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Mesenchymal stem cells – a promising therapy for Acute Respiratory Distress Syndrome

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Abstract

Acute Respiratory Distress Syndrome (ARDS) constitutes a spectrum of severe acute respiratory failure in response to a variety of inciting stimuli that is the leading cause of death and disability in the critically ill. Despite decades of research, there are no therapies for ARDS, and management remains supportive. A growing understanding of the complexity of the pathophysiology of ARDS, coupled with advances in stem cell biology, has lead to a renewed interest in the therapeutic potential of mesenchymal stem cells for ARDS. Recent evidence suggests that mesenchymal stem cells can modulate the immune response to reduce injury and also increase resistance to infection, while also facilitating regeneration and repair of the injured lung. This unique combination of effects has generated considerable excitement. We review the biological characteristics of mesenchymal stem cells that underlie their therapeutic potential for ARDS. We also summarise existing pre-clinical evidence, evaluate the potential and pitfalls of using mesenchymal stem cells for treatment, and examine the likely future directions for mesenchymal stem cells in ARDS.

Introduction

Acute Respiratory Distress Syndrome (ARDS) constitutes a spectrum of increasingly severe acute respiratory failure. It results from multiple causes (such as infection, trauma and major surgery), and is the leading cause of death and disability in the critically ill. ARDS is characterised clinically by an acute onset, severe hypoxia, stiff lungs, and the presence of an inflammatory pulmonary oedema [1]. It is a devastating disease process and is the leading cause of death and disability in critically ill adults and children [2]. In the US alone, there are 200,000 new cases annually, with a mortality rate of 40%, comparable to that seen from HIV and breast cancer [3]. The outlook for survivors of ARDS is also poor with a high incidence of post-discharge cognitive impairment, depression and muscle weakness, while the financial burden of ARDS on society is considerable [4-5].

Despite decades of research, there are no therapies for ARDS, and management remains supportive. Probable reasons for the failure to find a successful therapy include deficits in our understanding of the disease, coupled with a focus on strategies that inhibit one aspect of a multi-faceted injury process. More complex strategies, aimed at reducing early injury while maintaining the ability of the host to respond to insults, and/or enhance repair following injury, are needed. These insights have led, in part, to a renewed interest in the therapeutic potential of mesenchymal stem cells. We will review the biological characteristics of mesenchymal stem cells that underlie their therapeutic potential for ARDS. We will also summarise existing pre-clinical evidence, evaluate the potential and pitfalls of using mesenchymal stem cells, and examine the likely future directions for these cells in ARDS.

ARDS – a 'therapeutic' failure

Despite being a focus of ongoing intensive research efforts over four decades, there are no effective pharmacologic treatments for ARDS. Many therapies have been evaluated without success, including anti-oxidants [6], surfactant [7], nitric oxide [8], corticosteroids [9-11], immunomodulatory agents [12-13], and most recently beta-2 agonists [14]. Consequently, advances in the management of this devastating disease have relied on improvements in supportive measures, such as 'protective' mechanical ventilation strategies [15], restrictive intravenous fluid management approaches [16], and prone positioning of severely hypoxaemic patients [17-18]. These and other improvements in supportive care have decreased mortality from ARDS over the last decade [19]. Nevertheless, the failure of conventional pharmacologic approaches for ARDS underlines the need to consider alternative 'non-conventional' therapeutic approaches.

Why is it so difficult to find a therapy for ARDS?

ARDS is a challenging disease to study let alone treat. It is a syndrome identified by the presence of clinical parameters, including hypoxia, and bilateral infiltrates on chest x-ray in the absence of left atrial hypertension (to rule out cardiac failure). This leads to difficulties in diagnosis. The patient population is heterogeneous in terms of age, general health status, the cause of their ARDS, and whether other organs are also damaged as part of their critical illness. It is even uncertain if ARDS is a single disease or a collection of different disease processes with a similar phenotype. While about 40% of patients with ARDS die, hypoxia is usually not the reason for their deaths, with patients frequently dying from other complications of their critical illness, such as sepsis, shock, and failure of other organs [20].

More fundamentally, our understanding of the pathogenesis of ARDS remains limited. The disease progresses through relatively ill-defined stages, from the early acute 'hyper-inflammatory' stage to a later 'fibrotic' phase. The acute phase is characterised by a complex series of inter-related events, which may vary in response to the initial insult (e.g. bacteria, trauma, major surgery), and involves pro- and anti-inflammatory cytokines (e.g. TNF-α, IL-6, IL-10) and effector cells (e.g. neutrophils, macrophages). This inflammatory milieu increases alveolar-capillary permeability resulting in alveolar oedema and leukocyte infiltration, impaired surfactant function (normally it prevents alveolar collapse, and protects the lung from injury) with alveolar collapse, all resulting in impaired gas exchange. Patients surviving this acute phase may progress to a later fibrotic 'repair' phase, which can result in long term scarring and damage to the lungs. This phase may be complicated by impaired immunity, susceptibility to infections, muscle weakness and a need for prolonged respiratory support. However, the transition between these phases is poorly defined, and there is evidence of fibrosis and immune dysfunction from the earliest stage of ARDS [1].

Given these complexities, it is perhaps not surprising that strategies targeted at one aspect of the disease process have been unsuccessful. This has led to a shift in thinking towards more complex therapeutic approaches, aimed at reducing early injury while maintaining host immune competence, while facilitating (or at least not inhibiting) repair following the acute injury phase. Could mesenchymal stem cells fit this new therapeutic paradigm?

Mesenchymal stem cells and why they might be useful in ARDS

Mesenchymal stem cells are multipotent cells derived from adult tissues that are capable of self-renewal and differentiation into chondrocytes, osteocytes and adipocytes. They were first isolated from the bone marrow in 1976 by Friedenstein and colleagues [21] and have subsequently been isolated from many other tissues, including fat, muscle, dermis, placenta and lung. The derivation of mesenchymal stem cells from adult tissues, their relative ease of isolation and enormous expansion potential in culture make them attractive therapeutic candidates [22]. They are immunologically well tolerated [23], and can be transplanted from one individual to another individual of the same species, an important advantage for acute illnesses such as ARDS.

Mesenchymal stem cells are used in clinical trials for a variety of diseases, including diabetes, myocardial infarction, Crohn's disease, graft-versus-host disease, osteogenesis imperfecta, multiple sclerosis, and COPD (chronic pulmonary obstructive disease), attesting to their safety in humans. Interestingly, a recent study demonstrated that mesenchymal stem cells improved lung function in patients with myocardial infarction [24]. Also, a growing body of pre-clinical data shows that mesenchymal stem cells reduce lung injury caused by endotoxin [25-26], pneumonia [27] and systemic sepsis [28]. Recently, the clinical potential of mesenchymal stem cells for ARDS has been considerably enhanced by a study demonstrating that human mesenchymal stem cells can reduce endotoxin-induced injury in explanted human lungs [29]. All these findings offer considerable hope that mesenchymal stem cells may be a therapy for ARDS.

Do mesenchymal stem cells act by differentiating into lung cells?

Early studies suggested that mesenchymal stem cells might differentiate into lung epithelial cells, directly

Table 1: Postulated mechanisms of action of mesenchymal stem cells in pre-clinical models of ARDS

Study	Lung injury model	MSC delivery route	Postulated mechanism of action
Ortiz et al 2007 [33]	Murine IT Bleomycin induced ALI	IV delivery immediately post injury	• Secretion of IL-1 receptor antagonist • Inhibition of TNF-α production by macrophage and IL-1α dependent T cell line
Xu et al 2007[51]	Murine IP LPS induced ALI	IV delivery 1h and 24h post injury	• Production of soluble factors by mesenchymal stem cells that promote an anti-inflammatory cytokine milieu • Paracrine effect was enhanced by cell to cell contact • Production of chemoattractants for mesenchymal stem cells by lung cells
Gupta et al 2007 [25]	Murine IT LPS induced ALI	IT delivery 4h and 24h post injury	• Paracrine effect by mesenchymal stem cells in down-regulating the inflammatory response • Engraftment rate <5%
Lee et al 2009 [29]	Endotoxin induced ALI in ex-vivo perfused human lung	IT 1/24h post injury	• Secretion of KGF by mesenchymal stem cells resulting in improved endothelial permeability and restoration of alveolar epithelium fluid transport
Nemeth et al 2009 [28]	Murine CLP induced ALI	IV 24h pre- / 1h post-injury	• Prostaglandin E2 dependent reprogramming of macrophage to increase production of IL-10
Mei et al 2010 [35]	Murine CLP induced ALI	IV 6/24h post-injury	• Modification of inflammatory gene transcriptional activity • Down regulation of the acute inflammatory response and upregulation of pathways relevant to phagocytosis and bacterial clearance
Krasnodembskaya et al 2010 [27]	E.coli pneumonia induced ALI	IT 4/24h post-injury	• Secretion of the anti-microbial peptide LL-37 resulting in increased bacterial clearance
Danchuk et al 2011 [26]	Murine IT Endotoxin induced ALI	IV, OA and IP *human* mesenchymal stem cells	• Secretion of TSG-6 by mesenchymal stem cells resulting in reduced neutrophil recruitment and activation • Secretion of KGF

***Abbreviations*:** IV,intravenous; IP, intra-peritoneal; LPS, lipopolysaccharide; IT, intra-tracheal; KGF, keratinocyte growth factor; CLP, caecal ligation and puncture; OA, oropharyngeal aspiration; TSG-6, tumour necrosis factor alpha-induced protein 6; MSC, mesenchymal stem cell.

replacing the damaged and destroyed cells in the alveoli in ARDS. Krause *et al*. found that a single bone marrow-derived hematopoietic stem cell could give rise to cells of different organs, including the lung, and demonstrated that up to 20% of lung alveolar cells were derived from this single bone marrow stem cell [30]. Kotton *et al*. demonstrated that bone marrow derived cells engrafted into pulmonary epithelium and exhibited characteristics specific to lung epithelial cells [31]. Suratt and colleagues found significant rates of engraftment of transplanted hematopoietic stem cells in lung specimens from female allogeneic hematopoietic stem cell transplant recipients that received stem cells from male donors [32]. However, more recent studies demonstrate that, while mesenchymal stem cells reduce experimental lung injury, engraftment rates are low [25,33-34], suggesting that direct engraftment of mesenchymal stem cells in the lung is unlikely to be of therapeutic significance (Table 1).

How might mesenchymal stem cells benefit patients with ARDS?

While the precise mechanisms of action of mesenchymal stem cells remain unclear, a number of important insights have emerged.

Firstly, mesenchymal stem cells appear to modulate the immune response to lung injury [25,34-35]. In contrast to classic 'anti-inflammatory' strategies, mesenchymal stem cells appear to decrease host damage arising from the inflammatory response while enhancing host resistance to sepsis. Mesenchymal stem cells decrease pro-inflammatory cytokine expression [25-26], and secrete anti-inflammatory agents, including interleukin 1 receptor antagonist, interleukin-10, and prostaglandin E2 [28]. Mesenchymal stem cells also reduce lung neutrophil recruitment and modulate immune effector cell activity.

Secondly, mesenchymal stem cells may augment the host immune response to sepsis. Mesenchymal stem cells reduced systemic sepsis induced by lung injury in part again by secreting prostaglandin-E2, which stimulated host macrophage IL-10 secretion [28]. Mesenchymal stem cells also secrete anti-microbial peptides such as LL-37 (which may directly retard bacterial growth [27]) and tumour-necrosis-factor-alpha-induced-protein-6. *In vivo*, mesenchymal stem cells increased bacterial clearance and enhanced host cell phagocytosis in septic mice [35].

Thirdly, mesenchymal stem cells appear to aid the regenerative response following injury, in part via the secretion of cytoprotective agents [26,29,34,36]. mesenchymal stem cell secretion of angiopoeitin and

keratinocyte growth factor restores alveolar epithelial and endothelial permeability and enhances resolution of ARDS in pre-clinical models [26,29,34,36].

These diverse mechanisms of action of mesenchymal stem cells, whereby they may favourably modulate the immune response to reduce inflammatory injury while maintaining immunocompetence, and facilitating recovery and repair following injury, make them attractive therapeutic candidates for ARDS.

What are the hurdles to clinical translation of mesenchymal stem cells for ARDS?

A number of hurdles, however, remain before we can start using mesenchymal stem cells in the clinic for patients with ARDS. The optimal route of administration of mesenchymal stem cells is not known, with various studies supporting the intravenous [28], intra-tracheal [25,29] and intra-peritoneal [26] administration routes. The optimal dosage regimen for mesenchymal stem cells is also unclear. Specifically, the lower effective dose range and the efficacy of single versus multiple dose regimens are not known. In studies to date, the mesenchymal stem cells have generally been given either prior to the injury or immediately after the start of the injury process. This does not reflect the clinical setting where the disease is generally in progress for several days before treatment is possible. Encouragingly, mesenchymal stem cells have recently been demonstrated to enhance resolution and repair [37] following severe ventilation-induced lung injury [38]. This suggests that mesenchymal stem cells may have true 'therapeutic' potential.

Another problem is that pre-clinical studies to date have used relatively poorly defined, heterogeneous mesenchymal stem cells, which raises a number of issues. Firstly, distinct sub-populations of mesenchymal stem cells vary in terms of their differentiation potential and their ability to engraft *in vivo* [39-40]. This raises the possibility that specific mesenchymal stem cell subpopulations may have differing efficacies for ARDS. To complicate matters further, unlike haematopoietic stem cells, mesenchymal stem cells are not defined by a single marker and the markers they express are not uniquely expressed by stem cells [40-41]. While a set of minimal criteria for defining mesenchymal stem cells has been developed [42], there remains a lack of standardised protocols for isolation and characterisation of mesenchymal stem cells. Furthermore, there is no validated method of measuring mesenchymal stem cell bioactivity *in vivo* [43].

There are also deficits in our knowledge of the mechanisms of action of mesenchymal stem cells. One specific concern is their effects on host immunity. Recent experimental work showing that mesenchymal stem cells can elicit a memory T-cell response in mice has called into question their characterisation as 'immuno-privileged cells' that can be transferred without immunosuppression of recipients [44-45]. The picture is further confounded by the fact that most experimental experience in acute lung injury (ALI) is with murine and rodent mesenchymal stem cells, which differ from human mesenchymal stem cells on many grounds, including immunosuppression and genomic stability [26,46-47]. Reassuringly, however, clinical trials of mesenchymal stem cells in human subjects, to date, have not reported adverse immune side effects [48-49]. Nevertheless, caution is required in relation to immune-modulating therapy in the aftermath of the anti-CD28 monoclonal antibody trial [50], particularly given the very limited clinical experience with mesenchymal stem cells in critically ill patients to date [24].

Conclusions

Mesenchymal stem cells are a promising therapy for patients suffering from ARDS. Gaps remain in our knowledge regarding the mechanisms of action of mesenchymal stem cells and optimal mesenchymal stem cell administration and dosage regimens, and their safety in critically ill patients. However, the evidence that mesenchymal stem cells can favourably modulate the immune response to reduce lung injury, while maintaining host immune-competence and also facilitating lung regeneration and repair suggests that they fulfil the requirement for more complex therapeutic approaches to ARDS. We anticipate that these remaining deficits in understanding will be addressed in the future and that progression from pre-clinical studies to clinical trials in patients with ARDS is likely in the near future.

Abbreviations

ALI, Acute Lung Injury; ARDS, Acute Respiratory Distress Syndrome; CD-28, Cluster of Differentiation 28; HIV, Human immunodeficiency virus; IL, interleukin; TNF-α, tumour necrosis factor alpha.

Competing interests

The authors declare that they have no competing interests.

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