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Review article

Therapeutic potential of mesenchymal stem cells for pulmonary complications associated with preterm birth

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ABSTRACT

Preterm infants frequently suffer from pulmonary complications resulting in significant morbidity and mortality. Physiological and structural lung immaturity impairs perinatal lung transition to air breathing resulting in respiratory distress. Mechanical ventilation and oxygen supplementation ensure sufficient oxygen supply but enhance inflammatory processes which might lead to the establishment of a chronic lung disease called bronchopulmonary dysplasia (BPD). Current therapeutic options to prevent or treat BPD are limited and have salient side effects, highlighting the need for new therapeutic approaches. Mesenchymal stem cells (MSCs) have demonstrated therapeutic potential in animal models of BPD. This review focuses on MSC-based therapeutic approaches to treat pulmonary complications and critically compares results obtained in BPD models. Thereby bottlenecks in the translational systems are identified that are preventing progress in combating BPD. Notably, current animal models closely resemble the so-called "old" BPD with profound inflammation and injury, whereas clinical improvements shifted disease pathology towards a "new" BPD in which arrest of lung maturation predominates. Future studies need to evaluate the utility of MSC-based therapies in animal models resembling the "new" BPD though promising *in vitro* evidence suggests that MSCs do possess the potential to stimulate lung maturation. Furthermore, we address the mode-of-action of MSC-based therapies with regard to lung development and inflammation/fibrosis. Their therapeutic efficacy is mainly attributed to an enhancement of regeneration and immunomodulation due to paracrine effects. In addition, we discuss current improvement strategies by genetic modifications or precondition of MSCs to enhance their therapeutic efficacy which could also prove beneficial for BPD therapies.

Contents

Abbreviations: AF, amniotic fluid; AFC, alveolar fluid clearance; Ang-1, angiopoietin-1; ATII, alveolar type II (cells); BM, bone Marrow; BPD, bronchopulmonary Dysplasia; CFTR, cystic Fibrosis transmembrane conductance regulator; CCSP, Clara cell secretory protein; EGF, epidermal growth factor; ENaC, epithelial Na^+ channel; HGF, hepatocyte growth factor; IDO, indoleamine 2,3 dioxygenase; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; INF, interferon; KGF, keratinocyte growth factor; LPS, lipopolysaccharide; MHC, major histocompatibility complex; MSCs, mesenchymal stem cells; PGE_2, prostaglandin E_2; RDS, neonatal respiratory distress syndrome; SMA, smooth muscle actin; SP, surfactant protein; TGF, transforming growth factor; TNF, tumor necrosis factor; TSG-6, tumor necrosis factor-α-induced protein 6; UC, umbilical cord matrix; UCB, umbilical cord blood; VEGF, vascular endothelial growth factor.

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1. Pulmonary complications associated with preterm birth

Respiratory failure due to physiological and structural lung immaturity is a common morbidity associated with preterm birth. During fetal development the lung is filled with fluid which is actively secreted by lung epithelial cells to promote lung growth (Harding and Hooper, 1996). Prior to birth the lung switches from fluid secretion to absorption to enable air breathing. Mature alveolar epithelial cells achieve this alveolar fluid clearance (AFC) by unidirectional Na^+ transport through epithelial Na^+ channels (ENaC) and the Na,K-ATPase creating a driving force for fluid absorption (Fig. 1). Furthermore, mature alveolar type II (ATII) cells secrete surfactant into the lung lumen where it reduces lung collapse during end exhalation by lowering the surface tension within terminal airways and alveoli (Walsh et al., 2013). Surfactant consists of phospholipids, neutral lipids and proteins forming a film between the terminal airways/alveolar surfaces and the alveolar gas. In addition, surfactant enhances mucociliary clearance and reduces lung inflammation (Walsh et al., 2013). Impaired AFC due to insufficient expression of Na^+ channels (O'Brodovich, 1996), and surfactant deficiency as well as structural lung immaturity with low alveolar numbers lead to fluid accumulation and alveolar instability, which impair lung function and gas exchange.

Incidence of neonatal respiratory distress syndrome (RDS) is inversely correlated with gestational age resulting in a RDS risk of more than 50% for infants born at less than 30 weeks of gestation and weighing less than 1000 g (Ramanathan, 2006). Current therapeutic options include surfactant replacement therapy to compensate surfactant deficiency and antenatal glucocorticoid treatment, both of which have been shown to improve respiratory outcome. Antenatal glucocorticoids accelerate late-gestation lung maturation in low doses by enhancing surfactant synthesis, increasing the volume density of ATII cells and upregulating AFC (Ballard et al., 1997; Folkesson et al., 2000; Snyder et al., 1992). It is routinely administered in women at risk of preterm birth to improve perinatal survival and lung function (Roberts and Dalziel, 2006). Glucocorticoids are also prescribed postnatally to improve lung function and weaning from mechanical ventilation, however, they have been shown to decrease alveolar crest formation in animal experiments (Tschanz et al., 1995), and may thus worsen alveolar simplification. Furthermore, postnatal glucocorticoid administration has been associated with severe long term neurodevelopmental side effects (Yeh et al., 2004), and must be viewed as a double-edged sword.

Despite these clinical interventions, mechanical ventilation and oxygen supplementation are often required to ensure sufficient oxygen supply. However, the lung lacks antioxidant capacity and anti-inflammatory mediators, leading to enhanced oxygen toxicity and inflammatory processes, and ultimately to lung tissue destruction. Insufficient repair results in alveolar simplification and persistently low gas exchange capacity, which is the hallmark of bronchopulmonary dysplasia (BPD). Incidence of BPD, also called chronic lung disease of prematurity, rises in parallel with the increased survival rate of very-low-birth-weight infants who are treated for and recover from RDS (Walsh et al., 2006), affecting approximately 30% of preterm infants born before 29 weeks of gestation (Smith et al., 2005). BPD therefore represents a sequela arising from complications associated with RDS treatment, or when abnormal lung development occurs in older infants (Antunes et al., 2014).

The phenotype of BPD has changed over time. The so-called "old" BPD was characterized by severe lung injury, pronounced inflammation, lung edema, airway epithelial metaplasia, peribronchial fibrosis, and marked airway and pulmonary vascular smooth muscle hypertrophy (Hilgendorff et al., 2014; Northway, et al., 1967). In contrast, the "new" BPD differs from the "old" form with less structural damage due to optimized ventilation strategies, and treatment with surfactant and antenatal glucocorticoids. Unlike the "old" BDP, the "new" BPD exhibits only mild peribronchial inflammation and fibrosis, while structural lung immaturity predominates (Baraldi and Filippone, 2007; Jobe, 1999) (Fig. 2). Histologically, the "new" BPD is characterized by alveolar hypoplasia (fewer and larger alveoli), thickened alveolar septa, dysmorphic pulmonary microvascular networks, mild airway and vascular smooth muscle hypertrophy, interstitial fluid accumulation, abnormal deposition of extracellular matrix components and an arrest of lung development at the late canalicular to early saccular stage (Coalson et al., 1999; Thibeault et al., 2003). These conditions result in chronic pulmonary dysfunction associated with significant morbidity and mortality (Baraldi and Filippone, 2007). Lung damage and developmental arrest induced by BPD are mainly irreversible and the respiratory impairment may continue into adolescence and adulthood (Gross et al., 1998; Northway et al., 1990). Currently BPD therapy is mainly palliative and limited to moderately active substances such as caffeine, high caloric feeding and vitamin A or glucocorticoids (Baveja and Christou, 2006). As pharmacological approaches to treat BPD have limited efficacy, a therapeutic strategy to restart alveolar growth and induce the development of a more normal, complex alveolar structure would be a highly desired goal of therapy.

2. Mesenchymal stem cells

Adult, mesenchymal stem cells (MSCs) were first isolated by Friedenstein from bone marrow (BM) derived mononuclear cells (Friedenstein et al., 1970). Since then MSCs have been isolated from a broad range of tissues and organs including umbilical cord blood (UCB) (Erices et al., 2000), umbilical cord matrix (UC) (McElreavey et al., 1991), BM (Caplan, 1991; Friedenstein et al., 1970), adipose tissue (Zuk et al., 2001), skin (Bartsch et al., 2005), connective tissue (Young et al., 1995), synovial fluid (Jones et al., 2004), placenta (Di Bernardo et al., 2014b), amniotic fluid (AF) (Di Bernardo et al.,