Journal of Clinical and Translational Research 2022; 8(4): 276-291

Journal of Clinical and Translational Research

Journal homepage: http://www.jctres.com/en/home

REVIEW ARTICLE

Systemic anti-inflammatory effects of mesenchymal stem cells in burn: A systematic review of animal studies

Abdullah S. Eldaly[1]*, Sarah M. Mashaly[2], Eslam Fouda[3], Omar S. Emam[1], Amro Aglan[4], Jumanah Abuasbeh[5], Aditya Khurana[6], Hiba Hamdar[7], Ayman R. Fath[6]

[1]Division of Plastic Surgery, Mayo Clinic, Jacksonville, Florida, [2]Department of Dermatology, El-Menshawy General Hospital, Tanta, Egypt, [3]Division of Anesthesia and Perioperative Medicine, Mayo Clinic, Jacksonville, Florida, [4]Department of Internal Medicine, Lahey Clinic Beth Israel, Boston, Massachusetts, [5]Department of Public Health, University of Arizona, Phoenix, Arizona, [6]Department of Internal Medicine, Creighton University Health Education Alliance, Phoenix, Arizona, [7]Department of Emergency Medicine, Notre Dame Maritime Hospital, Byblos, Lebanon

ARTICLE INFO

Article history:
Received: February 20, 2022
Revised: May 18, 2022
Accepted: May 19, 2022
Published online: July 18, 2022

Keywords:
animal models
burn
exosomes
mesenchymal stem cells
systemic inflammation

**Corresponding author:*
Abdullah S. Eldaly, Division of Plastic Surgery, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida.
Tel.: +1 904-597-4771
Email: abdullaheldali@gmail.com

Abstract

Background: Despite the advances in burn care, severe burns still impose significant morbidity and mortality. Severe burns are associated with an inflammatory response that ranges from alterations in vital signs to shock, multiorgan failure, and death. Mesenchymal stem cells (MSCs) are known for their anti-inflammatory and immunomodulatory effects. Therefore, MSCs were investigated for their potential benefits in modulating burn-induced inflammation and organ damage in several studies.
Aim: We have conducted a systematic review of the literature to evaluate the efficacy of MSCs in modulating burn-induced systemic inflammation and organ damage in animal models.
Methods: Four databases were searched: PubMed, Cumulative Index of Nursing and Allied Health Literature, Scopus, and Web of Science. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis as our basis of organization.
Results: Eight studies were included in the study. Bone marrow derived MSCs, umbilical cord derived MSCs (UC-MSCs), and UC-MSCs exosomes were used to modulate the burn-induced inflammation. MSCs therapy reduced serum levels of pro-inflammatory cytokines, improved renal function, inhibited tissue damage, and improved survival after burn. Furthermore, MSCs reversed all the burn-induced pathological changes in blood brain barrier (BBB).
Conclusion: MSCs may attenuate the burn-induced inflammation by decreasing serum levels of inflammatory cytokines. However, the effect on anti-inflammatory cytokines is conflicting and mandates more substantial evidence. Furthermore, MSCs reduce tissue inflammation, tissue damage, and apoptosis in the lungs and kidneys. In addition, MSCs reversed the burn-induced pathophysiologic changes in the BBB. The underlying mechanisms of these effects are poorly understood and should be the focus of future stem cell research.
Relevance to Patients: Severe burn patients are liable to systemic inflammation due to the release of inflammatory cytokines into the circulation. This inflammatory response has a broad spectrum of severity that ranges from alterations in vital signs to multiorgan failure and death. Despite the advances in burn care, burn-induced inflammation still imposes significant morbidity and mortality. This systematic review evaluates the potential benefits of stem cells in modulating burn-induced systemic inflammation in animal burn models.

1. Introduction

Burn patients with or without inhalational injury are liable to systemic inflammation due to the release of inflammatory cytokines into the circulation. This pathophysiologic response takes place immediately or early post-burn and affects long-term outcomes of burn

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

patients [1,2]. The primary trigger of this inflammatory response is the tissue damage caused by the burn itself, and it has a broad spectrum of severity ranging from physiologic alterations in heart rate, blood pressure, respiratory rate, and body temperature to severe shock, multiorgan failure, and death [3-5].

Mesenchymal stem cells (MSCs) have regenerative, immunomodulatory, and anti-inflammatory potentials that might be of significant value for burn patients [6-11]; therefore, MSCs have been the focus of many preclinical studies to investigate their efficacy in burn animal models [12-15].

Animal models have contributed significantly to our understanding of burn pathophysiology and complications [16-20]. In addition, these models have been the spearhead of exploring new therapies in all aspects of burn care [21-24]. Recently, MSCs were investigated for their potential benefits in modulating burn-induced inflammation with promising results [25-27]. Therefore, we have conducted this systematic review to evaluate the efficacy of MSCs in attenuating burn-induced systemic inflammation and organ damage. Furthermore, we aim to provide researchers with a summary of the current models utilized for this purpose to guide them for the model that best fits their hypothesis-driven experiments.

2. Methods

2.1. Information sources, search strategy, and eligibility criteria

We utilized four electronic databases to run our search: PubMed (including MEDLINE), Cumulative Index of Nursing and Allied Health Literature, Scopus, and Web of Science. The databases were searched from inception to November 2021. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis as our basis of organization (Figure 1) [28]. The following search MESH terms were used: "Burn," "Animal model," and "MSCs." The search terms were adjusted according to each database, and Boolean expressions were used to create a complex search string to conduct our search. Details on search terms used for every database are provided in the supplementary material.

We included studies that (1) investigated the systemic anti-inflammatory effects of, (2) human or animal-derived MSCs, (3) in burn, (4) animal models with, (5) full-text available, and (6) reported in the English language. We have excluded (1) descriptive studies and studies that did not evaluate the outcomes, (2) the pre- and post- studies (studies without a control group), (3) editorials, (4) reviews, (5) conference papers, and (6) letters to the editors.

2.2. Study selection and data collection process

The first two authors independently searched and removed the duplicates using EndNote (Clarivate Analytics). After filtering the studies based on titles, abstracts were then screened according to the aforementioned eligibility criteria. The remaining studies were full text reviewed. Finally, any conflict was solved by a third author; one major conflict between the first two authors was regarding including studies evaluating the use of exosomes, and it was decided by the third author to include these studies.

2.3. Risk of bias (RoB) assessment

To assess the RoB in the included studies, we utilized the systematic review center for laboratory animal experimentation (SYRCLE) tool [29]. SYRCLE's RoB tool is based on Cochrane's RoB tool and was adjusted to detect bias that plays a specific role in animal intervention studies [29]. This tool contains ten entries related to selection bias, performance bias, detection bias, and attrition bias. Two authors independently evaluated the studies using the SYRCLE's tool, and a third author solved any disagreement.

3. Results

The initial search revealed 2353 non-duplicate results, of which, 40 papers underwent full-text readings resulting in eight studies included in our final analysis (Figure 1). Table 1 summarizes the included studies. In addition, we summarized the animal model, the sample size, the type and source of stem cells, the dose and route of administration, and the outcome variables for each included study.

3.1. Study characteristics

The earliest study was reported in 2010 [25] and the latest in 2020 [26]. All the studies reported using a rodent model; six reported using rats [25,27,30-33] while two reported using mice [26,34]. Sample sizes of 84 [31], 118 [30], and 134 [27] animals were reported in three studies, while the rest did not report the sample size [25,26,32-34]. Six studies reported scald burn injury model [25,26,30,32-34], and two studies reported flame burn injury [27,31]. Three studies did not specify the total burn surface area (TBSA) [26,27,31], while three studies reported a TBSA of 30% [25,32,33], and two studies reported a TBSA of 15 [34] and 20% [30].

3.2. Description of the intervention

One study reported using human bone marrow-derived MSCs (BMMSCs) [25], while Rat [30], mouse [26], and human [31] umbilical cored-derived MSCs (UC-MSCs) were reported in three studies. In addition, mouse BMMSCs [27,34] and human UC-MSC-exosomes [32,33] were reported twice each. The lowest passage for the used cells was 2 [31], and the highest was 7 [25]. The MSCs were administrated intravenously in five studies [26,30,32-34], while intramuscular (IM) [25], subcutaneous (SC) [31], and intradermal (ID) [27] delivery of the cells was reported in one study each.

3.3. Summary of the outcomes

IV administration of UC-MSCs and ID administration of BMMSCs improved survival in two studies [30]. IV and IM administration of rat UC-MSCs and human BMMSCs, respectively, reduced tissue damage and apoptosis in kidneys in two studies. Furthermore, a significant reduction in serum creatinine and blood urea nitrogen after MSCs administration was reported [25,30]. IM and IV administration of human MSCs and

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

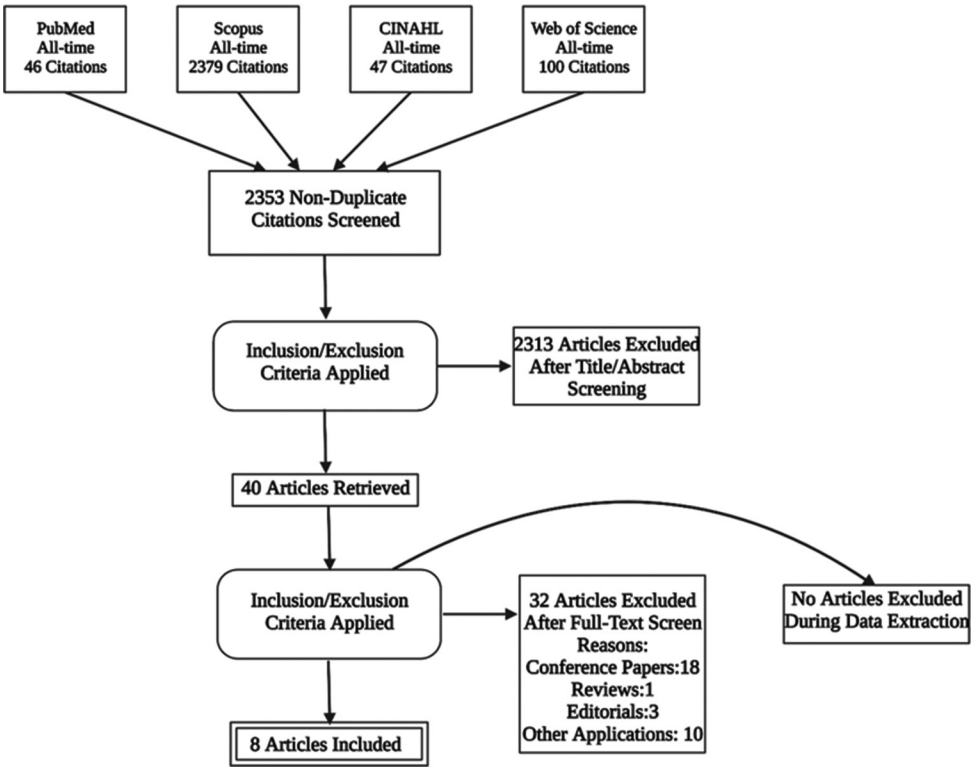

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flow chart diagram. *Created using BioRender.Com*

mouse BMMSCs, respectively, did not reduce apoptosis in the liver in two studies [25,34].

In two studies, IM and IV administration of human MSCs [25] and mouse BMMSCs [34], respectively, was associated with a significant reduction in inflammation in lung tissue. In a third study, IV administration of human UC-MSC-exosomes reduced the concentration of inflammatory cytokines in serum and lung tissue. Furthermore, histological analysis revealed a significant reduction in lung tissue damage and apoptosis compared to the control group [33].

One study investigated the effect of burn and MSCs therapy on the blood–brain barrier (BBB) [26]. Histological analysis of the brain tissue post-burn revealed increased BBB permeability and transcytosis. Furthermore, a marked increase in inflammatory markers, particularly interleukin (IL)-6 and IL-1β, was noted in serum and brain tissue. All these effects were reversed with a single dose of IV mouse UC-MSCs administrated 1 h after-burn.

Three studies attempted to evaluate the effect of MSC therapy on serum levels of pro-and anti-inflammatory cytokines post-burn. In the first study, Zhang *et al*. [31] investigated the potential benefits of human UC-MSCs in an SD rat model. SC administration of UC-MSCs in post-burn rats was associated with a significant decrease in serum levels of inflammatory cytokines, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and IL-6 compared to the control group. However, UC-MSCs therapy was also associated with lower anti-inflammatory cytokine IL-10. Finally, there was no significant difference in Interferon-gamma (IFN-γ) levels between the treatment and control groups.

In a different study, Caliari-Oliveira *et al*. [27] investigated the effect of mouse BMMSCs administrated intradermally on the serum levels of pro- anti-inflammatory cytokines in a rat flame burn model. The treatment group showed significantly higher anti-inflammatory cytokines, tissue growth factor-beta (TGF-β), and IL-10 than the control group. However, the treatment group also showed significantly higher pro-inflammatory cytokines, IL-6, and cytokine-induced neutrophil chemoattractant 1 (CINC-1).

The third study by Li *et al*. [32] investigated the influence of human UC-MSCs-exosomes on pro-and anti-inflammatory cytokines in a burn rat model. This study showed that UC-MSC-exosomes administrated intravenously were associated with lower levels of TNF-α and IL-1β. Furthermore, the UC-MSC-exosomes were associated with the lower expression of toll-like receptors 4 (TLR-4), which further inhibits the inflammatory response. Finally, the treatment group showed higher levels of IL-10 compared to the control group.

3.4. RoB

The RoB is summarized in Table 2. All the included studies were liable to a high risk of selection and performance bias. For selection bias, none of the included studies described how the allocation sequence was generated and applied. This is true even for the studies that stated that the animals were randomized. However, the authors know that reporting the sequence generation process is not a common practice in animal studies.

Regarding performance bias, none of the studies attempted to blind the investigators or caregivers to the treatment and control

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

Table 1. Summary of the included studies.

Author and Date	Animal Model	Number	Burn Type, Degree and TBSA	Stem Cell Therapy	Source	Passage	Dose and route of administration	Target of Therapy	Outcome Variables	Results	Summary
Yagi *et al.*[25] (2010)	Sprague-Dawley rats	-	Scald 3rd 30%	BMMSCs	Humans	3-7	2×10^6/rat IM	Kidney, Lung, Liver.	Gene expression in MSCs, BUN, AST, histological analysis.	MSCs versus Control MSCs gene expression in response to inflammation: ↑IL-10, ↑Akt1, ↑RAF1, ↓MAP3K1. BUN: ↓ AST: no difference from control. Histology: ↓ tissue injury, ↓ apoptotic cells in kidney and lung	MSCs react to inflammation on a genetic level. MSCs provide anti-inflammatory and anti-apoptotic effects in the lungs and kidneys of burned rats.
Caliari-Oliveira *et al.*[27] (2016)	Wistar rats	134	Flame 3rd	BMMSCs	Mice	3-4	5×10^6/rat ID	Inflammatory cytokines	TGF-β, IL-10, IL-6, CINC-1, survival rates	BMMSCs versus Control TGF-β, IL-10, IL-6, CINC-1: ↑ Survival rates: ↑	ID administration of BMMSCs increased both pro- and antiinflammaory cytokines and prolonged survival in rats
Curtis *et al.*[34] (2019)	C57BL/6 Mice	-	Scald 3rd 15%	BMMSCs	Mice	4	5×10^5/mouse IV	Liver, Lung	IL-6, AST, ALT, histological analysis	BMMSCs versus Control IL-6: ↓ AST, ALT: no difference from control. Histological analysis: no difference from control	IV administration of BMMSCs provided antiinflammatory effects in lung and liver in a mouse model of binge ethanol and burn
Lu *et al.*[30] (2013)	Sprague-Dawley rats	118	Scald 3rd 20%	UC-MSCs	Rats	3-5	1×10^6/rat IV	Kidney	Serum creatinine, BUN, histological analysis, survival rate.	UC-MSC versus Control Serum Creatinine: ↓ BUN: ↓ Histological analysis: ↓ tissue damage, ↓ apoptotic cells. Survival: ↑	IV administration of UC-MSCs protects from death caused by burn-indced acute kidney injury in rats
Zhang *et al.*[31] (2015)	SD rats	84	Flame 3rd	UC-MSCs	Humans	2-4	2×10^6/rat SC	Inflammatory cytokines	WBCs, CRP, IFN-γ, TNF-α, IL-6, IL-10	UC-MSC versus Control WBCs, CRP, TNF-α, IL-6, IL-10: ↓ IFN-γ: No significant difference	SC administration of UC-MSCs suppresses secondary inflammatory reaction by lowering inflamatory cytokines

(Contd...)

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

Table 1. *(Continued).*

Author and Date	Animal Model	Number	Burn Type, Degree and TBSA	Stem Cell Therapy	Source	Passage	Dose and route of administration	Target of Therapy	Outcome Variables	Results	Summary
Yang *et al.*[26] (2020)	C57BL/6J mice	-	Scald 3rd	UC-MSCs	Mice	3	1×106/mouse IV	BBB	BBB permeability and transcellular vesicular transport, IL-6, IL-1β	Burn: ↑ BBB permeability, ↑ IL-6 & IL-1β (brain and serum), ↑ transcytosis. UC-MSCs: reversal of all burn induced changes in BBB	Burn is associated with impaired function and integrity of BBB. IV administration of UCMSCs 1 h after burn reversed these effects
Li *et al.*[32] (2016)	SD rats	-	Scald 3rd 30%	UC-MSC-exosomes	Humans	3-8	800 µg UCMSC-exosomes IV	Inflammatory cytokines	WBCs, TNF-α, IL-1β, IL-10, TLR-4 expression	UC-MSC-exosomes versus Control WBCs: ↓ TLR-4, TNF-α, Il-1β: ↓ Il-10: ↑	IV administration of UCMSC-exosomes inhibited the post-burn inflammatory response in rats
Liu *et al.*[33] (2019)	SD rats	-	Scald 3rd 30%	UC-MSC-exosomes	Humans	-	800 µg UCMSC-exosomes IV	Lung	IL-6, IL-1β, TNF-α, histological analysis	UC-MSC-exosomes versus Control IL-6, IL-1β, TNF-α: ↓ (lung& serum) Histological analysis: ↓ tissue damage and apoptotic cells in lung	IV administration of UC-MSC-exosomes ameliorated burn induced lung injury. This effect was reversed when miR-451 expression in UC-MSC-exosomes was inhibited

MSCs: Mesenchymal stem cells, BMMSCs: Bone marrow-derived mesenchymal stem cells, IM: Intramuscular, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, IL-10: Interlukin 10, UC-MSCs: Umbilical cord derived mesenchymal stem cells, IV: Intravenously, SC: Subcutaneous, ID: Intradermal, CINC-1: Cytokine-induced chemotactant 1, BBB: blood brain barrier

Table 2. Summary of risk of bias assessment.

Study	Selection Bias (Sequence generation)	Selection bias (baseline characteristics)	Selection bias (Allocation concealmet)	Performance bias (random housing)	Performance bias (Blinding)	Detection bias (Random outcome assessment)	Detection bias (Blinding)	Attrition bias (Incomplete outcome data)	Reporting bias (Selective outcome reporting)
Yagi *et al.*[25] (2010)	High	Low	High	Unclear	High	Low	Low	Low	Low
Lu *et al.*[30] (2013)	High	Low	High	Unclear	High	Low	High	High	Low
Zhang *et al.*[31] (2015)	High	Low	High	Unclear	High	High	High	Low	Low
Caliari-Oliveira *et al.*[27] (2016)	High	Low	High	Unclear	High	High	Low	Low	Low
Li *et al.*[32] (2016)	High	Low	High	Unclear	High	High	Low	Low	Low
Curtis *et al.*[34] (2019)	High	Low	High	Unclear	High	High	Low	Low	Low
Liu *et al.*[33] (2019)	High	Low	High	Unclear	High	High	High	Low	Low
Yang *et al.*[26] (2020)	High	Low	High	Unclear	High	Low	High	Low	Low

groups. Therefore, all the studies had a high risk of performance bias, particularly the blinding domain.

Regarding the random housing domain, none of the included studies attempted to randomly place the cages/animals within the animal room or facility. The location of the animal in the room can affect many variables significantly. For example, the temperature in animals' room at the height of 1.5 m can be 3–4°C higher than at 0.5 m [35]; small changes in room temperature can influence the animal's metabolic rate significantly [36,37]. However, it was unclear if the housing would influence the outcomes evaluated in the included studies; therefore, we selected "unclear" for all studies regarding this domain.

4. Discussion

4.1. Burn induced systemic inflammatory response syndrome (SIRS)

The term SIRS was first coined by the American College of Chest Physicians/Society of Critical Care Medicine in 1992 to describe

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

a state of systemic inflammation, regardless of its cause [38]. SIRS diagnosis mandates the presence of two or more of the following criteria: body temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20/min or a $PaCO_2$ <32 mmHg; leukocyte count >12,000/μL, <4000/μL, or >10% immature (band) forms. These criteria must occur as an acute alteration from baseline that cannot be explained by any other cause. SIRS can be caused by a broad spectrum of infectious and non-infectious etiologies. The most common non-infectious causes include trauma, ischemia-reperfusion injuries, pancreatitis, and burn.

Burn patients commonly experience SIRS, with several factors influence the outcomes. Although the presence of SIRS in the first 24 h after burn does not predict mortality [39,40], the persistence of SIRS criteria for more than three days is associated with worse outcomes [41-43]. Furthermore, Talmor *et al*. [40] revealed that the persistence of SIRS for 2 days postoperatively in high-risk surgical patients was associated with an increased incidence of multiple organ dysfunction syndromes (MODS). In addition, the number of SIRS criteria existing in a patient seems to have a prognostic value. An analysis by Rangel-Frausto *et al*. [44] showed that the mortality rates for patients exhibiting two, three, and four SIRS criteria were 6%, 10%, and 17%, respectively. In addition several factors affect the prognosis of burn-induced SIRS. The magnitude of this inflammatory response depends on burn surface area and degree, presence of inhalation injury or other traumatic injuries, and patient-related factors such as age, pre-existing co-morbidities, and drug or alcohol intoxication [4]. Moreover, several other factors may compromise the patient's ability to adapt to SIRS. These factors include delayed or inadequate fluid resuscitation during the acute phase, infections, tissue necrosis, and bacterial translocation across the bowel [45].

Burn-induced SIRS occurs as a result of direct thermal trauma to tissues [5]. Severe burns result in an inflammatory response characterized by increased levels of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6 [3]. Although the cellular and molecular mechanisms of trauma-induced SIRS are complex, they are becoming increasingly understood. TLRs are expressed on leukocyte surface and respond to specific patterns of microbial components, named pathogen-associated molecular patterns (PAMPs), to initiate an innate immune response [46]. Furthermore, TLR can recognize damage-associated molecular patterns (DAMPs), which are endogenous particles released from cells upon their destruction by a burn injury, and they include heat shock protein, histones, mitochondrial DNA, extracellular ATP, and eosinophil-derived neurotoxin [47]. Since DAMPs are normally located intracellular, their presence in the extracellular matrix after cell damage can initiate the same TLR-mediated signaling pathway as PAMPs [48]. TLR activation by DAMPs/PAMPs up regulates the transcription of pro-inflammatory gene products, including TNF, IL-1, and IL-6 [49].

The two-hit hypothesis concept was proposed by some researchers to explain the exaggerated response to secondary stimuli (e.g., infections) in severely burned patients. Although the exact mechanism of the two-hit hypothesis is not fully understood, monocytes and macrophages are thought to play a critical role in mediating this effect [5]. For example, IFN-γ, which is produced early in SIRS might prime macrophages for an exaggerated inflammatory response if a second stimulus/hit is encountered. For example, TNF-α protein is not produced in significant amounts after the first inflammatory stimulus. However, if a second stimulus, such as bacterial infection, takes place, macrophages become primed by IFN-γ to produce large amounts of TNF-α [50]. Following burn, macrophages have increased sensitivity to ligands for TLR2 and TLR4. TLR2 and TLR4 are important components of receptor complexes of DAMPs, peptidoglycans, and lipopolysaccharides (LPS). After the initial burn injury, TLR2 and TLR4 responses become enhanced for secondary stimuli leading to the two-hit phenomenon [50].

On the other hand, SIRS is also thought to be associated with an anti-inflammatory response to restore immune homeostasis and prevent systemic inflammation. This response is referred to as the counter anti-inflammatory response syndrome (CARS) [51]. The hallmark of CARS is increased production of anti-inflammatory cytokines such as IL-10 and TGF-β, which results in leukocyte apoptosis and blunting of systemic inflammation [50,52]. However, prolonged CARS can result in excessive immunosuppression and predispose the patient to infections [5]. Furthermore, prolonged coexistence of SIRS and CARS results in persistent inflammation, immunosuppression, and catabolism syndrome, which can be further complicated by infections leading to MODS and death [53]. Therefore, the current models suggest that patients who rapidly resolve SIRS and CARS have more favorable outcomes.

4.2. The potential role of MSCs in controlling SIRS

MSCs are multipotent stem cells that can differentiate into multiple cell lines, including adipocytes, osteoblasts, chondrocytes, and pancreatic islet cells [8]. MSCs can be isolated from multiple tissues, including bone marrow, umbilical cord tissue, adipose tissue, menstrual blood, fallopian tubes, and endometrial polyps [54,55]. The anti-inflammatory and immunomodulatory effects of MSCs have been heavily investigated, mainly in the context of transplantation tolerance and allergic disorders [56-59]. Recently, several MSCs products were approved for clinical use, including Cartistem for degenerative arthritis, Cupistem for anal fistula in Korea, and Prochymal for graft versus host disease in Canada [8].

Current evidence from preclinical models and human studies suggest that MSCs influence the immune response in several ways, including inhibition of T-cell proliferation, cytokine production, and cytotoxicity [60,61]; induction and regulation of regulatory T cell (T_{reg}) [62] and regulatory B cells (B_{reg}) [63]; induction of IL-10 production [64-67]; inhibition of B cell proliferation and antibody production [68]; inhibition of antigen-presenting cells [69]; and inhibition of IL-2 mediated natural killer cell activation [70].

Although the exact mechanisms of immunomodulation by MSCs are not fully understood, several studies have attempted to investigate those mechanisms. In one model, MSCs' immunomodulation is explained by multiple soluble factors released from MSCs to mediate the immunosuppressive effects [8].

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

These soluble factors include TGF-β1, prostaglandin E2 (PGE2), nitric oxide, IL-10, and indoleamine-pyrrole 2,3-dioxygenase. MSCs release these factors in response to pro-inflammatory cytokines, including IFN-γ, TNF-α, and IL-1 [71-74]. In other models, MSCs' immunomodulatory effect relied on their cellular activities, such as secretomes and cellular cross-talk. Instead, the cells functioned through a mechanism involving phagocytosis of MSCs by monocytic cells [75]. After phagocytosis, monocytes produce less TNF-α and more IL-10. Thus, MSCs trigger other cells to perform the immunomodulatory effects [65,75].

Li *et al*. [32] investigated the potential role of human UC-MSC-exosomes in ameliorating burn-induced inflammation in a rat model. Exosomes are bilaminar membrane vesicles that can originate from any cell type and have the capacity to communicate with other cells and modulate local and distal microenvironments [76]. Exosomes are produced by double invagination of the plasma membrane and formation of intracellular multivesicular bodies (MVBs). These MVBs contain intraluminal vesicles which will be finally secreted as exosomes with a size that ranges from 40 to 160 nm in diameter through exocytosis [77]. Exosomes exhibit high levels of heterogeneity according to their size, content, functional impact on the recipient cells, and cellular origin [78]. The microenvironment and the cellular origin influence the content and the biological markers of exosomes. Exosomes contents vary and include membrane proteins, cytosolic proteins, nuclear proteins, metabolites, mRNA, and DNA [79]. In addition, exosomes exert biological activities similar to their parent cells [80]. Li *et al*. [32] showed that the exosomes lowered the burn-induced rise in leukocytes and serum levels of TNF-α and IL-1β. Moreover, exosomes induced the secretion of anti-inflammatory cytokine IL-10.

In addition, the exosomes inhibited the TLR-4 signaling pathway and reduced TLR-4 expression. The investigators attempted to investigate the mechanisms of TLR-4 signaling pathway inhibition. Quantification of TLR-4 mRNA and protein revealed higher levels in the burn group compared to sham controls. Although the administration of UC-MSC-exosomes reduced TLR-4 protein levels in the burned rats, they did not affect the TLR-4 mRNA levels. Therefore, the exosomes should have mediated their effect post-transcriptional (i.e., before the protein was produced). The investigators hypothesized that this effect is mediated through miRNA. Comparison of miRNA levels showed significantly lower levels of miR-181c in burned animals than sham controls. Furthermore, the levels of miR-181c in burned rats significantly increased after the administration of exosomes. To further investigate the integrity of this theory, the investigators transfected the exosomes with miR-181c and compared their effects on the TLR-4 pathway with control exosomes. The transfected exosomes showed higher miR-181c expression and significantly lowered TLR-4 protein levels compared to the control groups (Figure 2).

In a different study [27], mice BMMSCs - injected intradermally - were utilized to modulate the inflammatory response to burn in a rat model. Interestingly, the MSC therapy

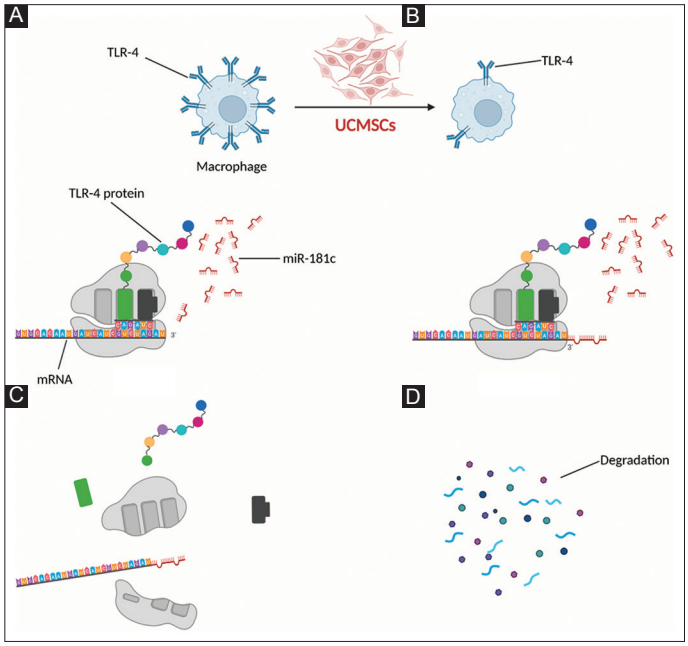

Figure 2. UC-MSCs-exosomes decrease the number of TLR-4 on macrophages. (A) miR-181c attach to the 3' end of TLR-4 mRNA. (B) The translation process stops. (C) The ribosome-mRNA complex is disassembled. (D) degradation of TLR-4 protein. UC-MSCs: Umbilical cord derived mesenchymal stem cells, TLR-4: Toll-like receptor-4, miR-181c: Micro RNA-181c. *Created using biorender.com.*

increased the serum levels of both anti-inflammatory cytokines TGF-β and IL-10 and pro-inflammatory cytokines IL-6 and CINC-1. The serum levels of TGF-β and IL-10 were significantly higher in the MSC treated animals compared to the control group on post-burn day 15 and 30, respectively ($P < 0.05$). On the other hand, the serum levels of IL-6 and CINC-1 were significantly higher in the MSC-treated animals on post-burn day 30 ($P < 0.05$ and 0.02, respectively) [27]. The late rise in pro-inflammatory cytokines may indicate that MSCs can reverse the systemic immunosuppression allowing the immune system to respond to bacterial infections. In other words, MSCs might play a role in inhibiting both SIRS and CARS at different time points. However, there is little evidence to support such a theory, and further studies should further expand on this point.

Zhang *et al*. [31] utilized human-derived UC-MSCs administrated subcutaneously to modulate the inflammatory response in a rat model. Although the MSC-treated animals showed significantly lower levels of the pro-inflammatory cytokines IL-6 and TNF-α at day 7 post-burn ($P < 0.01$ and 0.05, respectively), the same animals had lower serum levels of the anti-inflammatory cytokine IL-10 at the same timepoint ($P < 0.01$). The authors explained this contradictory effect as a weaker CARS due to a weaker inflammatory response. In other words, the MSCs blunted the inflammatory response to burn to level that is below the threshold to initiate CARS. Another explanation is that the MSCs unequally increase the production and consumption of IL-10, leading to the lower levels. Another

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

potential explanation is that MSCs might have different effects on pro- and anti-inflammatory cytokines at different time points. In one study investigating the effects of IV UC-MSCs on IL-10 levels in Sprague-Dawley rats, stem cell therapy was associated with a marked increase followed by marked reduction of IL-10 levels compared to control groups on days 3 and 14, respectively [81]. However, all these explanations lack substantial evidence and mandate further testing. Furthermore, the short follow-up period in this study (7 days) might have led to an inaccurate presentation of the MSC effects.

It is also worth mentioning that the studies included in this review show a marked variability regarding the type of stem cells, the dose, the route of administration, the experimental endpoints, TBSA, and the animal model used. This variability is expected to significantly affect the outcomes. Unfortunately, determining the stem cell type, dose, and route of administration that is associated with best outcomes requires conducting meta-analysis which is not possible currently due to the rarity of the studies.

4.3. Burn-induced liver, lung, and kidney injuries

4.3.1. Liver

Liver injury is a well-documented complication of severe burns [82]. Liver markers such as total bilirubin, glutamate-pyruvate transaminase, glutamic-oxaloacetic transaminase, alkaline phosphatase, and activated partial thromboplastin time may have a prognostic value [83].

Liver edema is the earliest sign of liver injury in severe burns and starts as early as 12 h postburn [84]. Edema of hepatocytes may result in cellular damage or altered membrane permeability, leading to the release of hepatic enzymes into the circulation. Therefore, a rise in plasma levels of liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may indicate a possible burn-induced liver injury. After severe burns, an elevation of 50–200% of AST and ALT is expected, with the peak happens early in the first 24 h postburn [3,85].

Burn-induced hepatocyte death is mediated through two pathways: apoptosis (programmed cell death) and necrosis [86]. An autopsy study of burned children revealed that 10–15% of severely burned descendants had signs of liver necrosis [82]. The molecular mechanisms of hepatocyte apoptosis are not entirely understood; however, several theories emerged to explain the phenomenon. In one theory, the post-burn decrease in blood flow to the bowel and possibly to the liver [87] was considered to be the initiating event of apoptosis. However, the theorized decrease in hepatic blood flow was not confirmed in human studies. Another theory suggests that the early rise in pro-inflammatory cytokines such as IL-1 and TNF-α mediate apoptosis [88,89]. This was endorsed by the synchronous rise in the serum levels of these cytokines with the liver injury onset.

Furthermore, some studies suggest that the elevation in the pro-inflammatory cytokines is not limited to the plasma as increased levels of IL-1, TNF-α, and IL-6 were also detected in the liver [90,91]. Since MSCs are known for their immunomodulatory effects, they can modulate the hepatic burn response. Therefore, several animal studies evaluated the effects of MSCs on burn-induced liver injury.

4.3.2. Kidney

Severe burns can lead to acute kidney injury (AKI) within the first 24–48 h of injury [92,93]. Although burn-associated AKI most commonly occurs as a result of hypovolemia, and it can develop despite aggressive fluid resuscitation and normal urine output [93]. Therefore, several other factors are believed to contribute to burn-associated AKI including systemic inflammation, extensive tissue destruction, iatrogenic agents as antibiotics, and cardiac dysfunction [92,94]. Some of the inflammatory mediators released in response to burn including TNF-α and endothelin compromise renal perfusion and can result in profound injury [95,96]. Therefore, MSCs can potentially ameliorate this injury by inhibiting inflammatory mediator release.

4.3.3. Lung

Lung injury in burn patients can result from inhalation of toxins, systemic inflammation, fluid overload and heart failure from aggressive fluid resuscitation, and iatrogenic ventilator injury [97]. The current guidelines of preventing pulmonary complications depend on early ventilator weaning, oral hygiene, and chest physiotherapy. Current treatments include nebulized heparin, albuterol, cortisol, epinephrine, and mucolytics; these treatments were found to improve pulmonary functions and outcomes [98].

4.4. The potential role of MSCs in reducing burn-induced liver, lung, and kidney injuries

Yagi *et al*. [25] evaluated the effects of human-derived BMMSCs in preventing organ damage induced by LPS or burn. The investigators conducted one *ex vivo* and another *in vivo* experiment. The *ex vivo* experiment was conducted to investigate the molecular response of MSCs to the inflammatory signals present in LPS-derived serum and burn-derived serum. Therefore, quantitative real-time RT-PCR was performed for four genes in MSCs after being incubated for 24 h in either burn-derived or LPS-derived serum. The four genes are IL-10, V-akt murine thymoma viral oncogene homolog 1 (Akt1), Mitogen-activated protein kinase kinase kinase 1 (MAP3K1), and V-raf-1 murine leukemia viral oncogene homolog 1 (RAF1); all of these genes are known for their anti-inflammatory and cell regulatory roles and should play a role in reducing organ injury. Gene expression analysis revealed an increased expression of IL-10, Akt1, and RAF1 in MSCs incubated in either type of inflammatory sera. However, MAP3K1 expression was increased in the MSCs incubated in LPS serum while decreased in the MSCs incubated in burn-derived serum (Figure 3). The results from the *ex vivo* experiment suggest that MSCs can alter their gene expression in response to the inflammatory signals present in their microenvironment.

The *in vivo* experiment involved IM injection of MSCs in endotoxemic and severely burned rats. Although MSCs

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

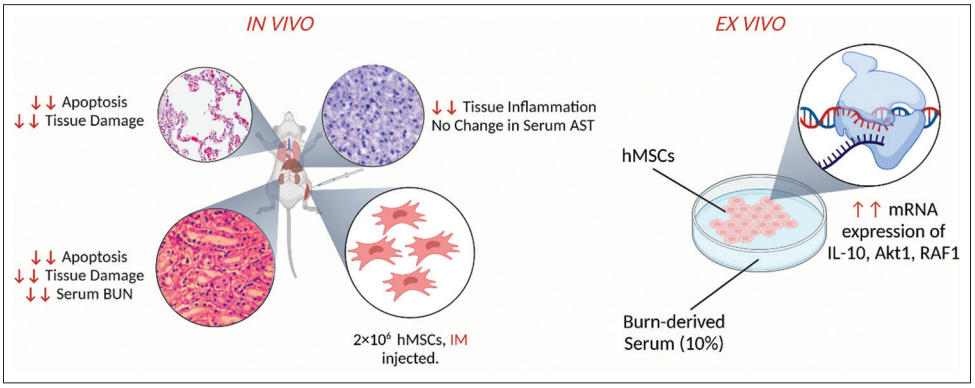

Figure 3. *In vivo*: IM injection of hMSCs reduced tissue damage in lungs and kidneys. However, MSCs did not reduce liver apoptosis. *Ex-vivo*: Incubation of hMSCs in 10% burn-derived serum increased mRNA expression of IL-10, Akt-1, and RAF-1. IM: Intramuscular, hMSCs: Human derived mesenchymal stem cells, BUN: Blood urea nitrogen, AST: Aspartate amino-transferase, IL-10: Interleukin 10. *Created using biorender.com.*

significantly reduced tissue injury and apoptotic cells in the lungs and kidneys in both groups, the effect in the liver was not similar. In the endotoxemic animals, the MSCs therapy was associated with significantly lower serum AST levels indicating less liver damage. However, in the burn model, AST levels were not significantly different from the control group suggesting a different response of MSCs in the burn model. These findings were further investigated in another study evaluating the effects of BMMSCs IV administrated in a mouse binge alcohol intoxication and burned model [34]. Although MSC therapy was associated with statistically significant lower levels of IL-6 and neutrophil chemokine, KC (CXCL1) gene expression in the liver, it did not significantly lower the AST and ALT serum levels compared to controls. Furthermore, the reduction in the number of apoptotic cells in the liver and lung was not significantly different from the control group.

The effects of UC-MSCs and UC-MSC-exosomes in preventing burn-induced lung and kidney injuries, respectively, were evaluated in two studies [30,33]. In both studies, UC-MSCs and their exosomes effectively reduced tissue inflammation and apoptosis in the lung and kidney. Furthermore, in the second study, the anti-inflammatory and anti-apoptotic effects of the exosomes were attributed to miRNA-451 expression, as these effects were reversed when the miRNA-451 expression was inhibited. The underlying mechanism is similar to that reported by Li *et al*. [32] as it is believed that miRNA-451 plays a role in reducing TLR4 protein levels.

4.5. Effects of burn on BBB

There is a lack of information on the effects of burn injury on the central nervous system in humans. However, neurological complications following inhalational injuries with or without coetaneous burn have been reported. These complications are variable and include persistent headaches, memory loss, paresthesia, impaired concentration and learning abilities, and anhedonia [99,100].

In a sheep model, Randolph *et al*. [101] investigated the pathophysiologic changes induced by inhalational smoke injury with or without third-degree skin burn. The results showed that smoke inhalation alone or in combination with third-degree skin burns was associated with a significant increase in the number of congested blood vessels in the brain compared to the sham-injured controls. Furthermore, damage to the basement membrane and rupture of blood vessels was also noted on histopathologic examination. These findings show that smoke inhalation can disrupt the BBB and lead to significant neurological consequences.

Yang *et al*. [26] utilized a mouse model to investigate the pathophysiologic effects of third-degree skin burns on BBB and whether these effects can be reversed with UC-MSCs treatment. BBB permeability was evaluated using several methods, including dextran tracer and transmission electron microscopy, to detect transcellular vesicular transport in BBB.

Burn injury increased BBB permeability to 10-kDa and 70-kDa dextran. Furthermore, burns decreased the level of tight junction proteins (TJs), including claudin-5, occludin, and ZO-1, which indicated increased BBB permeability due to the paracellular pathway. Administrating UC-MSCs 1-h post-burn successfully reversed all these effects and restored the integrity of BBB. In detail, UC-MSCs decreased IL-1β and IL-6 in blood and brain; attenuated the decrease of TJs; and inhibited transcytosis in cerebral endothelial cells. However, the underlying mechanisms of these effects are yet to be investigated.

4.6. Clinical trials reporting systemic administration of MSCs in patients with sepsis

The favored effects of MSCs on animal models encouraged investigating its safety and efficacy in clinical trials. Multiple studies investigated the safety of escalating doses of different types of MSCs and its effect on inflammatory mediators in septic and healthy patients (Table 3). He *et al*. [102] investigated the effect of different doses of freshly cultured UC- MSCs in patients with severe sepsis in the intensive care units (ICU). Although there was no significant change in the clinical outcomes, 100% of the patients tolerated the doses of MSCs with an evidence of a decreased level of inflammatory biomarkers L-6, IL-8, TNF-α, and CRP at day 8 after treatment. Two other studies [103,104]

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

Table 3. Summary of clinical trials utilizing mesenchymal stem cells in patients with septic conditions.

Study	Stem Cells Type	Dose	Administration Route	Type of Patients	Results
McIntyre *et al*. 2018 [103]	freshly cultured allogenic bone marrow–derived MSCs	0.3×10^6 cells 1.0×10^6 cells 3.0×10^6 cells	IV	ICU patients refractory to septic shock treatment (enrolled within 30 h of admission)	Intravenous delivery of a single dose of freshly cultured MSCs is safe and well tolerated up to a dose as high as 250 million cells in patients with septic shock that do not have significant severe comorbid illnesses No adverse safety (e.g., spike in cytokine concentrations after MSC administration) or efficacy signals in the measured cytokines
He *et al*.[102] 2018	Allogeneic freshly cultured Umbilical cord-derived MSCs.	low (1×10^6 cells/kg), intermediate (2×10^6 cells/kg), High (3×10^6 cells/kg)	IV	Intensive care units (ICUs) Age >18 years Onset of severe sepsis, defined as the presence of at least 2 of the 4criteria of the systemic inflammatory response syndrome within the previous 24 h	A single intravenous infusion of allogeneic MSCs up to a dose of 3£10^6 cells/kg was safe and well tolerated in15 patients with severe sepsis Reduced inflammatory biomarkers (L-6, IL-8, TNF-a, and CRP) at day 8 after MSC treatment
Perlee *et al*.[106] 2018	allogeneic adipose derived MSCs	0.25×10^6 1×10^6 4×10^6	IV	Healthy male subjects	Intravenous infusion of MSCs, at any dose, was well tolerated. MSCs infusion has mixed proinflammatory (enhanced IL-8 release) and anti-inflammatory effects (trend to reduce IL-12p40 and increased IL-10 and TFG-β release) on the cytokine network during human endotoxemia
Schlosser *et al*.[104] 2019	Allogeneic bone marrow-derived mesenchymal stem/stromal cells	0.3×10^6 1.0×10^6 3.0×10^6	IV	septic shock patients	No significant increase in pro-inflammatory cytokines was detected after MSC infusion MSC treatment appeared to attenuate levels of several pro-inflammatory cytokines in a dose-specific manner
Swaminathan *et al*.[105] 2021	SBI-101 is a combination of the allogeneic cells (bone marrow-derived) and a Food and Drug Administration-approved hollow fiber plasma separator	low dose of SBI-101 (250×10^6 MSCs)	*Ex vivo* administration	Patients with AKI of any etiology and had been, in the Investigator's opinion, stable for at least 12 hafter commencement of CRRT and were likely to require CRRT for an additional 48 h	Treatment with SBI-101 elicits an immunotherapeutic response that triggers an accelerated phenotypic switch from tissue injury to tissue repair

MSCs: Mesenchymal stem cells, IV: Intravenous, ICU: Intensive care unit

used escalating intravenous doses of allogenic BMMSCs on ICU patients with refractory septic shock. Both studies concluded the safety of using MSCs in this patient population with no change or attenuation in the level of pro-inflammatory cytokines.

Swaminathan *et al*. [105] studied a combination of the allogenic BMMSCs and a Food and Drug Administration-approved hollow fiber plasma separator (SBI-101). They concluded that infusion of this combination in patients with AKI on continuous renal replacement therapy triggered an immunotherapeutic response that promotes tissue repair. The effects of MSCs on healthy subjects were investigated through an IV infusion of allogenic adipose MSCs. In that study, Perlee *et al*. [106] conclusion came in line with the previously mentioned studies regarding the safety of different doses and the mixed cytokine response. All these human clinical trials which concluded the safety of MSCs were limited to small number of subjects in the interventional arm ranged from 9 to 24 (Table 3). We believe that this will open the door for more studies that investigate on a wider scale the effects of MSCs treatment modalities on different patient populations.

5. Conclusion

Although the anti-inflammatory and immunomodulatory characteristics of MSCs have been extensively investigated, only few studies investigated their potentials in burn. The evidence from the existing literature suggests that MSCs may attenuate the burn-induced SIRS by decreasing serum levels of inflammatory cytokines, including IL-1, IL-6, and TNF-α. However, the effect on anti-inflammatory cytokines such as IL-10 is conflicting and mandates more substantial evidence. Furthermore, MSCs reduce tissue inflammation, tissue damage, and apoptosis in the lungs and kidneys. However, these effects were not present in the liver. In addition, MSCs may reverse the burn-induced pathophysiologic

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

changes in the BBB. The underlying mechanisms of these effects are poorly understood and should be the focus of future stem cell research.

Limitations

As with most systematic reviews, this study is liable to the potential bias of misinterpreting data and results and bias in the study selection process. Specific to this study, the significant heterogeneity among the included studies, particularly the MSCs source and route of administration, precluded the possibility of conducting a sound statistical analysis. Furthermore, the small number of the included studies compromised the quality of driven conclusions.

Conflict of interest

The authors report no conflict of interest.

References

[1] Przkora R, Barrow RE, Jeschke MG, Suman OE, Celis M, Sanford AP, *et al*. Body Composition Changes with Time in Pediatric Burn Patients. J Trauma 2006;60:968-71.

[2] Finnerty CC, Herndon DN, Przkora R, Pereira CT, Oliveira HM, Queiroz DM, *et al*. Cytokine Expression Profile Over Time in Severely Burned Pediatric Patients. Shock 2006;26:13-9.

[3] Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman OE, Norbury WB, *et al*. Pathophysiologic Response to Severe Burn Injury. Ann Surg 2008;248:387-401.

[4] Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn iNjury. Nat Rev Dis Primers 2020;6:11.

[5] Toliver-Kinsky T, Kobayashi M, Suzuki F, Sherwood ER. The systemic inflammatory response syndrome. In: Total Burn Care. Amsterdam, Netherlands: Elsevier Inc.; 2018. p. 205-20.e204.

[6] Han Y, Li X, Zhang Y, Han Y, Chang F, Ding J. Mesenchymal Stem Cells for Regenerative Medicine. Cells 2019;8:E886.

[7] Fu X, Liu G, Halim A, Ju Y, Luo Q, Song AG. Mesenchymal Stem Cell Migration and Tissue Repair. Cells 2019;8:E784.

[8] Gao F, Chiu SM, Motan DA, Zhang Z, Chen L, Ji HL, *et al*. Mesenchymal Stem Cells and Immunomodulation: Current Status and Future Prospects. Cell Death Dis 2016;7:e2062.

[9] Jo H, Brito S, Kwak BM, Park S, Lee MG, Bin BH. Applications of Mesenchymal Stem Cells in Skin Regeneration and Rejuvenation. Int J Mol Sci 2021;22:2410.

[10] Mazini L, Rochette L, Admou B, Amal S, Malka G. Hopes and Limits of Adipose-Derived Stem Cells (ADSCs) and Mesenchymal Stem Cells (MSCs) in Wound Healing. Int J Mol Sci 2020;21:E1306.

[11] Cosenza S, Toupet K, Maumus M, Luz-Crawford P, Blanc-Brude O, Jorgensen C, *et al*. Mesenchymal Stem Cells-derived Exosomes are more Immunosuppressive than Microparticles in Inflammatory Arthritis. Theranostics 2018;8:1399-410.

[12] Li JY, Ren KK, Zhang WJ, Xiao L, Wu HY, Liu QY, *et al*. Human Amniotic Mesenchymal Stem Cells and their Paracrine Factors Promote Wound Healing by Inhibiting Heat Stress-induced Skin Cell Apoptosis and Enhancing their Proliferation Through Activating PI3K/AKT Signaling Pathway. Stem Cell Res Ther 2019;10:247.

[13] Amini-Nik S, Dolp R, Eylert G, Datu AK, Parousis A, Blakeley C, *et al*. Stem Cells Derived from Burned Skin the Future of Burn Care. EBioMedicine 2018;37:509-20.

[14] Shumakov VI, Onishchenko NA, Rasulov MF, Krasheninnikov ME, Zaidenov VA. Mesenchymal Bone Marrow Stem Cells more Effectively Stimulate Regeneration of Deep Burn Wounds than Embryonic Fibroblasts. Bull Exp Biol Med 2003;136:192-5.

[15] Xue L, Xu YB, Xie JL, Tang JM, Shu B, Chen L, *et al*. Effects of Human Bone Marrow Mesenchymal Stem Cells on Burn Injury Healing in a Mouse Model. Int J Clin Exp Pathol 2013;6:1327-36.

[16] Abdullahi A, Amini-Nik S, Jeschke MG. Animal Models in Burn Research. Cell Mol Life Sci 2014;71:3241-55.

[17] Hew JJ, Parungao RJ, Shi H, Tsai KH, Kim S, Ma D, *et al*. Mouse Models in Burns Research: Characterisation of the Hypermetabolic Response to Burn Injury. Burns 2020;46:663-74.

[18] Calum H, Høiby N, Moser C. Burn Mouse Models. Methods Mol Biol 2014;1149:793-802.

[19] Luze H, Kotzbeck P, Nischwitz SP, Kamolz LP. Importance of Accurate and Reproducible Animal Models for Burn Wounds. Burns 2020;46:1479-80.

[20] Reczyńska K, Tharkar P, Kim SY, Wang Y, Pamuła E, Chan HK, *et al*. Animal Models of Smoke Inhalation Injury and Related Acute and Chronic Lung Diseases. Adv Drug Deliv Rev 2018;123:107-34.

[21] Cetinkale O, Senel O, Bulan R. The Effect of Antioxidant Therapy on Cell-mediated Immunity Following Burn Injury in an Animal Model. Burns 1999;25:113-8.

[22] Hashemi SS, Pourfath MR, Derakhshanfar A, Behzad-Behbahani A, Moayedi J. The Role of Labeled Cell Therapy with and Without Scaffold in Early Excision Burn Wounds in a Rat Animal Model. Iran J Basic Med Sci 2020;23:673-9.

[23] Oryan A, Alemzadeh E. Comparison of Botulinum Toxin Type A and Aprotinin Monotherapy with Combination Therapy in Healing of Burn Wounds in an Animal Model. Mol Biol Rep 2020;47:2693-702.

[24] Kocaman N, Altun S, Bal A, Ozcan EC, Sarac M, Artas G, *et al*. Effects of Carnosine, Ankaferd, and Silver Sulfadiazine on an Experimental Burn Model: Roles of Irisin and HSP70. J Burn Care Res 2021;42:408-14.

[25] Yagi H, Soto-Gutierrez A, Kitagawa Y, Tilles AW,

Tompkins RG, Yarmush ML. Bone Marrow Mesenchymal Stromal Cells Attenuate Organ Injury Induced by LPS and Burn. Cell Transplant 2010;19:823-30.

[26] Yang J, Ma K, Zhang C, Liu Y, Liang F, Hu W, *et al*. Burns Impair Blood-Brain Barrier and Mesenchymal Stem Cells Can Reverse the Process in Mice. Front Immunol 2020;11:578879.

[27] Caliari-Oliveira C, Yaochite JN, Ramalho LN, Palma PV, Carlos D, Cunha Fde Q, *et al*. Xenogeneic Mesenchymal Stromal Cells Improve Wound Healing and Modulate the Immune Response in an Extensive Burn Model. Cell Transplant 2016;25:201-15.

[28] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA Statement for Reporting Systematic Reviews and Meta-analyses of Studies that Evaluate Healthcare Interventions: Explanation and Elaboration. BMJ 2009;339:b2700.

[29] Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's Risk of Bias Tool for Animal Studies. BMC Med Res Methodol 2014;14:43.

[30] Lu G, Huang S, Chen Y, Ma K. Umbilical Cord Mesenchymal Stem Cell Transplantation Ameliorates Burn-induced Acute Kidney Injury in Rats. Int J Low Extrem Wounds 2013;12:205-11.

[31] Zhang J, La X, Fan L, Li P, Yu Y, Huang Y, *et al*. Immunosuppressive Effects of Mesenchymal Stem Cell Transplantation in Rat Burn Models. Int J Clin Exp Pathol 2015;8:5129-36.

[32] Li X, Liu L, Yang J, Yu Y, Chai J, Wang L, *et al*. Exosome Derived From Human Umbilical Cord Mesenchymal Stem Cell Mediates MiR-181c Attenuating Burn-induced Excessive Inflammation. EBioMedicine 2016;8:72-82.

[33] Liu JS, Du J, Cheng X, Zhang XZ, Li Y, Chen XL. Exosomal miR-451 from Human Umbilical Cord Mesenchymal Stem Cells Attenuates Burn-induced Acute Lung Injury. J Chin Med Assoc 2019;82:895-901.

[34] Curtis BJ, Shults JA, Boe DM, Ramirez L, Kovacs EJ. Mesenchymal Stem Cell Treatment Attenuates Liver and Lung Inflammation after Ethanol Intoxication and Burn Injury. Alcohol 2019;80:139-48.

[35] Beynen A, Gärtner K, Van Zutphen L. Standardization of animal experimentation. In: Principles of Laboratory Animal Science: A Contribution to the Humane Use and Care of Animals and to the Quality of Experimental Results. 2nd ed. Amsterdam: Elsevier; 2001. p. 103-10.

[36] Clough G. Environmental Effects on Animals Used in Biomedical Research. Biol Rev Camb Philos Soc 1982;57:487-523.

[37] Johnston NA, Nevalainen T. Impact of the biotic and abiotic environment on animal experiments. In: Handbook of Laboratory Animal Science, Volume 1: Essential Principles and Practices. Boca Raton, Florida: CRC Press; 2002. p. 311.

[38] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, *et al*. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.

[39] Pittet D, Rangel-Frausto S, Li N, Tarara D, Costigan M, Rempe L, *et al*. Systemic Inflammatory Response Syndrome, Sepsis, Severe Sepsis and Septic Shock: Incidence, Morbidities and Outcomes in Surgical ICU Patients. Intensive Care Med 1995;21:302-9.

[40] Talmor M, Hydo L, Barie PS. Relationship of Systemic Inflammatory Response Syndrome to Organ Dysfunction, Length of Stay, and Mortality in Critical Surgical Illness: Effect of Intensive Care Unit Resuscitation. Arch Surg 1999;134:81-7.

[41] Sheridan RL, Ryan CM, Yin LM, Hurley J, Tompkins RG. Death in the Burn Unit: Sterile Multiple Organ Failure. Burns 1998;24:307-11.

[42] Ryan CM, Schoenfeld DA, Thorpe WP, Sheridan RL, Cassem EH, Tompkins RG. Objective Estimates of the Probability of Death from Burn Injuries. N Engl J Med 1998;338:362-6.

[43] Gando S, Nanzaki S, Kemmotsu O. Disseminated Intravascular Coagulation and Sustained Systemic Inflammatory Response Syndrome Predict Organ Dysfunctions after Trauma: Application of Clinical Decision Analysis. Ann Surg 1999;229:121-7.

[44] Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The Natural History of the Systemic Inflammatory Response Syndrome (SIRS). A Prospective Study. JAMA 1995;273:117-23.

[45] Wolf SE, Rose JK, Desai MH, Mileski JP, Barrow RE, Herndon DN. Mortality Determinants in Massive Pediatric Burns. An Analysis of 103 Children with > or = 80% TBSA Burns (> or = 70% full-thickness). Ann Surg 1997;225:554-65.

[46] Takeda K, Akira S. Toll-like Receptors. Curr Protoc Immunol 2015;109:14.12.1-10.

[47] Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, *et al*. Circulating Mitochondrial DAMPs Cause Inflammatory Responses to Injury. Nature 2010;464:104-7.

[48] D'Arpa P, Leung KP. Toll-Like Receptor Signaling in Burn Wound Healing and Scarring. Adv Wound Care (New Rochelle) 2017;6:330-43.

[49] Akira S. TLR signaling. Curr Top Microbiol Immunol 2006;311:1-16.

[50] Paterson HM, Murphy TJ, Purcell EJ, Shelley O, Kriynovich SJ, Lien E, *et al*. Injury Primes the Innate Immune System for Enhanced Toll-like Receptor Reactivity. J Immunol 2003;171:1473-83.

[51] Adib-Conquy M, Cavaillon JM. Compensatory Anti-inflammatory Response Syndrome. Thromb Haemost 2009;101:36-47.

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

[52] Yeh FL, Shen HD, Fang RH. Deficient Transforming Growth Factor Beta and Interleukin-10 Responses Contribute to the Septic Death of Burned Patients. Burns 2002;28:631-7.

[53] Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, Ungaro R, Davis R, Cuenca AG, *et al*. Persistent Inflammation, Immunosuppression, and Catabolism Syndrome after Severe Blunt Trauma. J Trauma Acute Care Surg 2014;76:21-9.

[54] Ding DC, Shyu WC, Lin SZ. Mesenchymal Stem Cells. Cell Transplant 2011;20:5-14.

[55] Colter DC, Class R, DiGirolamo CM, Prockop DJ. Rapid Expansion of Recycling Stem Cells in Cultures of Plastic-adherent Cells from Human Bone Marrow. Proc Natl Acad Sci U S A 2000;97:3213-8.

[56] Heo JS, Choi Y, Kim HS, Kim HO. Comparison of Molecular Profiles of Human Mesenchymal Stem Cells Derived from Bone Marrow, Umbilical Cord Blood, Placenta and Adipose Tissue. Int J Mol Med 2016;37:115-25.

[57] Denburg JA, Inman MD, Sehmi R, Uno M, O'Byrne PM. Hemopoietic Mechanisms in Allergic Airway Inflammation. Int Arch Allergy Immunol 1998;117:155-9.

[58] Denburg JA, Inman MD, Wood L, Ellis R, Sehmi R, Dahlback M, *et al*. Bone Marrow Progenitors in Allergic Airways Diseases: Studies in Canine and Human Models. Int Arch Allergy Immunol 1997;113:181-3.

[59] Steinberger Z, Xu H, Kazmers NH, Chen CD, Caron RJ, Qin L, *et al*. Robustness Testing of Mesenchymal Stem Cell Monotherapy Following Vascularized Composite Allotransplantation. J Reconstr Microsurg 2020;36:397-402.

[60] Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, *et al*. Immunomodulatory Effect of Human Adipose Tissue-derived Adult Stem Cells: Comparison with Bone Marrow Mesenchymal Stem Cells. Br J Haematol 2005;129:118-29.

[61] Yañez R, Lamana ML, García-Castro J, Colmenero I, Ramírez M, Bueren JA. Adipose Tissue-derived Mesenchymal Stem Cells Have *In Vivo* Immunosuppressive Properties Applicable for the Control of the Graft-versus-host Disease. Stem Cells 2006;24:2582-91.

[62] Selmani Z, Naji A, Zidi I, Favier B, Gaiffe E, Obert L, *et al*. Human Leukocyte Antigen-G5 Secretion by Human Mesenchymal Stem Cells is Required to Suppress T Lymphocyte and Natural Killer Function and to Induce CD4+CD25highFOXP3+ Regulatory T Cells. Stem Cells 2008;26:212-22.

[63] Chen CC, Chen RF, Shao JS, Li YT, Wang YC, Brandacher G, *et al*. Adipose-derived Stromal Cells Modulating Composite Allotransplant Survival is Correlated with B Cell Regulation in a Rodent Hind-limb Allotransplantation Model. Stem Cell Res Ther 2020;11:478.

[64] Zhang J, Rong Y, Luo C, Cui W. Bone Marrow Mesenchymal Stem Cell-derived Exosomes Prevent Osteoarthritis by Regulating Synovial Macrophage Polarization. Aging (Albany NY) 2020;12:25138-52.

[65] Németh K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, *et al*. Bone Marrow Stromal Cells Attenuate Sepsis via Prostaglandin E(2)-dependent Reprogramming of Host Macrophages to Increase their Interleukin-10 Production. Nat Med 2009;15:42-9.

[66] Zhou T, Sun Y, Wang Y, Chen X, Zhuo L, Bu L, *et al*. Umbilical Cord Blood Mesenchymal Stem Cells Enhance Lipopolysaccharide-Induced IL-10 and IL-37 Production in THP-1 Cells. Inflammation 2019;42:987-93.

[67] Ng SL, Leno-Duran E, Samanta D, Almo SC, Strominger JL. Genetically Modified Hematopoietic Stem/Progenitor Cells that Produce IL-10-Secreting Regulatory T Cells. Proc Natl Acad Sci U S A 2019;116:2634-9.

[68] Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, Cazzanti F, *et al*. Human Mesenchymal Stem Cells Modulate B-Cell Functions. Blood 2006;107:367-72.

[69] Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal Stem Cells Inhibit Dendritic Cell Differentiation and Function by Preventing Entry into the Cell Cycle. Transplantation 2007;83:71-6.

[70] Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell-natural Killer Cell Interactions: Evidence that Activated NK Cells are Capable of Killing MSCs, Whereas MSCs can Inhibit IL-2-induced NK-cell Proliferation. Blood 2006;107:1484-90.

[71] Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A, *et al*. Role for Interferon-gamma in the Immunomodulatory Activity of Human Bone Marrow Mesenchymal Stem Cells. Stem Cells 2006;24:386-98.

[72] Ryan JM, Barry F, Murphy JM, Mahon BP. Interferon-gamma does not Break, but Promotes the Immunosuppressive Capacity of Adult Human Mesenchymal Stem Cells. Clin Exp Immunol 2007;149:353-63.

[73] Ren G, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, *et al*. Mesenchymal Stem Cell-Mediated Immunosuppression Occurs Via Concerted Action of Chemokines and Nitric Oxide. Cell Stem Cell 2008;2:141-50.

[74] DelaRosa O, Lombardo E, Beraza A, Mancheño-Corvo P, Ramirez C, Menta R, *et al*. Requirement of IFN-gamma-mediated Indoleamine 2,3-dioxygenase Expression in the Modulation of Lymphocyte Proliferation by Human Adipose-derived Stem Cells. Tissue Eng Part A 2009;15:2795-806.

[75] Luk F, de Witte SF, Korevaar SS, Roemeling-van Rhijn M, Franquesa M, Strini T, *et al*. Inactivated Mesenchymal Stem Cells Maintain Immunomodulatory Capacity. Stem Cells Dev 2016;25:1342-54.

[76] Zhang L, Yu D. Exosomes in Cancer Development,

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

Metastasis, and Immunity. Biochim Biophys Acta Rev Cancer 2019;1871:455-68.

[77] Kalluri R, LeBleu VS. The Biology, Function, and Biomedical Applications of Exosomes. Science 2020;367:eaau6977.

[78] Zhang H, Freitas D, Kim HS, Fabijanic K, Li Z, Chen H, *et al*. Identification of Distinct Nanoparticles and Subsets of Extracellular Vesicles by Asymmetric Flow Field-flow Fractionation. Nat Cell Biol 2018;20:332-43.

[79] Keerthikumar S, Chisanga D, Ariyaratne D, Al Saffar H, Anand S, Zhao K, *et al*. ExoCarta: A Web-based Compendium of Exosomal Cargo. J Mol Biol 2016;428:688-92.

[80] Chen Z, Xue S, Zhang S, Cheng K, Ye Q. Exosomes from Donor-derived Adipose Mesenchymal Stem Cells Prolong the Survival of Vascularized Composite Allografts. J Cell Physiol 2021;236:5895-905.

[81] Sungkar T, Putra A, Lindarto D, Sembiring RJ. Intravenous Umbilical Cord-derived Mesenchymal Stem Cells Transplantation Regulates Hyaluronic Acid and Interleukin-10 Secretion Producing Low-grade Liver Fibrosis in Experimental Rat. Med Arch 2020;74:177-82.

[82] Jeschke MG. The Hepatic Response to Thermal Injury: Is the Liver Important for Postburn Outcomes? Mol Med 2009;15:337-51.

[83] Gong Y, Long X, Xu H, Yang X, Guo Q. The Changes and Prognostic Value of liver function in Young Adults with Severe Burn: A Retrospective Observational Study. Medicine (Baltimore) 2018;97:e13721.

[84] Barret JP, Jeschke MG, Herndon DN. Fatty Infiltration of the Liver in Severely Burned Pediatric Patients: Autopsy Findings and Clinical Implications. J Trauma 2001;51:736-9.

[85] Jeschke MG, Micak RP, Finnerty CC, Herndon DN. Changes in Liver Function and Size after a Severe Thermal Injury. Shock 2007;28:172-7.

[86] Steller H. Mechanisms and Genes of Cellular Suicide. Science 1995;267:1445-9.

[87] Ramzy PI, Wolf SE, Irtun O, Hart DW, Thompson JC, Herndon DN. Gut Epithelial Apoptosis after Severe Burn: Effects of Gut Hypoperfusion. J Am Coll Surg 2000;190:281-7.

[88] Bellas RE, FitzGerald MJ, Fausto N, Sonenshein GE. Inhibition of NF-kappa B Activity Induces Apoptosis in Murine Hepatocytes. Am J Pathol 1997;151:891-6.

[89] Strasser A, O'Connor L, Dixit VM. Apoptosis Signaling. Annu Rev Biochem 2000;69:217-45.

[90] Gauglitz GG, Song J, Herndon DN, Finnerty CC, Boehning D, Barral JM, *et al*. Characterization of the Inflammatory Response during Acute and Post-acute Phases after Severe Burn. Shock 2008;30:503-7.

[91] Jeschke MG, Boehning DF, Finnerty CC, Herndon DN. Effect of Insulin on the Inflammatory and acute Phase Response after Burn Injury. Crit Care Med 2007;35:S519-23.

[92] Carson J, Goverman J, Fagan SP. 31 Acute Renal Failure in Association with Thermal Injury. Total Burn Care E-Book. 2017;20:318-327.

[93] Kellum JA. Acute Kidney Injury. Crit Care Med. 2008;36(4 Suppl):S141-145.

[94] Cartotto R, Choi J, Gomez M, Cooper A. A Prospective Study on the Implications of a Base Deficit during Fluid Resuscitation. J Burn Care Rehabil 2003;24:75-84.

[95] Schrier RW, Wang W. Acute Renal Failure and Sepsis. N Engl J Med 2004;351:159-69.

[96] Hohlfeld T, Klemm P, Thiemermann C, Warner TD, Schrör K, Vane JR. The Contribution of Tumour Necrosis Factor-alpha and Endothelin-1 to the Increase of Coronary Resistance in Hearts from Rats Treated with Endotoxin. Br J Pharmacol 1995;116:3309-15.

[97] Kallinen O, Maisniemi K, Böhling T, Tukiainen E, Koljonen V. Multiple Organ Failure as a Cause of Death in Patients with Severe Burns. J Burn Care Res 2012;33:206-11.

[98] Kraft R, Herndon DN, Finnerty CC, Shahrokhi S, Jeschke MG. Occurrence of Multiorgan Dysfunction in Pediatric Burn Patients: Incidence and Clinical Outcome. Ann Surg 2014;259:381-7.

[99] de Albuquerque IM, Pasqualoto AS, Trevisan ME, Gonçalves MP, Badaró AF, de Moraes JP, *et al*. Role of Physiotherapy in the Rehabilitation of Survivors of the Kiss Nightclub Tragedy in Santa Maria, Brazil. Physiotherapy 2013;99:269-70.

[100] Tobe E. Progressive Neuropsychiatric and Brain Abnormalities after Smoke Inhalation. BMJ Case Rep 2012;2012:bcr0220125945.

[101] Randolph AC, Fukuda S, Ihara K, Enkhbaatar P, Micci MA. Blood-Brain Barrier Dysfunction after Smoke Inhalation Injury, With and Without Skin Burn. Shock 2019;51:634-49.

[102] He X, Ai S, Guo W, Yang Y, Wang Z, Jiang D, *et al*. Umbilical Cord-derived Mesenchymal Stem (Stromal) Cells for Treatment of Severe Sepsis: Aphase 1 Clinical Trial. Transl Res 2018;199:52-61.

[103] McIntyre LA, Stewart DJ, Mei SHJ, Courtman D, Watpool I, Granton J, *et al*. Cellular Immunotherapy for Septic Shock. A Phase I Clinical Trial. Am J Respir Crit Care Med 2018;197:337-47.

[104] Schlosser K, Wang JP, Dos Santos C, Walley KR, Marshall J, Fergusson DA, *et al*. Effects of Mesenchymal Stem Cell Treatment on Systemic Cytokine Levels in a Phase 1 Dose Escalation Safety Trial of Septic Shock Patients. Crit Care Med 2019;47:918-25.

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

[105] Swaminathan M, Kopyt N, Atta MG, Radhakrishnan J, Umanath K, Nguyen S, *et al*. Pharmacological Effects of *Ex Vivo* Mesenchymal Stem Cell Immunotherapy in Patients with Acute Kidney Injury and Underlying Systemic Inflammation. Stem Cells Transl Med 2021;10:1588-601.

[106] Perlee D, van Vught LA, Scicluna BP, Maag A, Lutter R, Kemper EM, *et al*. Intravenous Infusion of Human Adipose Mesenchymal Stem Cells Modifies the Host Response to Lipopolysaccharide in Humans: A Randomized, Single-Blind, Parallel Group, Placebo Controlled Trial. Stem Cells 2018;36:1778-88.

Publisher's note

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003

Journal of Clinical and Translational Research 2022; 8(4): 276-291

Journal of Clinical and Translational Research

Journal homepage: http://www.jctres.com/en/home

REVIEW ARTICLE

Systemic anti-inflammatory effects of mesenchymal stem cells in burn: A systematic review of animal studies

Data Base Search
PubMed
Search terms: ([Mesenchymal stem cells (MeSH Terms)] AND [burn (MeSH Terms)] AND [animal model (MeSH Terms)])
Results: 46.
CINAHL
Search terms: Mesenchymal stem cells AND Burn
Results: 47.
Scopus
Search terms: Mesenchymal Stem Cells AND Burn AND Animal Models
Filters: Article, Medicine, and Journal
Results: 2379.
Web of Science
Search terms: Mesenchymal Stem Cells AND Burn AND Animal Models
Results: 100.

DOI: http://dx.doi.org/10.18053/jctres.08.202204.003