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Disrupted Lung Development and Bronchopulmonary Dysplasia: Opportunities for Lung Repair and Regeneration

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Abstract

Purpose of review—Advances of medical therapy have increased survival of extremely premature infants, and changed the pathology of bronchopulmonary dysplasia (BPD) from one of acute lung injury to a disease of disrupted lung development. With this evolution, new questions emerge regarding: (i) the molecular mechanisms that control postnatal lung development; (ii) the effect of early disruptions of postnatal lung development on long-term lung function; and (iii) the existence of endogenous mechanisms that permit lung regeneration after injury.

Recent Findings—Recent data demonstrate that a significant component of alveolarization, the final stage of lung development, occurs postnatally. Further, clinical and experimental studies demonstrate that premature birth disrupts alveolarization, decreasing the gas exchange surface area of the lung and causing BPD. BPD is associated with significant short-term morbidity, and new longitudinal, clinical data demonstrate that survivors of BPD have long-standing deficits in lung function, and may be at risk for the development of additional lung disease as adults. Unfortunately, current care is mainly supportive with few effective therapies that prevent or treat established BPD. These studies underscore the need to further elucidate the mechanisms that direct postnatal lung growth, and develop innovative strategies to stimulate lung regeneration.

Summary—Despite significant improvements in the care and survival of extremely premature infants, BPD remains a major clinical problem. While efforts should remain focused on the prevention of preterm labor and BPD, novel research aimed at promoting postnatal alveolarization offers a unique opportunity to develop effective strategies to treat established BPD.

Keywords

alveolarization; prematurity; chronic lung disease; lung regeneration; stem cells

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Introduction

In contrast to other organs, the lung completes a significant portion of its development immediately prior to, and after, birth. During alveolarization, the final stage of lung development, the alveolar ducts divide into alveolar sacs by secondary septation and the pulmonary capillary bed expands via angiogenesis to markedly increase the gas exchange surface area of the lung [1]. However, postnatal completion of growth renders the lung highly susceptible to environmental insults that disrupt this developmental program. This is particularly evident in the setting of preterm birth, where disruption of alveolarization causes bronchopulmonary dysplasia (BPD), the most common complication of prematurity [2]. Infants with BPD require significant respiratory support early in life and many demonstrate long-term deficits in pulmonary function including persistent airway obstruction[3,4] and delayed distal lung growth [5].

While advances in the medical care of extremely premature infants have reduced mortality, the morbidities associated with severe BPD persist [6]. Accompanying this increase in survival, the clinical, radiographic, and pathological features of BPD have changed significantly. In contrast to the severe lung injury characterizing “old BPD” as originally described by Northway [7], premature birth earlier in gestation appears to disrupt the normal program of alveolar and vascular development, resulting in the “new BPD”, characterized by an arrest in alveolar development [8].

Evidence demonstrating that the new form of BPD results from impaired lung development rather than acute lung injury underscores the need to better understand the molecular pathways that direct normal alveolar development. Further, clinical studies demonstrating the long-term effects of disrupted alveolarization on lung growth and lung function, highlight the importance of determining whether the lung has the capacity to regenerate. In this review, we summarize the most recent studies linking BPD to a defect in distal lung growth, as well as the current knowledge regarding the capacity of the lung to regenerate after injury. This is followed by a discussion of emerging therapies currently under development as novel strategies to treat BPD.

Overview of Lung Development

Lung development begins when the primitive lung bud emerges from the ventral foregut during the embryonic stage of development (4–7 weeks gestation), and divides to form two lung buds that lie on either side of the future esophagus [9]. The remaining four stages follow sequentially (Figure 1), resulting in successive branching from the trachea to the terminal respiratory units, markedly increasing the cross-sectional surface area of the lung. During the pseudoglandular stage (7–17 weeks gestation), branching morphogenesis, a highly stereotyped pattern of repetitive sprouting and bifurcation [10], allows for the formation of the pre-acinar airways. This process is dependent upon the secretion of growth factors from the surrounding mesoderm, which signal to the endodermal cells of the developing airway epithelium. Branching morphogenesis is completed during the canalicular stage (17–25 weeks gestation), culminating in the formation of the terminal bronchioles. At the same time, the epithelium begins to thin in order to form a primitive

blood-gas interface, and near the end of this stage, differentiation of type II alveolar epithelial cells permits the onset of surfactant production [9,11]. Primitive terminal airspaces form during the saccular stage (24–36 weeks gestation), consisting of smooth walled saccules and ducts with thick primary septae containing a double pulmonary capillary layer [11]. During the final, alveolar stage of lung development, new tissue ridges lift off from the primary septae and extend into the airspaces via the process of secondary septation, forming the interalveolar walls and dividing the saccules into smaller alveoli [12]. It is in this final stage, beginning at 36 weeks gestation and extending for a number of years postnatally, where the gas exchange surface area of the lung increases by 20-fold [13].

An intricate and organized pulmonary microvascular circulation is a necessary component of the blood-gas interface in the lung. The pulmonary blood supply develops in close relationship to the airways throughout the stages of lung development [9], and evidence suggests that the airways provide a template for the development of the pulmonary arteries and veins. In the early stages of lung development, pulmonary vascular development appears to occur primarily via vasculogenesis, the de novo formation of vessels from the differentiation of primitive angioblasts and hemangioblasts [14,15]. Capillary endothelial cells deriving from these progenitor cells form tubules in the mesenchyme surrounding the branching airways, coalescing to form the peripheral pulmonary arteries and veins alongside the airways [9]. Beginning with the canalicular stage, angiogenesis appears to be the primary mode of further pulmonary vascular growth, with new capillaries arising from the proliferation of endothelial cells within existing capillaries rather than originating de novo from the mesenchyme. By the end of the saccular stage, the primary septae contain a double capillary layer, which extends into the secondary septae during the formation of the alveoli. At the end of the alveolar stage, a period of microvascular maturation begins, where the double capillary layer contained within the immature alveolar septa fuses to form a single pulmonary capillary [16].

The process of secondary septation is a complex, integrated series of events involving paracrine signaling between multiple cell types within the lung including fibroblasts, epithelial cells, and endothelial cells. Myofibroblasts, located at the tips of the new secondary crests secrete elastin and growth factors that promote the proliferation, migration and differentiation of epithelial cells. Extensive proliferation of alveolar type II cells provides a source of progenitor cells for the type I alveolar epithelial cells that line the alveolar walls, and ensures adequate surfactant production after birth [17]. Alveolar epithelial cells, in turn, promote the development of the pulmonary capillary bed by the paracrine secretion of factors that stimulate pulmonary endothelial cells including, vascular endothelial growth factor (VEGF). Each step in this intricate process is required for normal alveolarization, and disruption of signaling from any one cell type is often sufficient to disrupt the process as a whole.

Bronchopulmonary Dysplasia: A Disease of Disrupted Lung Development

The term bronchopulmonary dysplasia (BPD) was first used in 1967 to describe the chronic lung disease associated with preterm birth and neonatal respiratory distress that, at the time, was called hyaline membrane disease [7]. This form of BPD was associated with positive-

pressure ventilation and prolonged oxygen therapy, and characterized by evidence of severe lung injury including inflammation, protein-rich edema, airway epithelial metaplasia, peribronchial fibrosis, and marked airway and pulmonary vascular smooth muscle hypertrophy [18,19]. The cohort described by Northway was born at a mean gestational age (GA) of 32 weeks (corresponding to the late saccular stage of lung development).

Medical advances in the care of premature infants including, but not limited to, artificial surfactant, antenatal corticosteroids, and lung protective strategies of mechanical ventilation now permit relatively consistent survival of infants born much earlier during gestation (in the late canalicular and early saccular stages of lung development) [20,21]. While many of these extremely premature infants have minimal lung disease at birth, BPD remains a common complication, and results in significant short- and long-term morbidity [22,23]. However, the lung pathology observed in these more premature infants with BPD is distinct from that described by Northway and colleagues. The marked lung inflammation, fibrosis, and metaplasia frequently observed in the original form of BPD have now been replaced by histopathologic evidence of alveolar simplification, characterized by fewer and larger alveoli [24,25].

Impaired pulmonary capillary development also appears to be a key feature of the current form of BPD [26]. Preterm infants who die from severe BPD have highly abnormal alveolar microvessels and decreased VEGF expression [24,27]. These findings are recapitulated in animal models of BPD [28,29], and experimental inhibition of angiogenesis impairs alveolarization in newborn rats [30]. Furthermore, disruption of vascular growth predisposes preterm infants to pulmonary hypertension (PH) and other manifestations of pulmonary vascular disease (PVD) [31]. These findings suggest that proper development of the pulmonary microstructure requires intact angiogenesis that is disrupted in infants with BPD. Together, these disruptions in alveolar and vascular growth result in more simplified pulmonary acini and vascular structures, reducing the surface area for gas exchange to cause BPD [8,20].

Classically, BPD was defined in the clinical setting of a persistent oxygen requirement at 36 weeks GA, a chest radiograph with chronic changes, and respiratory distress (tachypnea, retractions, adventitious breath sounds)[32]. However, changes in both the underlying pathobiology and the clinical phenotype of BPD led to the need to define BPD with varying degrees of severity. In 2000, a consensus statement categorized BPD in extremely premature infants as follows: none (oxygen therapy needed for <28 days), mild (28 days of oxygen therapy, but not at 36 weeks GA), moderate ($FiO_2 < 0.3$ at 36 weeks), or severe ($FiO_2 \geq 0.3$ at 36 weeks or any form of positive pressure ventilation)[2,32]. This panel identified the need for a physiologic test to quantify oxygen status (rather than using a clinician-determined oxygen “requirement”). A physiologic assessment or oxygen reduction test (performed using an oxygen hood to avoid positive pressure ventilation) is now the preferred means of determining a child’s FiO_2 need [33]. Of note, heated high-flow nasal cannula (HHFNC) systems were not in common use at the time. HHFNC, which is reviewed below, delivers an elevated pharyngeal pressure[34] and thus may cause some infants with severe BPD to be incorrectly categorized as having moderate BPD when the clinical FiO_2 is used to determine BPD severity.

According to the most recent large-scale study in the U.S. (9575 subjects), the incidence of BPD is 68% in extremely low gestational age infants (born at 22–28 weeks; mean BW 836g) [35]. In these infants, both mortality and BPD were inversely associated with GA at birth. A study examining over 9.5 million neonatal hospitalizations between 1993 and 2006 revealed that the incidence of BPD decreased 4.3% per year during this period [36]. However, other recent studies have suggested that, although survival is increasing, the prevalence of BPD is not changing [37] and may even be increasing [38].

The early identification of preterm infants at greatest risk for BPD is critical for both clinical prognostication, and for the development of targeted clinical trials aimed at preventing BPD in the most severely affected individuals. BPD is a multifactorial clinical syndrome influenced by genetic predisposition, maternal complications of pregnancy, and the child's early postnatal course. Low gestational age and birth weight remain key predictors of BPD severity [23]. Although twin studies have shown that genetic predisposition may account for over 50% of BPD risk [39,40], a recent genome-wide association study (GWAS) of over 1700 infants in California was unable to identify single nucleotide polymorphisms (SNPs) associated with BPD, and failed to confirm candidate SNPs from previous studies [41]. Thus, additional research is necessary to better understand how genetic variation affects the risk for BPD in preterm infants. Other identified risk factors for BPD include: maternal preeclampsia [42–44], chorioamnionitis [45,46], sepsis [47,48], and fetal growth restriction [49].

Laughon and colleagues showed that, in addition to the degree of prematurity, early postnatal respiratory support (i.e., mechanical ventilation on day of life 7) was a risk factor for BPD [50]. A recent meta-analysis suggests that strategies to avoid mechanical ventilation have a small but significant impact on preventing BPD [51]. The presence of a patent ductus arteriosus (PDA) is associated with BPD risk and typically results in either prompt medical or surgical management [52]. However, it remains unclear whether PDA treatment increases or decreases the risk of BPD [53,54]. Finally, an increased score for neonatal acute physiology (SNAP), a valid indicator of the severity of neonatal illness, is associated with BPD or death in preterm infants and may thus prove useful in the early identification of preterm infants at greatest risk for BPD [55].

Current Management and Treatment

Although early interventions for the prevention of preterm birth and BPD are preferable to treatments for the condition after it has developed, the latter remains an important focus of both clinical and preclinical research to minimize its long-term sequelae. Our current therapies are largely supportive and are aimed at stabilizing the preterm infant with as little respiratory support and oxygen therapy as is needed. A recent meta-analysis of delivery room practices suggested that nasal continuous positive airway pressure (nCPAP) is less likely to result in death or BPD at 36 weeks as compared to endotracheal intubation (relative risk 0.91, 95% confidence interval 0.84–0.99), and that one additional infant could survive to 36 weeks without BPD for every 25 babies treated with nCPAP [56]. The ideal amount of supplemental oxygen for use in either the delivery room or the neonatal intensive care unit remains uncertain [57]. Numerous studies have investigated the appropriate amount of

oxygen to be delivered and the safest target saturations for clinical use [58–61]. In the recently published BOOST II study, retinopathy of prematurity was decreased, but death by 36 weeks was increased when targeting lower saturations (85–89%) [60]. This suggests that, although efforts to avoid excessive oxygen therapy are reasonable, this should be done with caution and oxygen therapy should not be withheld from the deteriorating child.

Over the past decade, heated high-flow nasal cannula (HHFNC) systems have been shown to be as effective as nCPAP with similar rates of BPD [62,63]. HHFNC does not require a tight seal and is thus, unlike nCPAP therapy, not associated with nasal trauma [62]. However, as noted above, these devices have been shown to deliver significant positive pharyngeal pressure [34]. Although HHFNC has clinical benefit, providers ought recognize that HHFNC provides significant respiratory support. Children requiring HHFNC may possess greater pulmonary compromise than apparent on cursory evaluation.

Long Term Effects of Prematurity and BPD on Lung Function

As survivors of extreme prematurity in the post-surfactant era are now reaching childhood and early adulthood, new evidence is emerging to suggest that the disruption of alveolarization seen in these patients durably impairs lung function. In the EPIcure study, over 50% of middle school aged children born at less than 25 weeks GA had abnormal baseline spirometry (primarily demonstrating significant lower airway obstruction), and these deficits were most pronounced in those patients with a history of BPD [64]. Further, less than half of the children with lower airway obstruction who demonstrated a positive response to bronchodilators had been treated with medication during the preceding 12 months, highlighting the need for continued and careful pulmonary follow up for patients with a history of extreme prematurity, even if asymptomatic. However, more comprehensive pulmonary function testing may be indicated, as spirometry alone is relatively insensitive in these patients, missing lung function abnormalities in up to 40% of childhood survivors of extreme prematurity [65]. Exercise tolerance may be impaired in school-age survivors of premature birth to a much greater degree than predicted by the amount of airway obstruction [66]. Further, Balinotti and colleagues demonstrated that pulmonary diffusion capacity was significantly lower in infants and toddlers with a history of BPD, thus providing some of the first physiologic data to support the histologic evidence that the “new” BPD results from arrested alveolar development and diminished loss of gas exchange surface area [5]. The high incidence of lung function abnormalities in children with a history of extreme prematurity even in the absence of BPD[67] highlights the vulnerability of the immature lung to premature birth.[67].

Mechanisms of Lung Regeneration

Experimental studies demonstrate that some species possess a remarkable capacity for lung regeneration. This is perhaps best exemplified by the regenerative neo-alveolarization that occurs following unilateral pneumonectomy in small rodents. In these models, the removal of a single lung invokes a rapid period of compensatory growth in the remaining lung characterized by the re-expression of growth factors and extracellular matrix components produced during developmental alveolarization, and the proliferation of pulmonary epithelial and endothelial cells, resulting in a complete restoration of total lung capacity

[68]. Mechanical stretch of the remaining lung and increased pulmonary blood flow have been hypothesized as initiating factors in invoking this compensatory growth, thought to occur via increases in both alveolar number and size of existing alveoli [69,70].

Early data in humans suggested that the majority of compensation after pneumonectomy resulted from the recruitment of reserve lung tissue rather than true lung growth [71]. However, more recent data suggest that the human lung also has some capacity for regeneration after injury, and this appears to be greatest in pediatric patients. While post-pneumonectomy adults demonstrate an increase in total lung capacity (TLC) in association with decreased residual volumes (i.e., due to recruitment of lung reserves), children were found to have similar increases in TLC without decreases in residual volume, suggesting compensatory growth [72]. In a group of patients undergoing pneumonectomy prior to age 5, the TLC reached 96% of the normal value for two lungs at 30 years post pneumonectomy, suggesting full compensation for the lost parenchyma [73]. In contrast, TLC reached a maximum of 70% in older patients post-pneumonectomy, demonstrating a greater ability of the immature lung to regenerate.

This increased capacity for lung regeneration in young patients may be better understood in light of new evidence suggesting that alveolarization may continue through the first two decades of postnatal life. Early data based on morphometric methods of counting alveoli, suggested that the number of alveoli increased rapidly postnatally, reaching a maximum by 2 years of age [74], with further increases in lung capacity resulting from increases in alveolar size and surface area, rather than additional increases in alveolar number. However, high resolution CT scans obtained during the first three years of life showed that growth of the lung parenchyma is primarily due to the addition of new alveoli, rather than the expansion of existing alveoli [75]. These images demonstrated that alveolar number increases through the first three years of life [75]. Moreover, recent animal studies using more advanced morphometric techniques have demonstrated that secondary septation and formation of new alveoli continue in rodents and non-human primates until time points that are analogous to early adulthood in humans [76,77].

Emerging Therapies to Promote Lung Growth

The recognition that alveolarization may extend until early adulthood suggests that therapeutic strategies could be developed to exploit these same mechanisms in order to promote lung regeneration. Many of the signaling pathways essential for lung development are suppressed during disease, and reactivated during lung repair. Thus, better delineation of these pathways and their cellular targets may provide novel therapeutic strategies to stimulate lung growth after injury. A number of putative resident progenitor cells have been identified in the lung, including proximal airway, distal lung epithelial, lung mesenchymal, and lung endothelial progenitor cells. Numerous experimental and clinical studies have tested the efficacy of these cell-based therapies in promoting lung regeneration after injury (comprehensively reviewed in [78]). Further, in a landmark report, Petersen et al. successfully engineered rat lungs *ex vivo* using a decellularized lung extracellular matrix entirely repopulated with neonatal rat epithelial and endothelial cells, that functioned for a short time when implanted in rats *in vivo* [79]. While certainly only an initial step, this

achievement raises the possibility that in the future, tissue-engineered lungs may represent an innovative alternative to lung transplantation for patients with end-stage lung disease, provided that a source of autologous lung progenitor cells can be identified.

Of these potential therapies, the efficacy of cell-based therapies for the treatment of bronchopulmonary dysplasia has been the focus of many recent investigative efforts. Many have speculated that circulating progenitors, such as umbilical cord blood-derived endothelial progenitor cells (EPCs) or mesenchymal stromal cells (MSCs), contribute to lung vascular development, are impaired in infants with BPD, and would thus serve as a potent stem cell therapy for treating or preventing BPD [26,80,81]. Two specific EPC sub-types, endothelial colony-forming cells (ECFCs) and circulating progenitor cells (CPCs) are decreased in the cord blood of infants with BPD [80,82,83]. Recent studies have shown that both ECFCs and MSCs help to prevent BPD and PH in newborn rodents with experimental BPD (Table 1), likely by augmenting angiogenesis through paracrine mediated mechanisms [84–88]. These promising preclinical results provide a rationale for studying ECFC and MSC therapy in human infants with severe BPD. However, the effects of stem cell therapy on other organs (such as the brain and the eye) are not well studied, and at this point, we suggest that umbilical cord stem cell therapy for BPD is not yet ready for clinical trials [89].

Conclusions

Increasing rates of survival for extremely premature infants has changed the pathology of bronchopulmonary dysplasia, resulting in a chronic lung disease that represents impaired microvascular and alveolar growth. Despite significant advances, BPD continues to be a major clinical problem. Recent longitudinal clinical data demonstrates that survivors of BPD suffer from long-term deficits in lung function, and may be at higher risk for developing emphysema as young adults. The lung may possess a greater capacity for regeneration than previously recognized as alveolarization occurs in young children postantally and after pneumonectomy. Emerging studies have identified resident progenitor populations in the lung that can stimulate lung growth. Future investigation will elucidate signaling pathways to promote and expand these populations in order to develop cell-based therapies. Innovative advances in lung tissue engineering hold promise for individuals with the most severe BPD. Further work is needed to bring these cutting edge advances to the bedside in order to cure this debilitating disease.

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Key Points

- Premature birth can disrupt normal alveolarization, resulting in long-term deficits in lung function that are most extreme in patients with a history of BPD.
- Many survivors of prematurity with lung function abnormalities are asymptomatic or lack a history of BPD. Therefore, patients with a history of extreme prematurity should be followed from a pulmonary perspective over the long-term.
- The lung has the capacity to regenerate, particularly during early childhood, raising the possibility that innovative therapeutic strategies could be developed to treat BPD by stimulating lung regeneration.

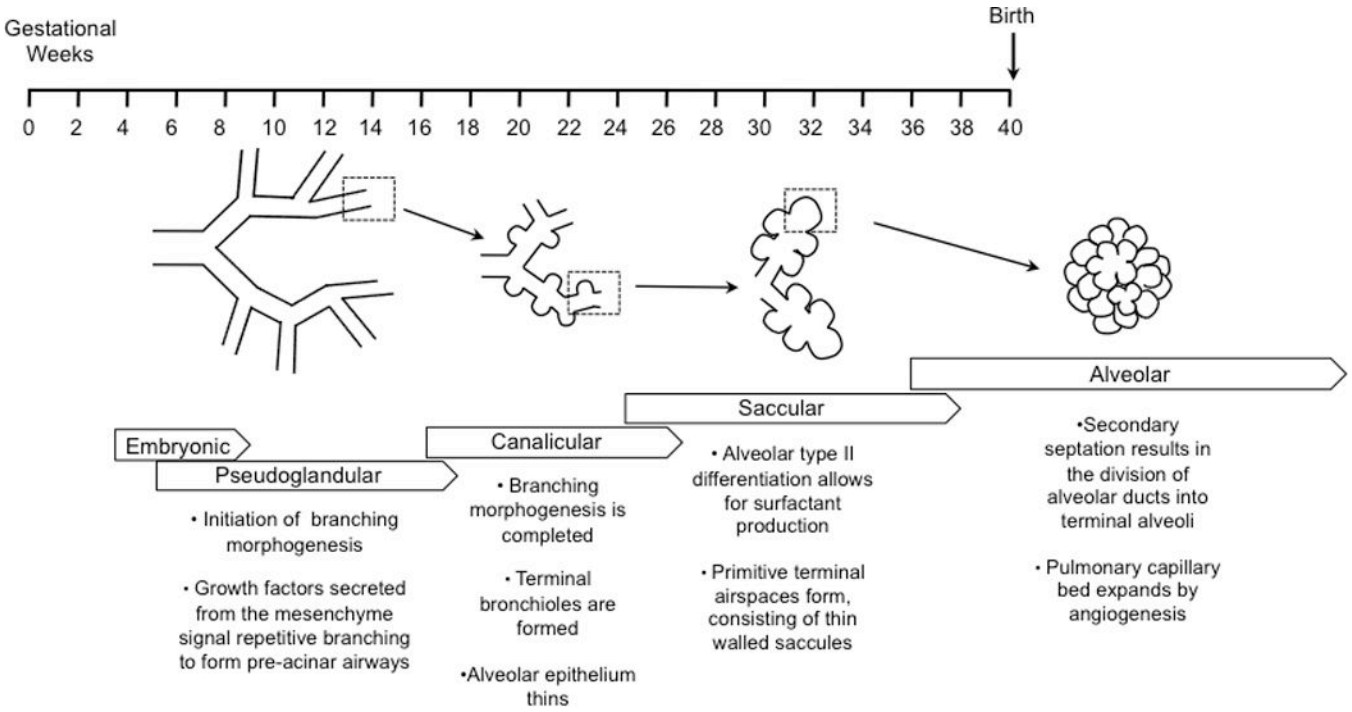

Figure 1.

Overview of the Stages of Lung Development. After formation of the primitive lung bud during the embryonic stage of development, the remaining four stages follow sequentially. During the pseudoglandular stage, repetitive sprouting and bifurcation results in the formation of the pre-acinar airways via branching morphogenesis. The terminal bronchioles form, and branching morphogenesis is completed during the canalicular stage. Primitive terminal airspaces form during the saccular stage of development, and alveolar type II cells differentiate and begin to produce surfactant. In the final, alveolar stage, beginning just before term birth and extending for a number of years postnatally, secondary septation and pulmonary angiogenesis markedly increase the gas exchange surface area of the lung.

Table 1

Cell-based Therapies in Experimental BPD

Therapy	Model of BPD	Route of Delivery	Physiologic Effect	Reference
MSC	Hyperoxia (neonatal mice)	Intravenous (temporal vein)	Modest improvement in alveolarization, suppression of lung inflammation, and prevention of pulmonary vascular remodeling	Aslam [84]
MSC	Hyperoxia (neonatal mice)	Intratracheal	Prevention and rescue of arrested alveolar growth, improved survival, attenuated alveolar and vascular injury and pulmonary hypertension.	Pierro [87] Van Haaften [88]
MSC	LPS Induced Lung Injury (Mice)	Intratracheal	Decreased LPS-induced lung inflammation, lung vascular permeability, and histologic lung injury.	Ionescu [86]
MSC-CM	Hyperoxia (neonatal mice)	Intravenous (temporal vein)	Marked improvement in alveolarization, suppression of lung inflammation, and prevention of pulmonary vascular remodeling	Aslam [84]
MSC-CM	Hyperoxia (neonatal mice)	Intraperitoneal	Improved alveolar growth and pulmonary vascular density, prevention of pulmonary vascular remodeling and RVH.	Pierro [87]
MSC-CM	LPS Induced Lung Injury (Mice)	Intratracheal	Decreased LPS-induced lung inflammation, lung vascular permeability, and histologic lung injury.	Ionescu [86]
ECFC	Bleomycin (neonatal rats)	Intravenous (jugular vein)	Decreased RVH, no effect on alveolarization or pulmonary vascular density	Baker [85]
ECFC-CM	Bleomycin (neonatal rats)	Intravenous (jugular vein)	Decreased RVH, no effect on alveolarization or pulmonary vascular density	Baker [85]
ECFC-CM	Bleomycin (neonatal rats)	Intraperitoneal	Decreased RVH, no effect on alveolarization or pulmonary vascular density	Baker [85]

MSC = mesenchymal stromal cell. ECFC = endothelial colony-forming cell. CM = conditioned media. LPS = lipopolysaccharide.