We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Current Status of Stem Cell Therapy for Sepsis and Acute Respiratory Distress Syndrome

Raquel Guillamat-Prats and Antonio Artigas

Abstract

Sepsis and acute respiratory distress syndrome (ARDS) are life-threatening diseases with high mortality, around 40%, and morbidity in all the critical care units around the world. After decades of research, and numerous pre-clinical and clinical trials, sepsis and ARDS remain without a specific and effective pharmaco-therapy and essentially the management remains supportive. Over the last years, cell therapies gained potential as a therapeutic treatment for ARDS and sepsis. Based on numerous pre-clinical studies, there is a growing evidence of the potential benefits of cell-based therapies for the treatment of sepsis and ARDS. Different cell subtypes have been used for the treatment of both syndromes; however, the major part of the studies is using mesenchymal stem/stromal cells (MSC). Also, other relevant groups performed some pre-clinical studies using induced pluripotent stem cells (iPSC) for the treatment of both syndromes and alveolar type II cells for ARDS treatment. Numerous questions need further study, including determining the best source for the progenitor cells isolation, their large-scale production, and cryopreservation. Also, the heterogeneity of patients with sepsis and ARDS is massive, and the stratification of the patients will help us to determine better the therapeutic effect of these cell therapies. In this review, we are going to describe briefly the different cell types, their potential sources, and characteristics and mechanism of action. We will review several pre-clinical and clinical studies in ARDS and sepsis.

Keywords: sepsis, ARDS, acute lung injury, cell therapy, critical care

1. Introduction

Sepsis and acute respiratory distress syndrome (ARDS) are life-threatening diseases with high mortality and morbidity in all the critical care units around the world [1–4]. Severe sepsis is a complex syndrome produced by the response to a systemic infection. The infection produces a general inflammatory response, such as tachycardia, elevated white cell count and systemic release of pro-inflammatory cytokines, and this can lead to an acute organ dysfunction. Sepsis is producing more than 5 million deaths per year worldwide [5–8].

The lung is one of the most affected organs during sepsis, and for that reason, one of the main indirect causes of ARDS is sepsis. ARDS can also be produced by a direct injury as a pulmonary infection or a trauma. ARDS is a multifactorial

syndrome characterized by increased lung permeability, hypoxemia, the absence of cardiogenic pulmonary edema, the disruption of the alveolar-capillary barrier, and widespread inflammation. Every year between 1.5 and 4.5 cases per 100,000 inhabitants/year in Europe is detected and in the United States approximately 200,000 new cases are identified per year [1, 5, 8].

There is no definitive therapy that targets the underlying pathobiology of sepsis exists. Nowadays, the treatment is based on antibiotics, infection source control, fluid resuscitation, and organ support [9, 10]. Moreover, several patients die due to secondary infections during the year after the hospital discharge. After decades of research, and numerous pre-clinical and clinical trials, sepsis and ARDS remain without a specific and effective pharmacotherapy and essentially the management remains supportive. Nowadays, patients with ARDS have been treated with several ventilator interventions such as lower tidal volumes, higher positive end-expiratory pressure (PEEP), and adjuncts such as prone positioning, neuromuscular blockade, and extracorporeal membrane oxygenation [11–14].

Current advances in the study and knowledge of stem cells have permitted to start using them as a novel treatment for ARDS and sepsis. Based on numerous pre-clinical studies, there is a growing evidence of the potential benefits of cell-based therapies for the treatment of sepsis and ARDS. Several cell types are used in the last years for the treatment of both syndromes showing high efficiency [15, 16].

In animal models, cell therapies have demonstrated noteworthy therapeutic properties including the modulation of the immune system, the release of several factors with growth factor, and antibiotic and anti-inflammatory properties. Cell therapies were tested in several animal models, such as mouse, rat, sheep, and pig models, using several septic and ARDS models. Moreover, different cell types and different administration pathways (intravenously, intraperitoneal, or local administration into the lung) were used as a treatment.

Furthermore, in the last years, a couple of clinical studies started using cell therapies for the treatment of sepsis and ARDS, and some safety and efficient results are published.

This chapter summarizes the different progenitor cells that can be used as a therapy, the mechanisms of action, and the results in pre-clinical and clinical studies in ARDS and in sepsis and future directions.

2. Cell sources for transplantation

We define cell therapy as a therapeutic product containing cells, which usually is administered into the patients to replace or repair damaged tissues or cells. Nowadays, several diseases are treated with cell therapies, for example, bone marrow transplants for the treatment of some specific cancers.

In the last years, several researchers and physicians are working to convert some cell therapies from potential treatments to real therapies. There is an effort to detect the factors that the cells are secreting and have this beneficial effect and also to set up the safety and efficacy. Additionally, these therapies are really expensive, and there are several problems associated such as the difficulty to obtain, expand, purify, and manipulate these cells. So, we also have to work on the cost-effective options.

Cell therapies have shown their potential in biomedicine, and their utility for several indications has been demonstrated and this utility will expand in the future. Nevertheless, progressing cell therapies from bench to bedside takes decades of hard and slow work.

Several pharmaceutical companies hold a number of stem cell lines and work to advance in cell therapies. Finding new culture mediums that able to maintain or differentiate into the desired cell type with high throughput and also diminish the risk of causing cancer is quite difficult. Afterwards, the laboratories and the companies will need to implement several protocols to work under good manufacturing practice guidelines (GMP) and follow specific storage rules of products that want to be used as a therapy. Several delicate conditions need to be fulfilled for these cells, to be approved by health authorities, and to be used in humans and in clinical trials.

First, we want to review the different cell types, their potential sources, and characteristics and underlie why mainly mesenchymal stem/stromal cells are used for the treatment of sepsis and ARDS. Some pre-clinical studies using induced pluripotent stem cells (iPSC) for the treatment of both syndromes and alveolar type II cells for ARDS treatment also presented some interesting results. The different cell subsets are summarized in **Table 1.**

2.1 Embryonic stem cells (ESCs)

ESCs are pluripotent cells derived from the inner blastocyst cell mass and constitute a potentially unlimited source of cells that could be differentiated into any progenitor cell and used in the clinical trials. ESCs have high plasticity and theoretically unlimited capacity for self-renewal; ESCs have been suggested for regenerative medicine and tissue replacement; however, their embryologic origin is linked to significant ethical issues regarding the use of these cells [17–19].

2.2 Induced pluripotent stem cells (iPSC)

A new type of pluripotent cells, iPSCs, can be obtained by reprogramming animal and human somatic (differentiated) cells. Usually, iPSCs are obtained from dermal fibroblasts because it is an easy source and did not produce any damage to the donor when we obtain them. The cells should be dedifferentiated following

Cell type	Harvest method	Advantages	Disadvantages	Benefits in ARDS	Benefits in sepsis
ESC	Embryos	Totipotent	High tumorigenic potential. Ethical problem	Easy to differentiate to AEC2. No tested *in vivo*	Reduces mortality and decreases lung inflammation
iPSC	Skin biopsy	Easy isolation No rejection	High tumorigenic potential	Easy to differentiate to AEC2. No tested *in vivo*	—
MSC	Bone marrow or adipose tissue	Easy isolation No rejection	High tumorigenic potential	Immunomodulatory effect. Reduces inflammation and lung edema	Reduces mortality and inflammation. Antibacterial activity and antiapoptotic activity
EnPC	Blood	Nontumorigenic	Difficult isolation and small amount	Maintains the integrity of the lung and improves the lung function	Reduces the sepsis damage re-establishing micro and macrocirculation
EpPC	Donor tissue	Nontumorigenic	Difficult isolation and small amount	AEC2 cells were tested improving lung function and reducing inflammation	—

Table 1.
Summary of the cell sources and their benefits.

reprogramming and finally are able to express four transcription factors such as Ocet3/4, Sox2, Klf-4, and c-Myc. They grow indefinitely and differentiate into all cell types of the human body, and also they can be obtained in autologous way reducing the graft-versus-host disease [20–22].

The main problem is that the dedifferentiation and reprogramming have low efficiency, and their genomic modification could create associated problems that until now are unknown or have not been studied and have a high tumorigenicity risk [23–25]. The potential applications of iPSCs in sepsis and ARDS are many [26, 27].

2.3 Endothelial progenitor cells (EnPC)

The endothelial damage is one of the main hallmarks of ARDS, and EnPCs have the ability to regenerate endothelial cells and could have an unlimited role in repairing the damaged endothelium. EnPCs have been defined as circulating cells that have ability to adhere to the endothelium at sites of hypoxia and ischemia secreting pro-angiogenic factors and generate a new vessel [28].

EnPCs express hematopoietic surface cell markers such as CD34. However, the role, isolation, and identification of these cells are not completely elucidated.

EnPCs can be useful as a regenerative instrument to treat several vascular diseases, but the ability to adhere to the endothelium at sites of hypoxia and ischemia secretes pro-angiogenic factors and generates a new vessel [29, 30].

Very few pre-clinical studies have been published, which have used EnPCs in sepsis and ARDS [31–34].

2.4 Epithelial progenitor cells (EpPC)

Some epithelial progenitors of the lung alveolar compartment have also been identified, but their isolation is really difficult and the number of cells that could be obtained is really low. EpPCs might be useful in the treatment of ARDS.

EpPCs are specified during development in each tissue and are highly regulated by epithelial-mesenchymal interactions. Different tissues have different EpPCs with small adjustments in their function; however, their maintenance, activation, and differentiation are regulated by the same pathways between all the tissues [35, 36].

The use of alveolar-epithelial type II cells (AE2C) for the treatment of ARDS has been demonstrated; these cells are more differentiated than EpPCs, but still can proliferate and differentiate into alveolar-epithelial type I cell, that are the complete differentiated cells in the lung epithelia. AE2C cells can only be isolated from the lungs of organ donors and may have problems in graft-versus-host disease [37–39]. The isolation of AE2C is laborious, but they have less ethical problems and tumorigenicity potential.

2.5 Mesenchymal stem cells (MSC)

MSCs are the best described cells and mostly used as a cell therapy. MSCs are multipotent cells that have been isolated from several tissues such as umbilical cord blood, placenta, adipose tissue, lung, and bone marrow.

The International Society of Cellular Therapy defined that MSCs should follow the three criteria: (1) MSCs must be adherent to plastic; (2) MSCs must express some cell surface markers, such as CD105, CD90, and CD73, but must not express other markers, including CD45, CD34, CD14, or CD11b; and (3) MSCs must have the capacity to differentiate into mesenchymal lineages (osteoblasts, adipocytes, and chondroblasts) in *in vitro* conditions [40].

MSCs have a high degree of plasticity and can be differentiated into a variety of cell lineages, but they do not possess the complete plasticity of ESCs. However, MSCs have some advantages because of their easy isolation and enormous propagation in culture and also because their use does not involve the ethical problems associated to the use of ESCs [41]. Moreover, they can be obtained in autologous way diminishing the immune rejection problem. In addition, MSCs are not immunogenic; they have an innate ability to avoid detection by a recipient's immune system because they express intermediate levels of major histocompatibility class I but do not express major histocompatibility class II [42–44].

Several experimental studies have indicated that MSCs may have potential therapeutic application in sepsis and ARDS [45–49]. It has also been reported that MSCs release several microvesicles that might have the therapeutic potential [50, 51].

3. Mesenchymal stem cell therapy for sepsis and acute respiratory distress syndrome

The complex pathophysiology of sepsis and also of ARDS requires a therapy with a wide range of properties. The heterogeneity of the host response in front of sepsis or ARDS makes it difficult to find a proper drug that works as a therapy. Stem cells are potential therapeutic agents with a diverse spectrum of action and can act at different levels of the pathophysiology of ARDS or sepsis, non only treating inflammation, moreover affecting coagulation, enhancing antimicrobial effect, modulating the innate and adaptive immune response, and reducing endothelium permeability and edema.

MSCs can be administered intravenously, but then only a small percentage of injected cells arrive to the injury site. Usually, MSCs get trapped into the lung's microvasculature, and after some hours, they are engulfed by macrophages and they disappear. It is well known that cells do not engraft into the tissue and their primary action mechanism is the secretion of soluble factors with therapeutic properties.

MSCs release into the extracellular media bioactive cytokines, chemokines, angiogenic factors, and/or growth factors. Moreover, it has been described that MSCs also release extracellular vesicles with bioactive compounds. Extracellular vesicles are small vesicles made by a phospholipid bilayer and encapsulate proteins, lipids, or miRNAs or other compounds that are protected from the media and can be phagocytosed by other cells and act on them. Nowadays, the use of extracellular vesicles to target specific cells is also a raising up therapy competing with cell therapies; however, there is still a lot to define about the secretome of the MSC to be able to mimic its therapeutic effects.

All these factors directly secreted to the media or inside extracellular vesicles regulate intracellular pathways from different cells and can act on the innate and adaptive immune system. The different effects or mechanisms are described in the following sections and in **Figure 1**.

3.1 Effects on the innate immune system

Inflammation is one of the main drivers of ARDS and sepsis pathogenesis. During ARDS, the injury of the lung endothelium and epithelium is producing a recruitment of pro-inflammatory cells such as neutrophils and monocytes into the alveolar space. These pro-inflammatory cells release several pro-inflammatory cytokines, for example, TNF-α, IL-1β, and IL-6 [52–54]. Moreover, neutrophils are secreting several ROS enhancing the damage of the endothelium and epithelial layers propagating the damage [55–57].
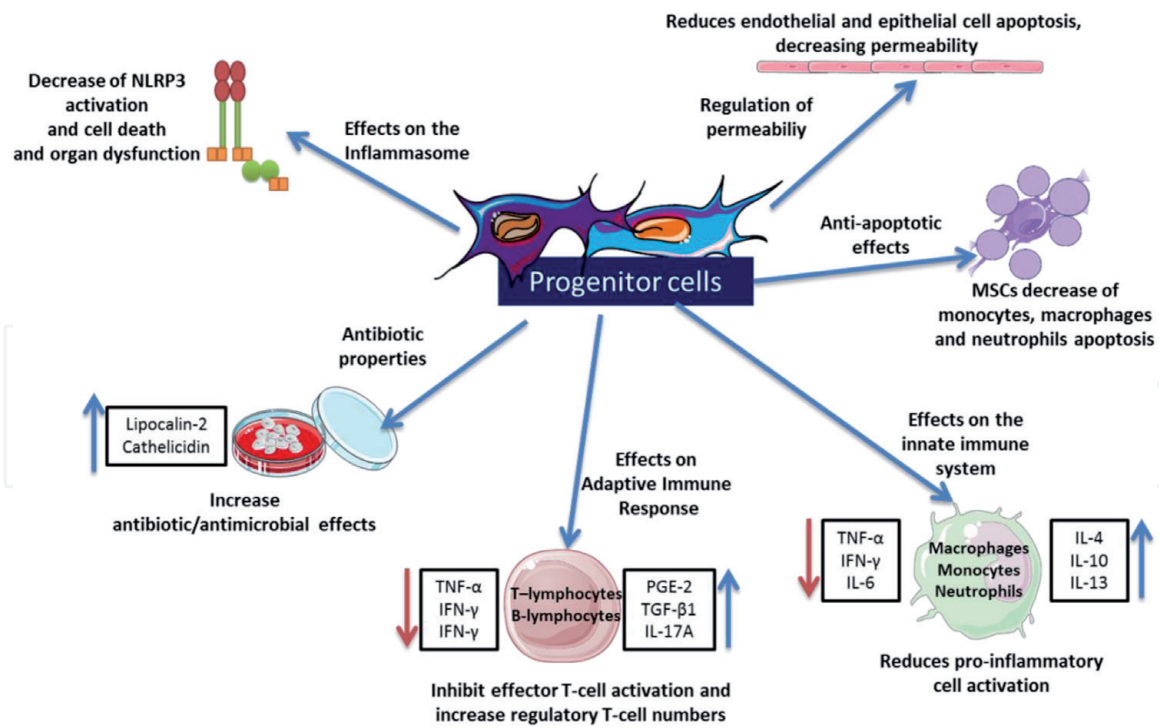
Figure 1.
Potential mechanisms of the cell therapies.

During sepsis, the infection activates TLR4, which leads to the activation of MyD88 and NF-kb and the transcription of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. After the first hours following the infection, there is a specific storm of cytokines [58].

MSCs have the ability to modulate the immune response and secrete several anti-inflammatory cytokines such as IL-4, IL-10, or IL-13 [59]. Furthermore, they regulate inflammation using different strategies and acting on different cells, which are described in the following sections.

3.1.1 Effects on humoral immune response

Numerous studies proved that MSCs decrease the pro-inflammatory cytokine response (TNF-α, IFN-γ, and IL-1α, -1β, -6, -12, and -17). They promote this effect while increasing concentrations of the anti-inflammatory agents, including IL-1 receptor antagonist (IL-1Ra), IL-10, tumor necrosis factor-inducible gene 6 protein (TSG-6), cyclooxygenase-2 (COX-2), insulin-like growth factor 1 (IGF-1), and prostaglandin-E2 (PGE2) [60, 61].

All these factors act on different cells; for example, IL-1Ra is able to reduce the production of inflammatory TNF-α in macrophages and also inhibits helper-T lymphocytes activation. TSG-6 has a potent anti-inflammatory effect acting in macrophages and polarizing them from a pro- to an anti-inflammatory phenotype while reducing the secretion of inflammatory chemokines by these cells. IGF-1 has been described as an anti-apoptotic compound, and during sepsis and ARDS, less apoptosis of the endothelium and epithelium cells reduces the damage and the associated inflammation [62, 63].

3.1.2 Effects on the inflammasome

The inflammasome is a multiprotein intracellular oligomer that detects pathogenic microorganisms and other factors and activates an inflammatory response. Inflammasome activates caspase-1 and caspase-1 cleaves the precursor cytokines

pro-IL-1β and pro-IL-18, generating the biologically active cytokines IL-1β and IL-18, respectively. Caspase 1 also activates following compounds derived from the host innate immune system that can lead to pyropotosis (an inflammatory form of cell death) [64].

Generally, myeloid cells such as neutrophils, monocytes, and macrophages are expressing inflammasome proteins such as pattern-recognition receptors (PRRs), toll-like receptors (TLR), or C-type lectin receptors in their membrane. NLRP3 is the best characterized and versatile inflammasome and is mainly expressed by myeloid lineage cells and stimulated by the activation of TLR and other signals [64, 65].

MSCs can regulate the NLRP3 inflammasome activation through the secretion of PGE2 that leads to an increase in IL-10 production by macrophages. The decrease in NLRP3 activation moderates cell death and organ dysfunction [65].

3.1.3 Effects on neutrophil response

Sepsis is associated with neutropenia, and it has been shown that MSCs are able to increase the neutrophil counts after their administration [66, 67]. The activity and survival of neutrophils were also increased in the lung during ARDS; this effect is produced through the stimulation of TLR-3 by MSCs.

During sepsis and ARDS, the injury or pathogen activates some recognition receptors that promote activated neutrophils recruitment. Neutrophils release some antimicrobial compounds and produce some traps to eliminate the pathogen. During sepsis, the general infection produces an overactivation of the neutrophils that migrate to inflamed and noninflamed tissue and can lead to an organ dysfunction [68].

Several pre-clinical studies have demonstrated that MSCs are able to modify neutrophils behavior, maintaining their bactericidal function but reducing the host injury.

In pre-clinical sepsis models, MSC therapy diminishes neutrophil infiltration into several organs such as lung, liver, gut, and kidney, reducing injury and improving organ function. Besides, MSCs augment neutrophil-mediated phagocytosis, improving the clearance of bacteria. It has been demonstrated that the protective effect of MSCs in systemic sepsis is clearly mediated by neutrophils, because their depletion abolishes the protective effect of MSCs [55, 69, 70].

3.1.4 Effects on monocyte/macrophage response

Monocytes and macrophages are present in practically all tissues. They have a wide range of functions like maintenance of the tissue homeostasis, immunologic functions, and participation in several metabolic pathways [71, 72].

It is well known that, in the course of sepsis and ARDS, macrophages get dysfunction and are not able to perform their activity as usual. Several groups focus in the use of MSCs as modulator of macrophages activity [73, 74]. Tissue resident macrophages and also circulating monocytes that migrate into the tissue and convert to macrophages can polarize to different phenotypes. Pro-inflammatory or M1 macrophages produce several pro-inflammatory cytokines and are involved in the elimination of pathogens. Anti-inflammatory/reparative or M2 macrophages secrete more anti-inflammatory compounds and are involved in the clearance of apoptotic cells. Alteration of M1 macrophages to a M2 phenotype has been demonstrated to be important to damage resolution.

MSCs have the ability to secrete several factors that polarize macrophages to a M2 phenotype, promoting a resolution phase, increasing phagocytic activity, and decreasing inflammation. It has been described that macrophages secrete PGE-2 that is able to increase the production of IL-10, SOCS-3, TGF-β, TSG-6, and others [60, 75]. All these factors are able to reduce the recruitment/migration of pro-inflammatory cells into the tissue, preventing organ dysfunction and also

decreasing the production of pro-inflammatory cytokines such as TNF-α or IFN-γ by macrophages [76].

Furthermore, complement activation pathway is also upregulated by MSCs infusion, what leads to a more efficient clearance of pathogens. MSCs, as we had previously described, secrete KGF that also promotes a M2 phenotype and can transfer mitochondria to macrophages, also reducing their pro-inflammatory phenotype [73, 77]. During ARDS, it has been shown that MSCs attenuate the damage induced by bacteria or LPS through the inhibition of Wnt/β-catenin pathway. The effects of MSCs on the macrophage activation varies quite a lot depending on the organ, the stage of the disease, and the steady-state of these macrophages when MSCs are infused.

3.2 Effects on adaptive immune response

In several diseases, there is an enhanced activation and proliferation of T and B cells, and this is also happening during sepsis. MSCs have the ability to diminish this cell activity and their proliferation [78, 79].

Explicitly, it has been shown that MSCs inhibit effector T-cell activation and can increase regulatory T-cell numbers, while suppressing propagation of CD4+ T-helper cells, CD8+ cytotoxic T lymphocytes, and natural killer cells [80, 81]. This effect is mediated through the secretion of PGE-2 and TGF-β1 [82]. Moreover, MSCs promote the formation of CD8+ regulatory T cells that might decrease cytotoxicity caused by cytotoxic lymphocytes [83, 84].

Regulatory T cells are a subclass of T cells, which functions in modulating the immune system and maintaining the antigen tolerance. These cells are able to limit inflammation and reduce organ dysfunction in sepsis, and MSCs have the capacity to regulate regulatory-T cell function [81, 85]. It has been verified that regulatory T cells subset is necessary to eliminate bacteria during infections.

MSCs induce regulatory T cells promoting their efficiency and enhancing sepsis or ARDS resolution [86, 87].

It has also been reported that MSCs modified the activity of other cells from the adaptive immune system such as NK, regulatory B cells, and dendritic cells.

3.3 Antibiotic properties

MSCs have been reported to have antibiotic/antimicrobial effects. They reduced bacterial levels in bronchoalveolar lavage, blood, spleen, and lung tissue. Generally, the antimicrobial effect of MSCs is due to their effect on host immune cells. MSCs have the ability to increase the phagocytic capacity of the host immune cells such as macrophages, monocytes, dendritic cells, and neutrophils [54, 73, 88]. It has been shown that this effect is produced through the production of keratinocyte growth factor (KGF) or also named fibroblast growth factor 7 (FGF7) [62, 69, 89].

Besides, MSCs are producing other factors with antibiotic properties per se. For example, in some pre-clinical models, it has been described that mouse MSCs secrete lipocalin-2, also known as neutrophil gelatinase-associated lipocalin (NGAL), which limits bacterial growth by iron sequestration. Human MSCs secrete LL-37, also known as cathelicidin antimicrobial peptide 18, described as antimicrobial peptide [90]. Patients with a high level of LL-37 were more likely to survive to a strong infection.

3.4 Antiapoptotic effects

During sepsis and ARDS, the apoptosis of endothelial, epithelial, and immune cells is one of the main descriptors of the severity of the disease. MSC therapy has been confirmed that it is able to limit the apoptosis of host cells.

The antiapoptotic capacity has been tested *in vitro* incubating neutrophils with MSCs or their supernatants and also *in vivo* where resident macrophages have presented less apoptosis [91, 92]. It seems that antiapoptotic effect of MSCs does not require cell-cell contact, and IL-6 and FGF7 have been described as the main drivers of this effect.

The role of MSCs in the decrease of monocytes, macrophages, and neutrophils apoptosis is directly associated with an increase in the clearance of bacteria and also can explain the antibiotic properties of MSCs [69].

3.5 Regulation of permeability

The endothelial and epithelial injury is a crucial characteristic of sepsis and ARDS. Throughout sepsis and ARDS, the barrier function of the endothelium and epithelium is destroyed due to the loss of their integrity and the disruption of the junction proteins between cells [1, 93].

MSCs have been described that they are able to decrease permeability and decrease the disturbance of the membrane, promoting the production of tight junction proteins and limiting the binding of inflammatory cells to the endothelium. It seems from some *in vitro* studies that the preserving effect of MSCs on permeability is due to the secretion of IL-1Ra and PGE-2, which decrease inflammation and reduce endothelial and epithelial cell apoptosis [94–96].

4. Mechanisms by which MSCs exert their effects

MSCs work by multiple mechanisms and can exert their effect through cell-cell contact, secreting several factors directly to the media or through the release of extracellular vesicles.

It seems that during sepsis and ARDS the MSC are not really engrafted in any tissue; however, it has been demonstrated that cells migrate to the site of the injury and they are retained there for a while. It has been shown that some effects are produced through cell-cell contact between MSCs and alveolar epithelial cells mainly to regulate endothelial integrity creating some junctions and transferring mitochondria or other cellular products with therapeutic effect [58, 60, 89].

In the last sections, we reviewed the effects of MSCs through the secretion of several factors such as antimicrobial peptides, antiapoptotic effectors, or immunomodulatory mediators.

Besides, MSCs release extracellular vesicles, which encapsulate several cellular components, including mitochondria and gene products such as miRNAs and mRNAs. Moreover, it has been described that some extracellular vesicles can also encapsulate lipids and proteins. Several studies have described the delivery of miR-223 that is transfer to macrophages and cardiomyocytes and reduces their inflammatory response. Also, the mRNA from KGF has also been detected inside these extracellular vesicles, producing its effect in the endothelium and epithelium and enhancing their repair [97–99].

5. Clinical trials

The encouraging preclinical data suggest that cell-based therapies capable of simultaneously affecting multiple processes constitute a promising new approach to sepsis and ARDS treatment [100]. MSCs can be efficiently cultured from bone marrow, umbilical cord blood, adipose tissue, and other sources and have a low

Study title	Register number	Sepsis/ARDS	Cell type	Phase	Dose and via	Start date	Finish date	Country	Reference
Adipose-derived mesenchymal stem cells in acute respiratory distress syndrome	NCT01902082	ARDS	MSC	Phase 1	1×10^6 intravenous	November 2012	November 2014	China	[104]
Russian clinical trial of mesenchymal cells in patients with septic shock and severe neutropenia	NCT01849237	Sepsis	MSC	Phase 1/2	1–2 millions/kg/day intravenous	December 2012	May 2015	Russia	[109]
Human mesenchymal stem cells for acute respiratory distress syndrome (START)	NCT01775774 NCT02097641	ARDS	MSC	Phase 1/2a	1 or 5 or 10 million cells/kg	July 2013	February 2018	USA	[102, 108]
Cellular immunotherapy for septic shock: a phase I trial (CISS)	NCT02421484	Sepsis	MSC	Phase 1	0.3 or 1 or 3 million cells/kg	May 2015	June 2017	Canada	[103]
Treatment of severe acute respiratory distress syndrome with allogeneic bone marrow-derived mesenchymal stromal cells	NCT02215811	ARDS	MSC	Phase 1	Not known. Cells are combined with ECMO	March 2014	December 2015	Sweden	
Human umbilical cord-derived mesenchymal stem cell therapy in acute lung injury (UCMSC-ALI)	NCT02444455	ARDS	MSC	Phase 1/2	5×10^5/kg intravenous	May 2015	December 2017	China	
A phase 1/2 study to assess MultiStem® therapy in acute respiratory distress syndrome (MUST-ARDS)	NCT02611609	ARDS	Multistem (MSC)	Phase 1/2	Not known	January 2016	November 2018	USA/UK	
Effects of administration of mesenchymal stem cells on organ failure during the septic shock (CSM choc)	NCT02883803	Sepsis	MSC	Phase 1	10^6/kg intravenous	December 2016	December 2019	France	
Mesenchymal stem cells (MSCs) for treatment of acute respiratory distress syndrome (ARD) in stem cell transplant patients	NCT02804945	ARDS	MSC	Phase 2	3×10^6 cell/kg intravenous	February 2017	February 2019	USA	
Repair of acute respiratory distress syndrome by stromal cell administration (REALIST)	NCT03042143	ARDS	MSC	Phase 1/2	2 doses, not specified	September 2017	September 2020	UK	

Table 2.
Phase 1 and phase 2 clinical studies with cell therapies for ARDS and sepsis (adapted from reference X).

expression of major histocompatibility antigens, permitting allogeneic therapy without need for immunosuppression, and no safety issues have been identified in hundreds of patients [101].

Two recent phase 1 dose-escalation safety of MSCs in patients with ARDS [102] and septic shock [103] raised no safety concerns adding a growing body of evidence that MSCs can be safety administered intravenously at several millions cells per kilogram to critically ill patients. Zheng et al. assigned 12 patients with moderate-to-severe ARDS to receive 1 million adipose-derived MSCs/kg or saline, reporting no adverse infusion-related events [104]. Nevertheless, the intravenous administration of high doses of MSCs may be associated with vascular thrombosis. Recently published trials of MSCs in ARDS and in sepsis and studies in progress are summarized in **Table 2**.

Larger phase 2 and phase 3 trials are required to define the adverse events related to cell therapy. These future studies should be designed considering the use of fresh versus cryopreserved cell product, the optimal dosing and route administration regimen, and which biologic and clinical outcomes should be assessed for insights into safety and efficacy. Central challenges in ensuring consistency in final product in the cell therapy field are the lack of consensus for *in vitro* potency assays to optimize donor selection, MSC tissue source, and optimal MSC culture condition. Without an accepted potency assay, the lack of a signal of biological effect in patients is difficult to interpret. One approach may be to measure paracrine factors such as angiopoietin-1 and KGF. Phase 2 trials should identify which biological markers are altered by cell-based therapy. However, the optimal approach for patient selection in sepsis and ARDS trials remains a challenge. ARDS and sepsis are clinical syndromes rather than a disease, with a lack of specificity of clinical criteria. Thirty-five percent of patients with ARDS have a hyperinflammatory phenotype, associated with a higher mortality and a different therapeutic response. Patients with a hyperinflammatory phenotype might be better candidates for therapy with MSCs [105, 106].

There is a growing evidence for the therapeutic effects of extracellular vesicles from MSCs, raising the possibility that cell-free therapy consisting of exosomes or microvesicles or MSC culture media might be produced and could be tested in patients with sepsis, ARDS, acute kidney injury, or traumatic brain injury. Several steps would be needed for this approach to become a reality, including optimization of purification methods for isolation of the required fractions of extracellular vesicles from MSCs accompanied by a comprehensive characterization of RNA, microRNA, lipids, and proteins in exosomes or microvesicles [50].

Although cell donors are extensively screened to rule out systemic illnesses, other donor-related variables, such as age, may be important. MSCs from aging (murine) donors demonstrated reduced efficacy [107]. Variations in production and cryopreservation methods may impact variability in the function of MSCs when tested in preclinical models or in patients for specific clinical disorders. Dimethyl sulfoxide and cell debris are removed by centrifugation after the cryopreserved MSCs have been thawed and cells are suspended in plasmalyte before intravenous administration in preclinical studies of lung injury. Current clinical studies are focused on a single dose of MSC administration via the less-invasive intravenous route with the START trial demonstrating safety for this approach [108].

6. Conclusions

Extensive progress has been made in the last years concerning cell therapy for sepsis and ARDS. Cell therapies have shown promising results in pre-clinical

studies. Several pathways, proteins, miRNAs, and lipids have been characterized and explain the mechanism of action of these cell therapies.

Several questions need further study, including determining the best source for the MSCs isolation, their large-scale production, and cryopreservation. Moreover, the therapeutic potential of MSCs and its conditioned media need to be studied for checking their efficacy in short-term and long-term follow-up studies.

The heterogeneity of patients with sepsis and ARDS is enormous, and establish a target population or the stratification of the patients will help us to determine better the therapeutic effect of these therapies.

There are many complications and concerns with using stem cells for cell-based therapy. The future may emphasis on the stimulation of other cells (growth factors, cytokines, and various other hematopoietic elements) that facilitate the formation or repair of endothelium and epithelium and the modulation of inflammatory cells.

We need to await evidence that these cell therapies have a benefit in patients with sepsis or ARDS and evaluate the phase I and II results from the ongoing studies.

Acknowledgements

Conflict of interest

The authors declare that they have no conflict of interest.

Abbreviation list

AE2C	alveolar-epithelial type II cells
ARDS	acute respiratory distress syndrome
COX-2	cyclooxygenase-2
EnPC	endothelial progenitor cells
EpPC	epithelial progenitor cells
ESC	embryonic stem cells
FGF7	fibroblast growth factor 7
GMP	good manufacturing practice guidelines
IGF-1	insulin-like growth factor 1
IL-1Ra	IL-1 receptor antagonist
iPSC	induced pluripotent stem cells
MSC	mesenchymal stem/stromal cells
NGAL	neutrophil gelatinase-associated lipocalin
PEEP	positive end-expiratory pressure
PGE2	prostaglandin-E2
PRRs	pattern-recognition receptors
TLR	toll like receptors
TSG-6	tumor necrosis factor-inducible gene 6 protein

Author details

Raquel Guillamat-Prats[1,2]* and Antonio Artigas[1,2,3,4]

1 Institut d'Investigació i Innovació Parc Tauli (I3PT), Sabadell, Spain

2 Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain

3 Universitat Autònoma de Barcelona, Bellaterra, Spain

4 Critical Care Center, Corporació Sanitària Universitaria Parc Taulí, Sabadell, Spain

*Address all correspondence to: r.guillamat.prats@gmail.com

IntechOpen

References

[1] Angus DC, van der Poll T. Severe sepsis and septic shock. The New England Journal of Medicine. 2013;**369**:2063

[2] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Medicine. 2003;**29**:530-538

[3] Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. The Journal of Clinical Investigation. 2012;**122**:2731-2740

[4] Ware LB, Matthay MA. The acute respiratory distress syndrome. The New England Journal of Medicine. 2000;**342**:1334-1349

[5] Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claessens Y-E, Avondo A, et al. Prognostic accuracy of Sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. Journal of the American Medical Association. 2017;**317**:301-308

[6] Martin-Loeches I, Levy MM, Artigas A. Management of severe sepsis: Advances, challenges, and current status. Drug Design, Development and Therapy. 2015;**9**:2079-2088

[7] Luo L, Shaver CM, Zhao Z, Koyama T, Calfee CS, Bastarache JA, et al. Clinical predictors of hospital mortality differ between direct and indirect ARDS. Chest. 2017;**151**:755-763

[8] Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. The New England Journal of Medicine. 2005;**353**:1685-1693

[9] Martínez ML, Ferrer R, Torrents E, Guillamat-Prats R, Gomà G, Suárez D, et al. Impact of source control in patients with severe sepsis and septic shock. Critical Care Medicine. 2017;**45**:11-19

[10] Ferrer R, Martínez ML, Gomà G, Suárez D, Álvarez-Rocha L, de la Torre MV, et al. Improved empirical antibiotic treatment of sepsis after an educational intervention: The ABISS-Edusepsis study. Critical Care. 2018;**22**:167

[11] Narendra DK, Hess DR, Sessler CN, Belete HM, Guntupalli KK, Khusid F, et al. Update in management of severe hypoxemic respiratory failure. Chest. 2017;**152**:867-879

[12] Patroniti N, Bonatti G, Senussi T, Robba C. Mechanical ventilation and respiratory monitoring during extracorporeal membrane oxygenation for respiratory support. Annals of Translational Medicine. 2018;**6**:386

[13] Alessandri F, Pugliese F, Ranieri VM. The role of rescue therapies in the treatment of severe ARDS. Respiratory Care. 2018;**63**:92-101

[14] Kallet RH. A comprehensive review of prone position in ARDS. Respiratory Care. 2015;**60**:1660-1687

[15] Horie S, Gonzalez HE, Laffey JG, Masterson CH. Cell therapy in acute respiratory distress syndrome. Journal of Thoracic Disease. 2018;**10**:5607-5620

[16] Gotts JE, Matthay MA. Cell-based therapy in sepsis. A step closer. American Journal of Respiratory and Critical Care Medicine. 2018;**197**:280-281

[17] Martin GR, Evans MJ. Differentiation of clonal lines of teratocarcinoma cells: Formation of embryoid bodies in vitro. Proceedings of the National Academy of Sciences of the United States of America. 1975;**72**:1441-1445

[18] Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. Embryonic stem cell lines derived from human blastocysts. Science. 1998;**282**:1145-1147

[19] Toya SP, Li F, Bonini MG, Gomez I, Mao M, Bachmaier KW, et al. Interaction of a specific population of human embryonic stem cell-derived progenitor cells with CD11b+ cells ameliorates sepsis-induced lung inflammatory injury. The American Journal of Pathology. 2011;**178**:313-324

[20] Yu J, Thomson JA. Pluripotent stem cell lines. Genes & Development. 2008;**22**:1987-1997

[21] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;**126**:663-676

[22] Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. Nature. 2007;**448**:313-317

[23] Ghaedi M, Mendez JJ, Bove PF, Sivarapatna A, Raredon MSB, Niklason LE. Alveolar epithelial differentiation of human induced pluripotent stem cells in a rotating bioreactor. Biomaterials. 2014;**35**:699-710

[24] Ghaedi M, Calle EA, Mendez JJ, Gard AL, Balestrini J, Booth A, et al. Human iPS cell-derived alveolar epithelium repopulates lung extracellular matrix. The Journal of Clinical Investigation. 2013;**123**:4950-4962

[25] Wang C, Hei F, Ju Z, Yu J, Yang S, Chen M. Differentiation of urine-derived human induced pluripotent stem cells to alveolar type II epithelial cells. Cellular Reprogramming. 2016;**18**:30-36

[26] Scudellari M. How iPS cells changed the world. Nature. 2016;**534**:310-312

[27] Heffernan C, Sumer H, Verma PJ. Generation of clinically relevant "induced pluripotent stem" (iPS) cells. Journal of Stem Cells. 2011;**6**:109-127

[28] Timmermans F, Plum J, Yöder MC, Ingram DA, Vandekerckhove B, Case J. Endothelial progenitor cells: Identity defined? Journal of Cellular and Molecular Medicine. 2009;**13**:87-102

[29] Hristov M, Erl W, Weber PC. Endothelial progenitor cells: Mobilization, differentiation, and homing. Arteriosclerosis, Thrombosis, and Vascular Biology. 2003;**23**:1185-1189

[30] Yoder MC. Human endothelial progenitor cells. Cold Spring Harbor Perspectives in Medicine. 2012;**2**:a006692

[31] Cao J-P, He X-Y, Xu H-T, Zou Z, Shi X-Y. Autologous transplantation of peripheral blood-derived circulating endothelial progenitor cells attenuates endotoxin-induced acute lung injury in rabbits by direct endothelial repair and indirect immunomodulation. Anesthesiology. 2012;**116**:1278-1287

[32] Li H, Qiang Y, Wang L, Wang G, Yi J, Jing H, et al. Repair of lipopolysaccharide-induced acute lung injury in mice by endothelial progenitor cells, alone and in combination with simvastatin. Chest. 2013;**144**:876-886

[33] Lam C-F, Liu Y-C, Hsu J-K, Yeh P-A, Su T-Y, Huang C-C, et al. Autologous transplantation of endothelial progenitor cells attenuates acute lung injury in rabbits. Anesthesiology. 2008;**108**:392-401

[34] Xu X, Yang J, Li N, Wu R, Tian H, Song H, et al. Role of endothelial progenitor cell transplantation in rats with sepsis. Transplantation Proceedings. 2015;**47**:2991-3001

[35] Blanpain C, Horsley V, Fuchs E. Epithelial stem cells: Turning over new leaves. Cell. 2007;**128**:445-458

[36] Rawlins EL. Lung epithelial progenitor cells: Lessons from development. Proceedings of the American Thoracic Society. 2008;**5**:675-681

[37] Guillamat-Prats R, Puig F, Camprubí-Rimblas M, Herrero R, Serrano-Mollar A, Gómez MN, et al. Intratracheal instillation of alveolar type II cells enhances recovery from acute lung injury in rats. The Journal of Heart and Lung Transplantation. 2018;**37**:782-791

[38] Adamson IY, Bowden DH. Derivation of type 1 epithelium from type 2 cells in the developing rat lung. Laboratory Investigation: A Journal of Technical Methods And Pathology. 1975;**32**:736-745

[39] Evans MJ, Cabral LJ, Stephens RJ, Freeman G. Transformation of alveolar type 2 cells to type 1 cells following exposure to NO_2. Experimental and Molecular Pathology. 1975;**22**:142-150

[40] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;**8**:315-317

[41] Pourrajab F, Forouzannia SK, Tabatabaee SA. Molecular characteristics of bone marrow mesenchymal stem cells, source of regenerative medicine. International Journal of Cardiology. 2013;**163**:125-131

[42] Bianco P, Cao X, Frenette PS, Mao JJ, Robey PG, Simmons PJ, et al. The meaning, the sense and the significance: Translating the science of mesenchymal stem cells into medicine. Nature Medicine. 2013;**19**:35-42

[43] Salmikangas P, Menezes-Ferreira M, Reischl I, Tsiftsoglou A, Kyselovic J, Borg JJ, et al. Manufacturing, characterization and control of cell-based medicinal products: Challenging paradigms toward commercial use. Regenerative Medicine. 2015;**10**:65-78

[44] Deskins DL, Bastakoty D, Saraswati S, Shinar A, Holt GE, Young PP. Human mesenchymal stromal cells: Identifying assays to predict potency for therapeutic selection. Stem Cells Translational Medicine. 2013;**2**:151-158

[45] Curley GF, Hayes M, Ansari B, Shaw G, Ryan A, Barry F, et al. Mesenchymal stem cells enhance recovery and repair following ventilator-induced lung injury in the rat. Thorax. 2012;**67**:496-501

[46] Chimenti L, Luque T, Bonsignore MR, Ramírez J, Navajas D, Farré R. Pre-treatment with mesenchymal stem cells reduces ventilator-induced lung injury. The European Respiratory Journal. 2012;**40**:939-948

[47] Curley GF, Ansari B, Hayes M, Devaney J, Masterson C, Ryan A, et al. Effects of intratracheal mesenchymal stromal cell therapy during recovery and resolution after ventilator-induced lung injury. Anesthesiology. 2013;**118**:924-932

[48] Sepúlveda JC, Tomé M, Fernández ME, Delgado M, Campisi J, Bernad A, et al. Cell senescence abrogates the therapeutic potential of human mesenchymal stem cells in the lethal endotoxemia model. Stem Cells. 2014;**32**:1865-1877

[49] Gonzalez-Rey E, Anderson P, González MA, Rico L, Büscher D, Delgado M. Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis. Gut. 2009;**58**:929-939

[50] Matthay MA. Extracellular vesicle transfer from mesenchymal stromal cells modulates macrophage function in acute lung injury: Basic science and clinical implications.

American Journal of Respiratory and Critical Care Medicine. 15 Nov 2017;**196**(10):1234-1236

[51] Zheng G, Huang R, Qiu G, Ge M, Wang J, Shu Q, et al. Mesenchymal stromal cell-derived extracellular vesicles: Regenerative and immunomodulatory effects and potential applications in sepsis. Cell and Tissue Research. 2018;**374**:1-15

[52] Mao M, Wang S-N, Lv X-J, Wang Y, Xu J-C. Intravenous delivery of bone marrow-derived endothelial progenitor cells improves survival and attenuates lipopolysaccharide-induced lung injury in rats. Shock. 2010;**34**:196-204

[53] Gupta N, Su X, Popov B, Lee JW, Serikov V, Matthay MA. Intrapulmonary delivery of bone marrow-derived mesenchymal stem cells improves survival and attenuates endotoxin-induced acute lung injury in mice. The Journal of Immunology. 2007;**179**:1855-1863

[54] Luo C, Zhang F, Zhang L, Geng Y, Li Q, Hong Q, et al. Mesenchymal stem cells ameliorate sepsis-associated acute kidney injury in mice. Shock. 2014;**41**:123-129

[55] Hall SRR, Tsoyi K, Ith B, Padera RF, Lederer JA, Wang Z, et al. Mesenchymal stromal cells improve survival during sepsis in the absence of heme oxygenase-1: The importance of neutrophils. Stem Cells. 2013;**31**:397-407

[56] Wang Y, Tan L, Jin J, Sun H, Chen Z, Tan X, et al. Non-cultured dermal-derived mesenchymal cells attenuate sepsis induced by cecal ligation and puncture in mice. Scientific Reports. 2015;**5**:16973

[57] Raffaghello L, Bianchi G, Bertolotto M, Montecucco F, Busca A, Dallegri F, et al. Human mesenchymal stem cells inhibit neutrophil apoptosis: A model for neutrophil preservation in the bone marrow niche. Stem Cells. 2008;**26**:151-162

[58] Xu J, Woods CR, Mora AL, Joodi R, Brigham KL, Iyer S, et al. Prevention of endotoxin-induced systemic response by bone marrow-derived mesenchymal stem cells in mice. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2007;**293**:L131-L141

[59] Rocheteau P, Chatre L, Briand D, Mebarki M, Jouvion G, Bardon J, et al. Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nature Communications. 2015;**6**:10145

[60] Németh K, Leelahavanichkul A, Yuen PST, 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. Nature Medicine. 2009;**15**:42-49

[61] Choi H, Lee RH, Bazhanov N, Oh JY, Prockop DJ. Anti-inflammatory protein TSG-6 secreted by activated MSCs attenuates zymosan-induced mouse peritonitis by decreasing TLR2/NF-κB signaling in resident macrophages. Blood. 2011;**118**:330-338

[62] Liang Z, Sun J, Wang P, Tian Q, Yang Z, Chen L. Bone marrow-derived mesenchymal stem cells protect rats from endotoxin-induced acute lung injury. Chinese Medical Journal. 2011;**124**:2715-2722

[63] Cóndor JM, Rodrigues CE, de Sousa Moreira R, Canale D, Volpini RA, Shimizu MHM, et al. Treatment with human wharton's jelly-derived mesenchymal stem cells attenuates sepsis-induced kidney injury, liver injury, and endothelial dysfunction. Stem Cells Translational Medicine. 2016;**5**:1048-1057

[64] Martinon F, Burns K, Tschopp J. The inflammasome: A molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Molecular Cell. 2002;**10**:417-426

[65] Miao C-M, Jiang X-W, He K, Li P-Z, Liu Z-J, Cao D, et al. Bone marrow stromal cells attenuate LPS-induced mouse acute liver injury via the prostaglandin E 2-dependent repression of the NLRP3 inflammasome in Kupffer cells. Immunology Letters. 2016;**179**:102-113

[66] Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nature Reviews Immunology. 2013;**13**:159-175

[67] Sônego F, Castanheira FVES, Ferreira RG, Kanashiro A, Leite CAVG, Nascimento DC, et al. Paradoxical roles of the neutrophil in sepsis: Protective and deleterious. Frontiers in Immunology. 2016;**7**:155

[68] Nourshargh S, Renshaw SA, Imhof BA. Reverse migration of neutrophils: Where, when, how, and why? Trends in Immunology. 2016;**37**:273-286

[69] Mei SHJ, Haitsma JJ, Dos Santos CC, Deng Y, Lai PFH, Slutsky AS, et al. Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. American Journal of Respiratory and Critical Care Medicine. 2010;**182**:1047-1057

[70] Zhao X, Liu D, Gong W, Zhao G, Liu L, Yang L, et al. The toll-like receptor 3 ligand, poly(I:C), improves immunosuppressive function and therapeutic effect of mesenchymal stem cells on sepsis via inhibiting MiR-143. Stem Cells. 2014;**32**:521-533

[71] Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. The Journal of Pathology. 2013;**229**:176-185

[72] Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Frontiers in Bioscience: A Virtual Library of Medicine. 2008;**13**:453-461

[73] Krasnodembskaya A, Samarani G, Song Y, Zhuo H, Su X, Lee J-W, et al. Human mesenchymal stem cells reduce mortality and bacteremia in gram-negative sepsis in mice in part by enhancing the phagocytic activity of blood monocytes. American Journal of Physiology: Lung Cellular and Molecular Physiology. 2012;**302**:L1003-L1013

[74] Devaney J, Horie S, Masterson C, Elliman S, Barry F, O'Brien T, et al. Human mesenchymal stromal cells decrease the severity of acute lung injury induced by *E. coli* in the rat. Thorax. 2015;**70**:625-635

[75] Luz-Crawford P, Jorgensen C, Djouad F. Mesenchymal stem cells direct the immunological fate of macrophages. Results and Problems in Cell Differentiation. 2017;**62**:61-72

[76] Kim J, Hematti P. Mesenchymal stem cell-educated macrophages: A novel type of alternatively activated macrophages. Experimental Hematology. 2009;**37**:1445-1453

[77] Brekke O-L, Christiansen D, Fure H, Fung M, Mollnes TE. The role of complement C3 opsonization, C5a receptor, and CD14 in *E. coli*-induced up-regulation of granulocyte and monocyte CD11b/CD18 (CR3), phagocytosis, and oxidative burst in human whole blood. Journal of Leukocyte Biology. 2007;**81**:1404-1413

[78] Deng W, Han Q, Liao L, You S, Deng H, Zhao RCH. Effects of allogeneic bone marrow-derived mesenchymal stem cells on T and B lymphocytes from BXSB mice. DNA and Cell Biology. 2005;**24**:458-463

[79] 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**:367-372

[80] Glennie S, Soeiro I, Dyson PJ, Lam EW-F, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood. 2005;**105**:2821-2827

[81] Najar M, Raicevic G, Fayyad-Kazan H, De Bruyn C, Bron D, Toungouz M, et al. Impact of different mesenchymal stromal cell types on T-cell activation, proliferation and migration. International Immunopharmacology. 2013;**15**:693-702

[82] Najar M, Raicevic G, Boufker HI, Fayyad Kazan H, De Bruyn C, Meuleman N, et al. Mesenchymal stromal cells use PGE2 to modulate activation and proliferation of lymphocyte subsets: Combined comparison of adipose tissue, Wharton's jelly and bone marrow sources. Cellular Immunology. 2010;**264**:171-179

[83] Djouad F, Plence P, Bony C, Tropel P, Apparailly F, Sany J, et al. Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. Blood. 2003;**102**:3837-3844

[84] Maccario R, Podestà M, Moretta A, Cometa A, Comoli P, Montagna D, et al. Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune response favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype. Haematologica. 2005;**90**:516-525

[85] Najar M, Raicevic G, Fayyad-Kazan H, De Bruyn C, Bron D, Toungouz M, et al. Bone marrow mesenchymal stromal cells induce proliferative, cytokinic and molecular changes during the T cell response: The importance of the IL-10/CD210 axis. Stem Cell Reviews. 2015;**11**:442-452

[86] Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007;**110**:3499-3506

[87] Mohammadpour H, Pourfathollah AA, Zarif MN, Tahoori MT. TNF-α modulates the immunosuppressive effects of MSCs on dendritic cells and T cells. International Immunopharmacology. 2015;**28**:1009-1017

[88] Alcayaga-Miranda F, Cuenca J, Martin A, Contreras L, Figueroa FE, Khoury M. Combination therapy of menstrual derived mesenchymal stem cells and antibiotics ameliorates survival in sepsis. Stem Cell Research & Therapy. 2015;**6**:199

[89] Gupta N, Krasnodembskaya A, Kapetanaki M, Mouded M, Tan X, Serikov V, et al. Mesenchymal stem cells enhance survival and bacterial clearance in murine Escherichia coli pneumonia. Thorax. 2012;**67**:533-539

[90] Krasnodembskaya A, Song Y, Fang X, Gupta N, Serikov V, Lee J-W, et al. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. Stem Cells. 2010;**28**:2229-2238

[91] Sung P-H, Chang C-L, Tsai T-H, Chang L-T, Leu S, Chen Y-L, et al. Apoptotic adipose-derived mesenchymal stem cell therapy protects against lung and kidney injury in sepsis syndrome caused by cecal ligation puncture in rats. Stem Cell Research & Therapy. 2013;**4**:155

[92] Pedrazza L, Lunardelli A, Luft C, Cruz CU, de Mesquita FC, Bitencourt S, et al. Mesenchymal stem cells decrease splenocytes apoptosis in a sepsis experimental model. Inflammation

Research: Official Journal of the European Histamine Research Society. 2014;**63**:719-728

[93] Bhattacharya J, Matthay MA. Regulation and repair of the alveolar-capillary barrier in acute lung injury. Annual Review of Physiology. 2013;**75**:593-615

[94] Pati S, Khakoo AY, Zhao J, Jimenez F, Gerber MH, Harting M, et al. Human mesenchymal stem cells inhibit vascular permeability by modulating vascular endothelial cadherin/β-catenin signaling. Stem Cells and Development. 2011;**20**:89-101

[95] Pati S, Gerber MH, Menge TD, Wataha KA, Zhao Y, Baumgartner JA, et al. Bone marrow derived mesenchymal stem cells inhibit inflammation and preserve vascular endothelial integrity in the lungs after hemorrhagic shock. PLoS One. 2011;**6**:e25171

[96] Lee JW, Fang X, Gupta N, Serikov V, Matthay MA. Allogeneic human mesenchymal stem cells for treatment of *E. coli* endotoxin-induced acute lung injury in the ex vivo perfused human lung. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**:16357-16362

[97] Xu Z, Zhang C, Cheng L, Hu M, Tao H, Song L. The microRNA miR-17 regulates lung FoxA1 expression during lipopolysaccharide-induced acute lung injury. Biochemical and Biophysical Research Communications. 2014;**445**:48-53

[98] Monsel A, Zhu Y, Gennai S, Hao Q, Hu S, Rouby J-J, et al. Therapeutic effects of human mesenchymal stem cell-derived microvesicles in severe pneumonia in mice. American Journal of Respiratory and Critical Care Medicine. 2015;**192**:324-336

[99] Wang X, Gu H, Qin D, Yang L, Huang W, Essandoh K, et al. Exosomal miR-223 contributes to mesenchymal stem cell-elicited cardioprotection in polymicrobial sepsis. Scientific Reports. 2015;**5**:13721

[100] Laffey JG, Matthay MA. Fifty years of research in ARDS. Cell-based therapy for acute respiratory distress syndrome. Biology and potential therapeutic value. American Journal of Respiratory and Critical Care Medicine. 2017;**196**:266-273

[101] Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): A systematic review and meta-analysis of clinical trials. PLoS One. 2012;**7**:e47559

[102] Wilson JG, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: A phase 1 clinical trial. The Lancet Respiratory Medicine. 2015;**3**:24-32

[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. American Journal of Respiratory and Critical Care Medicine. 2018;**197**:337-347

[104] Zheng G, Huang L, Tong H, Shu Q, Hu Y, Ge M, et al. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: A randomized, placebo-controlled pilot study. Respiratory Research. 2014;**15**:39

[105] Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. American Journal of Respiratory and Critical Care Medicine. 2017;**195**:331-338

[106] Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA, et al. Subphenotypes in acute respiratory distress syndrome: Latent class analysis of data from two randomised controlled trials. The Lancet Respiratory Medicine. 2014;**2**:611-620

[107] Bustos ML, Huleihel L, Kapetanaki MG, Lino-Cardenas CL, Mroz L, Ellis BM, et al. Aging mesenchymal stem cells fail to protect because of impaired migration and antiinflammatory response. American Journal of Respiratory and Critical Care Medicine. 2014;**189**:787-798

[108] Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): A randomised phase 2a safety trial. The Lancet Respiratory Medicine. Feb 2019;**7**(2):154-162

[109] Galstyan GM, Makarova PM, Parovichnikova EN. Use of mesenchymal stromal stem cells for the treatment of sepsis. Anesteziologiia i Reanimatologiia. 2015;**60**:59-65