Cell-Based Strategies to Reconstitute Lung Function in Infants with Severe Bronchopulmonary Dysplasia

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KEYWORDS

• Premature birth • Bronchopulmonary dysplasia • Oxygen • Lung injury • Stem cells • Regeneration • Cell therapy

KEY POINTS

- Various types of stem/progenitor cells have shown potential promise in preventing and/or repairing neonatal lung injury.
- Mesenchymal stem cells derived from both bone marrow and umbilical cord blood are being popularly studied and appear to function in a paracrine manner rather than through cell engraftment.
- Further knowledge and understanding in this novel and exciting area of research is necessary before safe clinical translation of cell-based therapies is warranted.
- Strong emphasis must be placed on developing and standardizing techniques for stem/progenitor cell definition, isolation, expansion, and therapeutic administration.
- Experimental studies also need to focus on the long-term outcomes of such therapies.
- By identifying the most appropriate "reparative cell(s)" and its source, combined with understanding alternative mechanisms of action beyond cell replacement, we can advance in the quest of providing therapeutic strategies to prevent/repair neonatal lung injury.

INTRODUCTION

Advances in perinatal care have led to improved survival following very preterm birth, with infants born as early as 23 to 24 weeks of gestation now being capable of survival. However, with this shift in the limit of viability toward a lower gestational age, the task of protecting the more immature lung from injury becomes increasingly challenging.

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Clin Perinatol 39 (2012) 703–725
http://dx.doi.org/10.1016/j.clp.2012.06.009 **perinatology.theclinics.com**
0095-5108/12/$ – see front matter

Extreme prematurity is one of the major risk factors for the development of chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD).[1] Preterm infants born between 24 and 28 weeks of gestation (ie, extremely preterm) have an immature pulmonary surfactant system, immature airway and vascular architecture, and an underdeveloped surface area for gas exchange (**Fig. 1**).[2] Many very preterm infants require prolonged respiratory support to ensure survival, which further increases their risk of developing BPD.

Recent evidence suggests that BPD may have long-term respiratory complications that reach beyond childhood. Numerous follow-up studies indicate that children and young adults who were born very preterm are at an increased risk of respiratory symptoms, poor lung function, and lower exercise capacity[3–7] this is especially apparent in infants who have developed BPD. More alarmingly, isolated case studies are surfacing of irreversible arrested alveolar development at adult age in former premature infants with BPD,[8,9] mirroring results from experimental models of BPD.[10]

Progress toward decreasing the incidence/severity of BPD over the next few years using currently available techniques and strategies is likely (ie, optimization of antenatal management combined with surfactant and early noninvasive ventilatory support targeting lower oxygen saturations).[11] However, further understanding of the mechanisms involved in lung development, injury, and repair are necessary to advance toward preventing lung injury and/or promoting lung development/regeneration in prematurely born infants. Exciting discoveries in stem cell biology in recent years may offer new insight into the pathogenesis of BPD and, more importantly, open new therapeutic avenues.

BASIC CONCEPTS OF STEM CELL BIOLOGY

Stem cells are primitive cells capable of extensive self-renewal with the potential to give rise to multiple differentiated cellular phenotypes.[12] These cells are not only critical for organogenesis and growth during the early stages of development but also contribute to organ repair and regeneration throughout life.

Developmental Potency of Stem Cells

The concept of developmental potency refers to the range of possible fates open to cells during differentiation. Stem cells exhibit varying differentiation potencies, and

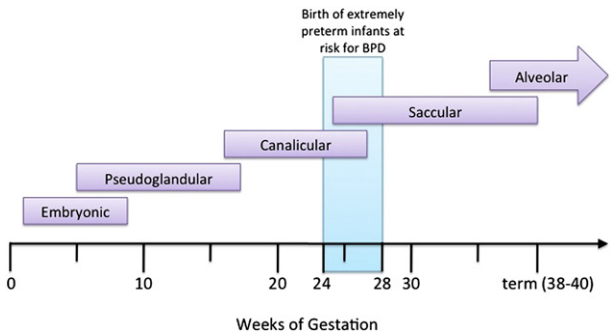

Fig. 1. Stages and gestational ages of normal lung development and preterm infants at risk of BPD. Schematic depicting stages of lung development in the human: embryonic (1–7 weeks), pseudoglandular (~5–16/17 weeks), canalicular (~16/17–24/26 weeks), saccular (~24–38 weeks), and alveolar (~36 weeks to postnatal) stages. Preterm infants at risk of developing BPD are born during the late canalicular to early saccular phase of lung development.