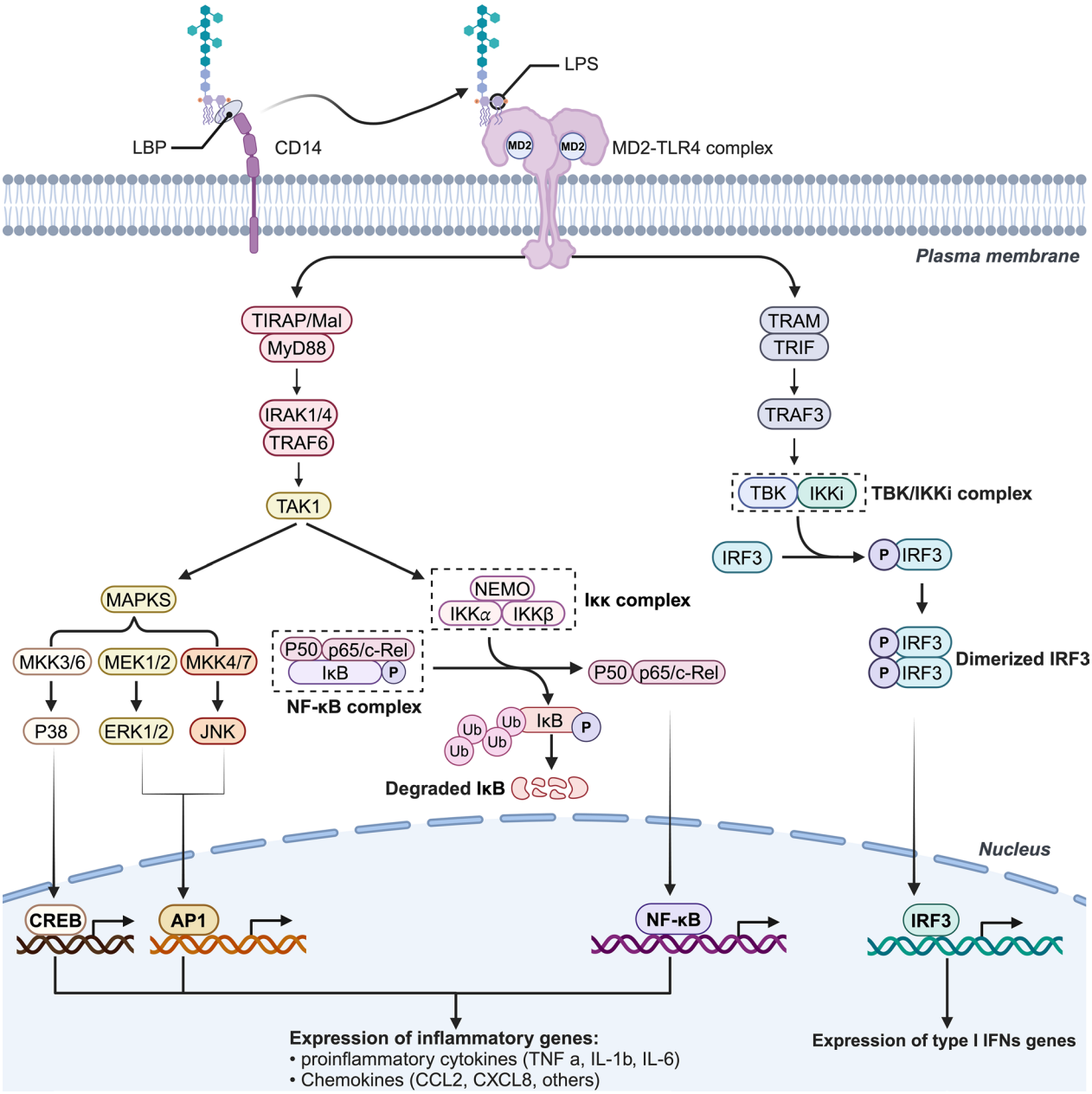


Fig. 2 LPS proinflammatory signaling pathway. LPS binds to host cell surface receptors, and TLR4 is activated and triggers two signaling cascades: The first signaling cascade involving the TIRAP and MyD88 adaptor proteins is induced in the plasma membrane, while the second signaling cascade involving the adaptor proteins TRAM and TRIF begins in the early endocytosis after eyhndocytosis. The transcription and expression of inflammatory cytokine genes are activated through many signal transduction pathways such as NF-κB and AP-1, and inflammatory response is induced to initiate the pathogenic process of bacterial infection. See the text for details. LPS, Lipopolysaccharide; LBP, LPS-binding Protein; TLR4, Toll-like Receptor 4; CD14, Cluster of Differentiation 14; MD2, Medullary Differentiation Protein 2; TRAF6, TNF Receptor-associated Factor 6; TAK,Transforming Growth Factor-β-Activated Kinase 1; IRAK, IL-1R-associated Kinase; TIRAP, TIR-domain-containing Adaptor Protein; MyD88, Myeloid Differentiation Factor 88; MAPK, mitogen-activated protein kinase; TRAM, TRIF-related Adaptor Molecule; TRIF, TIR-domain-containing Adaptor Inducing IFN-β; NF-κB, Nuclear Factor Kappa B; AP-1, Activator Protein 1. IKKi, IKK-related Kinase; IRF3, Interferon Regulatory Factor 3; IL, Interleukin (e.g., IL-1β, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17); TRAF3: TNF Receptor-Associated Factor 3; TBK: TANK-Binding Kinase; MKK3/6: Mitogen-Activated Protein Kinase Kinase 3/6; MEK1/2: MAPK/ERK Kinase 1/2; MKK4/7: Mitogen-Activated Protein Kinase Kinase 4/7; ERK1/2: Extracellular Signal-Regulated Kinase 1/2; JNK: c-Jun N-terminal Kinase; IκB: Inhibitor of NF-κB; NEMO: NF-κB Essential Modulator; CCL2: C–C Motif Chemokine Ligand 2; CXCL8: C-X-C Motif Chemokine Ligand 8. The image was created using BioRender (https://biorender.com/) with publication and licensing rights (Agreement number: TH27WBVDQD)

adipose tissue, olfactory mucosa, dental pulp, and synovial membrane [24–30], MSCs have become a research hotspot. MSCs not only possess multipotent differentiation potential, allowing them to develop into neurons, cardiomyocytes, bone, cartilage, and pancreatic cells under specific conditions [31], but they also exhibit low immunogenicity, making them relatively easy to isolate, culture, and expand [32]. They can be transplanted between individuals without triggering immune rejection. Furthermore, MSCs have strong anti-inflammatory and immunomodulatory properties, promoting tissue repair and regeneration, inhibiting inflammation progression, and enhancing the body's natural healing abilities. Therefore, stem cell therapy has garnered widespread attention as a novel treatment method and has become a popular topic in both basic research and clinical applications. This has brought hope to the treatment of various diseases. Numerous clinical trials have reported no adverse events following MSC infusion, indicating that these cells are safe for clinical use [33–36]. Stem cells can help repair the structure and function of damaged tissues, promote cell regeneration, regulate immune responses, and inhibit the progression of inflammation [37–39], showing beneficial effects in various conditions, particularly sepsis and septic shock.

Mechanisms and efficacy of stem cell therapy in LPS-induced animal models

MSCs can adapt their therapeutic effects depending on their local microenvironment. Increasing evidence suggests that the primary mechanism of MSC-based therapy is their paracrine function, where they secrete various soluble factors such as cytokines, chemokines, and growth factors, which exert anti-fibrotic, angiogenic, anti-apoptotic, and antioxidant effects [40, 41]. Stem cells exert immunosuppressive effects through cell–cell contact, for example, by reducing the toxicity of natural killer cells and modulating their immunosuppressive effects. They release IL-6, TSG-6, IGF1, and prostaglandin E2 to regulate immune responses, reduce excessive inflammation, and prevent immunosuppression to help restore immune balance and promote cell survival. MSCs can transfer mitochondria to damaged cells via tunneling nanotubes [42, 43]. Additionally, during tissue repair, MSCs reduce inflammation and promote cell proliferation by releasing extracellular vesicles that contain proteins, mRNA, and microRNA [44, 45]. These extracellular vesicles include exosomes and micro-vesicles. MSCs can differentiate into various cell lineages to replace damaged tissues, and they also possess antibacterial capabilities, acting on bacteria by secreting antimicrobial peptides such as lipocalin-2 [46], IL-37 [40, 47], and β-defensin-2 [48]. They can also be indirectly mediated by an increase in the phagocytic activity of macrophages and neutrophils. Therefore, LPS plays a significant role in the pathogenesis of host inflammatory diseases, and the application of stem cells in LPS-induced disease models has broad potential. Table 1 lists the preclinical trials of mesenchymal stem cell therapy in animal models of LPS-induced inflammatory diseases. Elucidating the specific mechanisms of stem cell therapy in the treatment of inflammatory diseases is crucial.

Sepsis model

Sepsis is a systemic inflammatory response syndrome. This severe and life-threatening syndrome can lead to shock and multiple organ dysfunction, and is a leading cause of morbidity and mortality in hospitalized patients. Sepsis models are widely used because of their importance. At the cellular and molecular levels, the pathogenesis of sepsis is relatively complex and involves various pathophysiological processes, such as imbalanced inflammatory responses, immune dysfunction [49], mitochondrial damage, coagulopathy, abnormalities in the neuroendocrine-immune network, endoplasmic reticulum (ER) stress, and autophagy, ultimately leading to organ dysfunction. Despite several years of research on the mechanisms of sepsis, clinical treatment remains primarily focused on symptomatic and supportive care. As a novel therapeutic strategy aimed at improving the prognosis of patients with sepsis, stem cells are intended to reduce inflammatory responses, enhance immune function, and improve tissue repair capabilities, demonstrating efficacy in LPS-induced sepsis models [50, 51]. Several preclinical studies have shown the beneficial effects of MSCs in sepsis models, including those using endotoxins or live bacteria. Systemic administration of MSCs may exert beneficial effects by inhibiting SIRS and organ damage caused by sepsis, reducing apoptosis and multiple organ failure rates through various mechanisms. MSCs can reduce anti-inflammatory factors such as IL-10 and IL-2 while reducing the production of inflammatory factors such as TNF-α and IL-6 [52]. Co-injection of endothelial progenitor cells (EPCs) and MSCs can modulate the TLR4/MyD88 signaling pathway, thereby reducing the inflammatory response in sepsis [53]. Recent studies have shown that exosomal KCNQ1OT1 inhibits sepsis by regulating miR-154-3p/RNF19A, thus providing a potential target for sepsis treatment [54]. In another study, mice injected with a lethal dose of LPS showed an increased phagocytic function of monocytes

Table 1 Preclinical trials of mesenchymal stem cell therapy in animal models of LPS-induced inflammatory diseases

Animal model	LPS delivery Route	MSCs used	Mechanism	Main findings	Year	References
ALI、ARDS	intratracheal injection	bone marrow-derived MSCs	exosome	MiR-23a-3p transmitted by MSC-exosome regulates the ubiquitination of IKKβ and MiR-182-5p transmitted by MSC-exosomes reverses EMT process	2020	[60]
	intratracheal injection	adipose-derived MSCs	transfer mitochondrial	AdMSC-Exos transfers mitochondria to macrophages, alleviating lung inflammation and injury	2022	[62]
	tracheal instillation	bone marrow-derived MSCs	exosome	BM-MSC-exosomes down-regulate transforming growth factor-β receptor 1 by delivering miR-130b-3p and reduce alveolar cell apoptosis to alleviate LPS-induced ALI in mice	2022	[61]
	intratracheally nebulization	umbilical cord-derived MSCs	activate the IL-17, JAK-STAT, NF-κB, and TNF-α signaling pathways	MSCs reduce inflammation, inhibit pulmonary fibrosis, and improve lung ventilation	2022	[63]
Liver failure	intraperitoneal injections	human amnioticl MSCs	HGF/c-Met Signal path	Hypoxia-mesenchymal stem cells can reduce inflammatory cell infiltration, inhibit liver cell apoptosis, and improve homing rate	2024	[66]
Acute pancreatitis	intraperitoneal injection	adipose-derived MSCs	paracrine	TSG-6 secreted by AD-MSCs protects PAC in SAP model mice by inhibiting ER stress and inflammatory response	2018	[68]
Intestinal barrier dysfunction	intraperitoneal injection	adipose-derived MSCs	immunomodulation	By preventing the infiltration of inflammatory cells in the intestines and downregulating the Th1 inflammatory response while upregulating the Th2 response, intestinal tissue damage is protected in GI colitis and LPS-induced sepsis	2009	[110]
	gavage feeding + hypoxia + oral	amniotic fluid stem cell	COX-2 dependent mechanism	AFS can modulate stromal cells expressing COX-2, reduce intestinal inflammation and intestinal epithelial cell apoptosis in NEC rats	2014	[70]
Interstitial cystitis	intravesical instillation	M-MSC		combination therapy with M-MSC and NAC effectively protect urothelium and decrease mast cell infiltration and apoptosis, improving urinary dysfunction	2019	[71]
	intravesical instillation	urine-derived stem cells		USCs restore bladder function by suppressing oxidative stress, inflammatory response, and apoptosis	2017	[72]

Table 1 (continued)

Animal model	LPS delivery Route	MSCs used	Mechanism	Main findings	Year	References
Acute kidney injury	intraperitoneal injection	adipose-derived MSCs	exosome	ADSC-derived exosomal circVMA21 alleviates LPS-induced AKI by targeting miR-16-5p, thereby inhibiting apoptosis, inflammation, and aerobic glycolysis	2023	[75]
	intraperitoneal injection	renal MSCs	paracrine	EPC-MSC promotes macrophage polarization and reduces levels of pro-inflammatory cytokines	2015	[76]
Neurological disease	substantia nigra injection	bone marrow-derived MSCs	neuronutrition	intra-nigral LPS administration induced localized microgliosis and GDNF-MSC treatment provided local neuroprotection of dopaminergic terminals	2015	[80]
	intraperitoneal injection	bone marrow-derived MSCs	extracellular vesicles	Microvesicles (mVs) extracted from MSC regulate inflammation, decreasing miR-155 and pAkt levels	2021	[81]
Myocardial injury	intraperitoneal injections	bone marrow-derived MSCs	down-regulated TLR4 and NF -kB	The expression levels of TLR- 4, NF kappa B, and phosphorylated p38 decrease, pro-inflammatory cytokines and the phagocytic activity of macrophages decreases	2016	[83]
	intravenous injection	bone marrow-derived MSCs		MSCs improve cardiac function as indicated by a reduction in EF and FS and decrease the level of TNF-a, IL-1b, and IL-6	2011	[84]
	intraperitoneal injections	bone marrow-derived MSCs	activation of mTORC2-Akt and inhibition of mTORC1-p70S6K signaling pathway	BMSCs activate the mTORC2-Akt signaling pathway and blocking the mTORC1-p70S6K signaling pathway	2017	[85]
Uveitis	foot pad injection	human uterine cervical stem cells		CM-hUCESC reduces pro-inflammatory cytokines and leukocytes in AqH and ocular tissues	2016	[102]

after MSC treatment, thereby exerting an antibacterial effect [55].

Respiratory disease model

Acute lung injury (ALI) is a common respiratory disease that can progress to lung fibrosis, and acute respiratory distress syndrome (ARDS) is its severe form. LPS is considered the most common cause of death in patients with lung injury [56]. ALI and ARDS are common in patients with severe sepsis who experience diffuse damage to alveolar and pulmonary capillary endothelial cells, which can lead to increased alveolar-capillary permeability, causing pulmonary edema [57, 58]. Clinically, it manifests as refractory hypoxemia and fatal respiratory failure [59]. Numerous studies have demonstrated that stem cells can alleviate lung injury through various pathways, and as novel biological treatments, stem cells have shown promising efficacy in animal models of LPS-induced lung injury. Researchers exploring the mechanisms by which MSCs reverse lung injury and fibrosis revealed that MSC-derived exosomes deliver miR-23a-3p and miR-182-5p, which inhibit Ikbkb and destabilize IKKβ, thereby inhibiting the NF-κB and Hedgehog pathways and reversing the progression of LPS-induced lung injury and fibrosis [60]. Moreover, MSC-derived exosomes delivered miR-130b-3p to alleviate LPS-induced ALI in mice [61]. Adipose-derived MSC exosomes can also alleviate ALI by transferring mitochondrial components to restore the homeostasis of alveolar macrophages [62]. MSCs release cytokines such as TNF-α, IL-1, and IL-6, which protect lung cells from damage and regulate inflammatory cell function, contributing to their therapeutic effects. RNA sequencing also shows that human umbilical cord MSCs (hUC-MSCs) activate the IL-17, JAK-STAT, NF-κB, and TNF-α signaling pathways. These activations enhance oxygen delivery, diminish extracellular matrix tissue, and alleviate ALI by reducing inflammation, suppressing pulmonary fibrosis, and improving respiratory function [63].

Digestive system disease models

The primary pathophysiological features of liver failure are inflammation and immune disorders in both the liver and entire body. LPS stimulates the immune cells to release inflammatory factors, leading to hepatocyte apoptosis and necrosis [64]. MSC transplantation has emerged as a new therapeutic strategy for treating acute liver failure (ALF). Numerous experimental studies on the stem cell treatment of LPS-induced ALI have provided valuable insights for clinical applications. Some researchers have explored the therapeutic effects of adipose-derived human adult stem cells in a rat model of endotoxemia, showing that MSCs can reduce the levels of liver injury biomarkers (such as ALT and AST), indicating less organ damage [65]. The paracrine effects of MSCs play an important role in liver injury. However, the low survival rate and poor homing ability of MSCs in damaged tissues limit their clinical application. Researchers have evaluated the effect of hypoxia-preconditioned human amniotic mesenchymal stem cell (hA-MSC) transplantation on the homing and repair of d-galactosamine/LPS-induced ALF. Hypoxic preconditioning promotes hA-MSC proliferation, migration, anti-apoptotic effects, and homing, thereby improving ALF repair, which is potentially mediated by the HGF/c-Met signaling axis [66].

Acute pancreatitis (AP) refers to a condition in which abnormal activation of pancreatic enzymes leads to digestion of the pancreas and surrounding organs. It is characterized by a localized inflammatory response, which may even cause organ dysfunction. Macrophage infiltration and activation are key steps in AP, and L-arginine, caerulein, and LPS induce pancreatic damage and systemic inflammation in mice [67]. Adipose-derived MSCs secrete TSG-6 to protect pancreatic acinar cells in a caerulein and LPS co-induced severe acute pancreatitis (SAP) model by inhibiting ER stress and the NF-κB signaling pathways, revealing new avenues for targeting ER stress in patients with SAP [68]. Injection of hcMSCs also reduced malondialdehyde levels and increased glutathione peroxidase and superoxide dismutase levels, effectively mitigating pancreatitis damage and making it a promising treatment for SAP, although further research is required [69].

Intestinal barrier dysfunction occurs when various factors cause damage and atrophy of the intestinal mucosa, leading to increased intestinal permeability and dysbiosis. This allows bacterial and endotoxin translocation, which induces or exacerbates systemic inflammation and multiple organ dysfunction. Intestinal barrier dysfunction is common in critically ill patients. However, there are currently no objective clinical diagnostic criteria or unified treatment protocols available. Zani et al. were the first to demonstrate that injecting amniotic fluid stem cells into a mouse model of LPS-induced necrotizing enterocolitis enhanced intestinal repair and improved survival, clinical status, intestinal structure, and function through a COX-2-dependent mechanism [70].

Urinary system disease models

Interstitial cystitis (IC) is a chronic inflammatory disease that mainly affects the submucosal and muscle layers of the bladder. Since the cause of IC remains unknown, no effective treatment is available. To date, few experimental

studies have been conducted on stem cell therapy for LPS-induced cystitis. Arifin et al. demonstrated that in a rat model of LPS-induced IC, multipotent MSCs and N-acetylcysteine-based therapies improved urinary dysfunction, regenerated urothelial cells, and alleviated tissue inflammation [71]. Li et al. showed that urine-derived stem cells restored bladder function and histological structure in PS/LPS-induced IC rodent models by inhibiting oxidative stress, inflammatory responses, and apoptosis, thus offering potential treatment options for patients with IC [72].

Acute kidney injury (AKI) is a common clinical syndrome. It is characterized by a sharp decline in kidney function, with a diagnosis based on increased serum creatinine levels and reduced urine output. Currently, there is no effective treatment for AKI, and renal replacement therapy is required in severe cases. In a mouse model of LPS-induced AKI, intraperitoneal administration of MSC secretions resulted in lower inflammation, necrosis, hemorrhage, and degeneration scores in the treatment group than in the AKI group [73]. In an animal model of sepsis-induced AKI, MSC therapy improved kidney function, reduced renal fibrosis, and decreased tubular cell apoptosis [74]. Exosomes derived from adipose-derived stem cells target miR-16-5p via circVMA21, alleviating LPS-induced AKI by inhibiting apoptosis, inflammation, and aerobic glycolysis, thus potentially offering a molecular target for treating sepsis-associated AKI [75]. Injecting LPS-induced AKI mice with EPCs improved kidney function. Co-encapsulation of EPCs and MSCs enhanced medullary blood flow in the kidneys, increased stress resistance, promoted M1 to M2 macrophage polarization, and improved kidney and vascular function when MSCs were preconditioned with hypoxia [76].

Neurological disease models

Neuroinflammation is primarily caused by chronic activation of glial cells (astrocytes and microglia) in the brain. It is a recognized feature of various neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, autism spectrum disorders, cerebral palsy, and amyotrophic lateral sclerosis. LPS, an inflammatory inducer, triggers both peripheral inflammatory processes and responses in the central nervous system (CNS). This is manifested by the activation of microglia in the brain, which then produces more pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These peripheral inflammatory signals reach the CNS through the blood–brain barrier via endothelial cells or secondary messengers, causing neuroinflammation. Hence, administering LPS peripherally or centrally can trigger microglial activation, inducing a series of inflammatory reactions that may lead to neurological and psychiatric disorders.

Such as depression, cognitive decline, anxiety, and post-traumatic stress disorder. MSCs regulate the inflammatory and immune responses by releasing various bioactive molecules, thereby protecting the CNS. Studies using in vitro LPS-induced BV2 microglial activation models have demonstrated the anti-inflammatory effects of MSCs, indicating that MSCs significantly suppress the expression of pro-inflammatory mediators in activated microglia. MSCs are ideal therapeutic agents for treating neurotraumatic injuries and neuroinflammatory diseases associated with microglial activation [77, 78].

Depression can be induced by LPS, which triggers strong immune activation and severe depression-like behaviors, as measured by increased immobility time in forced swim and tail suspension tests. Research has shown that the administration of HUCPVC reduces the surge in pro-inflammatory cytokines in the brain and significantly improves LPS-induced depression-like behaviors [79]. In another study, bone marrow-derived MSCs genetically engineered to overexpress glial cell line-derived neurotrophic factor (GDNF) were used to treat inflammation in LPS-induced Parkinson's disease models, emphasizing the neurotrophic role of GDNF in LPS-induced neuroinflammation and neurodegenerative diseases [80]. Additionally, the role of miR-155 in an LPS-induced Alzheimer's disease rat model was assessed. Researchers have studied the effects of MSC-derived microvesicles and H2S, either separately or in combination, on the regulation of proinflammatory signaling and improvement of neuroinflammation and cognitive function in LPS-induced Alzheimer's disease [81].

Cardiovascular disease models

Myocardial injury is a common LPD-induced cardiovascular disease. LPS stimulates TLRs on macrophages and monocytes, leading to the secretion of various pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8. These cytokines can cause fever, hypotension, and, ultimately, myocardial dysfunction, potentially resulting in heart failure [82]. Evidence suggests that MSCs regulate systemic and local cytokine production (TNF-α, IL-1β, and IL-6) by reducing the expression of macrophage receptors (TLRs) and inhibiting NF-kB signaling in macrophages.

Since the release of pro-inflammatory cytokines is associated with calcium imbalance, increased iNOS, and the generation of excessive toxic oxygen species, which in turn reduces contractile function, regulating pro-inflammatory cytokine secretion through MSCs may

be a potent strategy to alleviate cardiac suppression and improve heart function [83, 84].

Bone marrow-derived MSCs regulate the expression of inflammatory cytokines and mitigate LPS-induced myocardial injury by activating the mTORC2-Akt signaling pathway and blocking the mTORC1-p70S6K signaling pathway [85]. Exosomes derived from MSCs can alleviate myocardial injury in mouse models of sepsis, and non-coding RNAs, including miRNAs and lncRNAs secreted by exosomes, play a crucial role in this process [86]. MSC-derived exosomes promoted macrophage polarization to the M2 phenotype via miR-21-5p, thereby reducing inflammation and promoting cardiac repair [87]. Calcium is an important secondary messenger that plays a key role in myocardial contractility. In addition to regulating miRNAs, MSC-derived exosomes may reduce mitochondrial damage by alleviating calcium overload, thereby protecting cardiac function during sepsis.

Metabolic disease models

One key feature of type 2 diabetes (T2D) is insulin resistance. Increasing evidence suggests that insulin resistance is associated with chronic systemic inflammation, which plays a central role in the pathogenesis of T2D [88, 89]. Cani et al. investigated the effects of long-term, low-grade inflammatory stimulation on blood glucose levels in rats by inducing chronic inflammation through a single subcutaneous injection of low-dose LPS [90]. Blood glucose levels in the model group were significantly higher than those in the control group, thus meeting the criteria for the T2D model. MSCs alleviate insulin resistance [91, 92]. In an in vitro model, researchers explored the anti-inflammatory mechanisms of hUC-MSCs under insulin resistance induced by palmitic acid and LPS and identified the anti-inflammatory mechanisms of MSCs in improving insulin sensitivity [91]. However, no relevant studies on stem cell therapy using in vivo models of LPS-induced diabetes are currently available. The LPS-induced model mainly simulates insulin resistance and β-cell dysfunction caused by inflammation; however, it does not cover all the pathological mechanisms of diabetes, and further research is needed. Therefore, it can be hypothesized that in addition to directly differentiating into pancreatic β-cells, stem cells can secrete various insulin-promoting factors to enhance insulin secretion, inhibit autoimmune responses to reduce pancreatic cell damage and promote metabolism to increase insulin sensitivity, thereby improving T2D.

Other disease models

In addition to the aforementioned disease models, LPS also plays a role in the occurrence and development of autoimmune diseases. Rheumatoid arthritis (RA) is a systemic autoimmune disorder. Collagen-induced arthritis and complete Freund's adjuvant-induced arthritis are the most widely studied autoimmune RA models. The collagen antibody-induced arthritis model involves the administration of a mixture of endotoxins (LPS) and monoclonal antibodies, which can induce severe, persistent arthritis within a few days, suggesting that LPS-induced local inflammatory responses may play a role in RA pathogenesis [93, 94]. However, there are currently no studies on stem cell treatment for LPS-induced RA, and further research is needed. One study using LPS-stimulated HIG-82 synovial cells in vitro has shown that artificial cell-derived vesicles combined Exos derived from MSCs with Curc can significantly reduce the expression levels of anti-apoptotic proteins IAP1 and IAP2, as well as inflammatory mediators such as IL-6, TNF-α, matrix metalloproteinase 1, and prostaglandin E2 [95].

Ankylosing spondylitis (AS) is a chronic, progressive inflammatory arthritis that predominantly affects the spine, sacroiliac joints, and peripheral joints. Some studies have suggested that bacterial infections, particularly those caused by Gram-negative bacteria, may play an important role in the onset and progression of AS [96]. LPS-induced enthesitis is a key example of an inflammation-induced AS animal model, where mice, under certain conditions, spontaneously develop pathologies such as enthesitis and joint ankylosis, which resemble human spondyloarthritis in many aspects. Following LPS induction, mice may develop enthesitis in their hind paws [97]. However, reports on stem cell treatment in LPS-induced AS models are currently not available, and further research is warranted.

Uveitis refers to a range of conditions characterized by eye inflammation. It is a common, recurrent ophthalmic disease that can lead to secondary conditions, such as cataracts, glaucoma, or blindness [98]. Endotoxin-induced uveitis (EIU) is the most widely accepted uveitis animal model. The injection of LPS into an animal footpad induces an inflammatory response as early as the 6th hour, primarily manifesting as iridocyclitis and retinitis. Compared with melanin-induced uveitis models, the EIU model is relatively easy to induce and has no side effects [99, 100]. Corticosteroids are the first-line treatment for uveitis. However, their side effects highlight the need for new therapeutic approaches Existing studies have suggested that intraperitoneal administration of hMSCs can improve autoimmune uveitis by inhibiting the Th1/Th17 immune response [101]. Human cervical stem cells (CM-hUCESCs) reduce pro-inflammatory cytokines in human retinal pigment epithelial cell lines (ARPE-19) and significantly reduce ocular inflammation

in an EIU model. This suggests that MSCs may serve as potential therapeutic agents for patients with ocular inflammation [102].

Since uveitis can lead to secondary cataracts and LPS promotes the proliferation of human lens epithelial cells by upregulating epidermal growth factor receptor expression, contributing to the formation of posterior capsular opacification, it can be hypothesized that LPS may also induce cataract models. D-galactosamine combined with LPS can induce liver and heart failure [103, 104]. Recent studies have used this combination to induce cataracts in rats; however, reports of stem cell treatment in LPS-induced cataract models are not available, warranting further research.

LPS also stimulates human periodontal ligament cells to release matrix metalloproteinase 2 and activate NF-κB, leading to the production of various inflammation-related factors that play important roles in promoting the progression of periodontitis. Researchers have treated periodontal ligament stem cells (PDLSCs) in vitro with Pg-LPS from *Porphyromonas gingivalis* to study the immunoregulatory effects of exosomes derived from gingival MSCs (GMSC-Exos) on periodontal bone regeneration in the periodontitis inflammatory microenvironment, as well as their regulation of the NF-κB and Wnt/β-catenin pathways. GMSC-Exos can regulate the osteogenic differentiation of PDLSCs by activating the Wnt/β-catenin signaling pathway [105]. Stem cell-conditioned medium inhibited the activation of the NLRP3 inflammasome and expression of LPS-induced pro-inflammatory, thereby protecting human gingival epithelial cells [106].

Challenges and future directions

Over 50 years have passed since MSCs were first discovered, and significant progress has been made in MSC-based tissue engineering, with promising broad prospects in the field of regenerative medicine. Table 2 lists the disease models that can be induced by LPS. However, stem cell therapy has not yet been employed. Despite these challenges, MSC-based tissue engineering is a promising clinical approach for regenerative medicine. However, the malignant transformation potential of MSCs limits their clinical applications, and the oncogenic potential of uncontrolled MSC differentiation requires further investigation [107]. In addition, the low viability of cryopreserved MSCs may have affected their use. Donor age can also affect the proliferation and differentiation potential of MSCs, with MSCs from younger donors exhibiting less damage and better proliferation [108]. The differentiation potential, surface markers, and transcriptional levels of MSCs from various tissue sources vary, presenting a challenge for their clinical translation.

Numerous studies have proposed various strategies to enhance the efficacy of stem cell therapies from different perspectives. Among them, the method of modifying stem cell genes using genetic engineering has received significant attention, as it can overcome some of the limitations of using stem cells or genes alone. Genetically modified MSCs have greatly expanded their clinical applications. During tissue repair, modified MSCs promote healing and recovery by expressing neurotrophic factors, anti-inflammatory cytokines, and angiogenic factors. MSCs can also be combined with other therapies, such as gene therapy or drug treatment, to improve their efficacy [31].

Future research should focus on optimizing the therapeutic applications of novel stem cell therapies, including their mechanisms of action, delivery strategies, and potential for personalized treatment approaches. In recent years, olfactory mucosa-mesenchymal stem cells (OM-MSCs) have attracted significant attention due to their immunomodulatory and neuroregenerative properties. A recent study by Wang et al. demonstrated that OM-MSC-derived exosomes inhibit microglial pyroptosis through the lncRNA RMRP/EIF4A3/SIRT1 pathway, thereby reducing neuroinflammation and promoting spinal cord injury recovery [29]. These findings highlight the potential of OM-MSCs in developing novel therapies for neuroinflammatory and neurodegenerative diseases.Understanding how different stem cell-based therapies interact with the inflammatory microenvironment will be crucial for developing more

Table 2 Disease models induced by LPS but not treated with stem cells to date

Animal model	Study subject	LPS delivery route	Model details and timing of administration	Year	References
Preterm labour	Female BALB/c mice	intraperitoneal injections	two injections of 50 μg/kg LPS, 3 h apart	2020	[111]
	Female BALB/c mice	intraperitoneal injections	two injections of 0.4 mg/kg LPS	2016	[112]
Hemophagocytic Lymphohistiocytosis	Male SAMP1/TA-1 mice	intravenous injection	three injections of 25 μg LPS at weekly intervals	2019	[113]
Orchitis	Male C57BL/10 mice	intraperitoneal injections	100 μg of LPS in 1 ml of sterile PBS	2014	[114]
	Male adult sheep	intra-testicular injection	10 μg of LPS in 50 μL of saline	2020	[115]
Nasal Polyp	Male C57BL/6 J mice	instilled in each nostril	10 μL of LPS in each nostril for a total of 100 μg	2023	[17]

effective treatments for inflammation-associated diseases.

With the development of precision medicine, MSC therapies may become more personalized and tailored to meet the specific needs of individual patients [109]. Given the significant variations in individual inflammatory responses, designing tailored stem cell treatments based on specific inflammatory profiles may enhance efficacy and reduce side effects. For instance, by analyzing a patient's cytokine profile, gene expression levels, and immune microenvironment, the type, dosage, and delivery method of stem cells can be optimized to more precisely regulate inflammation. This approach not only improves the effectiveness of stem cell therapies but also advances precision medicine in inflammation-related diseases. Therefore, future research should further explore how personalized stem cell treatments can be tailored to individual inflammatory profiles to achieve more accurate and efficient disease management.

Conclusion

As a potent inflammation inducer, LPS is widely used to establish models of acute inflammation and various diseases, playing a significant role in medical research. At the same time, inflammation models continue to facilitate studies on the pathogenesis and treatment of inflammation and other diseases. In future inflammation research, LPS will remain a key tool, and we hope that LPS-based models will continue to contribute greater value to scientific experiments, further advancing medical research.

Stem cells show great potential in these models, demonstrating promising prospects for treating human diseases. Through paracrine, mitochondrial transfer and extracellular vesicles, mesenchymal stem cells secrete proteins to the damaged tissues or transfer mitochondria, exosomes and microvesicles to the damaged cells, and secrete antimicrobial peptides and immunomodulatory effects to exert antibacterial abilities, reduce excessive inflammation and prevent immunosuppression to help restore immune response balance and promote cell survival. Future research is needed to explore ways to overcome current challenges and fully unlock the therapeutic potential of stem cells.

Abbreviations

LPS	Lipopolysaccharide
MSCs	Mesenchymal stem cells
TLRs	Toll-like receptors
CLP	Cecal ligation and puncture
LBP	LPS-binding protein
CD14	Cluster of differentiation 14
TLR4	Toll-like receptor 4
MD2	Medullary differentiation protein 2
MyD88	Myeloid differentiation factor 88
IRAK	IL-1R-associated kinase
TRAF6	TNF Receptor-associated factor 6
IKK	IκB kinase complex
NF-κB	Nuclear factor kappa B
AP-1	Activator protein 1
CREB	CAMP response element-binding protein
TBK1	TANK-binding kinase 1
IKKi	IKK-related kinase
IRF3	Interferon regulatory factor 3
IFN-α/β	Interferon-alpha/beta
iNOS	Inducible nitric oxide synthase
HMGB1	High mobility group protein B1
MIP-1β	Macrophage inflammatory protein-1 beta
TNF-α	Tumor necrosis factor-alpha
IL	Interleukin (e.g., IL-1β, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17)
TIRAP	TIR-domain-containing adaptor protein
TAK	Transforming growth factor-β-activated kinase 1
TRAM	TRIF-related adaptor molecule
TRIF	TIR-domain-containing adaptor inducing IFN-β
TSG-6	Tumor necrosis factor-stimulated gene-6
MAPK	Mitogen-activated protein kinase
IGF1	Insulin-like growth factor 1
EPCs	Endothelial progenitor cells
SIRS	Systemic inflammatory response syndrome
KCNQ1OT1	KCNQ1 overlapping transcript 1
miR	MicroRNA (e.g., miR-154-3p, miR-23a-3p, miR-182-5p, miR-130b-3p)
RNF19A	Ring finger protein 19A
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
JAK-STAT	Janus kinase-signal transducer and activator of transcription
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALF	Acute liver failure
hA-MSC	Human amniotic mesenchymal stem cell
HGF	Hepatocyte growth factor
SAP	Severe acute pancreatitis
ER	Endoplasmic reticulum
COX-2	Cyclooxygenase-2
IC	Interstitial cystitis
AKI	Acute kidney injury
CNS	Central nervous system
BV2	BV2 microglial cells
HUCPVC	Human umbilical cord perivascular cell
GDNF	Glial cell line-derived neurotrophic factor
miR-155	MicroRNA-155
H2S	Hydrogen sulfide
LPD	Lipopolysaccharide-derived
mTORC2	Mechanistic target of rapamycin complex 2
Akt	Protein kinase B
mTORC1	Mechanistic target of rapamycin complex 1
p70S6K	Ribosomal protein S6 kinase beta-1; miRNAs, MicroRNAs
lncRNAs	Long non-coding RNAs
miR-21-5p	MicroRNA-21-5p
T2D	Type 2 diabetes
hUC-MSCs	Human umbilical cord mesenchymal stem cells
RA	Rheumatoid arthritis
AS	Ankylosing spondylitis
EIU	Endotoxin-induced uveitis
HLH	Hemophagocytic lymphohistiocytosis
hMSCs	Human mesenchymal stem cells
Th1/Th17	T Helper 1/T Helper 17
CM-hUCESCs	Conditioned medium from human umbilical cord epithelial stem cells
ARPE-19	Adult retinal pigment epithelial-19
Curc-Exos	Curcumin-loaded exosomes
IAP1	Inhibitor of apoptosis protein 1
IAP2	Inhibitor of apoptosis protein 2
EGFR	Epidermal growth factor receptor
PDLSCs	Periodontal ligament stem cells
Pg-LPS	Porphyromonas gingivalis lipopolysaccharide

GMSC-Exos	Gingival mesenchymal stem cell-derived exosomes
Wnt/β-catenin	Wnt/beta-catenin signaling pathway
NLRP3	NOD-like receptor family pyrin domain containing 3
TRAF3	TNF Receptor-associated factor 3
TBK	TANK-binding kinase
MKK3/6	Mitogen-activated protein kinase kinase 3/6
MEK1/2	MAPK/ERK kinase 1/2
MKK4/7	Mitogen-activated protein kinase kinase 4/7
ERK1/2	Extracellular signal-regulated kinase 1/2
JNK	C-Jun N-terminal kinase
IκB	Inhibitor of NF-κB
NEMO	NF-κB essential modulator
CCL2	C-C Motif chemokine ligand 2
CXCL8	C-X-C Motif chemokine ligand 8

Acknowledgements
We would like to thank Editage (www.editage.cn) for English language editing. The figures in this work were partially drawn using www.biorender.com. The authors declare that they have not use AI-generated work in this manuscript.

Author contributions
FG contributed to the conceptualization and methodology. FG developed the software used in the research and CW provided supervision. FG conducted the investigation, validation and visualization. The original draft was written by FG. The review and editing of the manuscript were jointly performed by JJ. All authors read and approved the final manuscript.

Funding
We acknowledge the financial support from the National Natural Science Foundation of China (Grant No. 82172230) and the Jilin Scientific and Technological Development Program (Grant No. 20240205001YY), Life Spring AKY Pharmaceuticals (No. 20210472), and College Students' Innovative Entrepreneurial Training Plan Program (No. X202410183444).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author details
[1]Scientific Research Center, China-Japan Union Hospital of Jilin University, Changchun 130033, Jilin Province, People's Republic of China. [2]School of Biology and Biological Engineering, South China University of Technology, Guangzhou, Guangdong Province, People's Republic of China. [3]Department of Breast Surgery, China-Japan Union Hospital of Jilin University, Changchun 130033, Jilin Province, People's Republic of China.

Received: 11 February 2025 Accepted: 19 March 2025
Published online: 12 April 2025

References

1. Netea MG, Balkwill F, Chonchol M, Cominelli F, Donath MY, Giamarellos-Bourboulis EJ, et al. Author correction: a guiding map for inflammation. Nat Immunol. 2021;22(2):254.
2. Park BS, Lee JO. Recognition of lipopolysaccharide pattern by TLR4 complexes. Exp Mol Med. 2013;45(12):e66.
3. Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, et al. Mesenchymal stem cells: cell therapy and regeneration potential. J Tissue Eng Regen Med. 2019;13(9):1738–55.
4. Maqsood M, Kang M, Wu X, Chen J, Qiu L. Adult mesenchymal stem cells and their exosomes: sources, characteristics, and application in regenerative medicine. Life Sci. 2020;256:118002.
5. Danchuk S, Ylostalo JH, Hossain F, Sorge R, Ramsey A, Bonvillain RW, et al. Human multipotent stromal cells attenuate lipopolysaccharide-induced acute lung injury in mice via secretion of tumor necrosis factor-alpha-induced protein 6. Stem Cell Res Ther. 2011;2(3):27.
6. Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. Nat Rev Nephrol. 2018;14(8):493–507.
7. Kay AG, Long G, Tyler G, Stefan A, Broadfoot SJ, Piccinini AM, et al. Mesenchymal stem cell-conditioned medium reduces disease severity and immune responses in inflammatory arthritis. Sci Rep. 2017;7(1):18019.
8. Meisel R, Brockers S, Heseler K, Degistirici O, Bulle H, Woite C, et al. Human but not murine multipotent mesenchymal stromal cells exhibit broad-spectrum antimicrobial effector function mediated by indoleamine 2,3-dioxygenase. Leukemia. 2011;25(4):648–54.
9. Brandau S, Jakob M, Hemeda H, Bruderek K, Janeschik S, Bootz F, et al. Tissue-resident mesenchymal stem cells attract peripheral blood neutrophils and enhance their inflammatory activity in response to microbial challenge. J Leukoc Biol. 2010;88(5):1005–15.
10. Mei SH, Haitsma JJ, Dos Santos CC, Deng Y, Lai PF, Slutsky AS, et al. Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. Am J Respir Crit Care Med. 2010;182(8):1047–57.
11. Niu H, Song H, Guan Y, Zong X, Niu R, Zhao S, et al. Chicken bone marrow mesenchymal stem cells improve lung and distal organ injury. Sci Rep. 2021;11(1):17937.
12. Alcayaga-Miranda F, Cuenca J, Martin A, Contreras L, Figueroa FE, Khoury M. Combination therapy of menstrual derived mesenchymal stem cells and antibiotics ameliorates survival in sepsis. Stem Cell Res Ther. 2015;6:199.
13. Qu M, Hou Q, Li X, Yu C, Xia J, Dong Z. Application of a flipped classroom incorporating modified team-based learning in molecular biology laboratory teaching: a mixed methods study. BMC Med Educ. 2024;24(1):1442.
14. Kulkarni HS, Lee JS, Bastarache JA, Kuebler WM, Downey GP, Albaiceta GM, et al. Update on the features and measurements of experimental acute lung injury in animals: an official american thoracic society workshop report. Am J Respir Cell Mol Biol. 2022;66(2):e1–14.
15. Zhang L, Mamillapalli R, Habata S, McAdow M, Taylor HS. Myometrial-derived CXCL12 promotes lipopolysaccharide induced preterm labour by regulating macrophage migration, polarization and function in mice. J Cell Mol Med. 2022;26(9):2566–78.
16. Shen J, Hu N, Wang Z, Yang L, Chen R, Zhang L, Wang X. Ghrelin alleviates placental dysfunction by down-regulating NF-kappaB phosphorylation in LPS-induced rat model of preeclampsia. Eur J Pharmacol. 2024;972:176569.
17. Lu X, Xu H, Shan L, Gao J, Tong J. DMBT1 alleviates nasal airway inflammatory response in the LPS-induced nasal polyp model. Int Arch Allergy Immunol. 2023;184(8):808–13.
18. Meng J, Gong M, Bjorkbacka H, Golenbock DT. Genome-wide expression profiling and mutagenesis studies reveal that lipopolysaccharide responsiveness appears to be absolutely dependent on TLR4 and MD-2 expression and is dependent upon intermolecular ionic interactions. J Immunol. 2011;187(7):3683–93.
19. Hajjar AM, Ernst RK, Fortuno ES 3rd, Brasfield AS, Yam CS, Newlon LA, et al. Humanized TLR4/MD-2 mice reveal LPS recognition differentially impacts susceptibility to *Yersinia pestis* and *Salmonella enterica*. PLoS Pathog. 2012;8(10):e1002963.
20. Hui B, Zhang L, Zhou Q, Hui L. Pristimerin inhibits LPS-triggered neurotoxicity in BV-2 microglia cells through modulating IRAK1/TRAF6/TAK1-mediated NF-kappaB and AP-1 signaling pathways in vitro. Neurotox Res. 2018;33(2):268–83.
21. Chiang CY, Veckman V, Limmer K, David M. Phospholipase cgamma-2 and intracellular calcium are required for lipopolysaccharide-induced

Toll-like receptor 4 (TLR4) endocytosis and interferon regulatory factor 3 (IRF3) activation. J Biol Chem. 2012;287(6):3704–9.
22. Ciesielska A, Matyjek M, Kwiatkowska K. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. Cell Mol Life Sci. 2021;78(4):1233–61.
23. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation. 1968;6(2):230–47.
24. Friedenstein AJ, Gorskaja JF, Kulagina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol. 1976;4(5):267–74.
25. Bunnell BA. Adipose tissue-derived mesenchymal stem cells. Cells. 2021;10(12):3433.
26. Fukuchi Y, Nakajima H, Sugiyama D, Hirose I, Kitamura T, Tsuji K. Human placenta-derived cells have mesenchymal stem/progenitor cell potential. Stem Cells. 2010;22(5):649–58.
27. Shareghi-Oskoue O, Aghebati-Maleki L, Yousefi M. Transplantation of human umbilical cord mesenchymal stem cells to treat premature ovarian failure. Stem Cell Res Ther. 2021;12(1):454.
28. Fernandes TL, Cortez de SantAnna JP, Frisene I, Gazarini JP, Gomes Pinheiro CC, Gomoll AH, Lattermann C, Hernandez AJ, Franco Bueno D. Systematic review of human dental pulp stem cells for cartilage regeneration. Tissue Eng Part B: Rev. 2020;26(1):1–2.
29. Wang C, Zhang J, Chen W, Gao L, He J, Xia Y. Exosomal lncRNA RMRP-shuttled by Olfactory Mucosa-Mesenchymal Stem Cells Suppresses Microglial Pyroptosis to Improve Spinal Cord Injury via EIF4A3/SIRT1. Mol Neurobiol. 2025.
30. Bami M, Sarlikiotis T, Milonaki M, Vikentiou M, Konsta E, Kapsimali V, et al. Superiority of synovial membrane mesenchymal stem cells in chondrogenesis, osteogenesis, myogenesis and tenogenesis in a rabbit model. Injury. 2020;51(12):2855–65.
31. Ullah I, Subbarao RB, Rho GJ. Human mesenchymal stem cells-current trends and future prospective. Biosci Rep. 2015;35(2):e00191.
32. Boquest AC, Collas P. Obtaining freshly isolated and cultured mesenchymal stem cells from human adipose tissue. Methods Mol Biol. 2012;879:269–78.
33. Song Y, Du H, Dai C, Zhang L, Li S, Hunter DJ, et al. Human adipose-derived mesenchymal stem cells for osteoarthritis: a pilot study with long-term follow-up and repeated injections. Regen Med. 2018;13(3):295–307.
34. Huang L, Zhang C, Gu J, Wu W, Shen Z, Zhou X, Lu H. A randomized, placebo-controlled trial of human umbilical cord blood mesenchymal stem cell infusion for children with cerebral palsy. Cell Transplant. 2018;27(2):325–34.
35. Molendijk I, Bonsing BA, Roelofs H, Peeters KC, Wasser MN, Dijkstra G, Van Der Woude CJ, Duijvestein M, Veenendaal RA, Zwaginga JJ, Verspaget HW. Allogeneic bone marrow–derived mesenchymal stromal cells promote healing of refractory perianal fistulas in patients with Crohn's disease. Gastroenterology. 2015;149(4):918–27.
36. Thompson M, Mei SHJ, Wolfe D, Champagne J, Fergusson D, Stewart DJ, et al. Cell therapy with intravascular administration of mesenchymal stromal cells continues to appear safe: an updated systematic review and meta-analysis. EClinicalMedicine. 2020;19:100249.
37. Gazdic M, Volarevic V, Arsenijevic N, Stojkovic M. Mesenchymal stem cells: a friend or foe in immune-mediated diseases. Stem Cell Rev Rep. 2015;11(2):280–7.
38. Zhang Y, Fan M, Zhang Y. Revolutionizing bone defect healing: the power of mesenchymal stem cells as seeds. Front Bioeng Biotechnol. 2024;12:1421674.
39. Yan W, Abu-El-Rub E, Saravanan S, Kirshenbaum LA, Arora RC, Dhingra S. Inflammation in myocardial injury: mesenchymal stem cells as potential immunomodulators. Am J Physiol Heart Circ Physiol. 2019;317(2):H213–25.
40. Liang X, Ding Y, Zhang Y, Tse HF, Lian Q. Paracrine mechanisms of mesenchymal stem cell-based therapy: current status and perspectives. Cell Transplant. 2014;23(9):1045–59.
41. Asgari Taei A, Khodabakhsh P, Nasoohi S, Farahmandfar M, Dargahi L. Paracrine effects of mesenchymal stem cells in ischemic stroke: opportunities and challenges. Mol Neurobiol. 2022;59(10):6281–306.
42. Cselenyak A, Pankotai E, Horvath EM, Kiss L, Lacza Z. Mesenchymal stem cells rescue cardiomyoblasts from cell death in an in vitro ischemia model via direct cell-to-cell connections. BMC Cell Biol. 2010;11:29.
43. Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, et al. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. Nat Med. 2012;18(5):759–65.
44. Lee C, Mitsialis SA, Aslam M, Vitali SH, Vergadi E, Konstantinou G, et al. Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension. Circulation. 2012;126(22):2601–11.
45. Zhang B, Yin Y, Lai RC, Tan SS, Choo AB, Lim SK. Mesenchymal stem cells secrete immunologically active exosomes. Stem Cells Dev. 2014;23(11):1233–44.
46. Gupta N, Krasnodembskaya A, Kapetanaki M, Mouded M, Tan X, Serikov V, Matthay MA. Mesenchymal stem cells enhance survival and bacterial clearance in murine Escherichia coli pneumonia. Thorax. 2012;67(6):533–9.
47. Devaney J, Horie S, Masterson C, Elliman S, Barry F, O'Brien T, Curley GF, O'Toole D, Laffey JG. Human mesenchymal stromal cells decrease the severity of acute lung injury induced by E. coli in the rat. Thorax. 2015;70(7):625–35.
48. Sung DK, Chang YS, Sung SI, Yoo HS, Ahn SY, Park WS. Antibacterial effect of mesenchymal stem cells against Escherichia coli is mediated by secretion of beta- defensin- 2 via toll- like receptor 4 signalling. Cell Microbiol. 2016;18(3):424–36.
49. Huang M, Cai S, Su J. The pathogenesis of sepsis and potential therapeutic targets. Int J Mol Sci. 2019;20(21):5376.
50. Keane C, Jerkic M, Laffey JG. Stem cell–based therapies for sepsis. Anesthesiology. 2017;127(6):1.
51. Wannemuehler TJ, Manukyan MC, Brewster BD, Rouch J, Poynter JA, Wang Y, et al. Advances in mesenchymal stem cell research in sepsis. J Surg Res. 2012;173(1):113–26.
52. Ou H, Zhao S, Peng Y, Xiao X, Wang Q, Liu H, et al. Comparison of bone marrow tissue- and adipose tissue-derived mesenchymal stem cells in the treatment of sepsis in a murine model of lipopolysaccharide-induced sepsis. Mol Med Rep. 2016;14(4):3862–70.
53. Hoseinnia S, Ghane M, Norouzi J, Hosseini F. Mesenchymal stem cell and endothelial progenitor cells coinjection improves LPS-induced lung injury via Tie2 activation and downregulation of the TLR4/MyD88 pathway. J Cell Biochem. 2021;122(12):1791–804.
54. Yuan H, Yu J, Liu C, Zhao H, Xue J, Liu J, et al. LncRNA KCNQ10T1 shuttled by bone marrow mesenchymal stem cell-derived exosome inhibits sepsis via regulation of miR-154-3p/RNF19A axis. Cell Tissue Res. 2023;393(3):507–21.
55. Krasnodembskaya A, Samarani G, Song Y, Zhuo H, Su X, Lee JW, et al. Human mesenchymal stem cells reduce mortality and bacteremia in gram-negative sepsis in mice in part by enhancing the phagocytic activity of blood monocytes. Am J Physiol Lung Cell Mol Physiol. 2012;302(10):L1003–13.
56. Domscheit H, Hegeman MA, Carvalho N, Spieth PM. Molecular dynamics of lipopolysaccharide-induced lung injury in rodents. Front Physiol. 2020;11:36.
57. Kim WY, Hong SB. Sepsis and acute respiratory distress syndrome: recent update. Tuberc Respir Dis (Seoul). 2016;79(2):53–7.
58. Lee FY, Chen KH, Wallace CG, Sung PH, Sheu JJ, Chung SY, et al. Xenogeneic human umbilical cord-derived mesenchymal stem cells reduce mortality in rats with acute respiratory distress syndrome complicated by sepsis. Oncotarget. 2017;8(28):45626–42.
59. Al-Husinat L, Azzam S, Al Sharie S, Araydah M, Battaglini D, Abushehab S, et al. A narrative review on the future of ARDS: evolving definitions, pathophysiology, and tailored management. Crit Care. 2025;29(1):88.
60. Xiao K, He W, Guan W, Hou F, Yan P, Xu J, Zhou T, Liu Y, Xie L. Mesenchymal stem cells reverse EMT process through blocking the activation of NF-κB and hedgehog pathways in LPS-induced acute lung injury. Cell Death Dis. 2020;11(10):863.
61. Wang X, Feng J, Dai H, Mo J, Luo B, Luo C, et al. microRNA-130b-3p delivery by mesenchymal stem cells-derived exosomes confers protection on acute lung injury. Autoimmunity. 2022;55(8):597–607.
62. Xia L, Zhang C, Lv N, Liang Z, Ma T, Cheng H, et al. AdMSC-derived exosomes alleviate acute lung injury via transferring mitochondrial

component to improve homeostasis of alveolar macrophages. Theranostics. 2022;12(6):2928–47.
63. Cui E, Zhang L, Pan X, Zhang Q, Zhang L, Wu F, et al. RNA-Sequencing approach for exploring the therapeutic effect of umbilical cord mesenchymal stem/stromal cells on lipopolysaccharide-induced acute lung injury. Front Immunol. 2022;13:1021102.
64. Farghali H, Kgalalelo Kemelo M, Wojnarova L, Kutinova CN. In vitro and in vivo experimental hepatotoxic models in liver research: applications to the assessment of potential hepatoprotective drugs. Physiol Res. 2016;65(Suppl 4):S417–25.
65. Shin S, Kim Y, Jeong S, Hong S, Kim I, Lee W, Choi S. The therapeutic effect of human adult stem cells derived from adipose tissue in endotoxemic rat model. Int J Med Sci. 2013;10(1):8–18.
66. Wang Q, Li Y, Yuan H, Peng L, Dai Z, Sun Y, et al. Hypoxia preconditioning of human amniotic mesenchymal stem cells enhances proliferation and migration and promotes their homing via the HGF/C-MET signaling axis to augment the repair of acute liver failure. Tissue Cell. 2024;87:102326.
67. Han X, Ni J, Wu Z, Wu J, Li B, Ye X, et al. Myeloid-specific dopamine D(2) receptor signalling controls inflammation in acute pancreatitis via inhibiting M1 macrophage. Br J Pharmacol. 2020;177(13):2991–3008.
68. Li Q, Song WJ, Ryu MO, Nam A, An JH, Ahn JO, et al. TSG-6 secreted by human adipose tissue-derived mesenchymal stem cells ameliorates severe acute pancreatitis via ER stress downregulation in mice. Stem Cell Res Ther. 2018;9(1):255.
69. Jung KH, Yi T, Son MK, Song SU, Hong SS. Therapeutic effect of human clonal bone marrow-derived mesenchymal stem cells in severe acute pancreatitis. Arch Pharm Res. 2015;38(5):742–51.
70. Zani A, Cananzi M, Fascetti-Leon F, Lauriti G, Smith VV, Bollini S, et al. Amniotic fluid stem cells improve survival and enhance repair of damaged intestine in necrotising enterocolitis via a COX-2 dependent mechanism. Gut. 2014;63(2):300–9.
71. Shin JH, Ryu CM, Ju H, Yu HY, Song S, Shin DM, Choo MS. Synergistic effects of N-acetylcysteine and mesenchymal stem cell in a lipopolysaccharide-induced interstitial cystitis rat model. Cells. 2019;9(1):86.
72. Li J, Luo H, Dong X, Liu Q, Wu C, Zhang T, et al. Therapeutic effect of urine-derived stem cells for protamine/lipopolysaccharide-induced interstitial cystitis in a rat model. Stem Cell Res Ther. 2017;8(1):107.
73. Arifin A, Purwanto B, Indarto D, Wasita B, Sumanjar T, Pamungkasari EP, Soetrisno S. Improvement of renal functions in mice with septic acute kidney injury using secretome of mesenchymal stem cells. Saudi J Biol Sci. 2024;31(3):103931.
74. Ranghino A, Bruno S, Bussolati B, Moggio A, Dimuccio V, Tapparo M, et al. The effects of glomerular and tubular renal progenitors and derived extracellular vesicles on recovery from acute kidney injury. Stem Cell Res Ther. 2017;8(1):24.
75. He Y, Li X, Huang B, Yang Y, Luo N, Song W, et al. Exosomal Circvma21 derived from adipose-derived stem cells alleviates sepsis-induced acute kidney injury by targeting mir-16-5p. Shock. 2023;60(3):419–26.
76. Zullo JA, Nadel EP, Rabadi MM, Baskind MJ, Rajdev MA, Demaree CM, et al. The secretome of hydrogel-coembedded endothelial progenitor cells and mesenchymal stem cells instructs macrophage polarization in endotoxemia. Stem Cells Transl Med. 2015;4(7):852–61.
77. Liu Y, Zhang R, Yan K, Chen F, Jiang X. Mesenchymal stem cells inhibit lipopolysaccharide-induced inflammatory responses of BV2 microglial cells through TSG-6. J Neuroinflammation. 2014;11(1):135.
78. Li W, Ali T, He K, Liu Z, Shah FA, Ren Q, et al. Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. Brain Behav Immun. 2021;92:10–24.
79. Shuster-Hyman H, Siddiqui F, Gallagher D, Gauthier-Fisher A, Librach CL. Time course and mechanistic analysis of human umbilical cord perivascular cell mitigation of lipopolysaccharide-induced systemic and neurological inflammation. Cytotherapy. 2023;25(2):125–37.
80. Hoban DB, Howard L, Dowd E. GDNF-secreting mesenchymal stem cells provide localized neuroprotection in an inflammation-driven rat model of Parkinson's disease. Neuroscience. 2015;303:402–11.
81. Aboulhoda BE, Rashed LA, Ahmed H, Obaya EMM, Ibrahim W, Alkafass MAL, et al. Hydrogen sulfide and mesenchymal stem cells-extracted microvesicles attenuate LPS-induced Alzheimer's disease. J Cell Physiol. 2021;236(8):5994–6010.
82. Zhang X, Lu C, Gao M, Cao X, Ha T, Kalbfleisch JH, et al. Toll-like receptor 4 plays a central role in cardiac dysfunction during trauma hemorrhage shock. Shock. 2014;42(1):31–7.
83. Wu Y, Zhou J, Bi L, Huang M, Han Y, Zhang Q, et al. Effects of bone marrow mesenchymal stem cells on the cardiac function and immune system of mice with endotoxemia. Mol Med Rep. 2016;13(6):5317–25.
84. Weil BR, Herrmann JL, Abarbanell AM, Manukyan MC, Poynter JA, Meldrum DR. Intravenous infusion of mesenchymal stem cells is associated with improved myocardial function during endotoxemia. Shock. 2011;36(3):235.
85. Huang W, Fan W, Wang Y, Han D, Li X, Li S, et al. Mesenchymal stem cells in alleviating sepsis-induced mice cardiac dysfunction via inhibition of mTORC1-p70S6K signal pathway. Cell Death Discov. 2017;3:16097.
86. Pei Y, Xie S, Li J, Jia B. Bone marrow-mesenchymal stem cell-derived exosomal microRNA-141 targets PTEN and activates beta-catenin to alleviate myocardial injury in septic mice. Immunopharmacol Immunotoxicol. 2021;43(5):584–93.
87. Shen D, He Z. Mesenchymal stem cell-derived exosomes regulate the polarization and inflammatory response of macrophages via miR-21-5p to promote repair after myocardial reperfusion injury. Ann Transl Med. 2021;9(16):1323.
88. Saad MJ, Santos A, Prada PO. Linking gut microbiota and inflammation to obesity and insulin resistance. Physiology (Bethesda). 2016;31(4):283–93.
89. Jung TW, Park HS, Choi GH, Kim D, Lee T. beta-aminoisobutyric acid attenuates LPS-induced inflammation and insulin resistance in adipocytes through AMPK-mediated pathway. J Biomed Sci. 2018;25(1):27.
90. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761–72. https://doi.org/10.2337/db06-149
91. Sun X, Hao H, Han Q, Song X, Liu J, Dong L, et al. Human umbilical cord-derived mesenchymal stem cells ameliorate insulin resistance by suppressing NLRP3 inflammasome-mediated inflammation in type 2 diabetes rats. Stem Cell Res Ther. 2017;8(1):241.
92. Xie Z, Hao H, Tong C, Cheng Y, Liu J, Pang Y, Si Y, Guo Y, Zang L, Mu Y, Han W. Human umbilical cord-derived mesenchymal stem cells elicit macrophages into an anti-inflammatory phenotype to alleviate insulin resistance in type 2 diabetic rats. Stem Cells. 2016;34(3):627–39.
93. Park MH, Yoon DY, Ban JO, Kim DH, Lee DH, Song S, et al. Decreased severity of collagen antibody and lipopolysaccharide-induced arthritis in human IL-32beta overexpressed transgenic mice. Oncotarget. 2015;6(36):38566–77.
94. Ye L, Mingyue H, Feng Z, Zongshun D, Ying X, Xiong C, Liang L. Systematic review of robust experimental models of rheumatoid arthritis for basic research. Digit Chin Med. 2021;4(4):262–72.
95. He X, Zhang C, Amirsaadat S, Jalil AT, Kadhim MM, Abasi M, Pilehvar Y. Curcumin-loaded mesenchymal stem cell-derived exosomes efficiently attenuate proliferation and inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. Appl Biochem Biotechnol. 2023;195(1):51–67.
96. Singh A, Karrar S. The role of intracellular organisms in the pathogenesis of inflammatory arthritis. Int J Inflam. 2014;2014:158793.
97. Capkova J, Hrncir T, Kubatova A, Tlaskalova-Hogenova H. Lipopolysaccharide treatment suppresses spontaneously developing ankylosing enthesopathy in B10. BR male mice: the potential role of interleukin-10. BMC Musculoskel Disord. 2012;13:1–9.
98. Papaliodis GN, Rosner BA, Dreger KA, Fitzgerald TD, Artornsombudh P, Kothari S, et al. Incidence of and risk factors for cataract in anterior uveitis. Am J Ophthalmol. 2023;254:221–32.
99. Smith JR, Hart PH, Williams KA. Basic pathogenic mechanisms operating in experimental models of acute anterior uveitis. Immunol Cell Biol. 1998;76(6):497–512.
100. Rosenbaum JT, Mcdevitt HO, Guss RB, Egbert PR. Endotoxin-induced uveitis in rats as a model for human disease. Nature. 1980;286(5773):611–3.
101. Oh JY, Kim TW, Jeong HJ, Lee HJ, Ryu JS, Wee WR, et al. Intraperitoneal infusion of mesenchymal stem/stromal cells prevents experimental autoimmune uveitis in mice. Mediators Inflamm. 2014;2014:624640.

102. Bermudez MA, Sendon-Lago J, Seoane S, Eiro N, Gonzalez F, Saa J, et al. Anti-inflammatory effect of conditioned medium from human uterine cervical stem cells in uveitis. Exp Eye Res. 2016;149:84–92.
103. Zhao S, Liu Y, Pu Z. Bone marrow mesenchymal stem cell-derived exosomes attenuate D-GalN/LPS-induced hepatocyte apoptosis by activating autophagy in vitro. Drug Des Devel Ther. 2019;13:2887–97.
104. Lin X, Zhang S, Huang R, Tan S, Liang S, Wu X, Zhuo L, Huang Q. Corrigendum to" Protective effect of tormentic acid from Potentilla chinensis against lipopolysaccharide/D-galactosamine induced fulminant hepatic failure in mice"[Int. Immunopharmacol. 19 (2014) 365–372]. Int Immunopharmacol. 2020;90:107244.
105. Hu Y, Wang Z, Fan C, Gao P, Wang W, Xie Y, Xu Q. Human gingival mesenchymal stem cell-derived exosomes cross-regulate the Wnt/beta-catenin and NF-kappaB signalling pathways in the periodontal inflammation microenvironment. J Clin Periodontol. 2023;50(6):796–806.
106. Li H, Sun L, Wang Y (2023) Inhibition of LPSinduced NLRP3 inflammasome activation by stem cellconditioned culture media in human gingival epithelial cells. Molecular Medicine Reports. 27(5):106
107. Holubova M, Lysak D, Vlas T, Vannucci L, Jindra P. Expanded cryopreserved mesenchymal stromal cells as an optimal source for graft-versus-host disease treatment. Biol J Int Assoc Biol Stand. 2014;42(3):139–44.
108. Zaim M, Karaman S, Cetin G, Isik S. Donor age and long-term culture affect differentiation and proliferation of human bone marrow mesenchymal stem cells. Ann Hematol. 2012;91(8):1175–86.
109. Hermann A, List C, Habisch HJ, Vukicevic V, Ehrhart-Bornstein M, Brenner R, et al. Age-dependent neuroectodermal differentiation capacity of human mesenchymal stromal cells: limitations for autologous cell replacement strategies. Cytotherapy. 2010;12(1):17–30.
110. Gonzalez-Rey E, Anderson P, Gonzalez MA, Rico L, Buscher D, Delgado M. Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis. Gut. 2009;58(7):929–39.
111. Zhang J, Luo X, Huang C, Pei Z, Xiao H, Luo X, et al. Erythropoietin prevents LPS-induced preterm birth and increases offspring survival. Am J Reprod Immunol. 2020;84(3):e13283.
112. Liu W, Xu C, You X, Olson DM, Chemtob S, Gao L, Ni X. Hydrogen sulfide delays LPS-induced preterm birth in mice via anti-inflammatory pathways. PLoS ONE. 2016;11(4):e0152838.
113. Tsuboi I, Harada T, Hirabayashi Y, Aizawa S. Senescence-accelerated mice (SAMP1/TA-1) treated repeatedly with lipopolysaccharide develop a condition that resembles hemophagocytic lymphohistiocytosis. Haematologica. 2019;104(10):1995.
114. Sliwa L, Macura B, Majewska-Szczepanik M, Szczepanik M. Lack of TCRalphabeta+ CD8+ and TCRgammadelta+ lymphocytes ameliorates LPS induced orchitis in mice–preliminary histological observations. Folia Biol (Krakow). 2014;62(1):67–71.
115. Deng SL, Zhang BL, Reiter RJ, Liu YX. Melatonin ameliorates inflammation and oxidative stress by suppressing the p38MAPK Signaling pathway in LPS-induced sheep orchitis. Antioxidants. 2020;9(12):1277.

Publisher's Note