Published in final edited form as:
Anesthesiology. 2014 November ; 121(5): 1099–1121. doi:10.1097/ALN.0000000000000446.

Cell-based Therapy for Acute Organ Injury: Preclinical Evidence and On-going Clinical Trials Using Mesenchymal Stem Cells

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Abstract

Critically ill patients often suffer from multiple organ failures involving lung, kidney, liver or brain. Genomic, proteomic and metabolomic approaches highlight common injury mechanisms leading to acute organ failure. This underlines the need to focus on therapeutic strategies affecting multiple injury pathways. The use of adult stem cells such as mesenchymal stem or stromal cells (MSC) may represent a promising new therapeutic approach as increasing evidence shows that MSC can exert protective effects following injury through the release of pro-mitotic, anti-apoptotic, anti-inflammatory and immunomodulatory soluble factors. Furthermore, they can mitigate metabolomic and oxidative stress imbalance. In this work, we review the biological capabilities of MSC and the results of clinical trials using MSC as therapy in acute organ injuries. Although preliminary results are encouraging, more studies concerning safety and efficacy of MSC therapy are needed to determine their optimal clinical use.

INTRODUCTION

In the intensive care unit (ICU), the care of patients with acute organ injuries leading to organ failure remains challenging. Organ failure was defined by the 1991 Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine as “the presence of altered organ functions in an acutely ill patient such that homeostasis cannot be maintained without intervention[1].” This disorder represents a dynamic continuum of change over time[2]. Multiple organ dysfunction syndrome (MODS) can lead to a mortality rate of 60% after severe trauma, 40% in sepsis, 50% in pancreatitis, 30% in burn injury and 30% in patients admitted post-cardiac arrest[3]. The higher the number of failed organs, the higher the mortality[4]. In the context of single organ injury without MODS, acute kidney injury (AKI)[5], acute respiratory distress syndrome (ARDS)[6] and acute liver failure (ALF)[7] are responsible for up to 60%, 40% and 30% of mortality respectively.

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The authors declare no competing interests.

The underlying mechanisms leading to cell death in organ injury are diverse: the pro-inflammatory nuclear factor-kappa B pathway, endothelial activation with coagulation disorders, lipid mediators, microcirculatory dysfunction, and ischemia-reperfusion (I/R) injury including oxydative stress (OS)-, metabolomic disruption- and pro-apoptotic-induced injuries. Aside from the diversity, many mechanisms are also dependent on the sequence in time of injury and/or are organ specific. For instance, nuclear factor-kappa B pathway can be either damaging in the acute phase of sepsis, and/or can be involved in the repair process during the resolution phase of injury. Similarly, the function of phagocytes is dual-faced. Although beneficial in sepsis by clearing pathogens, macrophages can also generate neuron damage through phagocytosis and apoptosis.

This complexity probably explains in part why treatment strategies geared toward a single pathway and/or during a specific timepoint have failed, highlighting the limited therapeutic strategies available to clinicians to target the multi-organ injuries which may result, aside from the treatment of the initial cause of injury. Clinical management currently focuses on supporting failed organs until they recover, a period where patients may be exposed to new iatrogenic complications[3]. Consequently, innovative therapies are needed. Therapeutic use of adult stem cells may be one of them. Stem cells are undifferentiated precursor cells capable of self-renewal and multi-lineage differentiation. They are classified by their potency (pluri-potent *vs* multi-potent) and origin (adult *vs* embryonic). Adult stem cells include hematopoietic stem cells, mesenchymal stem cells (MSC), endothelial progenitor cells, and organ specific stem cells. Although originally the beneficial effect of adult stem cells was thought to be through engraftment and regeneration[8], subsequent studies demonstrated the main therapeutic effects were mediated primarily through the secretion of soluble factors.

In this review, we focused on the potential therapeutic use of human MSC for acute organ injury, specifically in ARDS, AKI, ALF, acute brain injury encompassing stroke and traumatic brain injury (TBI), sepsis and MODS. To accomplish this goal, we searched PubMed for relevant studies published over the past ten years (2003–2013) and the proceedings of major relevant conferences, clinical trial databases, the reference lists of identified trials and major reviews. In this work, we decided to use the term “organ failure” and “organ injury” to define respectively the altered functional outcomes and the tissue lesions leading to this alteration in the corresponding organ.

DEFINITION OF MESENCHYMAL STEM CELLS

MSC are adult non-hematopoietic precursor cells derived from a variety of tissues such as the bone marrow, adipose tissue and placenta. The definition of MSC by the International Society of Cellular Therapy in 2006 is based on three criteria: (1) MSC must be adherent to plastic under standard tissue culture conditions; (2) MSC must express certain cell surface markers such as CD73, CD90, and CD105, but must not express CD45, CD34, CD14, or CD11b; and (3) MSC must have the capacity to differentiate into mesenchymal lineages including osteoblasts, adipocytes, and chondroblasts under *in vitro* conditions[9].

Engraftment Versus Paracrine Effects

Therapeutic properties of MSC were originally thought to derive from their engraftment in the organ of injury and regeneration. However, subsequent *in vivo* studies demonstrated limited replacement of damaged tissue by transdifferentiated stem cells (<5%). Thus, the role of paracrine soluble factors with its endocrine actions were studied as potential mechanisms mediating the therapeutic effects[10–13]. Despite the transient presence of MSC in the injured organ, ranging from several hours to several days[14,15], MSC are able to exert complex paracrine and endocrine actions, through the secretion of growth factors and cytokines[12]. Moreover, recent *in vivo* studies also underscore the new potential role of microvesicles, small (50–200 nm) anuclear membrane bound particles released from MSC as a paracrine vehicle to deliver messenger RNA (mRNA), micro RNA or proteins that may reprogram the injured cells or induce secretion of cytoprotective factors[16–21]. All these effects have been demonstrated in multiple organ injury models: acute lung injury (ALI)[22–24], AKI[14,15,25–27], ALF[28–30] and acute brain injury[31–33].

Mesenchymal Stem Cells Homing Capacity

The ability of stem cell to preferentially traffick to inflammatory sites is thought to play a crucial role in the success of cellular therapy for organ injury. Intravenous or intra-arterial infusion of MSC often initially result in the entrapment of the administered cells in organ capillary beds, especially in the lung and liver[34]. In non-injured states, intravenous MSC tend to migrate to the bone marrow[35,36]. However, following injury, MSC preferentially home to the site of inflammation where they migrate across the inflammed endothelium and enter the injured tissue bed[37–41]. MSC trafficking have been shown to be driven by different interactions between chemokines released from the injured tissue and chemokine receptors expressed by MSC. For instance, stromal cell-derived factor-1/CXCR4 pathway, which is upregulated under ischemic or hypoxic conditions, can mediate the localization of injected MSC into the injured brain or kidneys[42–46]. Interaction between CD44 expressed by MSC and hyaluronic acid in the injured tissue, expressed when the extra-cellular matrix is exposed[47,48], is another major pathway[38].

ORGAN INJURY PATHWAYS SPECIFICALLY IMPACTED BY MESENCHYMAL STEM CELLS

The multiple mechanisms involved in organ injury are diverse. Although organ injuries do not fit into a single common combination of pathways, we will highlight those impacted by MSC.

Acute Pro-inflammatory Pathway

In addition to “septic” inflammation, a severe inflammatory response can be triggered by non-infectious sources, such as danger associated molecular patterns[49,50]. In the acute phase of organ injury, multiple cells express pattern recognition receptors that can recognize either pathogen or danger associated molecular patterns. Pattern recognition receptors sense endogenous and exogenous danger signals and induce pro-inflammatory cytokines and type I interferons[49] (Figure 1). Monocytes-macrophages and polymorphonuclear neutrophils

migrate quickly to sites of injury and secrete reactive oxygen species (ROS) and pro-inflammatory cytokines/chemokines. Antigen-presenting cells also migrate to the site of injury and internalize and process either pathogen or danger associated molecular patterns and initiate the adaptive immune response. Adaptive immune cells such as natural killer cells, natural killer T cells, mast cells, T-lymphocytes and B-lymphocytes then converge, participating in the pro or anti-inflammatory response. T cells are essential players in the acute and intermediate inflammatory phase of organ injury, bridging together innate and adaptive immunity. CD4+ T helpers (Th) cells lead to polarization of the immune response in multiple pathways (Th1, Th2, Th17, Th22, Th3, T-regulatory), and CD8+ T cells are dramatically involved in the cytotoxic response leading to the lysis of the targeted cells. Rather than a patchwork process, acute organ injury is a continuum of responses from innate to adaptive immune cells.

Ischemia-Reperfusion Pathways: Oxydative Stress Injury, Metabolomic Disorders and Apoptosis

Oxidative stress is caused by increased production of reactive oxygen and nitrogen species or by depletion of protective antioxidants. Resulting oxidative products can damage DNA, promoting cell death/apoptosis and cause end-organ tissue damage. OS is present in many pathological situations, such as during reperfusion after ischemia or following toxic exposures. Whether through low regional blood flow or hypoxemia or both, ischemia is responsible for a dramatic shift in cell metabolism. The lack of oxygen to drive oxidative phosphorylation and other oxygen dependant metabolic reactions (aerobic glycolysis, fatty acid beta oxidation) results in inefficient anaerobic glycolysis as the major source of adenosine triphosphate (ATP) production and leads to ATP deficit[51–54]. Proteomic profiling indicate that during ischemia, metabolic key enzymes are decreased[53]. The resultant ATP-dependant metabolic reaction shutdown then produces deep imbalance in cellular homeostasis eventually leading to cell death[53,55–57]. Furthermore, any reduction in organ perfusion in terms of oxygen delivery[51] can lead to organ damage by generating I/R injuries[58]. I/R injury is present in most clinical conditions leading to acute organ injury such as shock, hypoxemia, sepsis, cardiac arrest, trauma, burn injuries or following certain surgeries (cardiac, aortic and organ transplantation surgeries). Although ischemia-induced tissue hypoxia can lead to irreversible tissue injury if the period of ischemia is prolonged, much of the tissue damage occurs following restoration of perfusion[59,60]. While reperfusion can induce mitochondria to generate ATP and restore cell metabolism in less damaged tissue, it can also paradoxically exacerbate ischemia-induced inury in severely ischemic cells leading to release ROS generated by damaged mitochondria and nicotinamide adenine dinucleotide phosphate oxidase[58,61–64]. Proteomic profiling show that reperfusion can lead to pro-glycolytic enzyme depletion, pro-apoptotic proteome shift and mitochondrial dysfunction inducing OS[65]. These I/R-induced pathways can lead to cell death and organ failure (Figure 2).

PROPERTIES OF MESENCHYMAL STEM CELLS

Immunomodulatory Properties

MSC can modulate innate and adaptive immune cells, by enhancing anti-inflammatory pathways in the injured organ milieu[66–68]. This immunomodulation is mediated by cell-contact-dependant and independant mechanisms through the release of soluble factors such as tumor necrosis factor-stimulated gene 6[69], prostaglandin E_2[70], interleukin (IL)-10[70,71], IL-1 receptor antagonist[72], transforming growth factor (TGF)-β[73], hepatocyte growth factor[73] or indolamine 2,3-dioxygenase[67]. Both decrease in pro-inflammatory mediators (IL-1β, tumor necrosis factor (TNF)-α, interferon-γ, IL-6) and increase in anti-inflammatory cytokines (IL-10, basic fibroblast growth factor, TGF-α, TGF-β) have been also pointed out as a key factor in preventing cell damage in acute kidney[15,26] and liver[30,74–76] injury models. Similar findings have been reported in acute stroke[77] and sepsis[78,79] animal models (Figure 3A).

Human MSC promote repolarization of monocytes and/or macrophages from a type 1 (pro-inflammatory) to a type 2 (anti-inflammatory) monocyte phenotype characterized by high levels of IL-10 secretion, increased phagocytosis and low levels of TNF-α and interferon-γ production and major histocompatibility class II expression[80–82]. This ability of MSC to reprogram monocytes/macrophages has been demonstrated *in vivo* in different models of sepsis[70,83–85], endotoxin[86] or live *E.coli* bacteria-induced ALI[87,88], ischemia[89] and regenerative medicine[82,90]. Often in these injury models, MSC reprogrammed type 2 monocytes produced large quantities of IL-10, which blocked polymorphonuclear neutrophil influx into the injured tissue and prevented further damage (Figures 3A). However, in a mouse model of TBI, intracerebral administred MSC modulated the inflammatory response through decreasing the phagocytic capability of microglia macrophages[91]. In this specific context, the reduction of phagocytosis by macrophages was beneficial, leading to better outcomes. These findings revealed the complexity of the crosstalk between MSC and macrophages, that may be organ specific and influenced by the injury milieu.

MSC can interfere with dendritic cells differentiation, maturation and function, skewing them toward a regulatory phenotype[92,93]. Dentritic cells generated in the presence of MSC have decreased capacity to induce activation of T cells, and exhibit an altered cytokine production pattern with lower pro-inflammatory and higher anti-inflammatory cytokines[66,92] (Figure 3A).

MSC also modulate natural killer cells, which are involved in both the elimination of virus-infected and damaged cells and the secretion of an array of pro-inflammatory cytokines such as interferon-γ. Several studies clearly show that MSC, when co-cultured with natural killer cells, impair their cytotoxic activity, cytokine production and granzyme B release[94–96] (Figure 3A). However, other studies have shown that MSC could enhance their pro-inflammatory phenotype depending on the culture conditions. Thus, the complex interplay between MSC and natural killer cells could result either in a pro-inflammatory or an anti-inflammatory phenotype depending on the type of the activation state of both cells and on the surrounding milieu[67].

In addition, MSC are able to suppress T cell activation and proliferation and decrease their response by shifting them from a T helper (Th)1 to a Th2 immune phenotype[72,73,97,98]. MSC have been shown to 1) inhibit the differentiation of naive T cells into Th17 cells[99–101], 2) inhibit secretion of pro-inflammatory cytokines by differentiated Th17 cells, 3) promote induction of immunosuppresive FoxP3+ T-regulatory cells[100,102], and 4) drive reprogramming of Th17 cells into FoxP3+ T-regulatory cells[100] (Figure 3B). MSC also potentially inhibit cytotoxic effect of antigen-primed cytotoxic T cells[98] and induce T cell anergy[67,73,103]. This T regulatory- skewed response has been also demonstrated *in vivo*. In an ALI model, Sun *et al.* showed that MSC could upregulate T-regulatory cells, reducing some key Th1 cytokines (interferon-γ, TNF-α, macrophage inflammatory protein-2) and increasing Th2 cytokines (IL-10). Others have also demonstrated that MSC decreased pro-inflammatory cytokines/chemokines such as macrophage inflammatory protein-1, B-lymphocyte chemoattractant, and IL-12, with subsequent decrease in Th cells[104].

Overall, an emerging body of data demonstrates at multiple levels the impact of MSC upon key cells involved in the continuum between innate and adaptive immunity, modulating inflammation in acute organ injury.

Antimicrobial Properties

Studies using bacteria-induced acute organ injury models demonstrated that MSC could exert direct and indirect antimicrobial properties. In *E.coli* pneumonia in mice, we demonstrated that MSC secreted antibacterial proteins/peptides such as LL-37[105] and lipocalin-2[87], leading to improved bacterial clearance. Other anti-bacterial mechanisms of MSC include tryptophan catabolism by indolamine 2,3-dioxygenase [106] or increased pathogen phagocytosis which inhibit overall bacterial growth[79,107–109]. Using different *in vivo* and *ex vivo* models of sepsis or pneumonia, MSC were found to increase phagocytosis of bacteria by macrophages by switching from a type 1 to type 2 monocyte phenotype[79,87,88,110]. In a mouse model of *Pseudomonas aeruginosa*-induced peritonitis, Krasnodembskaya *et al.* demonstrated that MSC reduced the number of colony-forming units of *Pseudomonas aeruginosa* in the blood by increasing the monocyte phagocytic potency[110]. The authors highlighted two potential underlying mechanisms: 1) the upregulation of phagocytosis receptor CD11b on monocytes and 2) the increase in CD163 and CD206-positive activated monocytes/macrophages in the spleen[110]. In a cecal ligation and puncture mice model of sepsis, Nemeth *et al.* showed a decrease in blood bacteria counts in the MSC treated group. The authors speculated that this increase in blood bacteria clearance could be explained by IL-10-mediated neutrophil retention within the vascular compartment[70]. Recently, toll like receptor 3-triggered human MSC were shown to promote polymorphonuclear neutrophil activity, viability and improve its respiratory burst, increasing ROS release which is bactericidal[108] (Figure 4).

Anti-oxidative Effect

Recent studies of organ injuries involving the heart[57], brain[111,112], kidneys[113–115] and liver[116–119] demonstrated that MSC could exert an antioxidative effect leading to a decrease in the severity of organ injury[56]. This anti-oxidative property has been best exemplified in sepsis-induced organ failure models. In this context, authors have shown that MSC can

reduce neutrophil-mediated oxidative injury in lungs, liver and kidneys[70,78]. This effect was primarily mediated through secretion of soluble factors, which prevent ROS accumulation through enhanced scavenging and antioxidant upregulation[57,120]. Interestingly, many of these studies focused on the adoptive transfer of anti-oxidant effects from exosomes by stem cells[59,60,121]. Similar to microvesicles, exosomes are bi-lipid membrane vesicles with a diameter < 50 nm They can carry a complex cargo of proteins, lipids, DNA, mRNA or microRNA which could be delivered into targeted cells and impact multiple cellular pathways[16,122]. MSC release a large quantity of exosomes in their environment upon diverse stimuli[120]. Both *in vitro* and *in vivo* studies have shown that MSC derived exosomes can decrease OS-induced injury by reversing the depletion of key enzymes in ROS metabolism and the resultant accumulation of toxic products from the electron transport chain[59,60,65,121,123]. For example, the transfer of peroxiredoxins and glutathione S-transferase by MSC derived exosomes into injured cells has been shown[65]. In addition, Zhou *et al.* recently demonstrated that the anti-oxidant effect of exosomes derived from human umbilical cord MSC in a cisplatin-induced AKI model may involve the inhibition of the p38 mitogen-activated protein kinases-caspase 3 pathway[121] (Figure 2).

Metabolomics

Any potential treatment aimed at reversing the metabolomic disorders in acute organ injury should ideally overcome ATP deficit, compensate the proteomic alteration and repair the mitochondrial electron transport chain. Several sudies demonstrate some direct beneficial effects from MSC on metabolomics disorders. Beiral *et al.* demonstrated in a rat kidney I/R model that MSC could restore ATP synthesis[124]. In addition, proteomic and genomic profiling of MSC-derived exosomes (Exocarta[125], Vesiclepedia[126]) showed that they contain key enzymes involved in the ATP-generating stage of glycolysis so that they could potentially restore proteomic alterations in injured tissue. Lai *et al.* showed in injured rat cardiomyoblast, that MSC-derived exosomes increased intracellular ATP levels by 75 and 55% after 15 and 30 minutes respectively[60]. In an *ex vivo* myocardial I/R injury model, MSC-derived exosomes increased ATP production in reperfused myocardium[59]. And in a model of lipopolysaccharide-induced ALI, Islam *et al.* demonstrated that mitochondrial transfer through connexin-43 may be involved in the restoration of ATP levels[127] (Figure 2).

Pro-mitotic/Anti-apoptotic Effects

Multiple groups have studied the underlying mechanisms of MSC anti-apoptotic effects in various organ injury models. Two main mechanisms have been proposed. 1) MSC secretion of growth factors. In animal models of AKI[27,128–131], acute stroke[132–135] and traumatic brain injury[91,136,137], a wide array of secreted growth factors such as insuline growth factor-1[128,131,133,134], vascular endothelial growth factor[27,130,135], hepatocyte growth factor[129], brain-derived neutrophic factor[91,132,136,137], nerve growth factor[91,133,134,136,137] and neurotrophin-3[91,136,137], have been linked to the pro-regenerative effects mediated by MSC. 2) And increased expression of pro-regenerative/anti-apoptotic genes and/or possibly mRNA transfer to injured cells by MSC or MSC derived microvesicles or exosomes. In ALF, MSC induced over-expression of genes involved in hepatocellular regeneration such as hepatocyte growth factor, epidermal growth factor, transforming growth factor-β, stem cell factor and tissue metalloproteinase 3[74]. In AKI, Bruno *et al.* showed that MSC released

microvesicles could transfer mRNAs or microRNAs involved in cell proliferation to damaged renal cells[18,19,138]. In a glycerol-induced AKI model in immunocompromised mice, MSC microvesicles had a proliferative effect in tubular epithelial cells [19]. RNAse pre-treated microvesicles lost their therapeutic potencies, suggesting a RNA-dependent effect. The underlying mechanisms were mainly attributed to a microvesicle induced up-regulation of anti-apoptotic genes (Bcl-xL, Bcl2) and to a down-regulation of apoptotic genes (caspase-1, caspase-8, lymphotoxin-α) in tubular epithelial cells. A similar decrease in apoptotic genes expression (caspase-3 pathway) and up-regulation of phosphorylated protein kinase B pro-survival pathway leading to new neuron generation[139,140] were found in TBI treated with MSC[136,141]. Finally, the over expression of genes involved in the anti-apoptotic pathways (such as growth hormone and insulin growth factor-1 signaling) also played a therapeutic role in a model of sepsis treated with MSC[78,79] (Figure 5).

Ischemia-Reperfusion Injury

Several *in vivo* studies have pointed out the beneficial effects of MSC with respect to I/R of the heart[142], lungs[71,104,143–145] brain[146], kidney[15,147,148] and gut[149,150]. More specifically, studies focused in I/R-induced ALI model, showed some beneficial effects through a combination of immunomodulation[71,143,145], anti-oxidant[71,143,145] or anti-apoptotic[143] properties. Others demonstrated that MSC could increase the activity of anti-oxidant enzymes in I/R[151]. Interestingly in a gut I/R model, MSC reduced rat intestinal I/R injury by increasing the expression of the intestinal tight junction protein zona occludens-1 and reducing tight junction disruption by suppressing the action of TNF-α[150]. The proteomic alteration in I/R injury[65] can be supplemented by the cellular contents of MSC-derived exosomes[60,123]. By replenishing depleted glycolytic enzymes, supplementing damaged cells with additional protein components of the cellular antioxidant system, and activating pro-survival phosphatidylinositide 3-kinases/phosphorylated protein kinase B pathway via cluster of differentiation 73, MSC exosomes can increase ATP level and decrease OS and cell death[59] (Figure 2).

Given the diversity of mechanisms involved in the potential therapeutic effect of MSC in various organ injuries (Figure 6), we will review the current literature underlying the rationale for the use of MSC in ARDS, AKI, ALF, acute brain injury and sepsis.

MESENCHYMAL STEM CELLS IN ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is major cause of acute respiratory failure in critically ill patients. Despite improvements in supportive care, mortality associated with ARDS remains high, up to 40%, depending on the etiology[152,153]. Current treatments remain focused on supportive care such as lung protective ventilation, fluid conservative strategy and prone positioning[154–156]. No pharmacological therapies from pre-clinical models have yet been translated to effective clinical treatment options. Past studies showed that focusing on either anti-inflammatory or anti-fibrotic pathways were too simplistic as a therapy. Pathophysiology of ARDS involves complex crosstalks between the immune system and the alveolocapillary barrier leading to an excess of pro-inflammatory Th1 polarized responses, increase in lung protein

permeability and formation of pulmonary edema. Pulmonary edema results in impaired gas exchange and eventual hypoxemia[153].

1. Mesenchymal Stem Cells Lung Specific Mechanism of Action

Aside from their immunomodulatory, anti-bacterial, anti-oxidant and anti-I/R injury properties, MSC can also display some lung specific functional effects.

Alveolar Fluid Clearance—ARDS is characterized by impaired alveolar fluid clearance, i.e. inability to decrease pulmonary edema, induced by excessive inflammation in the injured alveolar milieu[157]. Several studies have demonstrated that MSC secrete keratinocyte growth factor, which increases alveolar fluid clearance by upregulating key epithelial sodium channel gene expression and Na-K-ATPase activity, or by increasing trafficking of epithelial sodium channel proteins to the apical membrane[158]. These keratinocyte growth factor mediated effects were shown in animal models[83,159,160] as well as in an *ex vivo* perfused human[88,161] preparation. Most recently, we demonstrated that MSC-derived microvesicles could protect against lipopolysaccharide-induced ALI through delivery of the keratinocyte growth factor mRNA with subsequent expression of the protein in the injured alveolus[21].

Lung Permeability—In ARDS, the injured lung capillary endothelium leads to protein leakage from the vascular bed into the alveolar space. This phenomenon aggravates the ability of the lung epithelium to reduce pulmonary edema. Recently, MSC have been shown to secrete angiopoietin-1, a soluble factor capable of reducing endothelial permeability through enhanced endothelial survival and vascular stabilization, through the preservation of cell adhesion molecules and cell junctions and the prevention of actin “stress fiber” formation[162]. We and others have demonstrated that angiopoietin-1 secreted by human MSC was essential to prevent an increase in lung protein permeability[163–165].

2. Pre-clinical Acute Lung Injury Studies

A recent review reported the benefits of administering MSC in pre-clinical small animal lung injury models[6]. More than half of experimental studies concerned intra-tracheal lipopolysaccharide-induced ALI in rodents and intra-tracheal administration of MSC. Whereas, the intravenous route of deliver of MSC was prefered in bleomycin-induced, I/R or ventilator-induced lung injury. The beneficial effects of MSC were also been reported in bacterial-induced ALI models[84,87,88,105], such as pneumonia, peritonitis and sepsis from cecal ligation and puncture, highlighting the antibacterial properties of MSC. Gupta *et al.* found a survival advantage from syngeneic mouse MSC in an *E.coli* bacterial pneumonia-induced ALI model[87]. Lee *et al.* also showed beneficial effects of MSC in *E.coli* bacterial-induced ALI in an *ex vivo* perfused human lung preparation[88]. Although this model excluded other systemic organs, which may generate an inflammatory response, it replicated many of the injury patterns seen in patients with ARDS. Aside from bone marrow, other sources of MSC have been studied. Human umbilical cord-derived MSC is currently being investigated in clinical trials, due to their accessibility (from the placenta), lack of ethical concerns and their faster population doubling time[84,102,166]. Although promising, adipose derived human MSC[104,145], require further studies to clarify their potential therapeutic effects in ALI.

In ALI models in rodents, the mean dose of MSC typically was 20–30 × 10^6 cells/kg, and the timing of administration was within 6 hours following ALI. The maximum therapeutic effect of MSC was found 2 to 3 days following administration. One study using an ALI model in mice with a large dose of MSC (889 × 10^6 cells/kg) showed a delayed effect on day 28[167]. However, no dose response study has been yet published. Thus, it is still unclear whether there is a therapeutic ceiling or if a second dose of MSC is needed, especially during the resolution phase of ALI. Aside from the role of paracrine soluble factors, the role of MSC microvesicles or exosomes has been recently studied. Lee *et al.* found that murine MSC derived exosomes could prevent hypoxic pulmonary hypertension by reducing vascular remodeling, pulmonary influx of macrophages, and pro-inflammatory and proliferative mediators[20]. More recently, we demonstrated that human MSC microvesicles can reduce the severity of *E.coli* endotoxin-induced ALI in mice through the transfer of keratinocyte growth factor mRNA to the injured lung epithelium[21]. These recent findings shed first lights on a new stem cell-free therapy in ALI, circumventing caveats of MSC use such as genetic instability and potential malignant transformation.

3. Clinical Trials

Despite these multiple encouraging pre-clinical studies, translation into human clinical trials remains limited. Currently, two phase I/II clinical trials are underway (See table, Supplemental Digital Content 1, which lists the ongoing clinical trials). One Phase I/II study (NCT01775774) uses human bone marrow-derived MSC (BM-MSC) in ARDS patients. The aim of this multi-center, single group assignment study is to assess the safety and then the feasability of using escalating intravenous doses (1 to 10 × 10^6 cells/kg) of allogeneic human BM-MSC in patients with moderate or severe ARDS. Another randomized, double blind, placebo-controlled trial (NCT01902082), targets not only safety but also efficacy outcomes, using allogeneic adipose-derived MSC. In both studies, inclusion criteria are similar, the intravenous route is used and MSC therapeutic doses vary from 1 × 10^6 to 10 × 10^6 cells/kg. Both trials are still recruiting.

MESENCHYMAL STEM CELLS IN ACUTE KIDNEY INJURY

AKI is a clinical syndrome characterized by rapid loss of excretory function leading to accumulation of products of nitrogen metabolism and metabolic acids, increased potassium and phosphate serum concentration and decreased urine output. Incidence varies from 5000 cases per million people per year for non-dialysis-requiring AKI to 295 cases per million people per year for dialysis-requiring disease[168]. In critically ill patients, the AKI prevalence reachs 40% at admission to the ICU if sepsis is present[169] and 60% during ICU stay[170]. No pharmacological therapies are available. Treatment is essentially supportive, including renal replacement therapy if needed. Mortality from AKI ranges from 44.7 to 53% in critically ill patients[171]. Most patients who survive recover their renal function *ad integrum* after a few weeks. However, some remain in chronic renal failure requiring definitive renal replacement therapy.

Etiology of clinical AKI is often multifactorial involving diverse triggers such as hypovolemia, ischemia, I/R, sepsis and toxic injuries. Most of the AKI seen in the ICU, occur within 72 hours from a combination of pre renal and renal injuries[171]. Most existing

pre-clinical animal AKI models use ischemia induced by acute occlusion of the renal artery[172–174]. Although not wholly clinically relevant, these ischemic AKI models do imitate several activated pathways involved in AKI, such as coagulation system activation[175], leukocyte infiltration[176], endothelium injury[177] with over-expression of adhesion molecules[178], cytokines release[179], Toll-Like Receptors induction[180], intrarenal vasoconstriction pathway and apoptosis[181]. In addition, in septic and hepatorenal pre-clinical AKI models, triggered by a decrease in blood pressure secondary to a systemic or hepatosplanchnic vasodilation[182], the renal sympathetic system[183], the renin-angiotensin-aldosterone system[184] and the tubuloglomerular feedback system[184] are all activated. Depending on the intensity and the period of time of their association, these different factors contribute to a continuum ranging from tubular injuries to apoptosis/necrosis to renal failure[171].

1. Pre-clinical Acute Kidney Injury Studies

MSC therapy is effective in reducing AKI in diverse experimental models including those induced by cisplatin[19,25,38,128,130,185–190], glycerol[19,38] and I/R injury[14,15,26,129,191–193]. Systemic route of administration is widely used via intravenous or intra-peritoneal injection, except for I/R model where MSC are infused intra-arterial[14,15,26,129,191–193]. Delivered doses range from 8×10^{6} [187] to 2×10^{8} [186] cells/kg. In cisplatin-induced AKI models, MSC prevented renal function impairment, improved renal function and preserved tubular integrity[25,128], leading to an increase in the survival rate of mice following cisplatin injection[188–190] compared to saline control. Interestingly, Morigi *et al.* found that, in the cisplatin-AKI model, cord blood derived MSC[189] were more effective than BM-MSC[188] in terms of renal function improvement and survival, whereas MSC derived from human adipose tissue did not improve renal function[194]. In addition, mice treated by human adipose tissue-derived MSC showed some tubular alterations such as casts, nuclear fragmentations and necrosis. However, because these histological alterations are similar to those observed in a cisplatin-induced AKI, these lesions could not be interpreted as being harmful effects of MSC.

In a lethal AKI model induced by cisplatin administration, Bruno *et al.* showed MSC microvesicles could enhance survival in immunnocompromised mice[18]. In this model, a single administration of microvesicles increased survival rate and ameliorated renal failure but did not prevent chronic tubular injury. However, multiple injections of microvesicles not only improved survival but also normalized histology and renal function at day 21.

2. Clinical Trials

Despite strong pre-clinical evidence of the therapeutic effect of MSC in AKI, only three Phase I/II clinical trials have been carried out[12,195,196] (See table, Supplemental Digital Content 1, which lists the ongoing clinical trials). One on-going trial (NCT00733876)[12,196] aims to investigate safety and efficacy of allogeneic MSC in preventing and treating AKI following on-pump coronary artery bypass surgery, using suprarenal aortic MSC infusion. Patients at high risk of post-operative acute renal failure patients are included. Preliminary data from the trial indicates that MSC infusion is safe and feasible. Moreover, MSC infusion prevented any post-operative renal failure (0% *versus* 20% AKI incidence compared to case

control) and reduced by 40% the length of hospital stay and readmission rates[12,196]. A double-blind, placebo controlled, multicenter phase II trial is planned by the same investigators. Another clinical trial used allogeneic human BM-MSC in a multi-center, double-blind, placebo-controlled phase II study (NCT01602328) in patients with post cardio-pulmonary bypass-induced AKI. Safety and also efficacy outcomes such as time to kidney recovery and dialysis were the primary aims. The third ongoing pilot study (NCT01275612)[195] investigates the safety and the feasability of systemic infusion of donor *ex vivo*-expanded MSC in cisplatin-induced acute renal failure in chemotherapy treated patients with solid organ cancer. Preliminary data from these clinical trials are pending.

MESENCHYAML STEM CELLS IN ACUTE LIVER FAILURE

ALF still remains a leading cause of death in 30% of the cases[7]. Principal etiologies include acetaminophen-induced injury, idiosyncratic drug induced liver injury, viral hepatitis, autoimmune hepatitis, Budd-Chiari syndrome and Wilson disease. Up to 15% of the etiology of ALF are indeterminate. Depending on the cause, spontaneous recovery may vary from 30 to 60%[7]. However, supportive therapies in ALF are dramatically limited and liver transplantation remains the gold standard for treating end-stage liver failure[7,197].

In ALF, innate immunity with its resultant inflammatory cascade is activated. Uncontrolled hepatic inflammation with clinically high serum levels of pro-inflammatory cytokines such as IL-1, TNF-α, IL-6, IL-8 have been reported[198–200] with resultant hepatic cytotoxicity[201]. Necrosis and/or apoptosis may also take an important part in the loss of hepatic function, overwhelming hepatocyte regeneration[197]. I/R and OS injuries can also take place in different causes of ALF such as toxic, post hepatectomy or post transplantation injury. The prognosis of ALF is directly linked to liver regeneration, which in 40% of the cases can overcome the hepatocyte destruction.

1. Pre-clinical Acute Liver Failure Studies

To circumvent organ donnor shortage, replacing injured hepatocytes by stem cells initially appeared as the main aim of liver-oriented cell-based therapy. Although several studies showed that MSC can transdifferenciate towards a hepatocyte phenotype *in vitro* and *in vivo*[202], the beneficial effects of MSC are more complex, encompassing regenerative[203–207], immunoregulatory[206–208] and anti-OS injury[117] pathways.

Most preclinical studies using MSC used mice and rats with carbon tetrachloride[30,76,209–212], thioacetamide[118], D-galactosamine[29,74,75,213,214] or I/R-induced liver injury[116,215,216]. However, two studies used D-galactosamine induced fulminant hepatic failure in pigs[29,213]. Therapeutic dose ranged from 2 to 10×10^6 cells/kg[217]. Most of the studies used intravenous MSC administration, but others chose the intra-portal route[29,215] aiming at circumventing trapping in the pulmonary circulation[215]. Overall, MSC decreased the severity of histological liver injury[74,75,210,213–215], improved liver function[75,210–212,215] and finally enhanced survival[29,74,75,210,213–215]. In contrast, Boeykens *et al.* did not find any benficial effects of intraportally administrated MSC in terms of improved liver recovery[218]. However, the authors used MSC in a complex liver injury model, combining a partial hepatectomy in a previously steatotic liver which may not be

applicable to ALF. Regardless all these promising findings, no clinical trial has been carried out in this field.

MESENCHYMAL STEM CELLS IN ACUTE BRAIN INJURY STROKE

Stroke causes 15 million death worldwide every year[219]. In United States of America, it remains the leading cause of disability and the third leading cause of mortality behind cardiovascular disease and cancer[220]. Currently, tissue plasminogen activator administration within 4.5 hours of the onset of ischemia is the only validated treatment for ischemic stroke. Alternate or complementary therapeutics are urgently needed.

In acute stroke, reduction in the oxygen and glucose supplies lead to neuronal cell death through several mechanisms including intracellular calcium movement and energetic metabolism impairment[221–224]. Secondary, restoration of the cerebral blood flow leads to I/R. As in the other organs, I/R injury in the brain triggers ROS production as well as pro-inflammatory pathways[225,226]. Microglia cells secrete pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β[227,228]. Taken together, all these mechanisms increase neuronal cell damage.

1. Pre-clinical Stroke Studies

Most preclinical animal studies using MSC have involved rodent, preferentially rats, in models of middle cerebral artery occlusion. Although some teams carried out a permanent occlusion model[77,134,229–232], most of the studies used a transient middle cerebral artery occlusion model ranging from 90 to 120 minutes of ischemic time. Three routes of MSC administration have been investigated: intracerebral[77,132,229,231–236], intracarotid[237,238] and intravenous[133–135,230,239–242]. Time of treatment delivery after stroke varied from 2 hours[236] to 1 month[32]. Both routes of MSC administration, intracerebral[132,233–236] or intravenous[243], decreased infarct size and improved neurological outcomes in rats. Either intravenous or intracarotid administration of MSC also improved behavioral outcomes[244]. However, it remains unclear which route, intracerebral[243] or intravenous route[245], is more efficatious. The MSC doses range from 4×10^5 [77] to 1.2×10^8 [240] cells/kg depending on the model. A relation between cell dose and efficacy have been demonstrated with both neurological outcomes[240] and neurotrophic factors secretion[77].

2. Clinical Trials

Based on the accumulation of these preclinical studies, clinical trials using MSC in stroke have increased dramatically. The number of clinical trials involving MSC in stroke (ischemic, hemorrhagic, acute, subacute or chronic) rose from one completed phase I study in 2009[246,247] to 22 phase I/II clinical trials[248]. Bang *et al.* carried out the first phase I study for assessing feasibility and safety of intravenous administration of 10^8 autologous MSC in patients with severe neurological deficits due to subacute ischemic stroke[246]. Five patients were included in the treatment group versus 25 in the control group. Although intravenous cell infusion appeared safe and feasible, the small sample size in the treated group and the non-blinded design of this study prevented any conclusions concerning the potential therapeutic benefits of MSC on neurological outcomes. Five years later, the same authors

published a randomized placebo-controlled long-term follow-up study carried out on 52 subacute ischemic stroke patients[249]. In this study, 16 patients were included in the intravenous MSC group. No difference was observed between groups concerning adverse events. More importantly, some of the neurological recovery scores were improved in the MSC group compared to the placebo group. Currently 9 studies are underway to investigate the effect of intravenous or intra-arterial administration of MSC in acute ischemic stroke patients (See table, Supplemental Digital Content 1, which lists the ongoing clinical trials). All are phase I/II studies except one phase III. Four of the trials use autologous whereas 5 use allogeneic MSC. Time of MSC administration ranges from 1 day to 6 weeks after the onset of clinical signs of stroke. The therapeutic dose ranges from 1 to 2.5×10^6 cells/kg. Primary outcomes are safety, feasability, tolerance, improvement of functional recovery assessed by neurological scores, and size of infarct. The maximum follow-up ranges from 1 month to 24 months after MSC administration. Despite the number of clinical trials, little data is yet available to demonstrate the potential therapeutic use of MSC in stroke management. Results of on-going trials are expected soon, especially long-term safety data and the potential impact of MSC on neurological outcomes.

TRAUMATIC BRAIN INJURY

TBI remains a significant cause of morbidity, mortality and disability among patients[250]. After the initial trauma, multiple pathological pathways converge, generating secondary lesions and leading to increased neuronal cell death and brain damage. These different pathways include increased neurotransmitter release, ROS generation with OS injury, calcium-mediated signaling and increased apoptosis, mitochondrial dysfunction and pro-inflammatory response.

1. Pre-clinical Traumatic Brain Injury Studies

MSC can both suppress these different injury mechanisms and also express neuronal and glial markers[251], although regeneration may not be a significant therapeutic mechanism. Most preclinical studies in TBI have used BM-MSC[39,136,137,139,252–255], except two studies which used peripheral blood-derived[141] or umbilical cord-derived MSC[91]. Rats were the most frequent small animal used[39,137,139,141,252–256], although, a few studies with TBI have been performed in mice[91]. In these studies, MSC were typically given from 24 hours to 7 days following TBI and, doses varied from 6×10^6 [91] to 3.2×10^8 [254] cells/kg depending on the administration route, which included intravenous[39,136,137,139,140,252–255,257] or intracerebral[91,140,141]. MSC route of administration in TBI remains controversial. Multiple studies demonstrated that in rat models of TBI, most of the MSC are initially trapped in the lungs, liver and spleen, leaving a small portion of cells, ranging from 0.0005%[256] to 1.4%[33], to cross the blood brain barrier to reach the cerebral parenchyma. Harting *et al.* showed that intravenous MSC treatment failed to improve any motor or cognitive outcomes in a rat TBI model[256]. Although some studies highlighted the beneficial effects of intravenous MSC in TBI[39,136,137,140,253–255], most of studies were from the same experimental team. Interestingly, Mahmood *et al.* compared the intravenous with the intracerebral route of administration of MSC at doses of 3×10^6 and 7×10^6 cells/kg in a rat TBI model[140]. They found differences in terms of localization of the induced neuronal cells proliferation but

none regarding neurological functional recovery. Overall, the beneficial effects of MSC have been demonstrated in terms of functional neurologic improvements from 15 to 90 days after TBI[39,136,137,140,141,253–255,257]. MSC are believed to migrate into the injured brain parenchyma[91,141,255] with a high affinity for the periphery of the lesions[253], leading to a decrease in the contusion volume measured one month after the TBI[91]. Possibly due to the small number of published preclinical animal studies and to the unresolved issue of optiminal route of delivery, no clinical trial using MSC in TBI have been yet carried out.

MESENCHYMAL STEM CELLS IN SEPSIS AND MULTIPLE ORGAN DYSFUNCTION SYNDROME

Despite decades of clinical trials and improvement in antibiotic and supportive care, sepsis remains a challenging life-threatening disease in critically ill patients and the leading cause of morbidity and mortality in ICU patients[258]. In the United States, sepsis is responsible for more than 200,000 patient deaths and utilizes US$17 billion per year[259,260]. Sepsis results from a complex host-pathogen interaction leading to a dysregulation of the host response in terms of inflammation and coagulation. Pro-apoptotic pathways, metabolomic disorders, OS and I/R injuries are also involved in patients treated for sepsis. Eventually, sepsis can evolve toward septic shock, MODS, and death. Currently, all clinical trials using therapeutics targetting a single specific pathway have failed to demonstrate any clinical benefits[261–264] such as high dose corticoids[265,266] or activated protein C[267]. Consequently, immunomodulatory approach using a mutli-faceted therapy is required to overcome the inflammatory imbalance. MSC is an attractive approach due to its ability to home to injured sites, mitigate the pro-inflammatory cascade, modulate multiple immune cell types, promote cell survival, protect against OS injuries and exhibit some anti-bacterial properties. In addition, another advantage of cell-based therapy in sepsis is that stem cells can potentially interact with their environment, so that they can adopt some dynamic phenotypes and secrete a variety array of soluble factors depending on the pathological context[268,269].

1. Pre-clinical Sepsis Studies

In this review, we have excluded studies using endotoxin-induced injury models of sepsis and focused only on pre-clinical studies usings live bacteria. Although lipopolysaccharide represents one part of the multiple bacterial factors involved in the septic process, these models have obvious limitations[270]. Thus, we considered the live bacteria models more clinically relevant. The therapeutic use of MSC has been used in three different sepsis models: cecal ligation and puncture[70,78,79], *P. aeruginosa* peritonitis[110], and *E.coli* pneumonia[86,88]. The cecal ligation and puncture model is the only one that generates a polymicrobial sepsis, since the procedure exposes directly the peritoneum to the gut microbiome. Intravenous[70,79,110], intraperitoneal[78] and intratracheal[87,88] route of MSC administration have been used. Dose of MSC ranged from 1×10^{7} [79] to 4×10^{8} [88] cells/kg. The main findings were that MSC were able to enhance bacteria clearance and attenuate septic organ injury in lungs, liver and kidneys[70,78,79].

Although MSC have been extensievly studied in heart I/R injury and used in clinical trials in patients with acute myocardial infarction[271], no data have been published concerning their

potential therapeutic effects in sepsis-induced cardiac injury[272,273]. And yet, half of patients with severe sepsis and septic shock present with reversible left ventricular systolic or diastolic dysfunction[274] which is associated with increased mortality. Since the main pathways involved in this sepsis-related heart injury are those encountered in inflammation and I/R injuries, it seems to be important to study MSC in this context.

Beyond their ability of organ functional improvement in sepsis-induced injury, several studies showed a significant survival advantage in mice treated with MSC in peritonitis[70,78,79] or pneumonia models[87]. In addition, Lee *et al.* demonstrated a similar beneficial effect of MSC on macrophage phagocytosis and bacteria clearance in an *E.coli* bacterial-induced lung injury in an *ex vivo* human lung preparation[88]. Eventhough most of these studies highlighted promising therapeutic properties of MSC within the early inflammatory phase of sepsis, it is still unknown whether they could be beneficial or harmful during the later anti-inflammatory phases while immunity is impaired[275]. However, what makes the therpaeutic use of MSC unusual is that their phenotype can be skewed either towards a pro or anti-inflammatory side depending on the surrounding milieu[268,269,276]. This importance of this property of MSC needs to be studied, such as their use in the later phase of sepsis.

Possibly due to the heterogeneity of the animal septic models and the lack of data comparing MSC to the multiple therapeutics commonly used in sepsis, no clinical trial has been carried out yet.

REMAINING QUESTIONS AND LIMITATIONS IN CLINICAL USE OF MESENCHYMAL STEM CELLS

As we described previously, the dose of MSC used in the pre-clinical small animal studies are extremely large and varies substantially (from 4×10^5 to 4×10^8 cells/kg). The optimal dose remains unknown in clinical trials although the typical dose in human is $5 – 10 \times 10^6$ cell/kg per dose. Additionally, the optimal route of delivery to generate the best therapeutic effect is still largely unknown between systemic and local administration. For example, the two clinical trials (NCT02097641, NCT01902082) in ARDS use intravenous administration whereas, in bronchopulmonary dysplasia in neonates, the only clinical trial (NCT01297205) uses intra-bronchial administration.

Most injury models have shown benefits of MSC administration shortly after injury. Given that organ injury is a dynamic process over time, it is still unknown whether any beneficial effects might be found if MSC was given at a later phase such as during the resolution of injury; thus, it is unclear whether a second dose of MSC is needed for the resolution phase. Overall, the optimal dose, route and time-sequence remain to be determined.

Even though organ failure is associated with poor outcome, it remains unclear whether organ failure or the initial underlying cause of injury or both is responsible for death. Organ failure has been even seen by others as an adaptive process of the organism in response to injury. Consequently, MSC should be considered as an adjuvant therapy; treating the initial cause of injury still remain the priority. For example, MSC should be considered an adjuvant

therapy to ARDS caused by bacterial pneumonia, not supplanting antibiotics or other supportive therapies.

In addition, although MSC have anti-microbial properties in pre-clinical animal models, it is still worth questioning whether an immunosuppressive therapy such as MSC is appropriate during injury from an infectious etiology. For example, recent studies suggest that MSC fail to improve outcomes in acute phase of severe influenza[277]. Whether this is a limitation to the murine model used needs to be studied further.

And finally, although a recent meta-anaylsis demonstrated no severe adverse outcome associated with MSC therapy[278], the potential of malignant transformation of MSC or the ability of MSC to enhance pre-existing tumors still remains a serious clinical question, especially in light of the limitations of the tests available to detect cancer (i.e. computerized tomography scan).

CONCLUSION

The beneficial effects of cell-based therapy with MSC are apparent in multiple preclinical injury models involving all the organs in MODS. Attracted by signals from the injured and inflamed tissues, MSC appear to migrate to the site of damage and secrete an array of soluble factors and/or exosomes/microvesicles which suppress the injury. This review highlights the pre-clinical evidence which provided the underlying rationale for several phase I/II clinical trials in ARDS, AKI and stroke. Based on promising preliminary results, further phase II and III trials are underway, the results of which are pending. However, no clinical studies are underway for ALF, TBI, sepsis and MODS.

Some concerns still remain with MSC cell-based therapy which will need to be addressed in on-going Phase I/II clinical trials such as the long term adverse effects of systemic immune suppression, potential for ectopic tissue formation and MSC immunogenicity. Although very promising, the evidence is still unclear whether MSC cell-based therapy is superior to current therapies. We still await the results from the clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Monsel was funded by the International Research Grant from the Société Française d'Anesthésie-Réanimation (Paris, France). Dr. Lee was supported by the National Heart, Lung, and Blood Institute Grant HL-113022 (USA) & Hamilton Endowment Funds (UCSF Department of Anesthesiology, San Francisco, CA).

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Summary Statement

There are currently >350 clinical trials utilizing the adult stem cell, mesenchymal stem or stromal cells. The review summarizes the underlying rationale and pre-clinical studies using mesenchymal stem cells for acute organ injury.

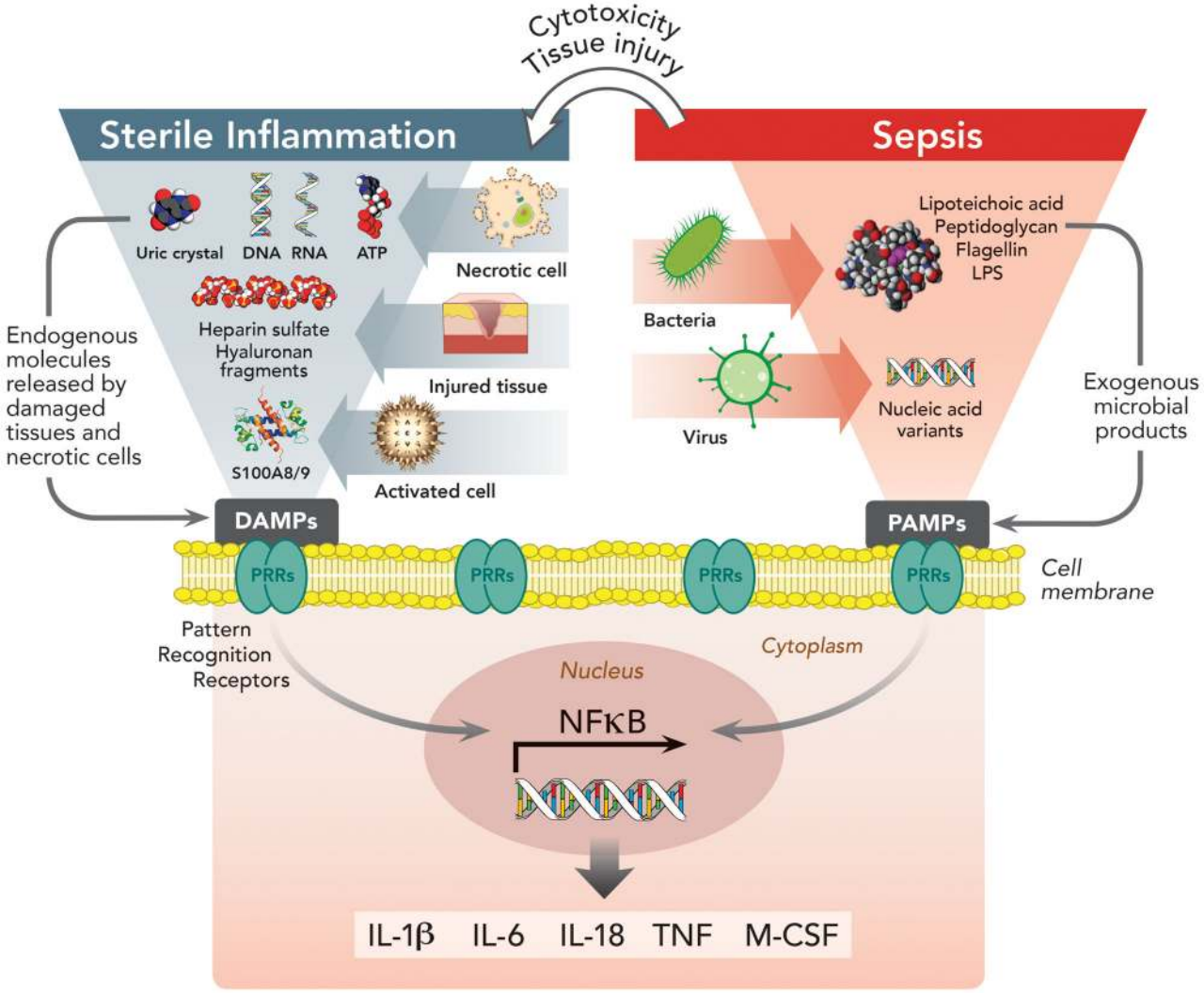


Figure 1. Pattern Recognition Receptors in Immunity and Their Involvement in Sterile and Sepsis-Related Inflammation

Pattern recognition receptors (PRRs) expressed by antigen presenting cells (dendritic cells, monocytes, macrophages) constitute the first interaction between the extra-cellular environment and innate immunity. They are proteins, which include membrane-bound and cytoplasmic receptors, that bind either pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) derived from exogenous microorganisms (i.e. sepsis from infection) or endogenous molecules (i.e. sterile inflammation). Interaction of PRRs with PAMPs/DAMPs induces nuclear factor-kappa B signaling pathways, resulting in the secretion of pro-inflammatory cytokines and co-stimulatory molecules. In sepsis, the initial immune response triggered by PAMPs/PRRs interaction can lead to tissue damage and the release of DAMPs, which may act synergistically with PAMPs to enhance inflammation. Nevertheless, even without microorganism involvement, DAMPs released from dead or dying cells in response to injury or stress, are able to induce similar pro-inflammatory cytokine production from tissues, driving “sterile inflammation.”

ATP = adenosine triphosphate; DAMPs = damage-associated molecular patterns; IL-1β = interleukin-1 beta; IL-6 = interleukin 6; IL-18 = interleukin 18; LPS = lipopolysaccharide; M-CSF = macrophage colony-stimulating factor; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; PAMPs = pathogen-associated molecular patterns; PRRs = pattern recognition receptors; S100A8/9 = (also known as calgranulins A and B, or MRP8 and MRP14 respectively) are members of the S100 multigene subfamily of cytoplasmic EF-hand Ca^{2+}-binding proteins which are endogenous activators of Toll-like receptor 4; TNF = tumor necrosis factor.

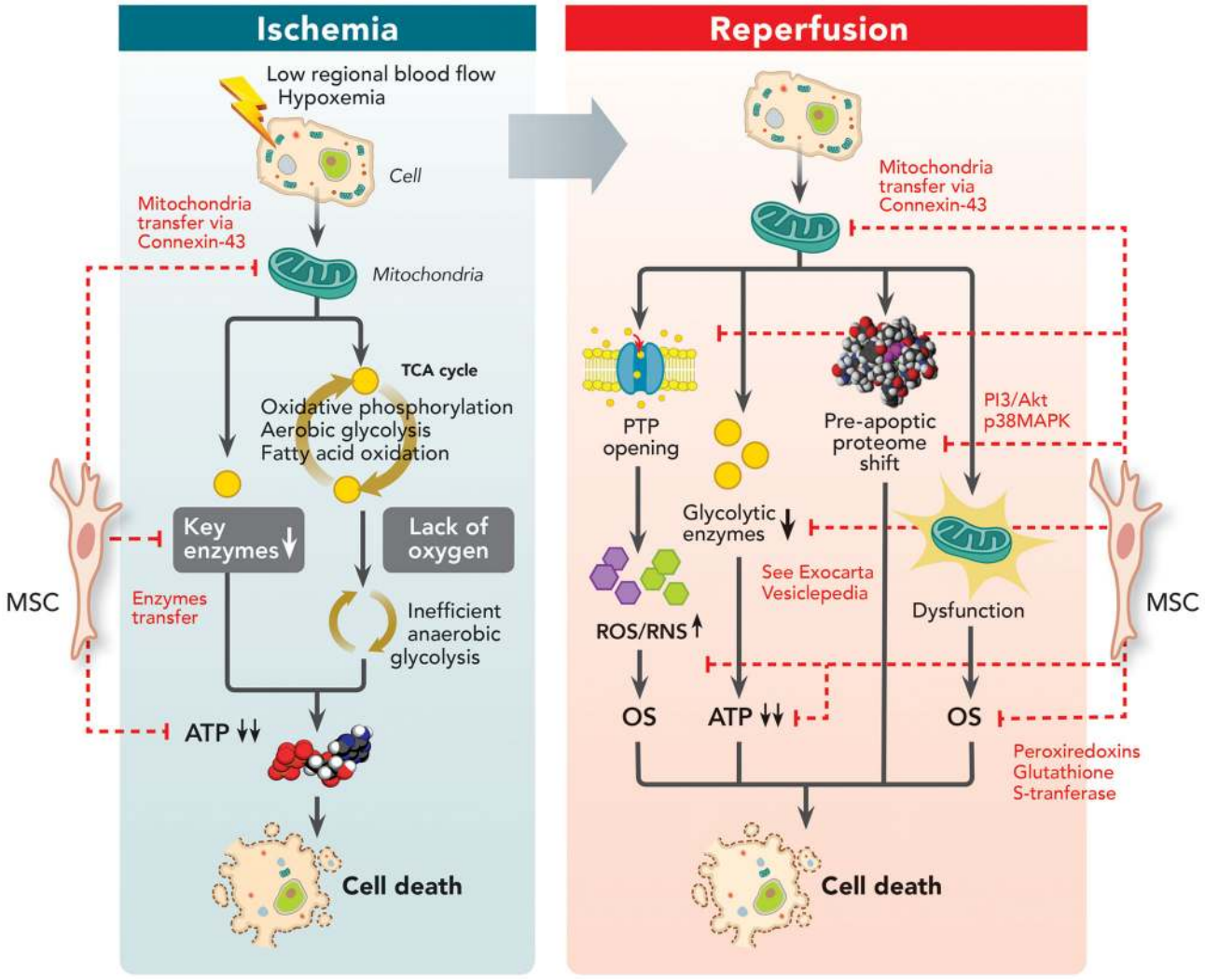
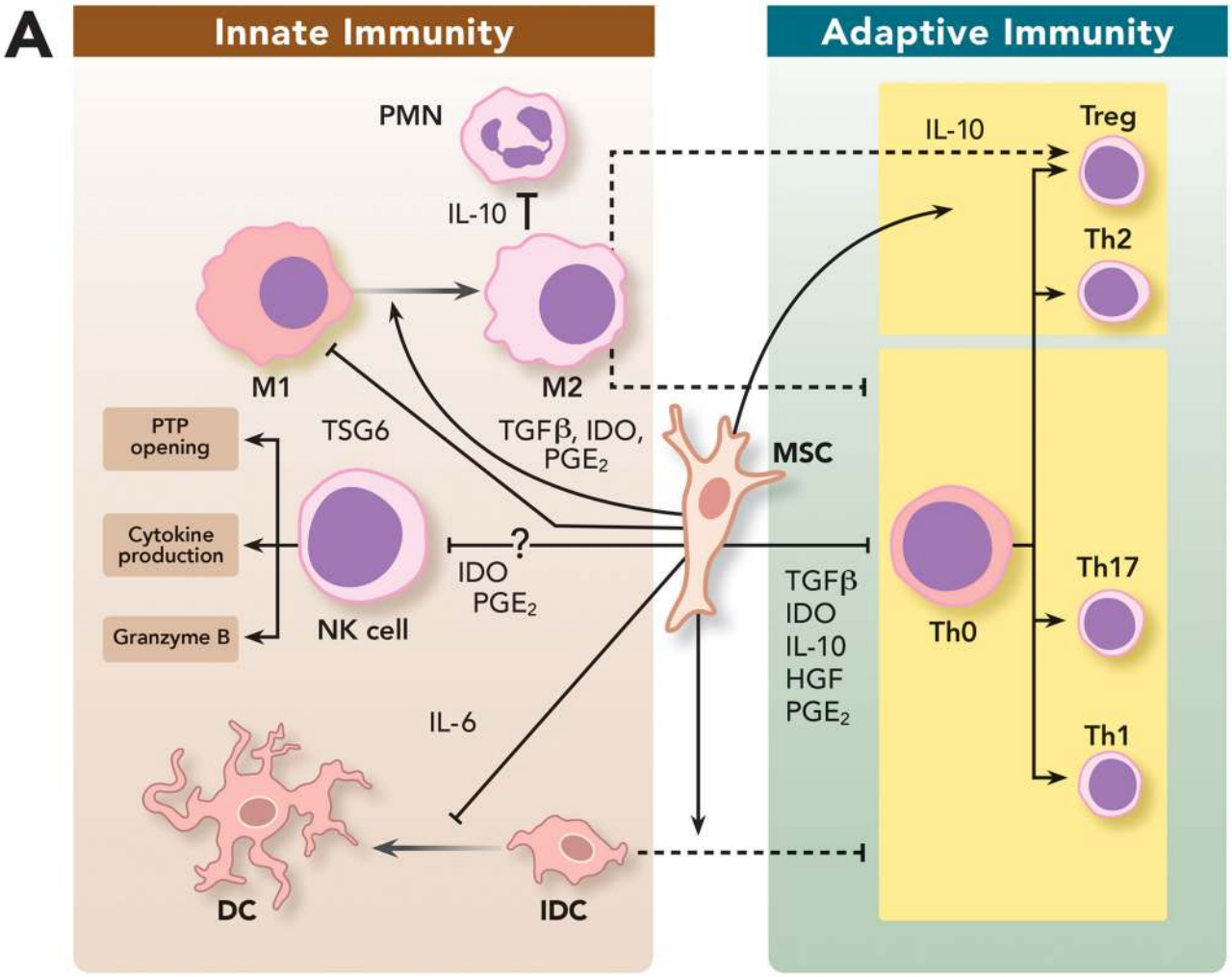


Figure 2. Impact of Mesenchymal Stem Cells on Ischemia-Reperfusion Injury Pathways

Ischemia is a significant cause of acute organ injury that results from a decrease in regional oxygen delivery (such as low blood flow or hypoxemia), leading to inefficient anaerobic glycolysis as the major source of ATP production and ATP deficit. However, much of the tissue damage occurs during the reperfusion phase, leading to mitochondrial permeability transition pore opening, pro-glycolytic enzyme depletion, pro-apoptotic proteome shift and mitochondrial dysfunction inducing oxidative stress. MSC can decrease ischemia-reperfusion induced injury by: (1) Restoring ATP levels by possibly mitochondrial transfer through connexin-43 channels and replenishing depleted glycolytic enzymes; (2) Decreasing reactive oxygen species/reactive nitrogen species generated during oxidative stress by either preventing their release, circumventing the depletion of key enzymes or by transferring reactive oxygen species scavengers (such as peroxiredoxins and glutathione S-transferase) into injured cells; (3) And restoring proteomic alterations by activating pro-survival phosphatidylinositide 3-kinases/protein kinase B pathway via cluster of differentiation 73 or inhibiting p38 MAPK-caspase 3 pathway.

ATP = adenosine triphosphate; CD73 = cluster of differentiation 73; MAPK = mitogen-activated protein kinases; MSC = mesenchymal stem cell; OS = oxidative stress; PI3/Akt = phosphatidylinositide 3-kinases/protein kinase B; PTP = permeability transition pore; ROS = reactive oxygen species; RNS = reactive nitrogen species; TCA = tricarboxylic acid cycle.



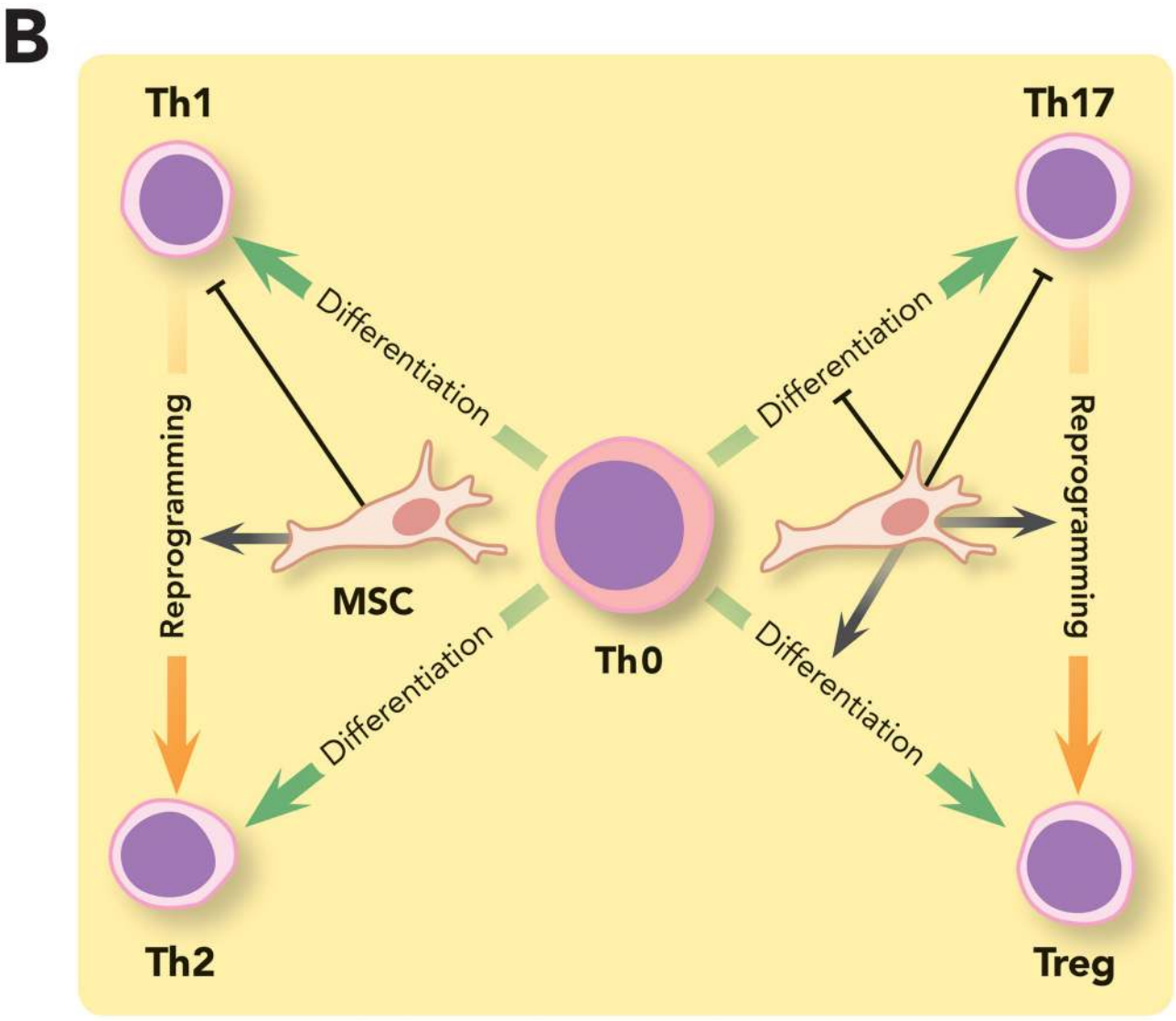


Figure 3. Immunomodulatory Properties of Mesenchymal Stem Cells on Innate and Adaptive Immunity

(A) MSC can modulate innate and adaptive immune cells by: (1) Promoting repolarization of macrophages from type 1 to type 2 phenotype characterized by high levels of interleukin-10 secretion, which can block polymorphonuclear neutrophil influx into the injured tissue and prevent further damage; (2) Interfering with dendritic cells differentiation, maturation and function, skewing them toward a regulatory phenotype and decreasing their capacity to induce activation of T cells; (3) And impairing natural killer cells cytotoxic activity, cytokine production and granzyme B release. However, recent studies suggest that the complex interplay between MSC and natural killer cells may depend on the surrounding milieu. **(B)** MSC can suppress T cell activation and proliferation and also decrease their response by shifting them from a T helper 1 to a T helper 2 immune response. MSC have been shown to (1) inhibit the differentiation of naive T cells into T helper 17 cells and prevent the secretion of pro-inflammatory cytokines by T helper 17 cells; (2) And promote

induction of immunosuppressive T regulatory cells in part by reprogramming T helper 17 cells into T regulatory cells.

DC = dendritic cell; HGF = hepatocyte growth factor; iDC = immature dendritic cell; IDO = indolamine 2,3-dioxygenase; IL-6 = interleukin-6; IL-10 = interleukin-10; M1 = type 1 phenotype; M2 = type 2 phenotype; MSC = mesenchymal stem cell; NK cell = natural killer cell; PGE2 = prostaglandin E2; PMN = polymorphonuclear neutrophil; TGFβ = transforming growth factor beta; Th = T helpers cell; Treg = T regulatory cell; TSG6 = tumor necrosis factor-stimulated gene 6.

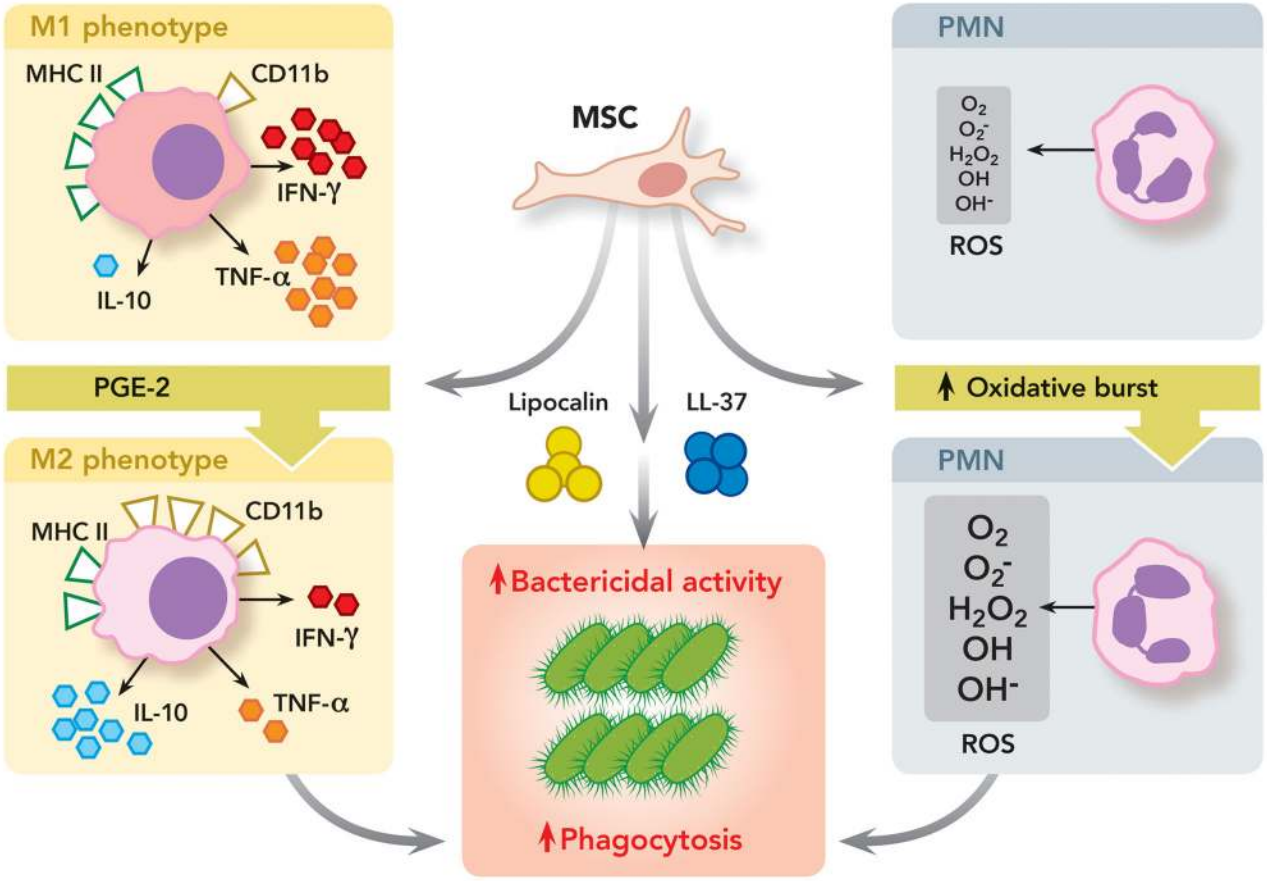


Figure 4. Antimicrobial Properties of Mesenchymal Stem Cells

MSC can exert direct and indirect anti-microbial activity by: (1) Secreting anti-bacterial proteins/peptides such as cathelicidin-related antimicrobial peptides and lipocalin-2, leading to improved bacterial clearance; (2) Promoting repolarization of monocytes and/or macrophages from a pro-inflammatory to an anti-inflammatory phenotype characterized by high levels of interleukin-10 secretion and phagocytosis receptor cluster of differentiation 11b expression, low levels of tumor necrosis factor-α and interferon-γ production and major histocompatibility class II expression. Type 2 monocytes-macrophages have increased phagocytosis capability against bacteria; (3) And promoting neutrophil activity and viability with improved respiratory burst and increased reactive oxygen species release, which are bactericidal.

CD11b = cluster of differentiation molecule 11b; H_2O_2 = hydrogen peroxide; IFN-γ = interferon gamma; IL-10 = interleukin-10; LL-37 = Cathelicidin-related antimicrobial peptides; M1 = type 1 phenotype; M2 = type 2 phenotype; MHC II = major histocompatibility class II; MSC = mesenchymal stem cell; O_2^- = superoxide anion radical; O_2 = oxygen; OH = hydroxide; OH^- = hydroxyl radical; PGE2 = prostaglandin E2; PMN = polymorphonuclear neutrophil; ROS = reactive oxygen species; TNF-α = tumor necrosis factor alpha.

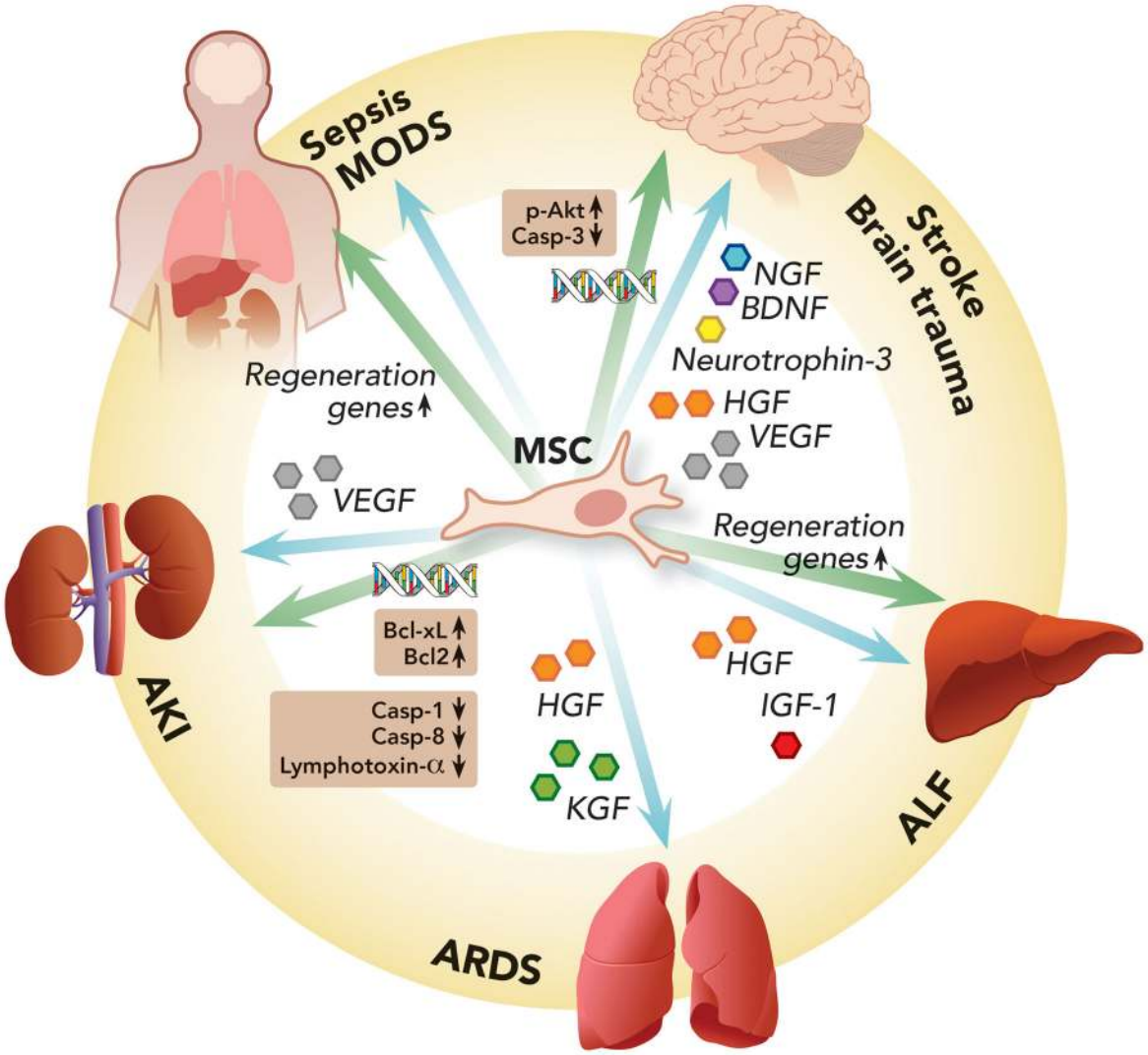


Figure 5. Pro-mitotic/Anti-apoptotic Properties of Mesenchymal Stem Cells

Mesenchymal stem cells can exert anti-apoptotic effects in different organs through two main mechanisms: (1) Secretion of a wide array of growth factors promoting cell regeneration and tissue repair; (2) And promotion of pro-regenerative/anti-apoptotic gene expression by either inducing their transcription or transferring mRNA or microRNA involved with cell proliferation to damaged cells.

AKI = acute kidney injury; ALF = acute liver failure; ARDS = acute respiratory distress syndrome; Bcl2 = B-cell lymphoma 2; Bcl-xL = B-cell lymphoma-extra large; BDNF = brain-derived neutrophic factor; Casp-1 = caspase 1; Casp-3 = caspase 3; Casp-8 = caspase 8; HGF = hepatocyte growth factor; IGF-1 = insulin growth factor 1; KGF = keratinocyte growth factor; MODS = multiple organ dysfunction syndrome; NGF = nerve growth factor; p-Akt = phosphorylated protein kinase B; VEGF = vascular endothelial growth factor.

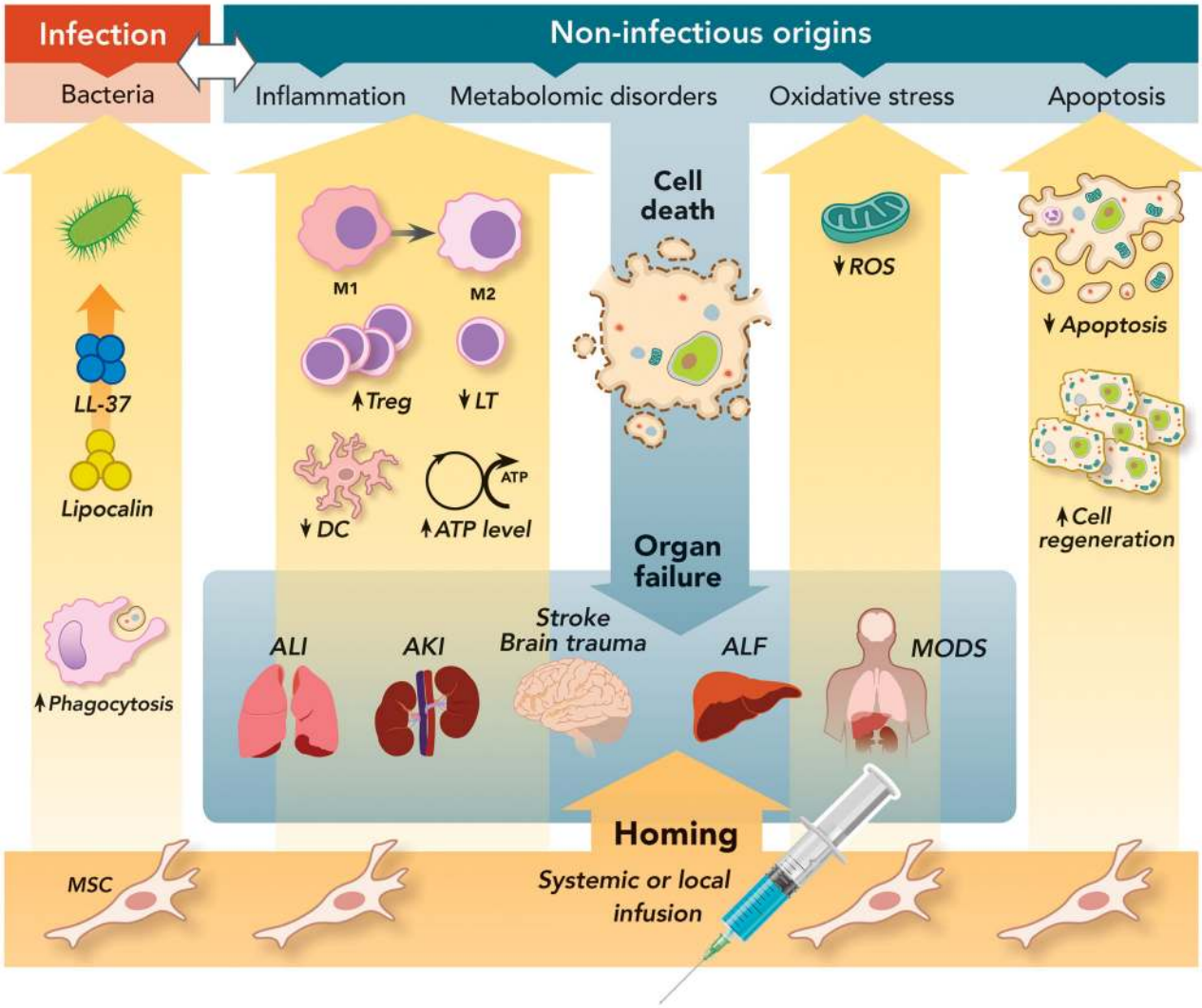


Figure 6. Therapeutic Effects of Mesenchymal Stem Cells on Multiple Signaling Pathways Leading to Acute Organ Injury

Both infection and non-infectious causes can trigger organ damage through the activation of diverse cell signaling pathways such as inflammation, metabolomic disorders, oxidative stress and apoptosis, eventually leading to organ injury and failure. MSC can exert pleiotropic therapeutic effects through the secretion of a wide array of soluble factors, which lead to: (1) Anti-microbial activity with secretion of cathelicidin-related antimicrobial peptides and Lipocalin and increased phagocytosis by monocytes and macrophages; (2) Anti-Inflammatory activity by switching the phenotype of monocytes or macrophages from a M1 to a M2 phenotype, which is characterized by an enhanced phagocytosis capacity and increased anti-inflammatory cytokine secretion; Inhibition of T-lymphocyte and dendritic cell activation and increase in T regulatory cells; (3) Increase in ATP cellular levels and decrease in ROS accumulation, reducing oxidative stress; (4) And switch from a pro-apoptotic to a pro-mitotic phenotype.

AKI = acute kidney injury; ALF = acute liver failure; ALI = acute lung injury; DC = dendritic cell; LL-37 = cathelicidin-related antimicrobial peptides; LT = T lymphocyte; M1

= type 1 monocyte/macrophage; MODS = multiple organ dysfunction syndrome; MSC = mesenchymal stem cells; ROS = reactive oxygen species; Treg = T regulatory cell.