World Journal of Stem Cells

Submit a Manuscript: https://www.f6publishing.com

*World J Stem Cells* 2023 July 26; 15(7): 654-664

DOI: 10.4252/wjsc.v15.i7.654

ISSN 1948-0210 (online)

OPINION REVIEW

# Could extracellular vesicles derived from mesenchymal stem cells be a potential therapy for acute pancreatitis-induced cardiac injury?

Long-Fei Pan, Ze-Qun Niu, Song Ren, Hong-Hong Pei, Yan-Xia Gao, Hui Feng, Jiang-Li Sun, Zheng-Liang Zhang

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Gupta R, India; Sharma V, India

**Received:** April 27, 2023
**Peer-review started:** April 27, 2023
**First decision:** May 19, 2023
**Revised:** June 11, 2023
**Accepted:** June 27, 2023
**Article in press:** June 27, 2023
**Published online:** July 26, 2023

**Long-Fei Pan, Ze-Qun Niu, Hong-Hong Pei, Yan-Xia Gao, Hui Feng, Jiang-Li Sun, Zheng-Liang Zhang,** Emergency Department, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China

**Song Ren,** Department of Geriatric Digestive Surgery, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China

**Corresponding author:** Long-Fei Pan, MD, Associate Chief Physician, Associate Professor, Emergency Department, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 Xiwu Road, Xincheng District, Xi'an 710004, Shaanxi Province, China. panlonf@yeah.net

## Abstract

Acute pancreatitis (AP) often leads to a high incidence of cardiac injury, posing significant challenges in the treatment of severe AP and contributing to increased mortality rates. Mesenchymal stem cells (MSCs) release bioactive molecules that participate in various inflammatory diseases. Similarly, extracellular vesicles (EVs) secreted by MSCs have garnered extensive attention due to their comparable anti-inflammatory effects to MSCs and their potential to avoid risks associated with cell transplantation. Recently, the therapeutic potential of MSCs-EVs in various inflammatory diseases, including sepsis and AP, has gained increasing recognition. Although preclinical research on the utilization of MSCs-EVs in AP-induced cardiac injury is limited, several studies have demonstrated the positive effects of MSCs-EVs in regulating inflammation and immunity in sepsis-induced cardiac injury and cardiovascular diseases. Furthermore, clinical studies have been conducted on the therapeutic application of MSCs-EVs for some other diseases, wherein the contents of these EVs could be deliberately modified through prior modulation of MSCs. Consequently, we hypothesize that MSCs-EVs hold promise as a potential therapy for AP-induced cardiac injury. This paper aims to discuss this topic. However, additional research is essential to comprehensively elucidate the underlying mechanisms of MSCs-EVs in treating AP-induced cardiac injury, as well as to ascertain their safety and efficacy.

**Key Words:** Acute pancreatitis; Cardiac injury; Mesenchymal stem cells; Extracellular vesicles; Inflammation; Therapeutic strategies

**Core Tip:** Acute pancreatitis (AP) often causes cardiac injury, leading to poor prognosis. Mesenchymal stem cells (MSCs) and their extracellular vesicles (EVs) possess anti-inflammatory properties and have been studied as a potential therapy for inflammatory diseases. Although preclinical studies on the use of MSCs-EVs for AP-induced cardiac injury are lacking, research has demonstrated their positive effects in various inflammatory diseases such as sepsis-induced cardiac injury and cardiovascular diseases. Therefore, MSCs-EVs may represent a promising strategy for treating AP-induced cardiac injury.

**Citation:** Pan LF, Niu ZQ, Ren S, Pei HH, Gao YX, Feng H, Sun JL, Zhang ZL. Could extracellular vesicles derived from mesenchymal stem cells be a potential therapy for acute pancreatitis-induced cardiac injury? *World J Stem Cells* 2023; 15(7): 654-664
**URL:** https://www.wjgnet.com/1948-0210/full/v15/i7/654.htm
**DOI:** https://dx.doi.org/10.4252/wjsc.v15.i7.654

## INTRODUCTION

Acute pancreatitis (AP) often results in important extra-pancreatic organ damage, including the lungs, kidneys, heart, liver, and intestines[1-3]. Cardiac injury associated with AP frequently manifests with non-specific symptoms, or is overshadowed by symptoms caused by AP itself, making it easy to be overlooked and leading to the misconception that cardiac injury is uncommon in AP[4]. However, studies have reported a 100% incidence rate of cardiac injury in all cases of AP, with cardiac injury occurring earlier than damage to organs such as the lungs and kidneys[5,6]. The severity of cardiac injury is closely related to the severity of AP, with severe acute pancreatitis (SAP) having the highest occurrence rate of severe cardiac injury, which can reach up to 60.5%, and in some severe cases, SAP can even lead to cardiac dysfunction[7,8]. Retrospective analysis has also confirmed significantly elevated serum cardiac injury markers in SAP patients upon admission[6]. Among SAP patients who succumbed to multiple organ dysfunction syndrome, approximately 86.4% experienced cardiovascular failure[9]. Cardiac injury is a significant contributing factor to the challenges in curing and increased mortality rates of SAP, with approximately 10%-30% of SAP fatalities attributed to SAP-induced cardiac injury[7]. Therefore, it is crucial to give adequate clinical attention to AP-induced cardiac injury. However, the exact mechanisms underlying AP-induced cardiac injury are complex, involving multiple factors, and the precise mechanism remains unclear, posing a significant challenge in the development of effective treatments.

Mesenchymal stem cells (MSCs) are among the most readily accessible types of stem cells, which can be extracted from sources such as bone marrow, adipose tissue, umbilical cord, and dental pulp. They possess unique characteristics of self-renewal and multi-directional differentiation, allowing them to differentiate into various cell types. MSCs participate in various inflammatory diseases through the paracrine secretion of bioactive molecules and can also promote tissue repair [10,11]. Moreover, MSCs can regulate the phenotype of immune cells and alleviate inflammatory responses[12]. However, the long preparation period required for MSCs transplantation makes it unsuitable for emergency situations. Additionally, MSCs carry the risks of immunogenicity and tumorigenicity, which to some extent limits their application [13].

The various biological functions of MSCs are primarily carried out through the secretion of bioactive molecules, encompassing a diverse range of chemical factors, cytokines, immunomodulatory factors, extracellular matrix components, as well as several other proteins, nucleic acids, and lipids[14]. MSCs also release extracellular vesicles (EVs) that serve as the principal mediators for MSCs to exert their immune and inflammatory regulatory effects. MSCs-EVs act as carriers, transporting bioactive molecules such as growth factors, cytokines, chemokines, mRNA, miRNA, lncRNA, *etc.*, which they transmit through paracrine or endocrine secretion[15]. EVs have been identified as effective therapeutic vehicles capable of delivering various proteins and regulatory genes to target organs. MSCs-EVs are believed to possess similar anti-inflammatory and other biological effects as MSCs, while offering advantages over MSCs such as smaller size, targeted transport, and low immunogenicity[16]. Therefore, MSCs-EVs hold the potential to replace MSCs in exerting therapeutic effects on certain diseases.

## MSCS-EVS HAVE EMERGED AS A PROMISING TREATMENT OPTION FOR VARIOUS INFLAMMATORY DISEASES

With the increasing focus on the immunomodulatory effects of MSCs, extensive research has been conducted to investigate their mechanisms in inflammatory diseases. MSCs-EVs, which possess similar anti-inflammatory effects as MSCs and the ability to avoid potential risks associated with cell transplantation, have been widely studied in the context of inflammatory diseases. Multiple studies have demonstrated the efficacy of MSCs-EVs in improving inflammatory responses in animal models of various diseases, including brain ischemia-reperfusion injury, acute lung injury/acute respiratory distress syndrome (ARDS), inflammatory bowel disease, acute liver injury, acute kidney injury, sepsis, AP, myocardial ischemia-reperfusion injury, and acute myocardial infarction[17]. For instance, MSCs-EVs can regulate inflammatory and immune responses following brain ischemia by modulating the central nervous system, peripheral immune system, and immune regulatory molecules, thereby promoting neurological function recovery[18]. By transmitting miRNA, MSCs-EVs can reduce the secretion of pro-inflammatory cytokines, oxidative stress, and prevent

lung tissue infiltration by inflammatory cells, thereby alleviating ventilator-associated lung injury[19]. Moreover, MSCs-EVs can regulate gene expression and inhibit the production of inflammatory cytokines by transmitting miRNA or other bioactive molecules, thereby reducing neutrophil infiltration, improving lung inflammation and oxidative damage, and promoting the survival, proliferation, and differentiation of alveolar epithelial cells and endothelial cells. This, in turn, facilitates lung tissue repair, regeneration, and improvement of lung function[19-22]. In acute liver failure, MSCs-EVs can inhibit inflammasomes, reduce levels of inflammatory factors, and alleviate inflammatory response, thus improving acute liver injury[23].

### *MSCs-EVs for the treatment of sepsis and sepsis-induced cardiac injury*

MSCs-EVs have shown promise in treating sepsis by modulating the immune response and mitigating inflammatory damage through various mechanisms. These mechanisms include regulating cytokine production, reducing oxidative stress, and promoting immune cell proliferation and differentiation[24]. In septic mice, MSCs-EVs have demonstrated the ability to decrease pro-inflammatory cytokine levels while promoting the production of anti-inflammatory cytokines, thus improving survival rates[25]. Furthermore, MSCs-EVs have been discovered to alleviate sepsis-induced acute lung injury by suppressing the mitogen-activated protein kinase (MAPK)/nuclear factor-κB (NF-κB) pathway. This regulation leads to the modulation of immune cell activity, reduction of oxidative stress levels, and promotion of cell survival and regeneration[26]. Additionally, MSCs-EVs can also improve the severity of sepsis-induced renal injury by directly delivering biologically active molecules, such as circRNA[27]. Moreover, through the delivery of miRNA and other biologically active molecules, MSCs-EVs can inhibit macrophage apoptosis, regulate macrophage polarization, and induce macrophage M2 polarization. These actions help to modulate immune responses and inflammation, promote tissue repair, and ultimately alleviate sepsis-induced acute lung and kidney injury[28-31].

Between 40% and 60% of sepsis patients experience cardiac injury[32]. Numerous studies have demonstrated the potential of MSCs-EVs in alleviating sepsis-induced cardiac injury. For example, MSCs-EVs carrying miR-223 can prevent myocardial cell apoptosis and suppress the inflammatory response by inhibiting the NF-κB signaling pathway, which in turn can help to prevent sepsis-induced cardiac injury[33]. MSCs-EVs enriched with miR-146a-5p can promote cell proliferation and survival by regulating Myb-like protein 1 expression, thus protecting septic myocardial cells or tissue[34]. In addition, the delivery of miR-223-3p by MSCs-EVs can suppress sepsis-induced cardiac inflammation, pyroptosis, and dysfunction[35]. Moreover, MSCs-EVs containing miR-141 can activate β-catenin by targeting phosphatase and tensin homolog deleted on chromosome 10 (PTEN), thereby mitigating septic mouse myocardial injury[36]. Furthermore, MSCs-EVs can also deliver circRTN4 to inhibit cardiac fibrosis and inflammation through the miR-497-5p/mitsugumin 53 signaling axis, thus preventing sepsis-induced cardiac injury[37]. Finally, the presence of PTEN-induced putative kinase 1 in MSCs-EVs can restore mitochondrial $_{m}Ca^{2+}$ efflux, thereby preventing septic myocardial cell mitochondrial calcium overload[38].

### *MSCs-EVs can be used for the treatment of AP*

Limited studies have been conducted on the role of MSCs-EVs in AP. Some studies have demonstrated the potential of human umbilical cord MSCs-EVs in reducing the severity of traumatic pancreatitis by colonizing injured pancreatic tissue, which in turn regulates inflammatory cytokine levels and inhibits acinar cell apoptosis[39]. Furthermore, human umbilical cord MSCs-EVs have shown promise in improving the inflammatory response in mild to moderate traumatic pancreatitis by suppressing inflammation, increasing cell proliferation, and inhibiting pancreatic acinar cell apoptosis. These effects promote the repair of pancreatic tissue, leading to effective relief of traumatic pancreatitis[40]. In addition, MSCs-EVs derived from hair follicles have also been found to promote pancreatic tissue repair and enhance pancreatic function by reducing inflammation in pancreatic cells and inhibiting cell pyroptosis-related signaling pathways[41]. These findings suggest that MSCs-EVs have therapeutic potential in treating AP and may offer a promising alternative to traditional treatments.

Table 1 presents a summary of the factors delivered by MSCs-EVs in inflammatory diseases, the signaling pathways that these factors mediate, and the ultimate effects of MSCs-EVs on inflammation or immunity.

## RESEARCH PROGRESS OF USING MSCS-EVS FOR TREATING AP-INDUCED CARDIAC INJURY

In recent years, there has been growing recognition of the therapeutic potential of MSCs-EVs in the treatment of inflammatory diseases. Sepsis and AP, which are closely associated with inflammatory reactions, can result in cardiac and other organ injuries due to the amplification of the inflammatory response during their course. MSCs-EVs, on the other hand, have been shown to have potential therapeutic effects for both conditions.

Although research on the use of MSCs-EVs for AP-induced cardiac injury is limited, several studies have confirmed their potential in treating sepsis-induced cardiac injury, as well as their potential as a therapeutic strategy for various cardiovascular diseases. For instance, MSCs-EVs have been demonstrated their ability to improve myocardial inflammation, reduce cell apoptosis, and promote cardiac remodeling and function following acute myocardial infarction. This is achieved by inhibiting the activation of the NF-κB signaling pathway through the transmission of miR-302d-3p[42]. Additionally, MSCs-EVs have been found to alleviate myocardial ischemia-reperfusion injury by suppressing M1 polarization of macrophages through the inhibition of Toll-like receptor 4 (TLR4) *via* the transmission of miR-182[43]. Based on these findings, it is reasonable to speculate that MSCs-EVs may also exert therapeutic effects on AP-induced cardiac injury.

**Table 1 Therapeutic potential of MSCs-EVs in inflammation disease**

| Cell model/animal model | Target cells in tissue | Source of MSCs | Cargo of MSCs-EVs | Factors or pathways involved | Therapeutic effects and mechanisms | Ref. |
|---|---|---|---|---|---|---|
| ALI | | | | | | |
| Mouse BMDMs stimulated with LPS/C57BL/6 mouse with LPS-induced ALI | Alveolar macrophages | Human AT-MSCs | miR-27a-3p | NF-κB1 | *In vitro*: MSCs-EVs facilitated M2 polarization of BMDMs through the inhibition of NF-κB1 expression; *in vivo*: Systemic or intratracheal administration of MSCs-EVs reduced NF-κB1 expression in alveolar macrophages *via* miR-27a-3p delivery, promoting macrophage M2 polarization and alleviating LPS-induced ALI | [20] |
| Mouse MLE-12 cells (lung epithelial cells) barrier model/ICR mouse with sulfur mustard-induced ALI | Lung epithelial cells | Mouse BM-MSCs | Not detected | GPRC5A/YAP axis | *In vitro*: MSCs-EVs dose-dependently inhibited sulfur mustard-induced lung epithelial cell apoptosis and promoted the repair of adherens and tight junction integrity through the regulation of the GPRC5A/YAP axis, ultimately facilitating the recovery of epithelial barrier function; *in vivo*: Administration of MSCs-EVs protected lung epithelial cells from apoptosis and epithelial barrier damage by regulating the GPRC5A/YAP axis, promoting the restoration of barrier function and exerting a protective effect against pulmonary edema in ALI | [21] |
| HLMVECs injured by a mixture of IL-1β, TNF-α, and interferon-γ which were often used as a surrogate for ALI pulmonary edema fluid/- | - | Human BM-MSCs | Ang1 mRNA | Not detected | *In vitro*: MSCs-EVs partially increased Ang1 secretion in injured HLMVECs through the transfer of Ang1 mRNA, subsequently promoting the secretion of anti-permeability factors, restoring intercellular junctions, and preventing the formation of "actin stress fiber", thereby dose-dependently restoring protein permeability across HLMVECs during ALI; *in vivo*: - | [22] |
| Sepsis | | | | | | |
| -/BALB/C mouse with LPS-induced sepsis | Not detected | Human UC-MSCs | Not detected | Not detected | *In vitro*: -; *in vivo*: Administration of MSCs-EVs effectively mitigated the destructive effects of inflammation caused by sepsis by reducing inflammatory factors, thereby alleviating tissue damage | [25] |
| -/C57BL/6 mouse with CLP-induced sepsis-induced ALI | Not detected | Human UC-MSCs | Not detected | MAPK/NF-κB pathway | *In vitro*: -; *in vivo*: MSCs-EVs can inhibit the phosphorylation and activation of the MAPK/NF-κB pathway, increase heme oxygenase 1 expression, enhance nuclear factor erythroid 2-related factor 2 expression, and upregulate antioxidant enzyme levels, thereby suppressing the infiltration of polymorphonuclear neutrophils to alleviate lung inflammation, improving pulmonary microvascular permeability to mitigate pulmonary edema, ultimately enhancing the survival rate of mice with sepsis-induced ALI | [26] |

| | | | | | | |
|---|---|---|---|---|---|---|
| -/C57BL/6N mouse with CLP-induced sepsis-induced renal injury | Not detected | Hypoxia pretreated mouse AT-MSCs | mmu_circ_0001295 | Not detected | *In vitro*: -; *in vivo*: EVs secreted by hypoxia-pretreated MSCs can mitigate the elevated levels of plasma chemokines and cytokines induced by sepsis through the delivery of mmu_circ_0001295, thereby improving renal microvascular dysfunction, suppressing renal vascular leakage, and ultimately mitigating sepsis-induced renal dysfunction to enhance the survival rate of septic mice | [27] |
| Mouse RAW264.7 cells (monocytes/macrophages) stimulated with LPS/C57 mouse with LPS-induced sepsis | BMDMs | Mouse BM-MSCs | miR-17 | BRD4/EZH2/TRAIL axis | *In vitro*: MSCs-EVs suppressed the inflammation caused by RAW264.7 cells under LPS stimulation by delivering miR-17 to regulate the BRD4/EZH2/TRAIL axis; *in vivo*: MSCs-EVs, through the delivery of miR-17 to regulate the BRD4/EZH2/TRAIL axis, decreased serum levels of pro-inflammatory cytokines and suppressed their expression in BMDMs, ultimately improving LPS-induced sepsis in mice and enhancing survival rates | [28] |
| Mouse BMDMs stimulated with LPS/C57BL/6 mouse with CLP-induced sepsis | Liver macrophages | IL-1β pretreated mouse MSCs (source not mentioned) | miR-21 | PDCD4 | *In vitro*: MSCs-EVs induced M2-like polarization of macrophages, and IL-1β-pretreated MSCs-derived EVs exhibited an enhanced capacity to promote macrophage polarization towards an M2-like phenotype; *in vivo*: MSCs-EVs, by delivering miR-21, suppressed the effects of PDCD4 and induced M2-like polarization of macrophages, resulting in reduced inflammation, alleviated symptoms, prevented the progression of sepsis, and ultimately improved the survival rate | [29] |
| -/C57BL/6 mouse with CLP-induced sepsis-induced ALI or LPS-induced ALI | Alveolar macrophages | Mouse BM-MSCs | SAA1 | LPS | *In vitro*: -; *in vivo*: MSCs-EVs delivering SAA1 induced LPS internalization by mouse alveolar macrophages, leading to a decrease in inflammatory cytokine levels and ultimately alleviating sepsis-induced ALI | [30] |
| Mouse MH-S cells (alveolar macrophages) stimulated with LPS/C57BL/6 mouse with LPS-induced ARDS | Alveolar macrophages | Mouse BM-MSCs | Not detected | HIF-1α/glycolysis-related protein | *In vitro*: MSCs-EVs suppressed M1 polarization and promoted M2 polarization of alveolar macrophages by inhibiting cellular glycolysis, thereby exerting anti-inflammatory effects; *in vivo*: Intratracheal administration of MSCs-EVs attenuated the LPS-induced inflammatory response by suppressing glycolysis in alveolar macrophages *via* regulation of HIF-1α, leading to improved lung pathology, reduced lung edema, increased $PaO_2/FiO_2$ ratio, and therefore enhancing survival rate | [31] |
| Mouse RAW264.7 cells (monocytes/macrophages) or primary cardiomyocytes stimulated with LPS respectively/C57BL/6 mouse with LPS-induced sepsis-induced cardiac injury | Cardiomyocytes | Mouse BM-MSCs | miR-223, STAT3 and Sema3A proteins | STAT3, Sema3A | *In vitro*: MSCs-EVs suppressed the release of inflammatory cytokines in LPS-induced macrophages through the delivery of miR-223 and reduced LPS-induced cardiomyocyte apoptosis and cell death; *in vivo*: MSCs-EVs | [33] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | carrying miR-223 suppressed the expression of STAT3 and Sema3A, resulting in reduced serum levels of TNF-α, IL-1β, and IL-6, which in turn decreased cardiomyocyte apoptosis, improved cardiac function, and conferred cardio-protection in sepsis, ultimately reducing mortality. Additionally, by inhibiting miR-223 to pre-treat MSCs, the protein cargo within the secreted EVs can be reprogrammed, leading to an increased delivery of Sema3A and STAT3 proteins that exert detrimental effects on recipient cells | |
| Rat H9c2 cells (cardiomyocytes) stimulated with LPS/C57BL/6 mouse with LPS-induced sepsis-induced cardiac injury | Myocardium | Rat BM-MSCs | miR-146a-5p | MYBL1 | *In vitro*: MSCs-EVs, by delivering miR-146a-5p, suppressed MYBL1 to inhibit the progression of LPS-induced cardiomyocyte inflammation, promoting cell proliferation, and inhibiting cell apoptosis; *in vivo*: MSCs-EVs administration can ameliorate cardiac injury and improve survival rates in septic mice | [34] |
| Human HL-1 cells (cardiomyocytes) model of cardiac dysfunction induced by LPS/C57BL/6 mouse with LPS-induced myocarditis | Cardiomyocytes | Mouse BM-MSCs | miR-223-3p | FOXO3/NLRP3 axis | *In vitro*: MSCs-EVs inhibited LPS-induced inflammation and pyroptosis in cardiomyocytes by delivering miR-223-3p, which targeted FOXO3 to suppress NLRP3 expression; *in vivo*: MSCs-EVs restricted myocardial tissue infiltration of inflammatory cells and inflammatory response, decreased cardiomyocyte pyroptosis, thus improving cardiac dysfunction by shuttling miR-223-3p, which targeted the FOXO3/NLRP3 axis | [35] |
| -/KM mouse with CLP-induced sepsis-induced cardiac injury | Cardiomyocytes | Mouse BM-MSCs | miR-141 | PTEN/β-catenin axis | *In vitro*: -; *in vivo*: MSCs-EVs ameliorated myocardial impairment and improved cardiac function by attenuating myocardial inflammatory infiltration and cell apoptosis in septic mouse myocardial tissues through the delivery of miR-141 and regulation of the PTEN/β-catenin axis | [36] |
| RAT H9c2 cells or human AC16 cells (cardiomyocytes) stimulated with LPS respectively/wistar rat with CLP-induced sepsis-induced cardiac injury | Cardiomyocytes | Human MSCs (source not mentioned) | circRTN4 | miR-497-5p/MG53 axis | *In vitro*: MSCs-derived exosomal circRTN4 improved cell survival and suppressed apoptosis in LPS-stimulated cardiomyocytes by targeting the miR-497-5p/MG53 axis; *in vivo*: MSCs-EVs, administered through injection into three different sites around renal tissue for three consecutive days after CLP, delivered circRTN4 to suppress oxidative stress, reduce inflammation factors, and alleviate apoptosis, resulting in the mitigation of cardiac injury | [37] |
| Human AC16 cells (cardiomyocytes) stimulated with LPS/C57BL/6 mouse with CLP-induced sepsis-induced cardiac injury | Cardiomyocytes | Human UC-MSCs | PINK1 mRNA | PKA/NCLX axis | *In vitro*: MSCs-EVs mediated the delivery of PINK1 mRNA to regulate cardiomyocyte $_{m}Ca^{2+}$ efflux through the PKA/NCLX axis; *in vivo*: MSCs-EVs mediated the transfer of PINK1 | [38] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | mRNA, leading to the maintenance of normal $_{m}Ca^{2+}$ efflux, alleviation of mitochondrial calcium overload, and subsequent mitigation of cardiomyocyte injury caused by mitochondrial damage, resulting in improved cardiac function and increased survival rate | |
| AP | | | | | | |
| -/SD rat with impactor-induced traumatic AP | Pancreatic tissue | Human UC-MSCs | Not detected | Not detected | *In vitro*: -; *in vivo*: MSCs-EVs inhibited the apoptosis of pancreatic acinar cells, controlled the systemic inflammatory response, and thereby attenuated pancreatic tissue injury and facilitated the repair of pancreatic tissue | [39, 40] |
| Mouse MPC-83 cells (pancreatic acinar cells) stimulated with caerulein/C57BL/6J mouse with caerulein-induced AP | Pancreatic acinar cells | Mouse HF-MSCs | Not detected | Pyroptosis-related protein | *In vitro*: MSCs-EVs enhanced cell viability, mitigated inflammation, and attenuated the expression of pyroptosis-related proteins in caerulein-stimulated pancreatic acinar cells; *in vivo*: Intraperitoneal or intravenous administration, especially intravenous injection, of MSCs-EVs, can mitigate pancreatic acinar cell pyroptosis, alleviate the inflammatory response and oxidative stress in AP, thus reducing the severity of pancreatic injury | [41] |
| Cardiovascular diseases | | | | | | |
| Mouse HL-1 cells (cardiomyocytes) hypoxia model/C57BL/6J mouse with LAD ligation-induced AMI | Cardiomyocytes | Mouse BM-MSCs | miR-302d-3p | BCL6/MD2/NF-κB axis | *In vitro*: MSCs-EVs carrying miR-302d-3p improved the viability of hypoxic cardiomyocytes, suppressed inflammation, and inhibited apoptosis by targeting the BCL6/MD2/NF-κB axis; *in vivo*: Intramyocardial injection of MSCs-EVs carrying miR-302d-3p near the infarcted area attenuated cardiomyocyte apoptosis and cardiac inflammation by targeting the BCL6/MD2/NF-κB axis, leading to reduced infarct size and myocardial fibrosis, thereby suppressing post-AMI cardiac remodeling and improving cardiac dysfunction | [42] |
| Mouse RAW264.7 cells (monocytes/macrophages) stimulated with LPS/C57BL/6J mouse with LAD ligation-induced ischemia-reperfusion injury | Cardiac macrophages | Mouse BM-MSCs | miR-182 | TLR4/NF-κB/PI3K/Akt signalling cascades | *In vitro*: MSCs-EVs carrying miR-182 facilitated the polarization of macrophages from an M1 to M2 phenotype in an inflammatory environment by inhibiting the TLR4/NF-κB signaling pathway and activating the PI3K/Akt signaling pathway through cross-talk between them; *in vivo*: MSCs-EVs carrying miR-182 regulated myocardial inflammation and reduced infarct size, thereby attenuating myocardial ischemia-reperfusion injury and improving cardiac function in mice through the promotion of macrophage M2 polarization *via* targeting the TLR4/NF-κB/PI3K/Akt signaling cascades | [43] |

MSCs: Mesenchymal stem cells; EVs: Extracellular vesicles; BM-MSCs: Bone marrow-derived MSCs; AT-MSCs: Adipose tissue-derived MSCs; UC-MSCs: Umbilical cord-derived MSCs; HF-MSCs: Hair follicle-derived MSCs; Akt: Protein kinase B; ALI: Acute lung injury; AMI: Acute myocardial infarction; Ang1: Angiopoietin-1; AP: Acute pancreatitis; BCL6: B-cell leukemia/lymphoma 6; BMDMs: Bone marrow-derived macrophages; BRD4: Bromodomain-containing protein 4; CLP: Cecal ligation and puncture; EZH2: Enhancer of zeste homolog 2; FOXO3: Forkhead box protein O3; GPRC5A: G protein-coupled receptor family C group 5 member A; HIF-1α: Hypoxia-inducible factor-1α; HLMVECs: Human lung microvascular endothelial cells; IL-1β: Interleukin-1β; LAD: Left anterior descending coronary artery; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; MD2: Myeloid differentiation protein 2; MG53: Mitsugumin 53; MYBL1: Myb-like protein 1; NCLX: Mitochondrial $Na^+/Ca^{2+}$ exchanger; NF-κB: Nuclear factor-κB; NF-κB1: Nuclear factor-κB subunit 1; NLRP3: NOD-like receptor thermal protein domain associated protein 3; PDCD4: Programmed cell death 4; PI3K: Phosphatidylinositol 3-kinases; PINK1: PTEN-induced putative kinase 1; PKA: Protein kinase A; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; SAA1: Serum amyloid A1; Sema3A: Semaphorin 3A; STAT3: Signal transducers and activators of transcription 3; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor-α; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; YAP: Yes-associated protein.

In a study conducted by Chen *et al*[44], MSCs-EVs were found to be effective in reducing oxidative stress and inflammatory damage in cardiac tissue, decreasing cell apoptosis, improving cardiac function, and ultimately increasing the survival rate of rats with SAP. These beneficial effects were attributed to the activation of the protein kinase B (Akt)/nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) signaling pathway. In our own research[45], we delved into the potential protective effects and mechanisms of MSCs-EVs in SAP-induced cardiac injury. Our findings suggest that MSCs-EVs can downregulate the high mobility group box-1/TLR4 signaling axis and activate the Akt signaling pathway by delivering miR-29a-3p. This, in turn, helps improve myocardial inflammation, enhance myocardial cell vitality, reduce cell apoptosis, and ultimately alleviate myocardial damage while preserving cardiac function. Therefore, we hypothesize that MSCs-EVs may play a crucial role in the onset and progression of SAP-induced cardiac injury.

## IS THERE POTENTIAL FOR USING MSCS-EVS IN THE TREATMENT OF AP-INDUCED CARDIAC INJURY?

Studies have demonstrated that injecting EVs derived from MSCs overexpressing macrophage migration inhibitory factor into the infarcted area of the heart can enhance myocardial angiogenesis, reduce cell apoptosis, decrease cardiac remodeling, and thereby improve cardiac function[46]. Pre-treatment of bone marrow-derived MSCs with fibronectin type III domain-containing protein 5 can promote the secretion of more EVs, which can inhibit the secretion of pro-inflammatory cytokines, increase anti-inflammatory cytokine levels, and promote M2 polarization of macrophages *via* NF-κB signaling pathway and Nrf2/HO-1 axis[47]. Furthermore, when bone marrow-derived MSCs are pre-treated with lipopolysaccharide, the EVs secreted by these MSCs can inhibit M1 polarization of macrophages, promote M2 polarization, alleviate inflammation and cell apoptosis, and thereby facilitate tissue repair in various inflammatory diseases[48]. These studies highlight the potential of MSCs-EVs for targeted interventions, as the cargo and level of bioactive molecules loaded in EVs can be modulated according to the specific therapeutic goals. The *In vitro* plasticity of MSCs-EVs suggests a promising avenue for their utilization in the treatment of specific diseases.

The potential of using MSCs-EVs for clinical therapy is being explored in the initial stages. A Phase I clinical trial has been conducted on MSCs-EVs containing KrasG12D siRNA for the treatment of metastatic pancreatic cancer, and Phase I and II clinical trials on MSCs-EVs transfected with miR-124 for the treatment of stroke have been initiated[49]. Encouraging results have been reported in some clinical studies. A Phase I clinical trial confirmed the safety and efficacy of intravenous injection of placenta-derived MSCs-EVs for treating complex anal fistula in non-Crohn's disease patients [50]. In another Pilot Randomized Clinical Trial, placenta-derived MSCs-EVs were injected intraparenchymally to patients who underwent decompressive craniectomy after malignant middle cerebral artery infarction, and no significant adverse events were observed[51].

Due to the membrane of MSCs-EVs can be modified with specific ligands or peptides, they can be engineered to effectively target specific tissues or cells[52]. Additionally, MSCs-EVs can be stored for extended periods of time. Therefore, when compared to cell-based therapies, MSCs-EVs offer several advantages, including lower risks of immune rejection and tumorigenesis, lower costs, and on-demand availability. As a result, MSCs-EVs may present a promising potential as a viable strategy for treating AP-induced cardiac injury. However, there are still challenges to overcome in optimizing the separation and characterization of EVs, ensuring their purity and potency, and determining appropriate doses and delivery routes for MSCs-EVs in the treatment of AP-induced cardiac injury. Furthermore, potential safety concerns associated with the use of MSCs-EVs, such as the risk of thrombosis formation, immunogenicity, and potential tumorigenicity due to targeted delivery failure, must be carefully evaluated in clinical trials.

## CONCLUSION

In conclusion, AP poses a significant global health threat, particularly when accompanied by cardiac injury, as it can complicate the treatment of SAP and worsen prognosis. Although there is currently limited preclinical research on the effectiveness of MSCs-EVs in treating AP-induced cardiac injury, multiple studies have demonstrated their ability to mitigate inflammation in various inflammatory diseases, including AP, regulate the immune response, promote tissue

regeneration, and improve sepsis-induced cardiac injury and various cardiovascular diseases. Therefore, we postulate that MSCs-EVs may hold promise as a potential treatment for AP-induced cardiac injury. However, further experimental research is necessary to explore their mechanisms, clarify treatment targets, and identify intervention pathways.

## ACKNOWLEDGEMENTS

Acknowledgements to Dr. Qiang Fu for assisting in recording the Audio Core Tip file.

## FOOTNOTES

**Author contributions:** Pan LF designed, reviewed, and was responsible for the manuscript; Pan LF and Niu ZQ wrote and revised the manuscript; Niu ZQ, Ren S, Pei HH, Gao YX, Feng H, Sun JL, and Zhang ZL conducted literature searches; and all authors have read and approve the final manuscript.

**Supported by** the Natural Science Basic Research Program of Shaanxi Province, China, No. 2021JM-284; Health Research Projects of Shaanxi Province, China, No. 2021A010; and Science and Technology Planning Project of Xi'an, China, No. 22YXYJ0111.

**Conflict-of-interest statement:** The authors declare that the research was conducted without any commercial or financial relationships that could be perceived as potential conflicts of interest.



**Country/Territory of origin:** China

**ORCID number:** Long-Fei Pan 0000-0002-8854-7646; Ze-Qun Niu 0009-0006-9503-7069; Song Ren 0000-0003-4237-8725; Hong-Hong Pei 0009-0002-1455-3047; Yan-Xia Gao 0009-0008-5223-2512; Hui Feng 0009-0005-5626-1431; Jiang-Li Sun 0009-0008-8008-4465; Zheng-Liang Zhang 0000-0003-2213-4483.

**S-Editor:** Chen YL
**L-Editor:** A
**P-Editor:** Chen YL

## REFERENCES

1 **Elder AS**, Saccone GT, Dixon DL. Lung injury in acute pancreatitis: mechanisms underlying augmented secondary injury. *Pancreatology* 2012; **12**: 49-56 [PMID: 22487475 DOI: 10.1016/j.pan.2011.12.012]
2 **Mao W**, Wu J, Zhang H, Zhou J, Ye B, Li G, Gao L, Li X, Ke L, Tong Z, Li W, Li J. Increase in serum chloride and chloride exposure are associated with acute kidney injury in moderately severe and severe acute pancreatitis patients. *Pancreatology* 2019; **19**: 136-142 [PMID: 30473463 DOI: 10.1016/j.pan.2018.11.006]
3 **Banks PA**, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2379-2400 [PMID: 17032204 DOI: 10.1111/j.1572-0241.2006.00856.x]
4 **Nadkarni N**, Bhasin DK, Rana SS, Bahl A, Sinha SK, Rao C, Talwar KK. Diastolic dysfunction, prolonged QTc interval and pericardial effusion as predictors of mortality in acute pancreatitis. *J Gastroenterol Hepatol* 2012; **27**: 1576-1580 [PMID: 22849657 DOI: 10.1111/j.1440-1746.2012.07229.x]
5 **Luo Y**, Li Z, Ge P, Guo H, Li L, Zhang G, Xu C, Chen H. Comprehensive Mechanism, Novel Markers and Multidisciplinary Treatment of Severe Acute Pancreatitis-Associated Cardiac Injury - A Narrative Review. *J Inflamm Res* 2021; **14**: 3145-3169 [PMID: 34285540 DOI: 10.2147/JIR.S310990]
6 **Zhao B**, Sun S, Wang Y, Zhu H, Ni T, Qi X, Xu L, Yao Y, Ma L, Chen Y, Huang J, Zhou W, Yang Z, Sheng H, Qu H, Chen E, Li J, Mao E. Cardiac indicator CK-MB might be a predictive marker for severity and organ failure development of acute pancreatitis. *Ann Transl Med* 2021; **9**: 368 [PMID: 33842589 DOI: 10.21037/atm-20-3095]
7 **Calleja GA**, Barkin JS. Acute pancreatitis. *Med Clin North Am* 1993; **77**: 1037-1056 [PMID: 7690443 DOI: 10.1016/s0025-7125(16)30209-7]
8 **Wang Y**, Chen M. Fentanyl Ameliorates Severe Acute Pancreatitis-Induced Myocardial Injury in Rats by Regulating NF-κB Signaling Pathway. *Med Sci Monit* 2017; **23**: 3276-3283 [PMID: 28680032 DOI: 10.12659/msm.902245]
9 **Kong L**, Santiago N, Han TQ, Zhang SD. Clinical characteristics and prognostic factors of severe acute pancreatitis. *World J Gastroenterol* 2004; **10**: 3336-3338 [PMID: 15484312 DOI: 10.3748/wjg.v10.i22.3336]
10 **Doorn J**, Moll G, Le Blanc K, van Blitterswijk C, de Boer J. Therapeutic applications of mesenchymal stromal cells: paracrine effects and potential improvements. *Tissue Eng Part B Rev* 2012; **18**: 101-115 [PMID: 21995703 DOI: 10.1089/ten.TEB.2011.0488]
11 **Ferreira JR**, Teixeira GQ, Santos SG, Barbosa MA, Almeida-Porada G, Gonçalves RM. Mesenchymal Stromal Cell Secretome: Influencing Therapeutic Potential by Cellular Pre-conditioning. *Front Immunol* 2018; **9**: 2837 [PMID: 30564236 DOI: 10.3389/fimmu.2018.02837]
12 **Regmi S**, Pathak S, Kim JO, Yong CS, Jeong JH. Mesenchymal stem cell therapy for the treatment of inflammatory diseases: Challenges,

opportunities, and future perspectives. *Eur J Cell Biol* 2019; **98**: 151041 [PMID: 31023504 DOI: 10.1016/j.ejcb.2019.04.002]
13 **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**: 280-287 [PMID: 25592610 DOI: 10.1007/s12015-014-9583-3]
14 **Barry F**. MSC Therapy for Osteoarthritis: An Unfinished Story. *J Orthop Res* 2019; **37**: 1229-1235 [PMID: 31081558 DOI: 10.1002/jor.24343]
15 **Harrell CR**, Jankovic MG, Fellabaum C, Volarevic A, Djonov V, Arsenijevic A, Volarevic V. Molecular Mechanisms Responsible for Anti-inflammatory and Immunosuppressive Effects of Mesenchymal Stem Cell-Derived Factors. *Adv Exp Med Biol* 2019; **1084**: 187-206 [PMID: 31175638 DOI: 10.1007/5584_2018_306]
16 **Tang Y**, Zhou Y, Li HJ. Advances in mesenchymal stem cell exosomes: a review. *Stem Cell Res Ther* 2021; **12**: 71 [PMID: 33468232 DOI: 10.1186/s13287-021-02138-7]
17 **Harrell CR**, Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Mesenchymal Stem Cell-Derived Exosomes and Other Extracellular Vesicles as New Remedies in the Therapy of Inflammatory Diseases. *Cells* 2019; **8** [PMID: 31835680 DOI: 10.3390/cells8121605]
18 **Shan XQ**, Luo YY, Chang J, Song JJ, Hao N, Zhao L. Immunomodulation: The next target of mesenchymal stem cell-derived exosomes in the context of ischemic stroke. *World J Stem Cells* 2023; **15**: 52-70 [PMID: 37007453 DOI: 10.4252/wjsc.v15.i3.52]
19 **Abdolmohammadi K**, Mahmoudi T, Alimohammadi M, Tahmasebi S, Zavvar M, Hashemi SM. Mesenchymal stem cell-based therapy as a new therapeutic approach for acute inflammation. *Life Sci* 2023; **312**: 121206 [PMID: 36403645 DOI: 10.1016/j.lfs.2022.121206]
20 **Wang J**, Huang R, Xu Q, Zheng G, Qiu G, Ge M, Shu Q, Xu J. Mesenchymal Stem Cell-Derived Extracellular Vesicles Alleviate Acute Lung Injury Via Transfer of miR-27a-3p. *Crit Care Med* 2020; **48**: e599-e610 [PMID: 32317602 DOI: 10.1097/CCM.0000000000004315]
21 **Mao GC**, Gong CC, Wang Z, Sun MX, Pei ZP, Meng WQ, Cen JF, He XW, Lu Y, Xu QQ, Xiao K. BMSC-derived exosomes ameliorate sulfur mustard-induced acute lung injury by regulating the GPRC5A-YAP axis. *Acta Pharmacol Sin* 2021; **42**: 2082-2093 [PMID: 33654219 DOI: 10.1038/s41401-021-00625-4]
22 **Hu S**, Park J, Liu A, Lee J, Zhang X, Hao Q, Lee JW. Mesenchymal Stem Cell Microvesicles Restore Protein Permeability Across Primary Cultures of Injured Human Lung Microvascular Endothelial Cells. *Stem Cells Transl Med* 2018; **7**: 615-624 [PMID: 29737632 DOI: 10.1002/sctm.17-0278]
23 **Lou G**, Chen Z, Zheng M, Liu Y. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. *Exp Mol Med* 2017; **49**: e346 [PMID: 28620221 DOI: 10.1038/emm.2017.63]
24 **Cheng Y**, Cao X, Qin L. Mesenchymal Stem Cell-Derived Extracellular Vesicles: A Novel Cell-Free Therapy for Sepsis. *Front Immunol* 2020; **11**: 647 [PMID: 32373121 DOI: 10.3389/fimmu.2020.00647]
25 **Eshghi F**, Tahmasebi S, Alimohammadi M, Soudi S, Khaligh SG, Khosrojerdi A, Heidari N, Hashemi SM. Study of immunomodulatory effects of mesenchymal stem cell-derived exosomes in a mouse model of LPS induced systemic inflammation. *Life Sci* 2022; **310**: 120938 [PMID: 36150466 DOI: 10.1016/j.lfs.2022.120938]
26 **Chen J**, Li C, Liang Z, Li Y, Zhao Z, Qiu T, Hao H, Niu R, Chen L. Human mesenchymal stromal cells small extracellular vesicles attenuate sepsis-induced acute lung injury in a mouse model: the role of oxidative stress and the mitogen-activated protein kinase/nuclear factor kappa B pathway. *Cytotherapy* 2021; **23**: 918-930 [PMID: 34272174 DOI: 10.1016/j.jcyt.2021.05.009]
27 **Cao S**, Huang Y, Dai Z, Liao Y, Zhang J, Wang L, Hao Z, Wang F, Wang D, Liu L. Circular RNA mmu_circ_0001295 from hypoxia pretreated adipose-derived mesenchymal stem cells (ADSCs) exosomes improves outcomes and inhibits sepsis-induced renal injury in a mouse model of sepsis. *Bioengineered* 2022; **13**: 6323-6331 [PMID: 35212606 DOI: 10.1080/21655979.2022.2044720]
28 **Su Y**, Song X, Teng J, Zhou X, Dong Z, Li P, Sun Y. Mesenchymal stem cells-derived extracellular vesicles carrying microRNA-17 inhibits macrophage apoptosis in lipopolysaccharide-induced sepsis. *Int Immunopharmacol* 2021; **95**: 107408 [PMID: 33915488 DOI: 10.1016/j.intimp.2021.107408]
29 **Yao M**, Cui B, Zhang W, Ma W, Zhao G, Xing L. Exosomal miR-21 secreted by IL-1β-primed-mesenchymal stem cells induces macrophage M2 polarization and ameliorates sepsis. *Life Sci* 2021; **264**: 118658 [PMID: 33115604 DOI: 10.1016/j.lfs.2020.118658]
30 **Lv Z**, Duan S, Zhou M, Gu M, Li S, Wang Y, Xia Q, Xu D, Mao Y, Dong W, Jiang L. Mouse Bone Marrow Mesenchymal Stem Cells Inhibit Sepsis-Induced Lung Injury in Mice *via* Exosomal SAA1. *Mol Pharm* 2022; **19**: 4254-4263 [PMID: 36173129 DOI: 10.1021/acs.molpharmaceut.2c00542]
31 **Deng H**, Wu L, Liu M, Zhu L, Chen Y, Zhou H, Shi X, Wei J, Zheng L, Hu X, Wang M, He Z, Lv X, Yang H. Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Attenuate LPS-Induced ARDS by Modulating Macrophage Polarization Through Inhibiting Glycolysis in Macrophages. *Shock* 2020; **54**: 828-843 [PMID: 32433208 DOI: 10.1097/SHK.0000000000001549]
32 **van der Poll T**, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol* 2017; **17**: 407-420 [PMID: 28436424 DOI: 10.1038/nri.2017.36]
33 **Wang X**, Gu H, Qin D, Yang L, Huang W, Essandoh K, Wang Y, Caldwell CC, Peng T, Zingarelli B, Fan GC. Exosomal miR-223 Contributes to Mesenchymal Stem Cell-Elicited Cardioprotection in Polymicrobial Sepsis. *Sci Rep* 2015; **5**: 13721 [PMID: 26348153 DOI: 10.1038/srep13721]
34 **Liu C**, Xue J, Xu B, Zhang A, Qin L, Liu J, Yang Y. Exosomes Derived from miR-146a-5p-Enriched Mesenchymal Stem Cells Protect the Cardiomyocytes and Myocardial Tissues in the Polymicrobial Sepsis through Regulating MYBL1. *Stem Cells Int* 2021; **2021**: 1530445 [PMID: 34691188 DOI: 10.1155/2021/1530445]
35 **Pan L**, Yan B, Zhang J, Zhao P, Jing Y, Yu J, Hui J, Lu Q. Mesenchymal stem cells-derived extracellular vesicles-shuttled microRNA-223-3p suppress lipopolysaccharide-induced cardiac inflammation, pyroptosis, and dysfunction. *Int Immunopharmacol* 2022; **110**: 108910 [PMID: 35978499 DOI: 10.1016/j.intimp.2022.108910]
36 **Pei Y**, Xie S, Li J, Jia B. Bone marrow-mesenchymal stem cell-derived exosomal microRNA-141 targets PTEN and activates β-catenin to alleviate myocardial injury in septic mice. *Immunopharmacol Immunotoxicol* 2021; **43**: 584-593 [PMID: 34308733 DOI: 10.1080/08923973.2021.1955920]
37 **Li J**, Jiang R, Hou Y, Lin A. Mesenchymal stem cells-derived exosomes prevent sepsis-induced myocardial injury by a CircRTN4/miR-497-5p/MG53 pathway. *Biochem Biophys Res Commun* 2022; **618**: 133-140 [PMID: 35724457 DOI: 10.1016/j.bbrc.2022.05.094]
38 **Zhou Q**, Xie M, Zhu J, Yi Q, Tan B, Li Y, Ye L, Zhang X, Zhang Y, Tian J, Xu H. PINK1 contained in huMSC-derived exosomes prevents cardiomyocyte mitochondrial calcium overload in sepsis *via* recovery of mitochondrial Ca(2+) efflux. *Stem Cell Res Ther* 2021; **12**: 269 [PMID: 33957982 DOI: 10.1186/s13287-021-02325-6]
39 **Han L**, Zhao Z, Chen X, Yang K, Tan Z, Huang Z, Zhou L, Dai R. Human umbilical cord mesenchymal stem cells-derived exosomes for treating traumatic pancreatitis in rats. *Stem Cell Res Ther* 2022; **13**: 221 [PMID: 35619158 DOI: 10.1186/s13287-022-02893-1]

40 **Zhirong Z**, Li H, Yiqun H, Chunyang H, Lichen Z, Zhen T, Tao W, Ruiwu D. Enhancing or inhibiting apoptosis? The effects of ucMSC-Ex in the treatment of different degrees of traumatic pancreatitis. *Apoptosis* 2022; **27**: 521-530 [PMID: 35612769 DOI: 10.1007/s10495-022-01732-1]

41 **Li S**, Li H, Zhangdi H, Xu R, Zhang X, Liu J, Hu Y, Ning D, Jin S. Hair follicle-MSC-derived small extracellular vesicles as a novel remedy for acute pancreatitis. *J Control Release* 2022; **352**: 1104-1115 [PMID: 36402231 DOI: 10.1016/j.jconrel.2022.11.029]

42 **Liu Y**, Guan R, Yan J, Zhu Y, Sun S, Qu Y. Mesenchymal Stem Cell-Derived Extracellular Vesicle-Shuttled microRNA-302d-3p Represses Inflammation and Cardiac Remodeling Following Acute Myocardial Infarction. *J Cardiovasc Transl Res* 2022; **15**: 754-771 [PMID: 35194734 DOI: 10.1007/s12265-021-10200-1]

43 **Zhao J**, Li X, Hu J, Chen F, Qiao S, Sun X, Gao L, Xie J, Xu B. Mesenchymal stromal cell-derived exosomes attenuate myocardial ischaemia-reperfusion injury through miR-182-regulated macrophage polarization. *Cardiovasc Res* 2019; **115**: 1205-1216 [PMID: 30753344 DOI: 10.1093/cvr/cvz040]

44 **Chen M**, Chen J, Huang W, Li C, Luo H, Xue Z, Xiao Y, Wu Q, Chen C. Exosomes from human induced pluripotent stem cells derived mesenchymal stem cells improved myocardial injury caused by severe acute pancreatitis through activating Akt/Nrf2/HO-1 axis. *Cell Cycle* 2022; **21**: 1578-1589 [PMID: 35422193 DOI: 10.1080/15384101.2022.2057762]

45 **Ren S**, Pan L, Yang L, Niu Z, Wang L, Feng H, Yuan M. miR-29a-3p transferred by mesenchymal stem cells-derived extracellular vesicles protects against myocardial injury after severe acute pancreatitis. *Life Sci* 2021; **272**: 119189 [PMID: 33571516 DOI: 10.1016/j.lfs.2021.119189]

46 **Liu X**, Li X, Zhu W, Zhang Y, Hong Y, Liang X, Fan B, Zhao H, He H, Zhang F. Exosomes from mesenchymal stem cells overexpressing MIF enhance myocardial repair. *J Cell Physiol* 2020; **235**: 8010-8022 [PMID: 31960418 DOI: 10.1002/jcp.29456]

47 **Ning H**, Chen H, Deng J, Xiao C, Xu M, Shan L, Yang C, Zhang Z. Exosomes secreted by FNDC5-BMMSCs protect myocardial infarction by anti-inflammation and macrophage polarization *via* NF-κB signaling pathway and Nrf2/HO-1 axis. *Stem Cell Res Ther* 2021; **12**: 519 [PMID: 34583757 DOI: 10.1186/s13287-021-02591-4]

48 **Xu R**, Zhang F, Chai R, Zhou W, Hu M, Liu B, Chen X, Liu M, Xu Q, Liu N, Liu S. Exosomes derived from pro-inflammatory bone marrow-derived mesenchymal stem cells reduce inflammation and myocardial injury *via* mediating macrophage polarization. *J Cell Mol Med* 2019; **23**: 7617-7631 [PMID: 31557396 DOI: 10.1111/jcmm.14635]

49 **Matsuzaka Y**, Yashiro R. Therapeutic Strategy of Mesenchymal-Stem-Cell-Derived Extracellular Vesicles as Regenerative Medicine. *Int J Mol Sci* 2022; **23** [PMID: 35742923 DOI: 10.3390/ijms23126480]

50 **Pak H**, Hadizadeh A, Heirani-Tabasi A, Soleimani M, Asbagh RA, Fazeli MS, Kazemeini A, Keshvari A, Keramati MR, Salahshour F, Nazari H, Tafti SMA, Behboudi B. Safety and efficacy of injection of human placenta mesenchymal stem cells derived exosomes for treatment of complex perianal fistula in non-Crohn's cases: Clinical trial phase I. *J Gastroenterol Hepatol* 2023; **38**: 539-547 [PMID: 36640153 DOI: 10.1111/jgh.16110]

51 **Dehghani L**, Khojasteh A, Soleimani M, Oraee-Yazdani S, Keshel SH, Saadatnia M, Saboori M, Zali A, Hashemi SM, Soleimani R. Safety of Intraparenchymal Injection of Allogenic Placenta Mesenchymal Stem Cells Derived Exosome in Patients Undergoing Decompressive Craniectomy Following Malignant Middle Cerebral Artery Infarct, A Pilot Randomized Clinical Trial. *Int J Prev Med* 2022; **13**: 7 [PMID: 35281985 DOI: 10.4103/ijpvm.ijpvm_441_21]

52 **Mendt M**, Kamerkar S, Sugimoto H, McAndrews KM, Wu CC, Gagea M, Yang S, Blanko EVR, Peng Q, Ma X, Marszalek JR, Maitra A, Yee C, Rezvani K, Shpall E, LeBleu VS, Kalluri R. Generation and testing of clinical-grade exosomes for pancreatic cancer. *JCI Insight* 2018; **3** [PMID: 29669940 DOI: 10.1172/jci.insight.99263]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com