Eur Respir J 2010; 36: 716–717
DOI: 10.1183/09031936.00070210

EDITORIAL

Lung development, lung growth and the future of respiratory medicine

S. Ranganathan

Most respiratory physicians will agree that the lung is a sexy organ and worthy of intense study. We understand its significance as an important biological system. Respiratory diseases are responsible for ~50% of acute medical conditions in children and rank second to cardiovascular disease in causing morbidity and mortality at a cost of well in excess of €100 billion to the European Community [1]. A major driver in research over the last two decades has been the unlocking of the so-called ''silent period'' in the preschool years where, until recently, there was a dearth of knowledge about early disease development, lung growth and physiology. As our knowledge increases, it is becoming apparent that these early years of life are extremely important, for it is the time during which many chronic respiratory diseases appear to have their origin. For example, persistent asthma arising from interactions between genetic predisposition and infection and allergy-induced airways inflammation results in airway remodelling that occurs during the first 3 yrs of life [2]. Lung function in older children with asthma appears to ''track'' into adulthood, and studies are currently investigating the interaction between childhood asthma and the development of chronic obstructive pulmonary disease in later life [3]. In cystic fibrosis, lung disease appears to start soon after birth, with pulmonary inflammation and infection leading to the development of structural [4] and functional changes [5] within the first few months of life. Lung function in those born prematurely but without chronic lung disease appears to be lower than term-born infants, and longitudinal studies suggest that ''catch-up'' in lung function does not occur [6]. This has been interpreted as suggesting that postnatal lung growth and development are affected in such infants, even in the absence of obvious direct insults to the lung. Our understanding of bronchopulmonary dysplasia (BPD) has evolved as our understanding of lung development has increased. In the presurfactant era, the histopathology of this condition was characterised by severe airway epithelial hyperplasia and squamous metaplasia, marked airway smooth muscle hyperplasia, extensive diffuse fibroproliferation and remodelling of pulmonary arteries in addition to decreased alveolarisation and surface area. In contrast, the introduction of exogenous surfactant therapy and improved medical management results in the ''new'' BPD, where the histology now appears to represent less a pattern of lung injury but more a developmental arrest in alveolarisation and vascular growth [7].

CORRESPONDENCE: S. Ranganathan, Brighton and Sussex Medical School, Dept of Paediatrics, 10th floor, Royal Alexandra Hospital for Children, Brighton, BN2 5BE, UK. E-mail: sarath.ranganathan@rch.org.au

Since common chronic respiratory conditions start in the early years of life better understanding of how the lung develops is essential so that novel therapies can be developed to prevent, limit or even reverse the impact of insults on the growing lung. Although the process of lung development is continuous, it is classically taught as consisting of five development epochs, the embryonic, pseudoglandular, cannalicular, saccular and alveolar stages, with the last being predominantly postnatal in humans. In the embryonic stage the lung develops as an outpouching of the ventral foregut. The distal portion develops into two venrolateral buds that grow into the adjacent splanchnic mesoderm and undergo dichotomous branching morphogenesis during the pseudoglandular stage, establishing the full complement of airways by about 17 weeks' gestation. The epithelium of the respiratory tract is endodermally derived but invested by cells of mesodermal origin. Subsequent stages of the lung are characterised by increased vascularisation and mesenchymal reduction to form airway smooth muscle, lymphatics, tracheal cartilage, the pleura and an efficient gas exchange interface. Growth factors such as fibroblast growth factor, hedgehog, retinoic acid, bone morphogenetic protein and responsive transcription factors orchestrate the complex process of epithelial–mesenchymal interactions required for primary lung bud induction, tracheo-oesophageal septation, branching morphogenesis and proximal–distal epithelial differentiation [8].

The majority of current knowledge on lung development is derived from studies conducted in mice, rats and cell models. Studying the role of individual growth factor signalling has involved experimental strategies such as using simplified models, immunolocalisation of signalling factors, blocking or inhibiting the actions of signalling molecules using neutralising antibodies, determining the timing of expression of genes coding for growth factors using *in situ* hybridisation and immunohistochemistry, and creation of animal models that overexpress or are deficient in signalling molecules or their receptors [8]. Such studies using knockout or transgenic animal models have resulted in significant progress in identifying determinants of embryonic lung morphogenesis and cell lineage differentiation over the last decade, partly because the action of these growth factors seems to be highly evolutionarily conserved with significant functional homology [9]. However, our understanding is certainly far from complete.

One example where current knowledge is limited is the role of members of the transforming growth factor (TGF)-β family in lung development. We do know that TGF-β has important

functions in pattern formation and tissue specification during embryonic development [10] and that both increased and decreased levels of TGF-β have been described in infants with BPD [11]. In cultured rat lung fibroblasts, TGF-β1 has been shown to increase elastin gene expression [12]. Elastin deposition by alveolar myofibroblasts is an essential component of the process of airspace septation and alveolarisation [13]. However, both gain [14] and loss of function [15] studies in mouse models suggest that TGF-β signalling is important, resulting in inhibition of branching morphogenesis and hypoplastic lungs when transgenically overexpressed or following selective abrogation of its signalling, and thus indicating that TGF-β signalling needs to be tightly regulated for normal development to occur.

Despite the evolutionary homology in growth signalling pathways, the abundance and localisation of the distinct cell types lining the lung vary considerably among species [16]. One recommendation of a recent workshop organised by the National Institutes of Health National Heart Lung and Blood Institute (Bethesda, MD, USA) was to ''develop and characterize biologically significant model systems that reproduce specific microenvironments and provide insights into niche-specific signalling events'' [16]. In the current issue of the *European Respiratory Journal*, TARANTAL *et al.* [17] assessed the role of excessive focal activation and overexpression of TGB-β at defined developmental stages in fetal Rhesus monkeys. Such a non-human primate model is likely to provide greater insight into human lung development than mouse models as Rhesus monkeys share 93% of their genes with humans [18]. The investigators used transabdominal ultrasound-guided fetal intrapulmonary injection of adenoviral vector expressing TGF-β1 in the late second or third trimester of pregnancy (representing the cannicular and saccular stages of lung development, respectively) of fetal monkeys in order to overexpress exogenous TGF-β1 transiently. Fetuses were sonographically assessed to confirm normal growth and development prior to gene transfer and then post-gene transfer until the animals were sacrificed near term. When the lungs were harvested the predominant phenotype was that of severe pulmonary and pleural fibrosis. Lung hypoplasia was also evident when transfection occurred in the cannalicular stage but was mild. Overexpression of TGF-β1 also triggered cell proliferation in mesenchymal cells that appeared to continue in a TGF-β1-independent manner after the overexpression of exogenous TGF-β1 had been discontinued. There was also evidence for an increase in extracellular matrix deposition. Does this experiment suggest a good model for the study of chronic lung disease in human infants? Not really. Although septal fibrosis is the predominant phenotype of the classic ''old'' BPD described by NORTHWAY *et al.* [19] in 1967, pleural fibrosis as identified here as a result of transient exogenous TGF-β1 was not a predominant feature, whereas ''new'' BPD is characterised by the lack of fibrosis. However, the study highlights the feasibility of studying growth factor signalling in the non-human primate lung and the potential importance for the future study of human lung development. Together with other groups working on lamb and baboon models, data will be crucial to our ability as clinicians to impact significantly on respiratory disease in the future. However, one caveat to bear in mind is that 25 million years of evolution separates humans from Rhesus monkeys and so caution will always be required when assessing the applicability and translation of results to humans [18].

STATEMENT OF INTEREST

None declared.

REFERENCES

1 European Respiratory Society and The European Lung Foundation. European Lung White Book. Sheffield, European Respiratory Society Journals Ltd, 2003.
2 Saglani S, Payne DN, Zhu J, *et al.* Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007; 176: 858–864.
3 Tran H, Tai A, Roberts M, *et al.* The development of COPD in a cohort study of childhood asthma. *Respirology* 2010; 14: Suppl. 1, A3.
4 Sly PD, Brennan S, Gangell C, *et al.* Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. *Am J Respir Crit Care Med* 2009; 180: 146–152.
5 Linnane BM, Hall GL, Nolan G, *et al.* Lung function in infants with cystic fibrosis diagnosed by newborn screening. *Am J Respir Crit Care Med* 2008; 178: 1238–1244.
6 Friedrich L, Pitrez PM, Stein RT, *et al.* Growth rate of lung function in healthy preterm infants. *Am J Respir Crit Care Med* 2007; 176: 1269–1273.
7 Kinsella JP, Greenough A, Abman SH. Bronchopulmonary dysplasia. *Lancet* 2006; 367: 1421–1431.
8 Kimura J, Deutsch GH. Key mechanisms of early lung development. *Pediatr Dev Pathol* 2007; 10: 335–347.
9 Warburton D, Lee M, Berberich MA, *et al.* Molecular embryology and the study of lung development. *Am J Respir Cell Mol Biol* 1993; 9: 5–9.
10 Lecart C, Cayabyab R, Buckley S, *et al.* Bioactive transforming growth factor-beta in the lungs of extremely low birthweight neonates predicts the need for home oxygen supplementation. *Biol Neonate* 2000; 77: 217–223.
11 Choi CW, Kim BI, Joung KE, *et al.* Decreased expression of transforming growth factor-beta1 in bronchoalveolar lavage cells of preterm infants with maternal chorioamnionitis. *J Korean Med Sci* 2008; 23: 609–615.
12 Kuang PP, Zhang XH, Rich CB, *et al.* Activation of elastin transcription by transforming growth factor-beta in human lung fibroblasts. *Am J Physiol Lung Cell Mol Physiol* 2007; 292: L944–L952.
13 Wendel DP, Taylor DG, Albertine KH, *et al.* Impaired distal airway development in mice lacking elastin. *Am J Respir Cell Mol Biol* 2000; 23: 320–326.
14 Zhou L, Dey CR, Wert SE, *et al.* Arrested lung morphogenesis in transgenic mice bearing an SP-C-TGF-beta 1 chimeric gene. *Dev Biol* 1996; 175: 227–238.
15 Chen H, Zhuang F, Liu YH, *et al.* TGF-beta receptor II in epithelia *versus* mesenchyme plays distinct roles in the developing lung. *Eur Respir J* 2008; 32: 285–295.
16 Cardoso WV, Whitsett JA. Resident cellular components of the lung: developmental aspects. *Proc Am Thorac Soc* 2008; 5: 767–771.
17 Tarantal AF, Chen H, Shi TT, *et al.* Overexpression of transforming growth factor-β1 in fetal monkey lung results in prenatal pulmonary fibrosis. *Eur Respir J* 2010; 36: 907–914.
18 Gibbs RA, Rogers J, Katze MG, *et al.* Evolutionary and biomedical insights from the rhesus macaque genome. *Science* 2007; 316: 222–234.
19 Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967; 276: 357–368.