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The pneumonectomy model of compensatory lung growth: Insights into lung regeneration

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ABSTRACT

Pneumonectomy (PNX) in experimental animals leads to a species- and age-dependent compensatory growth of the remaining lung lobes. PNX mimics the loss of functional gas exchange units observed in a number of chronic destructive lung diseases. However, unlike in disease models, this tissue loss is well defined, reproducible and lacks accompanying inflammation. Furthermore, compensatory responses to the tissue loss can be easily quantified. This makes PNX a potentially useful model for the study of the cellular and molecular events which occur during realveolarisation. It may therefore help to get a better understanding of how to manipulate these pathways, in order to promote the generation of new alveolar tissue as therapies for destructive lung diseases. This review will explore the insights that experimental PNX has provided into the physiological factors which promote compensatory lung growth as well as the importance of age and species in the rate and extent of compensation. In addition, more recent studies which are beginning to uncover the key cellular and molecular pathways involved in realveolarisation will be discussed. The potential relevance of experimental pneumonectomy to novel therapeutic strategies which aim to promote lung regeneration will also be highlighted.

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1. Introduction

Research in animals published more than one hundred years ago established that experimental pneumonectomy (PNX) stimulates compensatory growth of the remaining lung lobes. The first successful experimental pneumonectomies were performed in dogs and rabbits in 1881 (reviewed in Schilling, 1965). By the mid 1920s it was appreciated that dogs can live normally after PNX, with the remaining lung filling up the thoracic cavity by increasing to nearly the volume of two lungs (Heuer & Dunn, 1920; Heuer & Andrus, 1922; Andrus, 1923).

In humans, although PNX had been successfully performed dating back to 1895, the survival of the patient following early attempts was limited to a few days post-surgery (reviewed in Fuentes, 2003). It was early animal research which paved the way for the successful application of the procedure to humans, initially as a treatment for chest trauma, bronchiectasis or cancer. Indeed, in 1933 the first successful left PNX was reported as a treatment for carcinoma of the bronchus (Graham & Singer, 1974). This was shortly followed by the first successful right PNX in a patient with a carcinoid tumour (Overholt, 1935). It was, however, landmark studies in dogs published by Cohn in 1939 which would provide a basis for the ongoing research around PNX and compensatory lung growth (CLG) (Cohn, 1939). This research demonstrated that compensatory growth rapidly restores normal lung mass following PNX through pathways initiated by mechanical forces and regulated by age.

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The restoration of alveolar tissue may offer a novel therapeutic approach for lung diseases associated with the loss of alveolar septa and parenchyma. Current therapeutic options for diseases of this type are limited to the treatment of symptoms rather than the prevention or reversal of the alveolar pathology. Foremost amongst such diseases is chronic emphysema which represents the alveolar component of chronic obstructive pulmonary disease (COPD). Most often a consequence of tobacco smoking, COPD is predicted to become the third leading cause of death worldwide by 2020 (Stuckler, 2008). Bronchodilators alongside drugs targeting the inflammatory component of COPD represent the current mainstay of therapies for COPD. No therapies directed toward the emphysematous component are available at this time.

Bronchopulmonary dysplasia (BPD) occurs in very low birth weight (VLBW) neonates and is principally characterised by impaired alveolar and microvascular development. BDP affects approximately one third of VLBW neonates and is the most common chronic respiratory disease in premature infants (Baraldi & Filippone, 2007). Today, with the advent of surfactant therapy and use of optimal ventilation and oxygen supplementation the prognosis for preterm infants with BPD is much improved and the incidence of perinatal morbidity and mortality is reduced. However, respiratory symptoms in children with BPD persist beyond the first 2 years of life into the preschool years, adolescence, and early adulthood. Adults in whom BPD had been diagnosed have a potential for the early onset of chronic obstructive pulmonary disease (Wong et al., 2008). Furthermore, reduction in mortality rates has led to increases in the incidence of BPD amongst VLBW infants.

Despite obvious differences in their causes, both emphysema and BPD are characterised by a deficit in alveolar number and an increase in airspace size which leads to a reduction in the surface to volume ratio of the gas exchange tissues and, as a result, respiratory insufficiency. Therapies aimed at the restoration of normal alveolar tissue might, therefore, have the potential to provide clinical benefit for both COPD and BPD. Furthermore, such therapies could be effective in other diseases with distinct pathologies (e.g. Idiopathic Pulmonary Fibrosis (IPF)) where, nevertheless, restoration of normal alveolar tissue could be of benefit.

In chronic lung diseases, studying the responses of injured regions is not easily separated from regions that are normal due to the patchy or diffuse nature of the disease. Experimental PNX has proven pivotal in characterising the physiological and structural adaptation of the lung to the loss of functional gas-exchange units owing predominantly to a number of advantages which make it conducive for this research 1) PNX mimics the loss of functional lung units seen in destructive lung diseases. 2) The loss of tissue is well defined and reproducible. 3) The remaining lung is normal and not inflamed. 4) The compensatory responses can be easily quantified.

By facilitating a greater understanding of the cellular behaviours and interactions which take place during realveolarisation, the study of experimental pneumonectomy could be crucial in the advancement of therapeutic approaches aimed at restoring alveolar tissue. In particular, insight into the molecular pathways involved in realveolarisation may facilitate the identification of novel therapeutic targets, particularly if these pathways are found to be relevant to the restoration of lung tissue in the context of the disease. Therefore, in addition to discussing the physiological factors which promote compensatory lung growth in response to PNX as well as the importance of age and species in the rate and extent of this compensation, we will review our current understanding of the cellular and molecular pathways involved. This understanding may provide new opportunities for the field of lung regeneration and repair as a novel area for therapies of chronic destructive respiratory diseases.

2. Functional compensation with and without lung growth

It is well known that the lung possess a large amount of capacity that is not utilised for gas exchange at rest. The terms 'safety reserve' and 'physiological reserves' describe the differences between basal and maximal oxygen flux across gas exchange surfaces at peak exercise (Weibel et al., 1998). These reserves are recruited immediately following PNX to compensate for the loss of oxygen transport (Hsia et al., 1993). In part this occurs by the augmentation of gas exchange surfaces through the unfolding of alveolar epithelium which are not completely utilised prior to PNX. This is accompanied by increased pulmonary blood flow as a result of opening and distension of alveolar microvessels and redistribution of capillary blood flow. These adjustments are capable of increasing the diffusing capacity of the remaining lung by 40 to 50% (Hsia et al., 1991; Hsia, 2002) and through this exploitation of the remaining lungs' reserves, adequate lung function can be maintained following PNX without growth of alveolar tissues. Indeed, there is clinical evidence which supports the idea that the compensatory response which takes place following PNX in adults is the recruitment of these reserves rather than lung growth. A number of studies have demonstrated that the functional volume of the lung remaining after PNX in adults is greater than predicted values (reviewed by Tronc et al., 1999) however this is accompanied by increased residual volume which is consistent with compensation occurring through dilation of air spaces. For example, Jones et al. (1960) showed that in adult PNX patients, the remaining total lung capacity was 58% of that expected for an adult with both lungs intact, however, the residual volume was 85%. These results have been interpreted as evidence supporting an absence of true compensatory lung growth in adult humans.

This assertion was challenged by a clinical study in which serial CT scans and plethysmography as well as MRI was performed on a woman who had undergone a right-sided PNX 15 years earlier at the age of 33 years (Butler et al., 2012). The plethysmography and CT imaging were consistent with an increase in lung volume over time. In addition, MRI imaging after inhalation of hyperpolarised helium-3 gas was able to provide a measure of airway radial dimension which was homogenous across the remaining lung and similar in magnitude to a normal lung. It was suggested that these data were consistent with a significant increase in alveolar number in this patient.

Lung volume reduction surgery (LVRS), is a surgical treatment for emphysema where the most diseased and hyperinflated lung tissue is resected. A number of longitudinal studies have been performed in which improvements in lung function as well as exercise capacity and quality of life have been reported following LVRS in emphysema patients (Brown et al., 2012; Baldi et al., 2012; Fishman et al., 2003). Furthermore, increases in the volume of residual lobes have been reported in a subset of these studies, however the data presented does not address whether these changes occur through airspace dilation or compensatory lung growth. The debate over the ability of the adult human lung to undergo compensatory lung growth following PNX still remains unresolved.

In experimental PNX, the question of whether compensatory lung growth and consequent increases in lung volume are primarily due to the formation of new alveoli or the expansion of pre-existing alveoli is also controversial. A number of studies have reported the addition of new septa and hence the formation of new alveoli in the residual lung following PNX (Cagle et al., 1988; Sekhon & Thurlbeck, 1992; Hsia et al., 1993) whilst other studies have reported growth in the sizes of existing alveoli (Buhain & Brody, 1973; Fehrenbach et al., 2008). Much of the controversy is based on practical and theoretical difficulties in counting alveoli or calculating the number of alveoli per unit volume. This poses methodological problems because a) alveoli are not discrete but constitute a network of saccules opening into an alveolar duct, which makes it difficult to unambiguously define an individual alveolus in a single histological section and b) there is a high degree of diversity in the geometric shape of alveoli. Indeed, early studies were based on quantitative morphological methods for counting alveoli that are susceptible to bias because: 1) only single sections were used, 2) assumptions about specific geometric shapes of alveoli were made, 3) the samples studied were non-uniform, and 4) the data were not corrected for shrinkage (Weibel & Gomez, 1962; Weibel et al., 1998). More recently the use of stereology (i.e. the three-dimensional interpretation of planar sections) to eliminate bias when quantitating alveolar number