Battling Inflammation in Acute Lung Injury and Acute Respiratory Distress Syndrome: Stem Cell-Based Therapy Targeting the Root Cause of Acute Lung Injury

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Abstract

Acute lung injury (ALI) describes one or more initiating assaults either directly to the lungs or systemically that, if not treated in a timely manner, ultimately progresses to the development of acute respiratory distress syndrome (ARDS) a condition which is characterized by atelectasis, pulmonary hypertension, and an intense, overwhelming inflammatory response that leads to obliteration pulmonary fibrosis and ultimately respiratory failure. The long-term complications associated with ALI/ARDS can be subverted if the fibrotic phase of the disease is suppressed; therefore, it is essential to control inflammation in such a way that endogenous self-protection mechanisms are maintained while not allowing escalating inflammatory damage to occur in the local environment of the lungs. Current treatment strategies focus on optimal ventilator management and treatment of the underlying condition. Cell-based approaches are an attractive option for directed therapeutic intervention for ALI/ARDS. In particular, mesenchymal stem cells (MSCs) from bone marrow, adipose, umbilical cord, and lung tissue as well as induced pluripotent stem (iPS) cells have been shown to facilitate lung repair in several animal models of ALI. The exact mechanism(s) by which these cells accomplish this feat are as yet unknown; however, mounting evidence suggests that they possess potent immunomodulatory and anti-microbial capabilities which diminish the injury-induced inflammatory responses and reduce infection-mediated ALI, respectively, in these various models. Both direct delivery of stem cells to the lung and systemic administration have been somewhat effective, suggesting that stem cells utilize paracrine mechanisms, at least in part, to perform these functions. Aside from their endogenous ability to suppress inflammation and infection, gene-modified MSCs and iPS cells have recently been used as vehicles for carrying anti-inflammatory agents to the lung. Taken together, stem cell therapy is a promising alternative to current therapeutic intervention for ALI/ARDS.

Keywords: Inflammation; Lung; Acute Lung Injury; Acute Respiratory Distress Syndrome; Stem Cells; Mesenchymal Stem Cells; Cell Therapy

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by a serious, life-threatening onset of respiratory failure initiated by a myriad of assaults that lead to massive localized pulmonary inflammation-a condition collectively referred to as acute lung injury (ALI). Clinically, the criteria for defining ALI include respiratory failure with a PaO₂/FiO₂ ratio ≤ 300 mmHg regardless of positive end-expiratory pressure (PEEP), pulmonary vascular wedge pressure <18 mmHg or normal left atrial filling pressure, bilateral infiltrates (inflammatory cells) on chest radiograph, and acute onset of respiratory failure with pulmonary inflammation and increased capillary permeability; ARDS is defined by the same criteria as ALI except with a measure of a reduced limiting value of < 200 mmHg for PaO₂/FiO₂ [1]. Lung injury scoring has been used as a supplement to the above criteria for defining ALI/ARDS, taking into account diffuse alveolar damage (DAD) and oxygenation measurements influenced by PEEP [2-8]. ALI can be initiated directly by bacterial or viral infection, aspiration of gastric contents, aspiration of meconium in utero, blunt thoracic trauma involving lung, near-drowning, hyperoxia, irritant or toxicant inhalation, disseminated intravascular coagulation (DIC), and thoracic radiation. Other pathologies can indirectly lead to ALI; these include bacteremia (sepsis), hypovolemic shock, distant-site (non-thoracic) trauma, closed-space burn injury, and pancreatitis [9-14]. Ironically, clinical intervention for disease, including some of the aforementioned conditions, can also initiate the onset of ALI. Additionally, repeated transfusion, cardiopulmonary bypass, and ventilatory support have all been associated with development of ALI and ARDS.

Regardless of initiating insult, DAD is the most prevalent histopathological feature of ALI/ARDS and may be an indicator of prognosis [15,16]. The acute exudative phase of ALI/ARDS occurs within hours of the initiating injury event; DAD in this phase results from neutrophilic infiltrates which release enzymes such as elastase that further damage the epithelium and endothelium leading to increased permeability of the alveolar-capillary boundary and lung interstitial and parenchymal edema [17-21]. After several days, DAD is exacerbated to such a degree that denuding of alveolar basement membranes ensues, and cellular debris consisting of hyaline membranes, plasma...
treatment can reduce the mortality and morbidity associated with ALI because of their anti-inflammatory properties. Early trials using Pharmacological anti-inflammatory therapy in ALI or PMNs) [27]. Therefore, if the initial acute inflammatory response responds to danger signals in the lung by rapidly producing chemokines due to microvascular thrombosis and hypoxia-induced vasoconstriction [24,25]. Following these inflammatory pathological changes is a fibroproliferative phase occurring weeks after the initiating injury during which epithelial (alveolar type II) cells and fibroblasts propagate within the intra-alveolar exudates that accumulated during the acute phase. The fibroblasts subsequently differentiate into myofibroblasts, and extracellular matrix (ECM) proteins, predominantly collagens, are secreted within the alveolar space and accumulate throughout the parenchyma leading to marked fibrosis. Alveolar loss results from the increasing cellular mass and ECM deposition within the air space but may be exacerbated without prominent airspace occlusion if alveolar type II cells are damaged by ALI and, therefore, fail to provide sufficient surfactant to prevent alveolar collapse [14]. The lung vasculature also undergoes aberrant smooth muscle proliferation that leads to decreased vascular intraluminal diameter and associated pulmonary hypertension. Uncontrolled, the condition can progress to oblitative endarteritis (complete arteriolar obstruction), further hypoxic injury, and compromised right ventricular function.

Given the multiple etiologies of ALI/ARDS, the heterogeneity of clinical presentation, and co-morbidity associated with indirect ALI and lifestyle-associated risks (smoking, alcohol abuse, obesity, etc.), finding an appropriate course of therapeutic intervention is a substantial challenge. Ideally, treatment should be geared toward preventing the escalation of inflammatory processes at the early onset of disease before development of the devastating morphological changes that occur during the fibroproliferative phase of ARDS. Furthermore, treatments for late-stage disease must account for tissue remodeling and functional loss as a result of progressive lung fibrosis. Current treatment strategies for patients with ARDS/ALI involve general supportive measures combined with focused ventilatory strategies and palliative treatment of the underlying conditions [26]. There are no effective pharmacological therapies for ARDS. ARDS is characterized by an overwhelming inflammatory process followed by fibro-proliferative changes, therefore antinflammation has been a topic of interest for several years, and recent developments in immunomodulation therapy have generated new insights for treatment of diseases where inflammation is a central pathological feature. Resident macrophages are among the first cells to respond to danger signals in the lung by rapidly producing chemokines and cytokines that recruit polymorphonuclear leukocytes (neutrophils or PMNs) [27]. Therefore, if the initial acute inflammatory response of macrophages can be attenuated, the inflammation cascade may be dampened, thus contributing to the alleviation of ALI. This review will highlight current clinical therapies for ALI/ARDS with specific attention to controlling the root cause of morbidity in this disease -excessive inflammation- and novel pre-clinical cell-based approaches and gene therapy geared toward preventing long-term complications.

**Pharmacological anti-inflammatory therapy in ALI**

Corticosteroids have been investigated as a potential treatment for ALI because of their anti-inflammatory properties. Early trials using time-limited high-dose corticosteroids failed to demonstrate a survival benefit [28]. There is some evidence that low-dose corticosteroid treatment can reduce the mortality and morbidity associated with ALI [29]. However, controversy remains because other studies have provided conflicting data [30]. Other strategies to control inflammation and prevent ALI/ARDS have been proposed such as inhibition of thromboxane A2 synthesis [31], TNF blockers [32], neutrophil elastase inhibitors [33], and anti-oxidants [34]. However, most of these agents failed during clinical trials and did not provide protection to patients suffering from acute bacterial infections. Preclinical animal studies have shown promising results for reducing ALI-associated inflammation using anti-CD40 ligand (a mediator of proinflammatory cytokine production in pulmonary fibroblasts), and anti-IL-8 (a potent chemoattractant for PMNs) antibodies [35-37]. Schaefer et al. [38] showed that infusion of fish oil-based lipid emulsions reduced LPS-induced proinflammatory cytokines, alveolar leukocyte transmigration, and protein leakage in a murine ALI model. Another study demonstrated that administration of hesperidin down regulated the expression of pro-inflammatory cytokines and chemokines, reduced the infiltration of activated PMNs in the airways, decreased pulmonary edema, reduced nitrosative stress, and improved lung morphology in a murine ALI model [39]. A more lung-specific anti-inflammatory strategy is needed which can be used in combination with current physical and pharmacological therapies for ALI/ARDS.

**Stem cells and anti-inflammation: application to ALI/ARDS**

Mesenchymal stem cells (MSCs) and ALI: Stem cells are gaining increased attention as potential cell-based therapeutic agents for lung diseases. Mesenchymal stem cells (MSCs) are a heterogeneous subset of progenitor cells that have self-renewal and multilineage differentiation capacity [40-42]. In addition to their therapeutic potential for tissue regeneration, MSCs have been shown to possess potent immunomodulatory and immunosuppressive properties in several models [43,44]. MSCs can be isolated from many adult tissues (e.g. bone marrow, adipose, umbilical cord, and lung tissue) with high yield and can be expanded easily in vitro. MSCs are often considered to be hypoinmunogenic or immune privileged, since they express low levels of major histocompatibility complex (MHC) class I and II, and do not express of co-stimulatory molecules [45,46]. Furthermore, immunomodulation by MSCs is not MHC-restricted, making allogeneic treatment possible [47]. Thus, MSCs provide unique opportunities for developing novel treatments for a large array of inherited and acquired diseases. In 2008, the first clinical trial evaluating human mesenchymal stem cells (hMSCs) in a lung disease, chronic obstructive pulmonary disease (COPD), was initiated. Reports from the trial indicate that allogeneic hMSCs significantly decreased systemic inflammation in patients when compared to those receiving placebo, as determined by C-reactive protein. Although the pulmonary function in patients receiving hMSCs was not significantly improved compared to those receiving placebo despite the reduction in inflammation, the results indicate that hMSCs are safe in patients with compromised pulmonary function [46].

Whereas it was originally postulated that the greatest benefit of MSCs in lung repair may be their ability to reconstitute areas of damage by homing to sites of tissue injury, engrafting, and differentiating, it is generally accepted now that, given the low levels of engraftment, MSCs likely contribute to lung protection and repair via paracrine mechanisms [49,50]. An emerging body of data indicates that MSCs elicit immunomodulatory responses in different models of ALI [51-53]. Ortiz et al. [54,55] found that bone marrow-derived MSCs improved survival and dampened inflammation when delivered intravenously in a mouse bleomycin model of pulmonary fibrosis; later the same group presented evidence that the immunomodulatory...
effects of murine MSCs were mediated, at least in part, by their potent expression of interleukin-1 receptor antagonist (IL-1Ra) and its blockade of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and IL-1. Several groups have investigated the anti-inflammatory effects of MSCs in lung injury induced by intraperitoneal [56] or intrapulmonary [51,52] endotoxin exposure (Escherichia coli lipopolysaccharide, LPS). Xu et al. [56] found that intravenous delivery of syngeneic bone marrow-derived MSCs immediately after intraperitoneal challenge with endotoxin attenuated neutrophil infiltration in the lung and decreased Th1-related cytokines while Th2 cytokines were unchanged. Gupta et al. [51] reported that intrabronchial delivery of mouse bone marrow-derived MSCs to mice 4 hours after intratracheal endotoxin resulted in decreased lung edema and improved survival. This study also showed that bronchoalveolar lavage and plasma from endotoxin-challenged mice treated with MSCs had lower concentrations of TNF-α and macrophage inflammatory protein-2 (MIP-2) and higher concentrations of the anti-inflammatory cytokine IL-10 compared with untreated mice. In a recent publication, we reported that administration of human bone marrow-derived MSCs by oropharyngeal aspiration (OA) to immunocompetent mice 4 hours after intratracheal endotoxin significantly reduced the expression of pro-inflammatory cytokines, neutrophil counts, total protein in bronchoalveolar lavage, and pulmonary edema [52]. Our study demonstrated that xenogeneic bone marrow-derived MSCs recapitulated the observed immunomodulatory effects of syngeneic MSCs [52]. Most recently, lung-derived MSCs (LMSC) isolated from tissue homogenates were investigated for potential therapeutic benefits in ALI [57-59]. Hoffman et al. [58] found that LMSC contribute to repair of elastase-injured lungs (a model of emphysema) to a similar degree as bone marrow-derived MSCs (BMSC); however the LMSC showed a propensity toward extended lung retention time relative to BMSC [59].

Little is known about the mechanisms by which MSCs modulate lung inflammation and repair. The anti-inflammatory effects of mouse MSCs in the lung have been associated with MSC secretion of interleukin 1 receptor antagonist (IL1Ra) [54] and TGF-β1 [60]. TNF-α-induced protein 6 (TNFAP6/TSG-6) is emerging as a key factor in the immunosuppressive properties of MSCs [61-63]. TSG-6 is a 35 kDa, secreted protein produced by many cell types in response to TNF-α and IL-1β [64,65]. The anti-inflammatory properties of TSG-6 have been demonstrated in several different models including arthritis, myocardial infarction, and chemical injury to the cornea [62-65]. TSG-6 inhibits the inflammatory network of proteases by increasing the inhibitory activity of inter-alpha inhibitor and bikunin [66]. TSG-6 also specifically binds and sequesters hyaluronan fragments and has been shown to be a potent inhibitor of neutrophil activation and migration, as well as tissue remodeling [67], through upregulation of COX-2 and prostaglandin D2 expression [67,68]. We recently demonstrated that MSCs secrete high levels of TSG-6 in response to lung injury in vivo [52]. Using RNA interference we found that expression of TSG-6 is largely responsible for the anti-inflammatory effects of MSCs, including reduction in inflammatory cell infiltrates, in the endotoxin model of lung injury that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduces much of the model of lung injury and that intratracheal or intravenous delivery of recombinant human TSG-6 (rhTSG-6) reproduc...
phagocytic activity, *in vivo*. MSC treatment increased the survival rate of CLP-injured mice in the absence and presence of antibiotic therapy; these data suggest that MSC-mediated attenuation of ALI may be due to a combination of immunomodulatory and anti-microbial effects. It has also been recently reported that, in mouse models of *E. coli*-induced pneumonia, intratracheally-delivered human bone marrow- and umbilical cord-derived MSCs promoted bacterial clearance and attenuated ALI, respectively [75, 76].

Krasnodembskaya et al. [75] reported that human cathelicidin antimicrobial peptide-18 (hCAP-18/LL-37) mediates the direct inhibition of bacterial growth by human MSCs. LL-37 is an hCAP-18 cleavage product of 4 kDa and is a pro-inflammatory peptide that has been linked to prevention of bacterial infections and host defense against microbes, particularly in the lung where it is expressed by lung epithelial cells and submucosal glands [77, 78]. LL-37 is known to be expressed by PMNs, keratinocytes, and epithelial cells and can function as a chemotactic signal for neutrophils, monocytes, mast cells, and T-cells [79]. Additionally, LL-37 binds and neutralizes LPS, stimulates degranulation of mast cells, modifies transcriptional activity in macrophages, and participates in wound healing by promoting vascularization and re-epithelialization of healing skin [77, 80]. It has been shown that LL-37 administration can protect against *E. coli* or CLP-induced sepsis in rats [81]. Interestingly, LL-37 has been shown to promote recruitment of MSCs via the formyl peptide receptor (FPLR1) and alter the immunomodulatory properties of MSCs, perhaps by acting, in part, as a potential ligand for the toll-like receptor-4 (TLR4) [82, 83]. In addition to LL-37, the tryptophan catabolizing enzyme indoleamine 2,3-dioxygenase (IDO) has been linked to the antimicrobial activity of human MSCs, but not murine MSCs which do not express IDO [84]. IDO-mediated antimicrobial activity of human MSCs is not limited to bacteria but is also effective against protozoan parasites and viruses [84]. It is apparent that MSCs are both directly and indirectly involved in antimicrobial activity and that this ability is applicable to treating microbial complications in the lung potentially using either allogeneic or autologous cells.

**Gene-modified MSCs**

Early studies in adult stem cell biology suggested that MSCs could be genetically altered to enhance their homing to injured sites, particularly toward sites of infection; however, there has been much difficulty in achieving engraftment rates substantial enough to achieve therapeutic benefit [49, 85-87]. For this reason, the use of gene modification in stem cells has somewhat shifted in focus toward using the cells as vehicles for delivering therapeutic agents. In light of the numerous proteins and pathways involved in lung protective mechanisms that have been identified, many gene modification strategies have been developed to enhance the ability of MSCs to combat lung injury. Several of these strategies have targeted inflammatory processes.

**Keratinocyte growth factor (KGF):** KGF has been extensively studied as a key element in lung development, growth, and repair [88-91]. After lung injury, KGF stimulates the proliferation of alveolar epithelial cells and helps to facilitate alveolar epithelial fluid movement [92-94]. When used as a prophylactic measure, treatment with KGF has been shown to lessen the degree of radiation- and bleomycin-induced pulmonary fibrosis and improve survival [95]. Haddad et al. [96] showed that delivery of exogenous KGF preceding bone marrow transplant in a rat model of idiopathic pneumonia suppressed T-cell-mediated macrophage activation and release of pro-inflammatory cytokines. In a novel approach to delivery of KGF to the lung, Aguilar et al. [97] transduced bone marrow-derived MSCs and hematopoietic stem cells (HSCs) with a lentiviral vector carrying an inducible (Tet-On) KGF expression cassette; they showed that both MSC and HSC cell constructs were protective against bleomycin-induced fibrosis, but KGF-expressing HSCs, in particular, greatly attenuated histological damage typically associated with this model. This work supports the use of cell-based vehicles for delivery of therapeutic agents but also highlights the important fact that cell-type specificity is equally important when designing these types of strategies.

**Angiopoietin-1 (ANGPT-1):** ANGPT-1 ligand and its endothelial-specific receptor tyrosine kinase, Tie2, initiate pathways involved in angiogenesis and maturation of neovascularature [98]. ANGPT-1 has also been shown to be a protective factor which promotes the integrity of the vasculature by preventing endothelial permeability and apoptosis [99-101]. Leukocyte adhesion to the endothelium is suppressed by ANGPT-1, as is the expression of endothelial cell-surface adhesion molecules; moreover, in an experimental model of ALI, neutrophil infiltration, capillary leakage, and lung edema were associated with a down-regulation of ANGPT-1 [102-104]. McCarter et al. [105] employed a skin fibroblast-based cellular ANGPT-1 delivery system in a rat endotoxin model of ALI and showed marked improvement in lung inflammation and injury. Xu et al. [106] were the first to use MSCs as vehicles for delivering ANGPT-1 in an animal (mouse) model of ALI. In their experiments, either MSC or ANGPT-1 alone showed substantial reduction in lung neutrophil infiltrates or TNF-α expression, but MSCs expressing ANGPT-1 significantly reduced these parameters even further, implying that there is a synergistic effect of MSC and ANGPT-1 in the context of preventing ALI-induced inflammation.

**Inhibition of CCL2:** The monocyte chemotactic protein-1 (MCP-1), also referred to as CCL2, is a pro-inflammatory cytokine that recruits monocytes, T-cells, dendritic cells, and fibrocytes to areas of inflammation via CCR2 receptors [107]. Elevated levels of CCL2 are associated with heightened disease severity in patients with ALI/ARDS, and CCL2 has been implicated in the development of lung fibrosis in gene knockout mouse models [108-113]. Mutagenesis analysis uncovered a deletion mutant of CCL2, 7ND, that functions as a dominant negative inhibitor of CCL2 [114, 115]. In a very recent report, Saito et al. [116] expressed the 7ND mutant in adipose-derived MSCs from C57BL/6N mice using a lentiviral vector carrying the construct to stably transfect the cells. The CCL2-inhibited MSCs were then delivered intravenously to mice with bleomycin-induced pulmonary fibrosis. Their results demonstrated that CCL2 knockdown MSCs substantially reduced cell infiltrates in the lung, facilitated maintenance of weight, reduced plasma IL-6 and IL-1β, and improved survival relative to sham-treated controls.

Taken together, these cell-based techniques provide excellent evidence that gene-modified stem cells have the potential to function as novel therapeutic agents in the fight against inflammation in ALI/ARDS. Further investigation is warranted, however, to test the efficiency and safety of individual approaches as well as possible synergistic effects of combined methods.

**Summary/Conclusions**

To improve outcome in patients suffering from ALI/ARDS, it is imperative to prevent permanent lung damage (i.e. fibrosis) from occurring by early intervention in disease progression. Since inflammation is the initiating event through which the morbidity of ALI/ARDS develops, fighting inflammation early on is the best possible way to quench the onset of lung failure. Currently, stem-cell based therapy holds great promise for providing this necessary clinical intervention.
Early observations of engraftment of mesenchymal stem cells in the lung was a promising development in the fields of stem cell biology and lung disease; however, there has been no development towards improving the disappointingly low number of cells which can actually accomplish this feat. The discovery that stem cells have endogenous immunomodulatory and anti-microbial capabilities is sparking a robust push in the research community to uncover the mechanisms by which the cells can potentially protect against infection and inflammation and develop novel therapeutic strategies using stem cells. While there is an increasing amount of data suggesting that a large portion of the immunosuppressive effect of stem cells is mediated through paracrine mechanisms, more work is needed to elucidate the molecular components of this effect and the pathways through which they act. Identification of these paracrine factors and pathways will likely suggest strategies to improve the therapeutic potential of stem cells for treating ALI/ARDS and guide the development of cell-free therapies that have the potential to maintain a ready supply of therapeutic agents without the need to culture stem cells on-demand. In addition, the combination of cell and gene therapy that has been demonstrated to provide additive therapeutic benefits significantly expands the potential application of stem cell based therapy for ALI/ARDS.

Preclinical animal models of ALI/ARDS treated with cell-based therapies have been promising; however there are significant challenges that must be overcome before human clinical trials of stem-cell therapy for ALI/ARDS can begin. First, more research is needed to identify the optimal stem cell source, dose, route of delivery and timing of stem cell delivery in order to achieve the most efficient and effective treatment. Second, it is critical to understand the mechanisms integral to the therapeutic effects of stem cells in ALI/ARDS so that the human physiological response can be accurately predicted. Third, the lack of proper standardization and characterization of cell preparations is a serious impediment to the correlation of results from preclinical and early clinical studies. Finally, wide-ranging toxicology studies are required to increase our confidence in the safety of cellular therapies. The lack of human models of ALI has been a major limitation in overcoming these challenges. Recently, Lee et al. [117] employing an in vitro model of ALI/ARDS that incorporated an ex vivo human lung injured by endotoxin while being ventilated and perfused with human blood, demonstrated that human MSCs injected into the pulmonary circulation improved the clearance of fluid from the alveolar spaces. Although this model is limited by the short-term viability of the explanted lung and does not recapitulate the full inflammatory process, it provides valuable evidence that stem cell therapies hold great promise in treating human ALI/ARDS.

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