Role of mesenchymal stem cells in sepsis and their therapeutic potential in sepsis-associated myopathy (Review)

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Abstract. Sepsis-induced myopathy (SIM) is one of the leading causes of death in critically ill patients. SIM mainly involves the respiratory and skeletal muscles of patients, resulting in an increased risk of lung infection, aggravated respiratory failure, and prolonged mechanical ventilation and hospital stay. SIM is also an independent risk factor associated with increased mortality in critically ill patients. At present, no effective treatment for SIM has yet been established. However, mesenchymal stem cells (MSCs) have emerged as a promising therapeutic approach and have been utilized in the treatment of various clinical conditions. A significant body of basic and clinical research supports the efficacy of MSCs in managing sepsis and muscle-related diseases. This literature review aims to explore the relationship between MSCs and sepsis, as well as their impact on skeletal muscle-associated diseases. Additionally, the present review discusses the potential mechanisms and therapeutic benefits of MSCs in the context of SIM.

Contents

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1. Introduction

Sepsis is a life-threatening condition characterized by the dysregulated response of the body to infection, leading to multiple organ dysfunction syndrome. It is a major factor contributing to death in patients admitted to the intensive care unit (ICU) (1-3). Sepsis-induced myopathy (SIM), also known as ICU-acquired weakness, is a common complication associated with sepsis. SIM is characterized by symmetrical atrophy, and weakness of the respiratory system and limb skeletal muscles, leading to prolonged mechanical ventilation, challenges in weaning patients off ventilators and limb dysfunction (4-6). This condition substantially affects the clinical course and recovery of patients, exacerbating their overall morbidity and prolonging their stay in the ICU (7,8).

The incidence of SIM is as high as 40% among critically ill patients in the ICU (5-7). SIM is associated with an increased risk of mortality and long-term functional impairment (9-12). Muscle wasting in sepsis occurs early and rapidly within the first 10 days of ICU admission (13). A meta-analysis of 10 cohort studies including 2,396 patients with sepsis found that patients with sepsis with sarcopenia had a significantly higher risk of early mortality than patients with sepsis without sarcopenia (8). Furthermore, critically ill patients who survive often experience reduced quality of life after discharge, primarily owing to the decline in physical function caused by skeletal muscle atrophy (14-16). Despite marked advancements in medicine and technology, developing effective treatments for SIM remains challenging.

Mesenchymal stem cells (MSCs) are pluripotent stem cells derived from the mesoderm, and they are predominantly found in mesenchymal and connective tissues. MSCs can differentiate into bone, cartilage, muscle, fat and other tissues, and possess anti-inflammatory, immunoregulatory and paracrine properties. MSCs have shown efficacy in the treatment of cardiovascular diseases (17,18), respiratory diseases (19,20), motor system disorders (21) and sepsis (22). Furthermore, several studies have indicated that MSCs can

enhance the function of organs affected by sepsis, including the heart, lungs, liver and kidneys (23-26). These findings suggest that MSCs may possess considerable potential in treating SIM. The present review aims to summarize the sources and biological characteristics of MSCs and their therapeutic potential in SIM.

2. Definition and properties of MSCs

Definition of MSCs. MSCs are a class of pluripotent stem cells originating from the mesoderm. They were first described by Friedenstein *et al* (27) in 1968 as adherent, fibroblast-like, non-hematopoietic precursor cells. In 2006, the International Society for Cellular Therapy established three primary criteria for defining MSCs: i) Adherence to plastic in standard culture conditions; ii) expression of the surface markers CD105, CD90 and CD73, along with the absence of HLA-DR, CD34, CD45, CD19 and CD11b; and iii) the ability to differentiate into osteoblasts, chondrocytes and adipocytes under appropriate culture conditions *in vitro* (28).

Origin and properties of MSCs. MSCs were initially isolated from the bone marrow, which remains their primary source; therefore, they are often referred to as bone marrow-derived mesenchymal stromal cells (BMSCs). In addition, MSCs are found in the adipose tissue, muscle, tendon, umbilical cord, placenta, spleen, peripheral blood and dental pulp (29-31). Some studies have identified perivascular cells as another source of MSCs. These supportive cells of the vessel wall exhibit chemotactic activity in response to inflammation and injury, and have an MSC-like phenotype (32).

Owing to their robust proliferative capacity and multi-directional differentiation potential, MSCs can differentiate into myocytes, osteoblasts, chondrocytes, adipocytes, hepatocytes, stromal cells and other cell types under suitable culture conditions (29-32). Furthermore, MSCs possess anti-inflammatory (33) and immunomodulatory properties (34,35). Upon injury or inflammation, MSCs migrate to the site of damage and interact with immune cells to secrete cytokines, scavenge pathogens, suppress inflammatory responses, and reduce oxidative stress and apoptosis (36). The mechanisms through which MSCs repair tissue damage include: i) Direct differentiation or cell fusion; ii) transfer of exosomes, cytokines or organelles to injured cells through tunnelling nanotubes (TNTs); and iii) promotion of tissue repair by releasing cytokines in a paracrine manner (37). MSCs are widely available, and easy to extract, culture and expand. The lack of major histocompatibility complex II or co-stimulatory factors endows MSCs with specific immune-privileged properties (38). These characteristics make MSC transplantation a viable treatment option for various diseases (39,40).

3. MSCs and organ failure in sepsis

In numerous preclinical studies (25,26,36,39,41), MSCs have been shown to serve an immunomodulatory and protective role in organ function impairment associated with sepsis, including in the brain, lungs, liver, kidneys, heart, intestines and blood vessels (Fig. 1).

MSCs and septic lung injury. The respiratory system is particularly vulnerable to sepsis (41). The primary pathological changes observed in sepsis include intrapulmonary inflammatory cell infiltration, release of inflammatory mediators, pulmonary capillary thrombosis, interstitial pulmonary edema and pulmonary fibrosis. These changes manifest primarily as progressive dyspnea and intractable hypoxemia in patients with acute lung injury secondary to sepsis (42). The activation and recruitment of inflammatory cells, such as neutrophils and macrophages, in pulmonary circulation serve a crucial role in the onset and progression of septic lung injury (43,44). Neutrophils activate Toll-like receptor (TLR)4 and $CD14^+$ T cells, promoting the release of inflammatory mediators such as IL-1β, TNF-α, NO and reactive oxygen species (ROS). These mediators damage the alveolar-capillary interface, and the cellular barrier between the alveolar epithelium and endothelium, increasing the permeability of the alveolar-capillary membrane and leading to interstitial lung edema (45-47). Additionally, endotoxins and inflammatory factors stimulate the release of tissue factor in the lungs, activating the exogenous coagulation pathway, which releases thrombin, and leads to pulmonary capillary embolism and interstitial fibrosis. Thrombin further promotes neutrophil adhesion and activation, exacerbating lung injury (48-50).

Owing to their immunomodulatory properties, MSCs can inhibit the release of inflammatory cytokines in the lungs during sepsis, thereby alleviating lung injury. Studies have demonstrated that MSCs can reduce the number of inflammatory cells in the alveolar lavage fluid of septic mice and inhibit the release of inflammatory factors, such as IL-1β, IL-6 and TNF-α, thereby correcting the immune imbalance (51-53). Chen *et al* (54) revealed that MSCs used in combination with melatonin reduced the number of $CD14^+$ and $CD68^+$ T cells, and the levels of IL-6 in the lungs during acute lung injury in sepsis, thereby attenuating the inflammatory response. Moreover, MSCs secrete antimicrobial peptides (such as LL-37), complement components (such as C5a) and other antimicrobial substances to inhibit the proliferation of pathogenic microorganisms and promote macrophage polarization toward the M2 phenotype, enhancing the phagocytic activity of macrophages and reducing the intrapulmonary microbial load (55-59). Activation of the exogenous coagulation pathway and formation of microthrombi in pulmonary capillaries are other crucial causes of septic lung injury. Tan *et al* (60) validated that MSCs reduced thrombin levels in pulmonary microcirculation, alleviated microcirculation embolism and improved pulmonary blood circulation. Furthermore, MSCs can alleviate sepsis-induced lung injury by regulating the expression of microRNAs (miRNAs) in exosomes (61,62).

MSCs and myocardial injury in sepsis. Sepsis-induced myocardial dysfunction (SIMD) is one of the most common complications of sepsis. The pathogenic factors of SIMD include the release of myocardial depressant factor, upregulation of NO, impairment of myocardial calcium homeostasis and mitochondrial dysfunction. SIMD manifests primarily as myocardial ischemia and hypoxia, systolic myocardial dysfunction, and reduced left ventricular ejection fraction (EF), resulting in inadequate tissue and organ perfusion (63,64). TLRs on cardiomyocyte membranes activate downstream

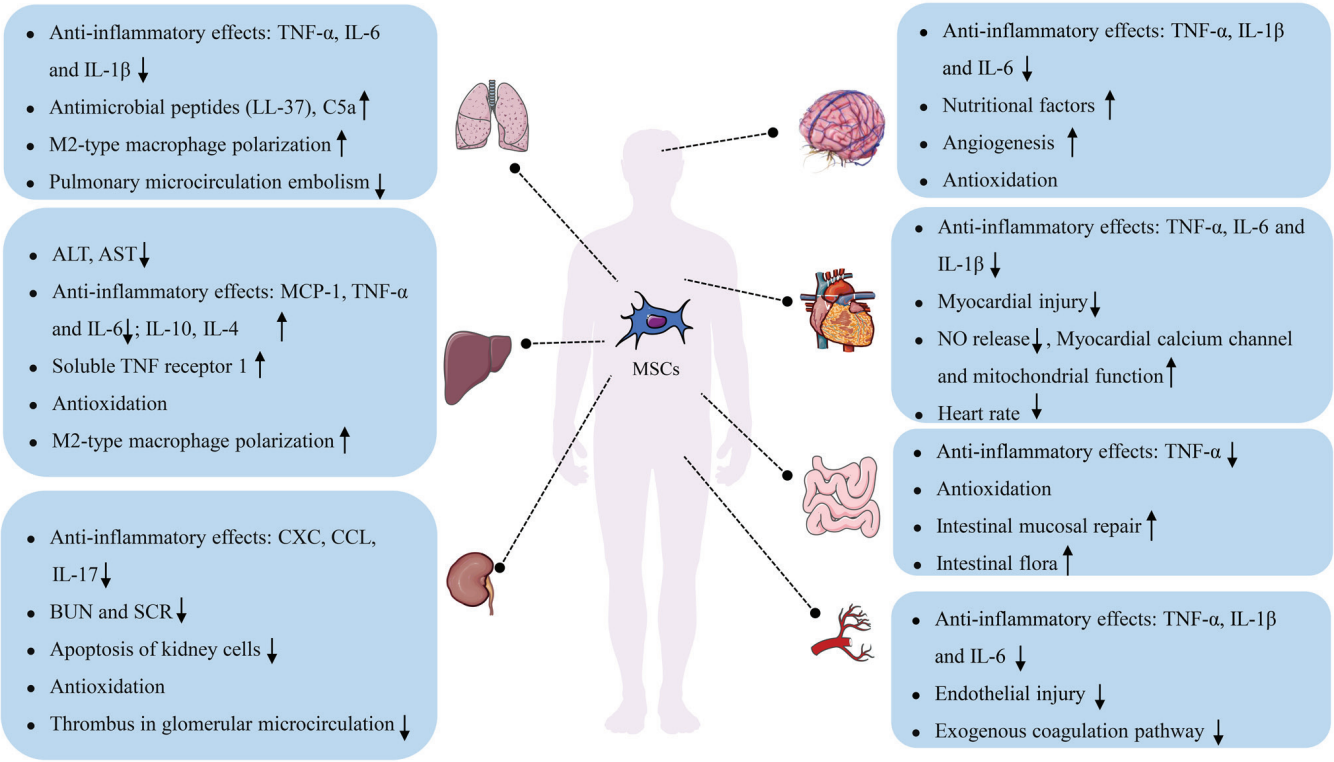

Figure 1. Protective effect of MSCs on organ function in sepsis and its mechanism. In numerous preclinical studies, MSCs have been found to serve an immunomodulatory and protective role in organ function impairment associated with sepsis, including the brain, lungs, liver, kidneys, heart, intestines and blood vessels. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; MCP-1, monocyte chemotactic protein 1; MSCs, mesenchymal stem cells; SCR, serum creatinine.

mTOR/NF-κB and mTOR/Akt signaling pathways by recognizing pathogen-associated molecular patterns and danger-associated molecular patterns, resulting in the release of inflammatory factors, such as TNF-α and IL-6, which directly contribute to myocardial injury (65-67). These inflammatory factors activate myocardial endothelial cells, leading to increased secretion of inducible NO synthase (iNOS) and excessive production of NO. Excess NO inhibits type I calcium channels and myocardial mitochondrial function, resulting in systolic dysfunction and decreased cardiac output (68-70). Additionally, the ratio of anti-apoptotic to pro-apoptotic proteins decreases in sepsis, leading to myocardial damage (71).

Several studies have reported that MSCs attenuate inflammatory cell infiltration in cardiomyocytes during sepsis, alleviate myocardial injury, and improve myocardial contractility. Wu *et al* (72) reported that MSCs can markedly improve cardiac EF by reducing the expression of TLRs; inhibiting the NF-κB signaling pathway; and decreasing the levels of inflammatory factors, such as IL-1β, IL-6 and TNF-α, in the plasma and myocardium of septic mice. Weil *et al* (73) showed that, in addition to reducing the levels of myocardial inflammatory factors, MSCs can decrease the frequency of myocardial contraction, thereby improving myocardial function. Additionally, MSCs have been shown to secrete exosomes enriched with miRNA-223, which inhibits myocardial inflammatory responses and alleviates myocardial injury (74). Taken together, MSCs can attenuate the inflammatory response, inhibit NO release, improve myocardial calcium channel activity and mitochondrial function, and alleviate myocardial injury in sepsis by inhibiting inflammatory signaling pathways and secreting exosomes.

MSCs and septic liver injury. The liver exhibits the most robust inflammatory response to sepsis (75,76). Lipopolysaccharide in the peripheral blood stimulates Kupffer cells to secrete high-mobility group protein B1 (HMGB1); in the presence of HMGB1, immune cells release inflammatory factors, such as TNF-α and IL-6 (77,78). Studies have confirmed that TNF-α serves a crucial role in septic liver injury (77,78). Liver cells are rich in TNF-α receptors and TNF-α can directly cause liver injury. Additionally, TNF-α stimulates the release of other inflammatory factors, such as IL-6 and IL-1β; HMGB1 interacts with these factors, forming an inflammatory cascade that exacerbates liver injury. Moreover, TNF-α induces hepatocyte apoptosis, and recruits and activates inflammatory cells, such as neutrophils, further aggravating liver injury (77,78). Oxidative stress can increase the levels of ROS and NO in the liver, disrupting epithelial integrity, increasing hepatic permeability and triggering cholestasis (79).

Amplification of the inflammatory response is the primary cause of sepsis-induced liver injury. MSCs can inhibit the inflammatory response and the migration of inflammatory cells to the liver, thereby alleviating liver injury. Several studies have shown that MSCs can inhibit the release of TNF-α, IL-6 and monocyte chemotactic protein (MCP)-1, and upregulate the anti-inflammatory factors IL-10 and IL-4 to correct immune imbalance. In addition, MSCs can suppress the migration and activation of neutrophils in the liver, thereby alleviating liver damage caused by inflammation (80-82). Studies have demonstrated that adipose tissue-derived MSCs secrete TNF receptor 1, and attenuate apoptosis and inflammatory responses in the liver, thus improving the survival of

septic mice (83,84). Furthermore, MSCs can promote macrophage polarization toward the M2 phenotype, clear pathogens, increase intrahepatic glycogen reserves, reduce hepatic oxidative stress, and decrease the plasma levels of aspartate aminotransferase and alanine aminotransferase (59).

MSCs and septic kidney injury. Sepsis-associated kidney injury (SAKI) involves the development of structural and functional abnormalities in the kidney following sepsis in patients without pre-existing kidney injury (85,86). Crucial factors involved in the pathogenesis of SAKI include inflammatory responses, abnormal intrarenal microcirculation, and altered bioenergetic processes of renal cells (85,86). The global incidence of SAKI in patients with sepsis ranges from 19 to 23%, whereas that in patients with septic shock is substantially higher, ranging from 51 to 66.9% (85,86). The excessive release of inflammatory factors in sepsis causes damage to glomerular capillary endothelial cells and tubular epithelial cells, resulting in increased glomerular capillary permeability and decreased glomerular filtration rate (GFR) (87,88). Furthermore, inflammatory factors can induce the release of tissue factor and activate the exogenous coagulation pathway, leading to the formation of microthrombi in renal microcirculation. Owing to ischemia and hypoxia, the production of ROS is increased in renal tissues, causing increased mitochondrial permeability and decreased mitochondrial membrane potential, leading to mitochondrial dysfunction and worsening of renal injury (89,90).

Studies have shown that MSCs can reduce the incidence of SAKI and attenuate renal tissue damage. Luo *et al* (91) showed that treatment with 10^6 MSCs within 3 h of induction of sepsis in mice reduced the incidence of SAKI when compared with control mice. After 24 h of induction, MSCs reduced the release of inflammatory factors, such as CXC, CCL and IL-17, and inhibited the migration of neutrophils to the kidney, improving renal tubular function and prolonging survival in mice with sepsis. Cóndor *et al* (92) demonstrated that umbilical cord Wharton's jelly-derived MSCs suppressed renal cell apoptosis, NF-κB expression, and the release of IL-1 and IL-6, thereby improving GFR and renal tubular function in sepsis. The combined use of adipose-derived MSCs (AMSCs) and exendin-4 (a glucagon-like peptide-1 analogue) can reduce renal oxidative stress and fibrosis in sepsis (93), and the combined use of MSCs and melatonin has been shown to substantially reduce NF-κB expression and the release of inflammatory factors (94). Additionally, MSCs can inhibit thrombosis in glomerular microcirculation, prevent the destruction of glomerular endothelial cells and restore renal function (90,92).

MSCs and sepsis-associated encephalopathy. Sepsis-associated encephalopathy (SAE) is characterized by confusion, coma and other changes in consciousness (95,96). Notably, 10-20% of patients with SAE experience long-term cognitive dysfunction worldwide (97). The pathogenesis of SAE primarily involves neuroinflammation, blood-brain barrier (BBB) impairment, cerebrovascular microcirculation disorder and mitochondrial dysfunction (95,96). MSCs can inhibit neuroinflammatory responses and promote the restoration of intracerebral microcirculation, thereby improving cognitive dysfunction following sepsis. Studies have demonstrated that MSCs injected via the internal jugular vein and peripheral vein can cross the BBB and colonize damaged sites in the brain (98,99). These infiltrating cells have been shown to inhibit the secretion of IL-6, IL-1β and TNF-α, and the proliferation and activation of microglia, consequently attenuating the inflammatory response (100-102). Tan *et al* (103) and Silva *et al* (104) demonstrated that MSCs improved cognitive function in septic mice by inhibiting neurological and peripheral inflammation. Studies have demonstrated that MSCs can secrete various trophic factors, including brain-derived neurotrophic factor, which promotes the differentiation of new neurons, and vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which promote local vascular regeneration and improve blood circulation in brain tissue (105-108). MSCs can transfer their mitochondria to damaged cells via membrane channels (TNTs), thereby continuing aerobic respiration and reducing ROS production. In addition, they can alleviate mitochondrial dysfunction and reduce oxidative stress (109). Liu *et al* (110) showed that olfactory mucosa-derived MSCs may promote the expression of UBIAD1, improving mitochondrial function. Cao *et al* (111) and Wang *et al* (112) demonstrated that MSCs could inhibit the expression of brain-iNOS and NADPH oxidase, and that MSC-derived exosomes contain antioxidant components, such as miRNAs, which may alleviate damage caused by oxidative stress (113).

MSCs and intestinal dysfunction in sepsis. Intestinal dysfunction can increase the global morbidity and mortality rates of patients with sepsis in the ICU to as high as 41.9% (114). MSCs can protect against sepsis-induced intestinal dysfunction by attenuating the intestinal inflammatory response, enhancing mitochondrial function and improving microbial diversity. Studies have demonstrated that MSCs may inhibit the production of the inflammatory factor TNF-α and promote the secretion of the anti-inflammatory factor IL-10 by modulating dendritic cell function (115,116). Chen *et al* (117) and Koliaraki *et al* (118) showed that MSCs can respond to TNF, inhibit the production of TNF-α and IL-12, and promote the secretion of IL-4 and IL-10. Parikh *et al* (119) and Zheng *et al* (120,121) showed that MSC-derived microvesicles could deliver mfn2 and PGC-1α to endothelial cells, promoting mitochondrial production and delivering the mitochondria directly to damaged endothelial cells to improve cellular energy metabolism and reduce oxidative stress-induced damage. Phinney *et al* (122) demonstrated that MSCs can promote mitochondrial autophagy. Additionally, MSCs have been shown to promote intestinal mucosal repair and increase the diversity of intestinal flora (123). For example, Valcz *et al* (124) showed that MSCs can colonize damaged intestinal mucosa and differentiate into intestinal mesenchymal or epithelial cells. Hayashi *et al* (125) also found that MSCs can secrete VEGF and TGF to promote the repair of damaged intestinal mucosa. Furthermore, MSCs may improve the diversity of intestinal flora, regulate the secretion of IgA and maintain intestinal symbiotic homeostasis (126).

MSCs and sepsis-induced coagulopathy (SIC). SIC is characterized by an enhanced coagulation response and impairment of anticoagulation mechanisms, leading to extensive

microthrombosis (127). The incidence of SIC in patients with sepsis is 50-70%, with ~35% of patients progressing to disseminated intravascular coagulation worldwide (128). The pathogenesis of SIC primarily includes the release of inflammatory mediators, endothelial cell injury, activation of the exogenous coagulation pathway, and inhibition of the anticoagulation and fibrinolytic systems (129). Studies have validated that MSCs possess potent anti-inflammatory and immunomodulatory functions. For example, Wang *et al* (130,131) and Miao *et al* (82) demonstrated that MSCs could inhibit the activity of the NLRP3 inflammasome, reduce the levels of IL-1β, IL-6 and TNF-α, and promote the secretion of IL-10. Furthermore, MSCs can alleviate vascular endothelial cell injury, thereby improving the anticoagulant function of protein C. Notably, Baudry *et al* (132) showed that MSCs pretreated with interferon-γ (IFNγ) reduced selectin-E levels and increased intercellular adhesion molecule-1 levels, thereby accelerating leukocyte flow in the blood, reducing leukocyte adhesion and attenuating vascular endothelial cell injury in septic mice (132). By improving the anticoagulant function of protein C, MSCs can substantially decrease the levels of von Willebrand factor and tissue factor in plasma, inhibit the exogenous coagulation pathway and reduce thrombin production, consequently ameliorating SIC (60).

4. Pathophysiological relationship between MSCs and skeletal muscle

MSCs possess a notable capacity for directed differentiation, which enables them to transform into skeletal muscle cells under appropriate conditions (133,134). *In vitro* studies have demonstrated that the transcription factor Pax-3 can induce the differentiation of MSCs to myogenic cells (135), whereas intracellular structural domain genes can drive the differentiation of MSCs to skeletal muscle cells (136). Additionally, mechanical traction can stimulate BMSCs to differentiate into skeletal muscle cells (137). An *in vivo* study validated that embryonic MSCs (EMSCs) promoted the repair of injured tibialis anterior muscle in mice, with >60% of EMSCs differentiating into skeletal myocytes (138).

In addition to their ability to differentiate into skeletal muscle cells, MSCs can enhance the functional recovery of injured skeletal muscles. In a previous study, BMSCs isolated from the tibia and femur of green fluorescent protein-expressing transgenic Sprague-Dawley rats were cultured and expanded *in vitro*. After these BMSCs were transplanted at the site of skeletal muscle injury, the contractile force of the injured muscle reached close to pre-injury levels after 1 month. By contrast, the contractile force in control rats recovered to only ~80% of the pre-injury levels (139). Another study showed that MSCs improved skeletal muscle function in a cell density-dependent manner, with the most significant treatment effect being observed when the number of transplanted MSCs was $10x10^6$ (140). Notably, the treatment effect was not influenced by the timing of MSC transplantation or the sex of rats (141,142). Furthermore, MSCs have been shown to promote skeletal muscle angiogenesis and increase blood flow. In a previous study, transplantation of hypoxic MSCs in the hindlimb of mice resulted in a 2-fold increase in the number of skeletal muscle capillaries and a 7-fold increase in the number of vascular connections and branches when compared with the control group (139). Additionally, studies have shown that MSCs hold great promise in the treatment of various skeletal myopathies, such as Duchenne muscular dystrophy (143), skeletal muscle denervation atrophy (144) and traumatic skeletal muscle injury (145). These studies provide diverse avenues for further research on MSCs and the treatment of SIM using MSCs.

5. Potential mechanisms of MSCs in the treatment of SIM

Skeletal muscle, accounting for 35-45% of body weight in adult humans, is essential for maintaining all physiological activities. Promoting muscle regeneration and repair in patients with SIM is crucial for improving prognosis and quality of life. Factors that lead to skeletal muscle injury and dysfunction following sepsis include increased protein hydrolysis and decreased protein synthesis (146,147), oxidative stress (148), release of inflammatory mediators (149,150), skeletal muscle apoptosis (151), and skeletal muscle vascular damage. Skeletal muscle repair involves three stages, as follows: Inflammatory response, repair and remodeling. MSCs may enhance skeletal muscle function in SIM through numerous mechanisms (Fig. 2).

Myogenic differentiation. Owing to their multidirectional differentiation potential, MSCs can differentiate into skeletal muscle cells under appropriate conditions to directly repair muscle injury (152). Orlic *et al* (153) suggested that different environments lead to varying MSC differentiation rates, and that direct contact with injured organs or target cells is crucial for myogenic differentiation of MSCs. Egusa *et al* (154) showed that arranging BMSCs according to skeletal muscle fibers markedly improved the efficiency of the transformation of BMSCs to skeletal muscle. Studies have shown that treatment of MSCs with 5-azacytidine (5-AZA) may result in the formation of multinucleated myotubes expressing myosin after 7-11 days (155-157). Meligy *et al* (158) treated BMSCs, AMSCs and skeletal muscle-derived MSCs with 5-AZA and demonstrated that MSCs highly expressed myostatin after 1 week of treatment. In addition, microsatellite cells serve an essential role in the development and regeneration of skeletal muscles. These cells are dormant under physiological conditions but are activated upon muscle injury. Activated microsatellite cells can differentiate into myogenic cells that fuse to form myotubes (159,160). MSCs have been reported to secrete fibroblast growth factor (FGF), HGF and insulin-like growth factor-1 (IGF-1) to induce myogenic differentiation of microsatellite cells (161,162).

Homing of MSCs. Homing refers to the process by which MSCs are captured in the vascular system of the target tissue and subsequently migrate across the vascular endothelium to the target tissue (163). During inflammation or injury, various signaling molecules, such as chemokines, adhesion factors and growth factors, are locally released from the injured tissue, inducing MSCs to migrate to that tissue. Homing is crucial for the safe and effective clinical application of MSCs (164,165). The stromal cell-derived factor 1 (SDF-1)/CXCR-4 axis, comprising SDF-1 and its ligand CXCR-4, serves a vital role in

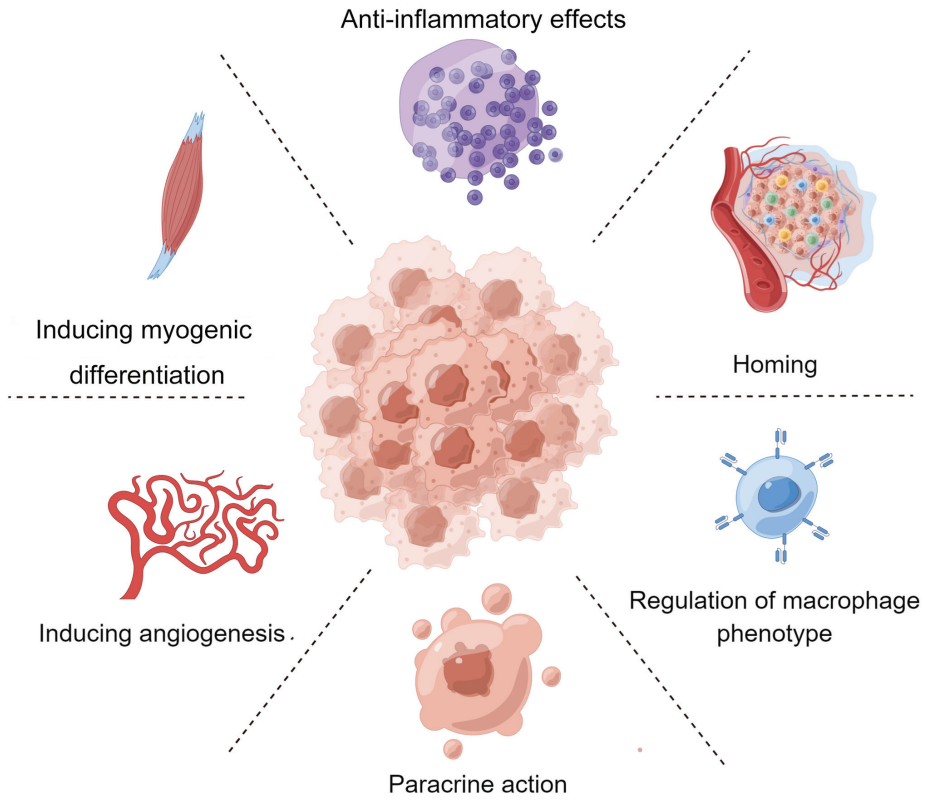

Figure 2. Possible mechanisms of MSCs in the treatment of sepsis-induced myopathy. MSCs have a protective role in skeletal muscle through anti-inflammatory, homing, regulating macrophage phenotype, paracrine action, and inducing angiogenesis and inducing myogenic differentiation in different skeletal muscle myopathy models, demonstrating its therapeutic potential for sepsis-induced myopathy. MSCs, mesenchymal stem cells.

MSC homing. Upon tissue injury, SDF-1α secretion increases, and MSCs expressing CXCR-4 migrate to the injury site along the SDF-1α concentration gradient to participate in tissue repair (166-169). Additionally, MCP (170,171), VEGF (172), HGF (173) and integrins (174) are essential for MSC homing. Ferrari *et al* (175) used BMSCs to treat injured muscles and found that BMSCs can migrate to the injury site, differentiating into skeletal muscle cells and promoting the regeneration of injured muscle fibers. Winkler *et al* (176) used MRI to visualize that labelled MSCs migrated to damaged muscle fibers and fused with them 24 h post-transplantation.

Anti-inflammatory effect of MSCs. In sepsis, the immune function becomes dysregulated, resulting in an uncontrolled inflammatory response, and the release of large amounts of TNF-α, IL-6 and other inflammatory factors. TNF-α promotes the secretion of iNOS, leading to muscle injury, whereas IL-6 has been shown to inhibit the myogenic differentiation of the C2C12 myotube cell line and the elongation of muscle protein peptide chains, causing muscle atrophy (149). The excessive release of inflammatory factors is a key driver of muscle injury (149). MSCs have powerful anti-inflammatory functions and can restore immune balance, an essential mechanism by which MSCs repair tissue damage (177). AMSCs have been shown to inhibit the expression of inflammatory factors, such as TNF-α, IL-6 and ROS, in injured gastrocnemius muscle while upregulating IL-4 and IL-10 levels to suppress the inflammatory response and repair muscle injury (178). BMSCs can reduce muscle fibrosis by inhibiting TGF-β1 expression. Moreover, MSCs can inhibit the activity of natural killer cells, preventing IFN-γ and TNF-α from exerting their effects, and can attenuate the muscle inflammatory response by inhibiting dendritic cell maturation.

MSCs modulate macrophage phenotype. Macrophages are heterogeneous immune cells that can be classified into two phenotypes: M1 and M2, based on their function and markers. M1-type macrophages secrete inflammatory factors, such as TNF-α, IL-1α, IL-6 and IL-12, which can inhibit the myogenic differentiation of C2C12 myotubes and lead to skeletal muscle injury (179-181). Conversely, M2-type macrophages can secrete anti-inflammatory factors, remove pathogens and apoptotic cells, promote myogenic differentiation of C2C12 cells, attenuate the skeletal muscle inflammatory response and facilitate muscle repair (179-181). When MSCs are co-cultured with macrophages *in vitro*, the inflammatory factors secreted by M1-type macrophages have been shown to activate MSCs. In turn, MSCs secrete anti-inflammatory factors, such as IL-10, IL-4 and TGF-β, which can promote the conversion of M1-type macrophages to M2-type macrophages. The release of these mediators is crucial for mediating M2-type macrophage polarization (182). MSCs can also induce M2-type macrophage polarization through the exosome pathway. MSC-derived exosomes have been reported to promote the conversion of M1-type macrophages to M2-type macrophages in infarcted myocardium, thereby reducing the local inflammatory response in a mouse model (182). Exosomal miRNA sequencing has revealed that miRNA-182 in MSC exosomes

may mediate M2-type macrophage polarization (183-185). Additionally, MSCs can facilitate M2-type macrophage polarization via the regulatory T cell pathway (186).

Paracrine effects of MSCs. Paracrine secretion underpins the application of stem cells in tissue regeneration and constitutes a critical mechanism by which MSCs repair skeletal muscle injury. MSCs regulate skeletal muscle repair by releasing various growth factors and exosomes through the paracrine pathway. Studies have confirmed that MSCs secrete IGF-1, VEGF, sphingosine 1-phosphate (S1P) and other cellular growth factors involved in skeletal muscle injury repair (122,137). VEGF has been shown to promote capillary endothelial cell proliferation and the myogenic differentiation of C2C12 cells (187), while IGF-1 can enhance endothelial cell migration to the injury site and repair local blood circulation (188). S1P reduces skeletal muscle apoptosis, promotes myogenic proliferation, and stimulates satellite cell proliferation and differentiation (189). Moreover, MSC-derived exosomes serve an essential role in skeletal muscle repair. It has been found that BMSC-derived exosomes contain FGF-2, platelet-derived growth factor-BB and recombinant granulocyte colony-stimulating factor, which are associated with skeletal muscle regeneration (137,188). Exosomes are also enriched with miRNAs and proteins crucial for skeletal muscle injury repair. For example, miRNA-21 in exosomes inhibits apoptosis, and miRNA-494 promotes MSC myogenic differentiation and vascular regeneration (122,190). Studies have demonstrated that exosomes are enriched in annexin A1, which is essential for myofilament repair after skeletal muscle injury (191,192). Similarly, it has been shown that exosomes contain various proteins related to skeletal muscle injury repair, such as filament proteins and myosins, which can promote the proliferation of skeletal muscle satellite cells and muscle repair (193-195).

MSCs promote skeletal muscle vascular regeneration. Vascular regeneration has a crucial role in repairing skeletal muscle injury, and studies have shown that MSCs can promote this process by secreting cytokines. In 2000, Oswald *et al* (196) first applied VEGF to induce BMSCs to differentiate into vascular endothelial cells, although the differentiation efficiency was low. Since then, researchers have significantly increased the efficiency of vascular endothelial cell differentiation by adding VEFG, IGF-1, FGF and S1P to MSC culture media (197,198). Sassoli *et al* (187) found that MSCs secrete large amounts of VEGF, which promotes skeletal muscle vascular regeneration by activating the Notch-1 signaling pathway. MSCs also activate the TLR-2/TLR-6 pathway to enhance vascular regeneration through paracrine secretion. Grote *et al* (199) significantly increased the secretion of growth factors and cytokines, such as VEGF and granulocyte-macrophage colony-stimulating factor, by adding the TLR-2/TLR-6 agonist MLP-2 to MSC culture media. Additionally, Leroux *et al* (200) found that hypoxia-pretreated MSCs transplanted into skeletal muscle showed increased Wnt4 expression, and a significant increase in skeletal muscle vascular regeneration and blood flow, suggesting that MSCs promote vascular regeneration through the Wnt4 signaling pathway.

6. Limitations of MSCs therapy

MSCs have significant differentiation potential and can repair skeletal muscle injury through various mechanisms. However, several limitations hinder the clinical application of MSCs in treating skeletal muscle injuries.

Firstly, the optimal tissue source of MSCs remains undetermined. MSCs are primarily derived from bone marrow, adipose tissue, cord blood, peripheral blood and dental pulp, with bone marrow being the most common source. However, acquiring BMSCs requires invasive procedures, the isolation rate is low (0.001-0.01%), and the multi-directional differentiation ability of BMSCs decreases with age. Peripheral blood-derived MSCs are easy to obtain and possess the most potent immunosuppressive function, but they take longer to cultivate *in vitro* (201,202). AMSCs have a similar immunomodulatory capacity to dental pulp-derived MSCs (DPMSCs); AMSCs are easy to obtain and have a high cell isolation rate (3%), whereas DPMSCs have strong proliferative capacity (203). However, cord blood-derived MSCs exhibit a higher potential for multi-directional differentiation (203).

Secondly, the administration route for MSCs, whether local or systemic, remains controversial in terms of effectiveness. Local application at the injury site is fast-acting but carries a risk of bleeding (204). Systemic administration methods include subcutaneous, intramuscular, intravenous and intraperitoneal injections, each with varying efficacy. Castelo-Branco *et al* (205) reported that intraperitoneal but not intravenous administration of MSCs exhibited better homing and anti-inflammatory effects, while Gonçalves *et al* (206) reported conflicting findings. Roux *et al* (207) preferred intraperitoneal injection due to the lower probability of pulmonary embolism. Intramuscular and subcutaneous injections can prolong the duration of MSCs *in vivo*, with intramuscular injections showing retention for up to 100 days; however, data on intramuscular injections remain insufficient (204,208).

Finally, the optimal therapeutic dose of MSCs is not well-defined. Although studies have shown that administering $12x10^9$ MSCs is safe, it does not imply that higher doses are more effective. MSCs possess anti-apoptotic, self-replicating and growth-regulating abilities, similar to tumor cells, and administering large doses may pose safety risks (209,210). Some studies have indicated that the effective minimum dose ranges from $10x10^8$ to $15x10^8$, with an optimal dose for aging patients at $10x10^8$. Dose response data showing differential efficacy for improved outcomes were reported in three trials, which indicated that there was no significant difference between the therapeutic effects of $10x10^8$ and $20x10^8$ (211-213). Therefore, further studies are needed to validate the optimal dose for treating skeletal muscle diseases.

7. Discussion of the therapeutic potential of MSCs in SIM

Although advancements in medical technology have improved the early diagnosis and treatment of sepsis, multiple organ failure remains a leading cause of death in patients with sepsis (214). MSCs have emerged as a promising therapeutic option owing to their immunomodulatory, anti-inflammatory and regenerative properties (60,82,104,121). The present review highlights the therapeutic role of MSCs in sepsis-induced organ

failure, focusing on lung injury, myocardial injury, kidney injury, encephalopathy and intestinal dysfunction. Existing studies have suggested that MSCs possess marked potential in the treatment of sepsis-induced organ failure. An in-depth understanding of the mechanisms of MSCs and a comparison of their efficacy across different organs may expand their application, eventually improving the outcomes and reducing the mortality rate of sepsis.

SIM results from a complex interplay of inflammation, oxidative stress and metabolic dysregulation (4-6,215,216). It not only results from sepsis but also influences the progression and outcomes of the disease (215). It contributes to malnutrition and negative nitrogen balance, weakening the overall condition and immune response of patients, thus making it more challenging to combat the infection (8,217). Additionally, atrophy of respiratory muscles, such as the diaphragm, can impair breathing and increase the likelihood of respiratory failure (218), necessitating prolonged mechanical ventilation, which in turn increases morbidity and mortality (218). Therefore, SIM is closely associated with the progression of sepsis in a cycle that worsens clinical outcomes. Addressing skeletal muscle atrophy through early intervention, nutritional support, physical rehabilitation and novel therapeutic approaches can help disrupt this cycle, and improve recovery and survival rates in patients with sepsis.

MSCs possess several characteristics that make them promising candidates for treating SIM. First, MSCs exert anti-inflammatory and immunomodulatory effects, which can attenuate the excessive inflammatory response caused by sepsis (111). Second, MSCs can secrete various growth factors and cytokines that promote tissue repair and regeneration (219). They can enhance the repair and regeneration of skeletal muscles by secreting exosomes and microvesicles that deliver beneficial molecules to the damaged site (220). Third, the antioxidant activity of MSCs can alleviate oxidative stress-induced damage in muscle cells. In particular, MSCs decrease the production of free radicals by improving the intracellular redox balance, thereby protecting muscle cells from oxidative stress-induced injury (221). Although preclinical studies have strongly supported the potential benefits of MSCs in the treatment of sepsis, further clinical research is warranted to translate the findings into effective treatments. A better understanding of the use of MSCs may help improve clinical outcomes and reduce the long-term impact of sepsis on skeletal muscle health.

8. Outlook and conclusion

SIM is a common complication in patients with sepsis, significantly affecting prognosis and quality of life, with a lack of effective therapeutic measures. MSCs have emerged as a novel treatment for certain refractory diseases, and have demonstrated good clinical efficacy in treating tissue repair, skeletal muscle diseases and sepsis-related conditions. The present review specifically focused on the mechanisms and therapeutic potential of MSCs in SIM. While there have been some studies on the application of MSCs in sepsis, a focused review on SIM is still lacking. Secondly, this review integrated the latest experimental and clinical data, providing comprehensive evidence for the application of MSCs in SIM. By synthesizing these data, this review not only highlighted the therapeutic potential of MSCs but also detailed their mechanisms of action. This may help to fill the current gaps in the literature, and offers valuable guidance for future research and clinical practice. Finally, a detailed comparison of the efficacy of MSCs in treating damage across different organs was conducted, including the lungs, heart, kidneys, brain and intestines. This comparative analysis offers a new perspective, demonstrating the role of MSCs in multi-organ protection. By elucidating how MSCs can mitigate damage in various organs, the present study provides a holistic view of their therapeutic potential, which is crucial for developing effective treatment strategies for SIM. Therefore, the present study may improve the understanding and application of MSCs in SIM, and their underlying mechanisms. However, skeletal muscle repair is a highly complex biological process. The mechanisms, efficiency and safety of MSCs in treating SIM have not yet been fully elucidated, necessitating further research to clarify these aspects. More clinical studies are required to obtain sufficient data to verify the safety and therapeutic effects of MSCs in treating SIM. As research on MSCs progresses, there is reason to believe that MSCs will become an effective treatment for SIM in the near future.

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Authors' contributions

All authors contributed to the design of the study and writing of the manuscript. DW, SQ, LX, YL and CW contributed to the literature collection, analysis and interpretation for writing this review. DW and YW wrote the main manuscript text and prepared the figures. ZL, XB and YL revised the article critically for important intellectual content. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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