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REVIEW ARTICLE

Mechanisms of bronchopulmonary dysplasia

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Abstract Bronchopulmonary dysplasia (BPD) is a chronic lung disease affecting premature infants with long term effect on lung function into adulthood. Multiple factors are involved in the development of BPD. This review will summarize the different mechanisms leading to this disease and highlight recent bench and clinical research targeted at understanding the role of the mesenchyme (both its cellular and extracellular components) in the pathogenesis of BPD.

Keywords Bronchopulmonary dysplasia · Extracellular matrix · Growth factors · Hyperoxia · Lung development · Prematurity

Introduction

First described by Northway and colleagues in 1967 (Northway et al. 1967), bronchopulmonary dysplasia (BPD) is a chronic lung disease which develops in premature infants. Most of these infants suffered from surfactant deficiency (respiratory distress syndrome, or RDS) and subsequent lung injury due to some combination of oxygen toxicity, mechanical ventilation, inflammation and infection. The term BPD was chosen to emphasize the involvement of all tissues of the lung in the pathologic process. Pathologic findings included inflammation, airway fibrosis and smooth muscle hypertrophy, alveolar collapse and hyperinflation and interstitial fibrosis (Bonikos et al. 1976). Infants frequently died of respiratory failure.

In the past two decades, advances in perinatal care including antenatal steroid therapy, surfactant use, novel ventilator strategies and aggressive treatment of patent ductus arteriosus, have led to increased survival of very preterm newborns (Fanaroff et al. 2007). Increased survival, in turn, has led to increase in the incidence of BPD. In 2009, there were 3,987,108 singleton live births in the U.S., of which 1.6 % were very preterm (<32 weeks gestation) and 1.1 % had very low birth weight (<1,500 g) (Martin et al. 2011). Over 25 % of premature infants with birth weights <1,500 g develop BPD (Jobe and Bancalari 2001). Thus, there are over 10,000 new cases of BPD annually. Today's surviving premature infants have different lung pathology, defined as "new BPD," with preserved airway structure and homogeneous lung inflation. However, there are also larger and fewer alveoli, as well as poorly formed secondary crests, indicating interference with septation (Hussain et al. 1998; Coalson 2003). Infants with BPD are more likely to be hospitalized in the first year of life and to require medications for pulmonary disease (Furman et al. 1996; Greenough et al. 2001; Ehrenkranz et al. 2005). There is broad agreement that survivors have abnormal lung function even as adults (Kennedy 1999; Eber and Zach 2001), making BPD a leading cause of pediatric lung disease.

Over the years, with the change in lung pathology and clinical presentation, different definitions of BPD have been used. In a 1979 workshop, BPD was defined as 28 days of oxygen therapy with radiographic changes (Tooley 1979). Later, an oxygen requirement at 36 weeks postmenstrual age was used as a better predictor of long terms respiratory outcomes (Shennan et al. 1988). In 2000, a workshop organized by the National Institute of Child Health and Human Development, the National Heart, Lung and Blood Institute, and the Office of Rare Diseases defined diagnostic criteria for BPD based on gestational age (<32 weeks versus ≥32 week) and severity (mild, moderate or severe based on oxygen supplementation at 28 days of age and 36 weeks postmenstrual age) (Jobe and Bancalari 2001). A limitation of these definitions is that criteria for oxygen administration may vary among different centers. To minimize the variations introduced by different practices for oxygen use, a new physiologic definition of BPD was recently described using a stepwise timed oxygen reduction test (Walsh et al. 2003).

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The development of BPD is a complex interaction between normal growth and developmental patterns superimposed with acute and chronic responses to environmental factors deleterious to the lung. Understanding the underlying mechanisms of BPD may provide insight into development of new therapeutic and preventive strategies. In recent years, the molecular and cellular basis of BPD has been studied, primarily using animal models. Human studies of premature infants have provided additional understanding of the different factors involved.

The lung at 24 to 26 weeks gestation is in the late canalicular stage of development. Transition to the saccular stage (starts at 26–28 weeks) and alveolar stage (starts at 36 weeks) is defined by a rapid increase in lung volume and alveolar surface area (Langston et al. 1984). Beginning at about 28 weeks, the complexity of the saccules increases, secondary crests begin to form. Extensive vasculogenesis within the developing terminal saccules occurs, along with a decline in airspace wall thickness. By 36 weeks alveoli are uniformly present and the total number of alveoli increases exponentially in proportion to gestational age. In a premature infant, this process is disrupted by prenatal and/or postnatal inflammatory processes, particularly injury due to supplemental oxygen and volutrauma.

Oxygen- and ventilation-mediated lung injury

The structure of the lung in the canalicular and saccular stages of development, together with the mechanics of the respiratory system, do not provide an optimal environment for adequate ventilation and gas exchange: diffusion of oxygen and carbon dioxide through the thickened airspace walls is limited; surfactant deficiency decreases lung compliance. The highly compliant chest wall of the premature infant exerts insufficient outward recoil, contributing to low functional residual capacity and respiratory failure. Thus, to sustain physiological function, a higher concentration of inspired oxygen and/or mechanical ventilation must be used. In addition to the benefit provided by these modalities, their injurious effects have been extensively studied. The role of hyperoxia in the pathogenesis of BPD has been reviewed extensively (Bhandari 2010; Saugstad 2010). Animal studies have shown that hyperoxia alone can arrest septation of lungs in the saccular stage of development (Coalson et al. 1995; Warner et al. 1998). Infants with BPD who were exposed to higher levels of supplemental oxygen to achieve higher levels of oxygen saturation were found to have more persistent lung disease (The STOP-ROP Multicenter Study Group 2000). Recent studies have shown that even short term exposure to hyperoxia affects the developing lung. When infants born between 24 and 28 weeks gestation were resuscitated in the delivery room with 30 % instead of 90 % oxygen, the incidence of BPD at 36 weeks gestation was reduced from 37.7 % to 15.4 % (Vento et al. 2009). Hyperoxia is a powerful proinflammatory stimulus. Infants exposed to 90 % oxygen have significantly elevated TNF-α and IL-8 levels (Vento et al. 2009). Oxygen toxicity is mediated through reactive oxygen species (ROS). Antioxidants have been considered as possible preventive or therapeutic options for BPD (Asikainen and White 2004; Welty and Smith 2001, 2003). Some antioxidant defenses, such as glutathione peroxidase, are greater in the premature neonate than in the adult, while other defenses, such as catalase, are lower in neonates (Asikainen et al. 1998).

Mechanical ventilation alone in animal models can interfere with lung development and induce lung phenotype reminiscent of BPD (Coalson et al. 1999; Albertine et al. 1999; Mokres et al. 2010). Mechanical ventilation at high lung volumes (by stretching normal and deceased alveoli) and low lung volumes (by periodic opening and closing of distal airspaces during ventilation with a reduced functional residual capacity) may cause ventilator-induced lung injury (Dreyfuss and Saumon 1998). Preterm lambs subjected to large tidal-volume ventilation show upregulation of multiple proinflammatory markers including IL-1β, IL-6, IL-8, and Toll-like receptors 2 (TLR-2) and 4 (TLR-4) (Hillman et al. 2007). Strategies to minimize ventilator induced lung injury due to conventional mechanical ventilation have been developed, including volume-targeted ventilation (Cheema and Ahluwalia 2001) and early discontinuation of positive pressure ventilation and substitution with continuous positive airway pressure (CPAP) (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010).

Role of inflammation or infection

The role of inflammation and infection in the pathogenesis of BPD has been reviewed extensively (Jobe 2003; Speer 2003; Li and Tullus 2002) and will not be discussed in detail. Elevated levels of IL-6 and IL-8 precede the influx of neutrophils observed in RDS (Munshi et al. 1997) and may be the initiators of the inflammatory cascade that predisposes to the development of BPD (Kotecha et al. 1996). Preterm infants developing BPD demonstrate higher numbers of inflammatory cells – neutrophils and macrophages, in their bronchoalveolar lavage fluid compared with infants who recovered from RDS (Merritt et al. 1983; Arnon et al. 1993; Groneck et al. 1994). Previous studies have examined the role of neutrophils and macrophages in the pathogenesis of neonatal hyperoxic lung injury. In neonatal rats, hyperoxia induces neutrophil influx and hypoalveolarization which is attenuated by neutralizing antibodies against the neutrophil chemoattractants CXCL1 (Auten et al. 2001) or CXCL2 (Deng et al. 2000). Neutrophilic inflammation in hyperoxia is also prevented by a selective chemical antagonist of CXCR2 (Yi et al. 2004). Neutralizing antibodies against CCL2, a monocyte chemoattractant, also decrease lung

hypoalveolarization, as well as lung macrophage and neutrophil counts, in hyperoxia-exposed rats (Vozzelli et al. 2004).

NF-κB signaling in activated fetal lung macrophages disrupts airway morphogenesis (Blackwell et al. 2011). In fetal mouse lungs, chorioamnionitis stimulates angiogenesis and inflammatory lung phenotype reminiscent of the inflamed lungs of infants developing BPD (Miller et al. 2010). In addition to proinflammatory lung phenotype, antenatal infection (chorioamnionitis) in sheep causes lung maturation (Kramer et al. 2009). The question about a relationship between antenatal infection (chorioamnionitis) and respiratory outcomes of prematurely born infants remains unsettled. (Laughon et al. 2009; Soraisham et al. 2009; Been et al. 2010).

Genetic risk factors

Genetic influences in the development of BPD have also been considered. An early twin study by Parker et al. (Parker et al. 1996) reported that, for twin pairs with birth weights less than 1,500 g, the BPD status of the first twin was a highly significant predictor of BPD in the second twin, independent of birth weight, gestational age, gender, severity of RDS, PDA and other potentially significant risk factors, suggesting that genetic factors are affecting the susceptibility of very low birth weight premature infants to BPD. In a study of 450 sets of twins born at less than 32 weeks of gestation, after controlling for covariates, genetic factors accounted for 53 % of the variance in liability for BPD (Bhandari et al. 2006). A number of studies have reported on potential candidate genes, including polymorphisms in surfactant protein (Weber et al. 2000; Makri et al. 2002; Rova et al. 2004; Pavlovic et al. 2006) and tumor necrosis factor-alpha genes (Kazzi et al. 2004; Strassberg et al. 2007). From the large number of genes involved in normal lung growth and development, it is likely that other specific sequence variations may also be recognized in the future.

Role of peptide growth factors

Various epithelium- and mesenchyme-derived peptide growth factors and other molecules are involved in continuous cross-talk during normal lung development. The establishment of a localized domain in the ventral wall of the anterior foregut expressing the transcription factor *Nkx2-1* (also known as *Ttf1*) is the earliest known step in the development of the respiratory system. Within this domain, at E9.5 in the mouse and ~28 days in the human, the two primary lung buds appear. This specification is regulated by mesoderm derived Wnt and fibroblast growth factor (FGF) signals (Goss et al. 2009; Serls et al. 2005). Once the primary lung buds form, they extend into the surrounding mesenchyme, beginning the process of branching morphogenesis. The development of the lung buds is dependent on localized expression of FGF10 in the mesoderm overlying the buds and Fgfr2 in the endoderm (Min et al. 1998; Sekine et al. 1999). At the distal tip of the branching endoderm and the surrounding mesoderm, a core group of evolutionary conserved signaling pathways, including bone morphogenic protein (BMP)/transforming growth factor (TGF)-β, Wnt, Sonic hedgehog (Shh) and retinoic acid, establish a signaling network (Cardoso and Lu 2006). The different pathways cross-regulate one other. For example, Shh stimulates Wnt2 and Bmp4 in the mesenchyme (Pepicelli et al. 1998), Wnt7b/β-catenin signaling promotes the expression of Bmp4 and Fgfr2 in the epithelium (Rajagopal et al. 2008; Serls et al. 2005) and Fgf9 (secreted by both the early epithelium and the mesothelium) promotes the expression of Fgf10 in the distal mesoderm (del Moral et al. 2006). During the saccular and alveolar stages of lung development, the functional units for gas exchange develop. The timing of alveolar development varies between species. In mice it occurs postnatally (~P5-30), whereas in humans some alveoli are formed before birth and the process continues for many months or years afterwards. A critical role for the Fgf pathway in alveolar development is demonstrated by the phenotype of lungs of Fgfr3/Fgfr4 double null mice that fail to undergo secondary septation (Weinstein et al. 1998). Retinoic acid receptor-β deficient mice have defects in distal airspace development and a progressive loss of respiratory function (Snyder et al. 2005). In mice, PDGF-A, which signals solely through PDGF-Rα, is required for secondary alveolar septal formation and elastic fiber deposition (Boström et al. 1996).

Vascular growth factor signaling has been closely linked to alveolarization. Impaired signaling of growth factors involved in vasculogenesis and angiogenesis (e.g. vascular endothelial growth factor) plays a role in the development of BPD in the preterm baboon model (Maniscalco et al. 2002) and in human infants (Bhatt et al. 2001; Lassus et al. 2001). During lung injury and repair, these peptide growth factors, in combination with other growth factors involved in the acute response to injury and repair, may erroneously (spatially and temporally) exert their effect, leading to abnormal tissue architecture and impaired function.

In the remainder of this review, we will focus on role of transcription factors, signaling molecules, extracellular matrix proteins and matricellular proteins within the cellular and matrix components of the lung mesenchyme, and discuss their implication in the pathogenesis of BPD.

Role of the mesenchyme – mesenchymal cells, myofibroblasts, extracellular matrix and matricellular proteins

In early mouse embryonic lung explants, soluble factors released by peripheral lung mesenchyme can induce ectopic branching from the trachea, as well as induce expression of

genes specific to peripheral lung epithelium, including surfactant protein (SP)-A, -B, -C and Clara cell-specific 10 kD protein (CC-10) (Shannon 1994). Progenitor cells in the distal lung mesoderm expressing Pdgfrα and the transcription factors Twist 2, Foxf1 and Tbx4 are multipotent. During development, they are exposed to a series of signals, including Shh, Bmps, Wnts, VEGF, Pdgfs, FGFs, TGFβ and retinoic acid, which regulate commitment to different specialized cell types, including pericytes, parabronchial smooth muscle, myofibroblasts and lipofibroblasts.

In addition to the cellular component, the lung mesenchyme is composed of fibrous structural proteins (mainly type I and IV collagen, elastin, fibronectin and laminin), glycosaminoglycans, proteoglycans and matricellular proteins. Elastin and collagen provide the supportive structure for the airways and alveolar spaces. Fibronectin and laminin fascilitate linking of cells to the larger fibrillar proteins of the matrix. Alterations in mesenchyme-associated proteins and growth factors and their receptors, e.g., fibroblast growth factors (FGF7, FGF10, FGFR-2, -3, -4), epidermal growth factors, transforming growth factor β, connective tissue growth factor and vascular endothelial growth factor, have been associated with the development of impaired alveolarization (Ahlfeld and Conway 2012). The role of the mesenchymal cells and their interaction with matricellular proteins, non-structural extracellular matrix proteins that regulate cell-matrix interactions, thereby influencing fiber deposition, adhesion, migration, proliferation, and survival will be discussed below.

Recent studies have drawn attention to the role of mesenchymal cells in lung development and neonatal lung disease, in support of Northway and colleagues' emphasis that all lung tissues are involved in the pathologic process of developing BPD (Northway et al. 1967). As lung saccules form, there is distal spread of platelet-derived growth factor receptor-α-expressing myofibroblasts from more proximal airway sites to the tips of secondary alveolar septa (Boström et al. 1996; Lindahl et al. 1997). These cells, which express α-smooth muscle actin and elastin, are required for alveogenesis (Noguchi et al. 1989; Boström et al. 1996; Lindahl et al. 1997; McGowan and Torday 1997; Wright et al. 1999; Yamada et al. 2005; McGowan et al. 2008). During normal lung development, a second type of interstitial cell, containing intracellular lipids, are present at the bases of the developing septa (Vaccaro and Brody 1978). These lipofibroblasts mediate the uptake and trafficking of lipid to the type II cells for surfactant phospholipid synthesis (Schultz et al. 2002; Torday et al. 1995). By contrast, hyperoxia-exposed lungs with arrested alveolar development show a paucity of α-actin-positive myofibroblasts at the septal tips (Hirakawa et al. 2007) and an increase in the number of α-smooth muscle actin-, transforming growth factor (TGF)-β-positive interstitial myofibroblasts (Toti et al. 1997; Bhatt et al. 2001; Kaarteenaho-Wiik et al. 2002; Kaarteenaho-Wiik et al. 2004). Overexpression of TGF-β in neonatal mouse lungs induces proliferation of α-actin-positive cells within the alveolar septal walls and hypoalveolarization (Vicencio et al. 2004), implying a critical role for TGF-β in the development of BPD. Together, these data suggest that, in BPD, there is impaired mesenchymal cell migration combined with abnormal proliferation and differentiation.

We have isolated mesenchymal stromal cells (MSCs) from the tracheal aspirates of premature infants with respiratory distress syndrome. These cells undergo TGF- β-induced myofibroblastic differentiation and may also be stimulated to undergo adipocytic differentiation (Hennrick et al. 2007), suggesting that these cells may represent a common progenitor of the two alveolar mesenchymal cell subtypes. Neonatal lung MSCs are almost never isolated from the tracheal aspirates of infants with good pulmonary outcomes, whereas approximately half of the infants from whom MSCs are isolated develop BPD (Popova et al. 2010). Low passage unstimulated MSCs from infants developing BPD show a higher α-actin content when compared to MSCs from infants not developing this disease, suggestive of more advanced myofibroblastic differentiation. GSK-3β/β-catenin signaling, which has been implicated in myofibroblastic differentiation in vitro (Armstrong and Esser 2005; Haq et al. 2003) is upregulated in cells from infants developing BPD. Similar changes are found in lungs of infants with BPD (Popova et al. 2012). These findings suggest that GSK-3β/β-catenin signaling pathway is activated in lung mesenchymal cells from patients with BPD and may play an important role in the pathogenesis of neonatal lung injury.

The GSK-3β/β-catenin pathway may be initiated (and GSK-3β kinase activity suppressed) by a number of physiologic stimuli, including TGF-β, Wnts, Shh, BMPs, cardiotrophin, endothelin, serotonin (Deng et al. 2008; Deng et al. 2010) and the matricellular protein CCN2 (also called connective tissue growth factor or CTGF) (Fig. 1). In addition to their independent effects, matricellular proteins enhance TGF-β receptor binding and downstream signaling responses (Abreu et al. 2002), and are required for a subset of TGF-β responses (Snider et al. 2008)(Fig. 2). Like TGF-β (Vicencio et al. 2004), CCN2 overexpression during development results in a lung phenotype analogous to BPD (Wu et al. 2009). CCN2 and another matricellular protein, SPARC (for Secreted Protein, Acidic, Rich in Cysteine) are early markers of fibrosis in various diseases and lung injury models (Leask et al. 2009; Wu et al. 2008; Chang et al. 2010; Strandjord et al. 1999). Neonatal lung mesenchymal stromal cells have high levels of mRNAs encoding matricellular proteins, including CCN2, SPARC and periostin (Bozyk et al. 2011).

CCN2 is a cysteine-rich protein possessing a secretory signal peptide, a non-functional IGF binding domain, a

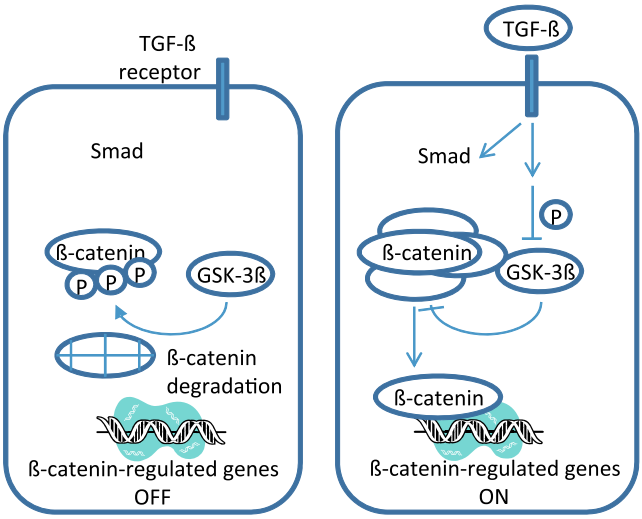

Fig. 1 GSK-3β, a constitutively-active kinase normally phosphorylates β-catenin. Phosphorylation of β-catenin targets it for degradation, thereby preventing gene expression of regulated genes (e.g. α-actin, collagen, fibronectin, laminin, matrix metalloproteinases, VEGF). Phosphorylation of GSK-3β inactivates it, allowing β-catenin to accumulate in the cytoplasm, translocate to the nucleus, and activate gene expression

VonWillebrand factor-like domain for TGF-β binding, a thrombospondin-like domain for binding to sulfated glycoconjugates, and a heparin-binding cysteine knot domain which binds the cell surface and allows dimerization. In Mink lung epithelial cells and embryonic fibroblasts, CCN2 enhances binding of TGF-β to its three receptors and is required for a subset of TGF-β responses, inducing a cellular response not achieved by either factor alone (Abreu et al. 2002; Shi-wen et al. 2006). Conversely, TGF-β is required for a subset of CCN2 responses (Qi et al. 2005; Sohn et al. 2006). Overexpression of CCN2 in respiratory epithelial cells during the neonatal period induces thickening of the alveolar septa, decreased secondary septal formation, myofibroblast differentiation (Wu et al. 2009) and pulmonary hypertension (Whitehead et al. 2006). CCN2 expression is increased within 30 min of

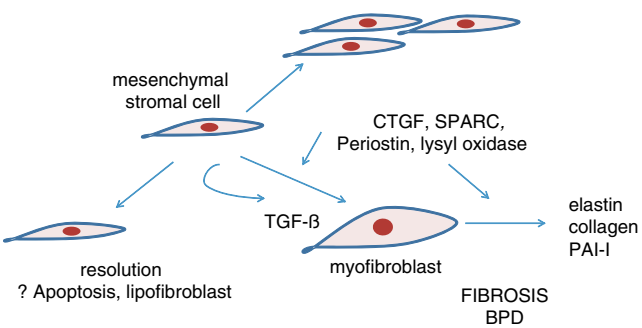

Fig. 2 Proliferation and myofibroblastic differentiation of mesenchymal stromal cells, mediated by matricellular proteins such as CCN2 and periostin, leads to fibrosis and development of BPD. (Apoptosis or adipogenic differentiation lead to resolution of lung injury.)

mechanical ventilation in preterm lambs (Wallace et al. 2009) and after high tidal volume ventilation in newborn rat lungs (Wu et al. 2008). Hyperoxic exposure increases lung CCN2 mRNA and protein expression, not only in epithelial cells, but in lung mesenchyme and thickened alveolar interstitia. (Popova et al. 2012). Overexpression of CCN2 in mouse lungs also increases whole lung Ser^9 GSK-3β phosphorylation and nuclear localization of β-catenin, and CCN2 induces β-catenin nuclear translocation in primary alveolar type II epithelial cells (Whitehead et al. 2006). CCN2 induces GSK-3β phosphorylation and β-catenin accumulation in neonatal lung MSCs, and CCN2 expression is also increased in the lungs of infants with BPD. Together, these data are consistent with the notion that CCN2, perhaps in combination with TGF-β, is responsible for GSK-3β/β-catenin signaling and myofibroblastic differentiation observed in neonatal mice, as well as in human infants with BPD (Popova et al. 2012).

SPARC is a secreted extracellular matrix glycoprotein possessing an N-terminal secretory signal peptide, a combined follistatin-like region and acid protease-like inhibitor region and a collagen-binding region. SPARC allows efficient incorporation of collagen into extracellular matrix and formation of mature, insoluble fibers by diminishing its association with cell surfaces, favoring its degradation by cell surface-associated collagenases (Rentz et al. 2007). SPARC is increased in fibroblasts from patients with idiopathic pulmonary fibrosis (Chang et al. 2010) and required for maximum collagen accumulation in bleomycin-treated mice (Strandjord et al. 1999).

Periostin is a secreted protein with an N-terminal secretory signal sequence and 4 fasciclin domains. It directly interacts with other extracellular matrix proteins and is a ligand for αvβ3, αvβ5 and α4β6 integrins. In the heart, periostin is induced by TGF-β but also required for normal TGF-β responsiveness (Snider et al. 2008). Periostin promotes myofibroblast differentiation of palmar fascia mesenchymal cells (Vi et al. 2009) and is a component of subepithelial fibrosis in asthma (Takayama et al. 2006). Lysyl oxidase, which cross-links collagen and elastin, is proteolytically activated by CCN2 and periostin (Hong et al. 1999; Maruhashi et al. 2010). Lung lysyl oxidase immunoreactivity is increased in BPD (Kumarasamy et al. 2009). We examined the role of periostin in hyperoxia-induced neonatal lung injury. Hyperoxic exposure of neonatal mice increases alveolar wall periostin expression, particularly in areas of interstitial thickening. Periostin colocalizes with α-smooth muscle actin, suggesting synthesis by myofibroblasts (Bozyk et al. 2012). A similar pattern is found in lung sections of infants dying of BPD. Periostin knockout mice are protected from hyperoxia-induced alveolar simplification and show absence of α-smooth muscle-positive interstitial myofibroblasts. Compared to hyperoxia-exposed wild-type mice, hyperoxia-exposed periostin null mice also

showed reduced mRNA expression of α-smooth muscle actin, elastin, CXCL1, CXCL2, CCL4. Together, these data suggest that excess periostin deposition promotes hyperoxia-induced lung inflammation in neonatal mice. In addition, these data show that, in addition to mediating lung fibrosis, periostin may regulate lung inflammation.

Summary

Alterations in lung development following premature birth involve a complex interplay between cellular and molecular components with diverse structural (epithelial, mesenchymal or vascular) origins. Both resident and recruited cells of hematogenous origin participate. The use of advanced molecular and genomic techniques has improved the understanding of these interactions and provides a source for future therapeutic or preventive strategy development.

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