Stem/Progenitor Cell Therapy in Acute Lung Injury/Acute Respiratory Distress Syndrome

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Acute lung injury (ALI) is diffuse but heterogeneous lung parenchyma changes associated with increased capillary leakage and non-cardiogenic pulmonary edema, manifested with severe hypoxemia. Acute respiratory distress syndrome (ARDS) is a more severe condition first established in a case series by Ashbaugh et al. [1] based upon 5 clinical features; (1) the presence of a defined risk; (2) severe hypoxemia despite administration of supplemental oxygen; (3) bilateral pulmonary infiltrates; (4) reduced lung compliance; (5) the absence of congestive heart failure. The new Definition of ARDS was recently announced at Berlin which includes acute lung injury as mild form of ARDS [2].

The reported incidence of ARDS in the United States is approximately 58/100000 [3]. A multi-centered clinical study among ICU patients in Shanghai, China found an ARDS incidence of 2% [4]. Global ARDS mortality rate remains significantly constant and fluctuates between 40% - 50% [5]. Such high morbidity and mortality boosted ALI/ARDS research yet scarcely resulted in satisfactory prescriptions: beta-2 agonists [6], activated protein C (APC) [7], antioxidants [8], surfactant [9] and vasoactive drugs [10-15] all yielded limited effect among ALI/ARDS patients even given substantial benefit in animal models. Except small tidal volume ventilation strategy, such failures on pharmacology led to emphasis in repair, host immunity maintenance and lung injury suppression of therapeutic research instead. Stem/progenitor cell therapy and cell-based gene therapy are currently under investigation for their potential therapeutic effects.

Stem cells present properties of self-renewal and potency, their subdivision into adult and embryonic stem cells relevant to plasticity. Mesenchymal stem cells (MSCs) are adult stem cells which gain particular interest because of their ease to obtain and isolate. They derive from different human tissues like bone marrow; adhere to plastic under standard tissue culture conditions; express certain cell surface markers (CD105, CD90 and CD73) instead of others (CD34, CD14 or C11b) and differentiate into mesenchymal lineages like osteoblasts, adipocytes and chondroblasts under in vitro conditions [16]. MSCs have been implied clinically in lung injury induced by bleomycin [17] and endotoxin [18,19]. Their effect may be explained by mechanisms including engraftment and paracrine secretion, immunomodulation, alveolar fluid clearance and lung endothelial permeability [20]. Though further investigation is essential, MSC engraftment was supported by expression of Clara cell secretory protein (CCSP) [21-23] or lung epithelial markers [20] in cultured MSCs. Duality of immunosuppression and immunostimulation has been implied in MSCs via inflammatory mediator release [24,25] and protection over neutrophil apoptosis, degranulation and functions [26]. Paracrine secretion of growth factors by MSCs were also verified in alterations of endothelial and epithelial responses against injury [24,27-29]. For example, keratinocyte growth factor (KGF) secretion was associated with alveolar fluid clearance in ex vivo perfused human lung through increased trafficking of sodium transport proteins to the alveolar surface [30-32]. MSC-secreted hepatocyte growth factor (HGF) and KGF were also suggested in integrity maintenance of the lung microvascular endothelium [33,34].

Progenitor cells resemble parent stem cells but are more specific in target cell differentiation. Circulating endothelial progenitor cells (EPCs) differentiate into mature endothelial cells and are readily mobilized from bone marrow to peripheral circulation for endothelial repair in response to cytokines, growth factors, ischemic conditions and drugs like statins [35]. EPCs were also verified to alleviate ALI in rabbit models through (i) suppressed polymorphonuclear cell (PMN) infiltration in lung parenchyma which reduced inflammation; (ii) enhanced neovascularization and vasculogenesis which facilitated pulmonary artery and alveolar-capillary membrane regressions [36-39]. Further, increased number of EPCs colonies in ALI patients was associated with higher overall survival [40]. To summarize, EPCs serve potential therapeutic effect over ALI/ARDS.

Advancements in ALI/ARDS research acknowledged certain genes relevant to its pathogenesis and development. Genes coding for endothelial nitric oxide synthase (eNOS), inhibitory kappa B, KGF and angiopoietin-1 (Angpt1) have been implicated for their therapeutic significance [41]. Yet, gene therapy delivered by viral vectors was associated with risks of tumorigenesis and host immune responses so alternatives like stem/progenitor cells were suggested to replace conventional vectors. Indeed, retrovirally transduced bone-marrow-derived stem cells were seen to generate up to 20% lung epithelial cells [42] while MSCs transfection with Ang-1 yielded more favorable therapeutic effect over lipopolysaccharide (LPS)-induced ALI murine models. EPCs transfected with eNOS were also found to be more effective than EPCs alone in treating pulmonary hypertension [43], implying their clinical significance in prevention/treatment of pulmonary hypertension related to ALI/ARDS. Indeed, cell-based gene therapy overcame short protein half-life and improved efficiency of targeted treatment thus it might be more useful than cell or gene therapy alone.

Past investigation in prescriptions for ALI/ARDS proved to be a failure because it concentrated on particular aspects but not the complex nature of the disease. At present, more diversifying approaches including stem/progenitor cell therapy and cell-based gene therapy are vividly studied in hope to establish effective and promising therapy for ALI/ARDS.

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References


