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# Compensatory Lung Growth After Pneumonectomy

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## 1. Introduction

Pneumonectomy, the surgical removal of a lung, elicits a number of anatomical changes within the thoracic cavity that augments the diffusion capacity of the remaining lung. Pneumonectomy directs the entire cardiac output into the remaining lung and creates an empty hemithorax that results in a shift of the mediastinum toward the vacated thoracic compartment. In a number of experimental animal models, pneumonectomy initiates compensatory, regenerative growth of the remaining lung tissue that restores normal mass, structure and function. This growth process, called compensatory lung growth (CLG), is qualitatively similar across species, but differs with gender, age and hormonal status. CLG involves unique structure-function interactions not seen in solid organs. Little is known about the regenerative potential of human lungs. Although CLG has been reported in children after major lung resection, CLG in adults rarely occurs and remains a significant challenge. Mechanical feedback between the lung and thorax constitutes a major signal that sustains both post-natal lung development as well as post-pneumonectomy CLG. After pneumonectomy, increased mechanical stress and strain on the remaining lung induce adaptive responses to augment oxygen transport, including 1) recruitment of alveolar-capillary reserves, 2) remodeling of existing tissue, and 3) regenerative growth of acinar tissue when strain exceeds a critical threshold. This chapter will discuss the clinical aspects of pneumonectomy and will primarily review cellular and molecular mechanisms of CLG via experimental pneumonectomy models, which offers powerful insights into regenerative organ growth.

## 2. Clinical pneumonectomy

### 2.1 Historical perspective

Before the 1930s, all pneumonectomies in humans were fatal due primarily to complications such as hemorrhage and sepsis. Another major challenge was to perform lung surgery with an open pneumothorax. A significant step to solve this problem was taken in 1903 by Ferdinand Sauerbruch, who designed a negative pressure chamber that allowed a team of surgeons to operate within the open chest without collapse of the lung (Sauerbruch, 1953). Sauerbruch brought his machine to New York in 1908, where Willy

Meyer modified it to work with positive and negative pressure. Meyer successfully performed pulmonary resections in dogs in 1909 using suture closure of the bronchus and individual vessel ligation (Meyer, 1909), but he did not attempt his technique in humans. Years later, Quinby and Morse used a modification of this technique in dogs and showed that after pneumonectomy, the hemithorax fills with fluid and the remaining lung will shift to this empty side (Quinby & Morse, 1911). After the experimental use of endotracheal delivery of oxygen and anesthetics (Meltzer & Auer, 1909), Howard Lilienthal performed the first thoracotomy under endotracheal anesthesia at Mount Sinai Hospital (Lilienthal, 1910). He also had the largest published series of lobectomies, which he considered dangerous, reaching a mortality rate of 70% if more than one lobe was removed (Lilienthal, 1922). The first successful case of total pneumonectomy was described in 1931 by Roudolph Nissen in Berlin. The patient was a 12 year-old girl with trauma injury of the left chest (Naef, 1987). She recovered completely after two months, and Nissen was quoted saying that the occlusion of the pulmonary artery did not cause cardiopulmonary collapse as predicted 20 years earlier by Quinby and Morse. A year later, Cameron Haight was the first surgeon to perform a successful pneumonectomy in the west at the University of Michigan, USA (Haight, 1934). This time, a 13 year-old girl developed pneumonia in the left lung and subsequent pyopneumothorax. After a small bronchial fistula, she recovered 3.5 months later. On April 1933, Evarts Graham performed the first successful pneumonectomy for cancer disease in a 48 year-old patient with a squamous cell cancer of the left upper lobe bronchus that survived almost 30 years after surgery (Graham & Berck, 1933). In his paper, Clarence Crawford standardized the pneumonectomy technique used for many years, including the use of periscapular incision, individual vessel ligation, suture closure of the bronchus and a new rhythmic ventilatory technique (O'Shaughnessy & Crawford, 1938). In 1950, the introduction of a new double lumen tube allowed the ventilatory exclusion of the operated side (Bjork & Carlens, 1950). By the 1970s, a new technique changed the surgical method with the design of surgical staplers for lung resection. The first successful thoracic surgery performed using video assisted thoracic surgery (VDATS) was for treatment of pneumothorax in 1990. Shortly thereafter the first descriptions of pulmonary lobectomies and pneumonectomies appeared (Davies & Panasuk, 1992). There has been steady progress in thoracic surgery and pneumonectomy in particular through the years, with advances in knowledge of respiratory physiology, anesthetics and ventilation techniques, as well as more sophisticated methods of lung resection. These advancements have transformed pneumonectomy surgery from a "dangerous procedure" to become a very useful treatment for both malignant and non malignant diseases of the lung and airways.

## **2.2 Indications and risk factors**

Pneumonectomy is known to be associated with high morbidity and mortality. However, in certain instances, it offers the only chance for a cure. The indications for pneumonectomy are usually classified in two major groups: pneumonectomy for benign disease and pneumonectomy for malignant disease. Due to the improvement of antimicrobial therapies and better control of inflammatory diseases, pneumonectomy for benign diseases is not a routine procedure in our times. The conditions considered in this group belong to several categories including inflammatory, traumatic, congenital and other miscellaneous

conditions (Conlan & Kopec, 1999). These conditions carry a high mortality rate in most cases, but some examples of non-malignant disease have an excellent cure rate. Indications for pneumonectomy in cases of bacterial or fungal infections include symptomatic patients with hemoptysis, productive cough or chronic empyema, as well as unilateral lung destruction documented by CT or bronchography (Blyth, 2000). In patients with pulmonary tuberculosis, pneumonectomy is indicated for either multidrug resistance disease or for complications or sequelae of tuberculosis infection. The most common fungal infection that requires pneumonectomy is produced by *Aspergillum*, which can produce severe infections with recurrent or massive hemoptysis in over 75% of patients (Conlan, et al., 1987). Pneumonectomy for trauma is uncommon, but is associated with high morbidity and mortality (66-75%). The most obvious indication of the procedure is the laceration of the lung and airways, which can produce massive hemorrhage and air leakage. Complications of congenital and other miscellaneous lung diseases, as well as completion pneumonectomy are rare indications for pneumonectomy, which can be associated with high mortality. Pneumonectomy for malignant disease has become the most common indication for lung resection today, which includes both primary lung tumors and metastatic lung disease. It is regarded as the only curative treatment for non small cell lung cancer (Shields, 1982) and also as an effective therapeutic option for pulmonary metastasis; however, these can be associated with high mortality (Spaggiari, et al., 1998).

### **2.3 Morbidity and mortality**

Pneumonectomy is associated with a 38-59% rate of morbidity and a 30-day mortality ranging from 3-12%. Postoperative cardiac dysrhythmias (e.g., atrial fibrillation and supraventricular tachycardia) are relatively common complications occurring in approximately 20-40% of patients following pneumonectomy. Postpneumonectomy pulmonary edema (PPE) and acute respiratory distress syndrome (ARDS) occur in 4-7% of patients and are increasingly believed to be the same disease process. PPE/ARDS results in noncardiogenic pulmonary edema and is manifest by diffuse pulmonary infiltrates on chest radiograph combined with profound hypoxia and respiratory failure frequently requiring mechanical ventilation. One of the more devastating complications of pneumonectomy is an empyema involving the postpneumonectomy space. A postpneumonectomy empyema is usually associated with a bronchopleural fistula (BPF), which is a communication between the mainstem bronchial stump and the pleural cavity. The incidence of BPF and empyema ranges from 2-8%, but both complications are significantly more common in patients who undergo pneumonectomy for septic pulmonary disease (e.g., tuberculosis or fungal disease) (Deschamps, et al., 2001). Postpneumonectomy syndrome is a rare complication characterized by stridor, dyspnea and recurring pneumonia. Postpneumonectomy syndrome is more common following right pneumonectomy and results from severe shifting of the mediastinum and contralateral lung into the postpneumonectomy pleural space, which in turn leads to compression of the contralateral mainstem bronchus between the vertebral bodies and descending aorta (Kopec, et al., 1998).

### **2.4 Physiological changes**

Pneumonectomy results in reduced lung function. Although residual volume (RV) declines after pneumonectomy, it decreases less than expected as a result of the hyperexpansion that

occurs in the remaining lung. Forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) both typically decrease by 25-40%. Diffusion capacity usually decreases by less than 50% whereas PaO<sub>2</sub> and PaCO<sub>2</sub> typically remain unchanged from preoperative levels (Kopec, et al., 1998).

### **3. Experimental CLG following pneumonectomy**

The removal of a lung entails profound mechanical, metabolic and vascular changes in response to the reduction in lung volume and the empty space in the hemithorax. These changes trigger a compensatory response in experimental models, known as CLG, which are directed toward reestablishing the normal rate of oxygen exchange capacity. This section describes a number of experimental animal models of CLG that are currently used to study this process, as well as a detailed evaluation of the CLG response in these models, including lung morphometry and imaging.

#### **3.1 Animal models**

In many animal models, pneumonectomy (or lobectomy) induces CLG of the remaining lung, resulting in rapid restoration of total lung volume, compliance, mass, DNA, protein, alveolar number, and normal lung cell populations. Pneumonectomy has proven to be a reliable model for characterizing the sources, mechanisms, and functional limits of the compensatory growth response after removal of lung tissue. Pulmonary resections in animals began in 1881 when it was documented that the remaining lung eventually expands to the same size as both lungs. Early animal studies established the basis for application of the procedure to humans, beginning in the 1900s. Cohn in 1939 first established mechanical forces as a major signal for the compensatory increase in lung mass following lobectomy. In the 1950s, Schilling detailed the well-preserved functional status in dogs that underwent removal in stages of up to nearly 70% of lung mass (Schilling, et al., 1958). The use of small animals (e.g. rabbit, rat, and mouse) from the 1960s to the current day has had a great impact in uncovering the hormonal, cellular, and molecular responses to pneumonectomy (Bennett, et al., 1985; Buhain & Brody, 1973; Rannels, et al., 1979; Romanova, et al., 1967). Significant progress in understanding the cellular and molecular pathways of tissue regeneration in vertebrates were achieved using both transgenic mice and molecular biology techniques (Leuwerke, et al., 2002; Sakamaki, et al., 2002; Sakuma, et al., 2002). Functional compensation to pneumonectomy has been described mainly in dogs to define the limits of such compensation (Ravikumar, et al., 2004; Takeda, et al., 1997).

#### **3.2 Alveolar growth**

Alveolar epithelial cells in pneumonectomized rats exhibit metabolic changes typical of accelerated cell growth. Studies in mice and rats indicate that type II epithelial cell hypertrophy, proliferation and differentiation into type I cells characterize CLG in a fashion similar to early postnatal lung growth and lung repair after injury (Kaza, et al., 2002).

The post-pneumonectomy CLG response is independent of the lobe or lobes removed in small animals; and all remaining lobes grow rapidly until normal total lung mass is

restored. Increases in lung volume after pneumonectomy parallel accumulation of tissue growth. However, the increase of growth in the remaining lobes is not uniform (Fernandez, et al., 2007). Development of sophisticated morphometric methods has permitted accurate analysis of lung volume and alveolar number, and studies indicate that new alveoli are formed during post-pneumonectomy CLG (Kaza, et al., 2002; Sakamaki, et al., 2002). In dogs, however, it appears that the CLG response is initiated after a certain threshold is achieved (removal of >50% of total lung mass) (Hsia, et al., 1994). Bronchoalveolar stem cells (BASC) have also been implicated in CLG. Their proliferation and differentiation into alveolar epithelial cells type II and I, contribute between 0-25% to the regenerative lung growth process (Nolen-Walston, et al., 2008).

### 3.3 Vascular growth and angiogenesis

Vascular growth and angiogenesis during CLG has not been well characterized. Stimuli known to initiate angiogenesis include hypoxia, inflammation, and mechanical factors such as shear stress and stretch. Our laboratory has shown that angiogenesis is necessary for successful CLG by demonstrating that angiogenesis inhibitors such as fumagillin or thalidomide prevented increased lung weight and volume after pneumonectomy (Maxey, et al., 2003). We have also shown that pneumonectomy induces arterial growth including the increase in length and number of branches of pulmonary arteries and that these changes are proportional to the amount of tissue removed (Le Cras, et al., 2005). When a bilobectomy was performed in rats (24% of lung tissue removed), the arterial area of the remaining lung increased by 26% compared to sham animals. Furthermore, when lung resection was more extensive (trilobectomy, 52%) we found that the increase in arterial area increased by 47% (Le Cras, et al., 2005). Other researchers have shown the effects of exogenous angiogenic factors, such as vascular endothelial growth factor (VEGF) in the mouse model. Additional VEGF therapy accelerated the CLG response, which was completed in only 4 days compared to 10 days in the pneumonectomy control group (Sakurai, et al., 2007).

## 4. Initiation of CLG

Several general hypotheses have been advanced to account for events that initiate the cellular and molecular changes that lead to CLG. Mechanical signals, transient hypoxia associated with thoracotomy, and elevated blood flow have been considered; however, no single event has been proven to account for the growth response.

### 4.1 Mechanical forces

After resection of the lung, increased inflation of the remaining lung and increased blood flow will induce stretch in both alveolar and endothelial structures. The displacement of the lung to the empty hemithorax is also a feature of CLG. These mechanical forces have an important role in initiating and regulating CLG as it was demonstrated when lateral displacement of the lung was restricted by the use of an inflatable prosthesis. This prevention of the mediastinal shift significantly limited mechanical lung strain, and CLG was thus significantly impaired by 30-60% (Hsia, et al., 2001). Another factor, increased alveolar inflation, was also implicated when experiments using *in vitro* perfusion of lungs

with or without constant positive pressure ventilation (CPAP) of 20 cmH<sub>2</sub>O, demonstrated that lungs with increased inflation had cellular hyperplastic changes, such as elevated levels of cAMP and PKA activity, but perfusion alone did not account for these changes (Russo, et al., 1989). It is clear that CLG is very complex with multiple metabolic factors. Hyperinflation and stretch applied to the remaining lung after pneumonectomy are powerful signals to initiate CLG, and it is known that stretch of alveolar cells induces important changes associated with cell growth and septal formation, including signal transduction, protein turnover, growth factor production, proliferation, and apoptosis (Brody, 1975; Davies, et al., 1982; Fehrenbach, et al., 2008; Karl, et al., 1989). It appears that lung stress and strain generated after pneumonectomy, overlaid on a background of heightened developmental lung strain generated by the expanding thorax, intensifies the CLG responses. Importantly, minimizing post-pneumonectomy strain of the remaining lung with space-occupying, inert material blunts the CLG response.

#### **4.2 Elevated blood flow**

Post-pneumonectomy changes in pulmonary blood flow have been considered as possible signals for CLG. Increased perfusion, reflecting elevated cardiac output to the remaining lung, likely causes physical distention of the pulmonary vasculature, resulting in a mechanical signal for lung growth and a concurrent increase in the growth factor and/or nutrient availability to the lung. It has been described that, after banding of the left caudal pulmonary artery in ferrets that reduced blood flow to the lung by 25%, CLG still occurred after pneumonectomy. However, the caudal lobes in the banded animals were 17% smaller than those of non-banded animals and tended to have lower protein content (McBride, et al., 1992). In our laboratory, we have shown that after left pneumonectomy, increases in growth and proliferation were not uniform among the right lobes but were greater in the upper and cardiac lobes. These unequal changes coincided with a predominant vascular growth in the upper lobe, which received the highest fraction of relative blood flow (Fernandez, et al., 2007).

#### **4.3 Hypoxia**

Hypoxia has been shown to stimulate alveolar growth either directly or via interaction with other signals. The effects of hypoxia after pneumonectomy were initially described in the rat model, where pneumonectomized rats that recovered at hypoxic levels showed significant increases in lung weight and volume indices, increased alveolar surface area and total alveolar numbers compared to normoxic and hyperoxic rats (Sekhon, et al., 1993). Hypoxia-inducible factors (HIFs), which are activated in response to oxidative stress, hypoxia, injury, and physical forces, regulate transcription of genes involved in a wide array of functions including glycolysis, erythropoiesis, apoptosis, and angiogenesis. Most of these stressors are directly or indirectly associated with a change of intracellular oxygen tension, which leads to stabilization of the HIF-1 $\alpha$  protein and increases the transcriptional activation of target genes. Elevated hypoxia-induced mitogenic factor (HIMF) and HIF-1 $\alpha$  mRNA and protein expression has been documented during CLG, thus these pathways may play an important role in mediating CLG (Li, et al., 2005; Zhang, et al., 2006; Zhang, et al., 2007).

## 5. Molecular mediators of CLG

The molecular mediators of CLG remain poorly understood. CLG involves regulated pathways of cell cycle activity, cell differentiation, synthesis and organization of connective tissue components, tissue remodeling, and angiogenesis. Studies in animals have led to several hypotheses that various pathways play a role in the induction of CLG including post-operative release of hormones and growth factors, as well as changes in cellular behavior. This section describes several important aspects of post-pneumectomy CLG regulatory mechanisms.

### 5.1 Hormones

The most substantial evidence for hormonal regulation of CLG stems from investigations that involved surgical ablation of the adrenal glands, or adrenalectomy, which alone does not stimulate lung growth. Adrenalectomy performed prior to pneumectomy increases the rate and extent of CLG above that observed in rats after pneumectomy alone. This stimulatory effect on lung growth was blocked by daily doses of hydrocortisone acetate, evidenced by parameters such as dry lung weight and DNA content, which were similar to the pneumectomy group (Bennett, et al., 1985). This blocking effect was found only if the therapy was used continuously for the entire period after surgery (Rannels, et al., 1987). A combination of dexamethasone, 8-bromo-3'-5'-cAMP and isobutylmethylxanthine (DCI) has been successfully used to accelerate CLG in mice, represented by an increase in lung dry weight index and an increased number of alveoli by morphometric analysis. The effect of a single airway dose was enough to maintain the effect for the entire 28-day period of study. This effect seems to be modulated by thyroid transcription factor 1 (TTF-1), since its transient inhibition attenuated CLG (Takahashi, et al., 2011). Adrenal glucocorticosteroids seem to have a role in the modulation of the accelerated CLG initiated by pneumectomy. Several lines of evidence suggest a possible role of growth hormone in the regulation of CLG. Significantly higher serum levels of growth hormone were detected in pregnant rats 3 days after pneumectomy when compared with sham and unoperated rats (Khadempour, et al., 1992). In diabetic rats, which normally have greater levels of growth hormone and adrenal corticosteroids, pneumectomy was accompanied by an increased dry lung weight index as well as higher elastin and collagen content, when compared to control pneumectomy and sham rats (Ofulue & Thurlbeck, 1995). Following pneumectomy, rats implanted with a subcutaneous growth hormone-secreting tumor (MtTF4) underwent a CLG response similar to non-tumor-bearing controls; however, lung growth in MtTF4 rats was associated with a greater lung volume.

### 5.2 Growth factors

There is ample evidence that growth factors regulate CLG, and the production of many growth factors is known to be sensitive to mechanical strain. Each growth factor modulates different aspects of cellular growth, but any one growth factor cannot recapitulate the entire CLG response, and there is much functional overlap among growth factors. Our laboratory, among others, has demonstrated important roles for epidermal growth factor (EGF), hypoxia-induced mitogenic factor (HIMF), keratinocyte growth factor (KGF) and retinoic



acid in CLG. Other growth factor signaling pathways have been found to be activated after PNx including insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), erythropoietin receptor, and hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ). These growth factors will be discussed below.

### 5.2.1 Epidermal growth factor (EGF)

It is been shown that EGF via its receptor (EGFR) plays a role in prenatal and postnatal lung development. Its actions involve the synthesis of surfactant precursors and the differentiation of type 2 epithelial cells. Using a pig lobectomy model, our laboratory demonstrated an upregulation of EGFR expression two weeks after lobectomy, which coincided with an increased alveolar cell proliferation index of the remaining lung. At 3 months after surgery, there was an increase in the lung protein/DNA ratio in the lobectomy group compared to controls (Kaza, et al., 2001; Kaza, et al., 2002). We also have documented the effects of EGF in CLG using a rodent pneumonectomy model. When exogenous EGF was administered to rats after pneumonectomy, it caused significantly higher lung weight and volume indices when compared to pneumonectomy control animals. We also detected an upregulation of EGFR after exogenous EGF supplementation (Kaza, et al., 2000), suggesting that the upregulation of EGF signaling is a feature of this process and is capable of modulating post-pneumonectomy CLG.

### 5.2.2 Erythropoietin (EPO)

Erythropoietin (EPO) actions have been classically associated with the induction of erythropoiesis; however, organ specific EPO receptor (EPOR) signaling is also involved in development, angiogenesis and organ growth. Researchers have shown that EPOR is upregulated both during postnatal lung maturation and during CLG in adult dogs (Foster, et al., 2004). Furthermore, they demonstrated an upregulation of one of its upstream activators, HIF-1 $\alpha$ , during the same processes. Using an *in vitro* system, the same group showed that upregulation of HIF-1 $\alpha$  in cultured HEK-293 cells also caused the upregulation of endogenous EPOR expression (Zhang, et al., 2006). This also provided evidence of a possible role of EPOR in CLG after pneumonectomy.

### 5.2.3 Hepatocyte growth factor (HGF)

HGF is known to selectively stimulate epithelial and endothelial cells, and the major sources for HGF in the lung are macrophages, fibroblasts, and endothelial cells. The increase of serum HGF during the first week after major lung resections in humans has been documented (Dikmen, et al., 2006; Sugahara, et al., 1998). A more comprehensive study of the role of HGF in CLG was performed using a mouse pneumonectomy model (Sakamaki, et al., 2002). In this study, the authors demonstrated an increased level of both lung mRNA and protein expression of HGF after pneumonectomy, and serum HGF levels were also higher when compared to sham operated animals. These findings were accompanied by an increased proliferation index of alveolar and airway epithelial cells, which peaked at day 5 after surgery. They also detected an upregulation of the HGF receptor (c-Met) at day 3 post-pneumonectomy. In addition, injections of HGF twice daily enhanced the proliferative response of these cells as well as increased lung weight index at day 3 when compared to controls. Use of a neutralizing antibody against HGF resulted

in the inhibition, although incomplete, of the increase in lung weight and DNA synthesis observed. Another interesting study evaluated the effects of CLG in a rat model of elastase-induced emphysema, with transfection of the human HGF cDNA into the lung (Shigemura, et al., 2005) or implantation of adipose tissue-derived stromal cells (ASCs), which produce a large amount of angiogenic factors including HGF (Shigemura, et al., 2006). Therapy with gene transfection was performed using the hemagglutinating virus of Japan (HVJ) envelope-plasmid complex. In the HGF- and ASC-treated animals, increased levels of both exogenous and endogenous HGF were detected; and furthermore, HGF enhanced the CLG response by increasing lung cell proliferation and improving functional parameters. Taken together, these studies provide strong evidence for a role of HGF in the proliferative responses during CLG.

#### **5.2.4 Hypoxia-induced mitogenic factor (HIMF)**

In a collaborative study, we demonstrated the role of HIMF in the context of CLG (Li, et al., 2005). The mRNA and protein expression of HIMF, which is known by its mitogenic and angiogenic properties, was upregulated after pneumonectomy (days 3-14) when compared to sham operated mice. The elevated HIMF expression also coincided with an increase in cell proliferation index in lungs of these animals. HIMF expression after pneumonectomy was mainly detected in airway epithelial, endothelial and type 2 epithelial cells. Intratracheal instillation of exogenous HIMF increased the proliferative activity in these cells, documenting its mitogenic properties and establishing its role in CLG.

#### **5.2.5 Hypoxia-inducible factor-1 $\alpha$ (HIF-1 $\alpha$ )**

Researchers have shown that HIF-1 $\alpha$  expression is upregulated both during postnatal lung maturation and during adult CLG in dogs and that this coincides with the upregulation of one of its downstream targets, EPOR. *In vitro* experiments also provided evidence that upregulation of HIF-1 $\alpha$  in cultured HEK-293 cells triggers the upregulation of endogenous EPOR expression (Zhang, et al., 2006). Another study found that lung expansion is a major contributor to the activation and stabilization of HIF-1 $\alpha$ . Acute deflation of prosthesis in the chest cavity of pneumonectomized dogs triggered the increase of both HIF-1 and several HIF-1 targets including EPOR and VEGF compared to non-deflated animals. They concluded that these increases did not depend on hypoxia but instead were due to stretch-related signals after lung resection (Zhang, et al., 2007).

#### **5.2.6 Insulin-like growth factor-I (IGF-I)**

IGF-1, its receptor and binding proteins are naturally expressed in the lung during development, and IGF-1 is known to contribute to the regulation of postnatal lung cell proliferation. Researchers have shown that 2 and 6 days after pneumonectomy in rats, the bronchoalveolar lavage fluid from these animals demonstrated significantly increased mitogenic activity when applied *in vitro* to fibroblasts compared with controls. Importantly, such activity was partially inhibited by the use of neutralizing antibody against IGF-1, and the levels of IGF-1 were elevated by 100% at day 2 after pneumonectomy (McAnulty, et al., 1992). In a separate study, IGF-1 mRNA expression was again significantly increased after 21 days post-pneumonectomy in a model of neonatal CLG in lambs (Nobuhara, et al., 1998).

### 5.2.7 Keratinocyte growth factor-I (KGF)

KGF has been shown to play an important role in alveolar epithelial cell proliferation and lung development. In our laboratory, exogenous KGF administered to rats after pneumonectomy further enhanced several parameters of CLG compared to control animals. Changes in lung weight index, lung volume index as well as morphometric parameters were accompanied by a significant increase in pulmonary cell proliferation index, providing the first evidence for a role of KGF in CLG (Kaza, et al., 2002). A more recent study corroborated our findings where epithelial cell proliferation was further enhanced after *in vivo* transfection of a KGF cDNA vector in a model of CLG in rats, confirming KGF as an important lung mitogenic factor (Matsumoto, et al., 2009).

### 5.2.8 Retinoic acid

Retinoic acid, a metabolite of vitamin A, has been implicated in normal lung development and cell proliferation. Our laboratory described the effects of exogenous retinoic acid during CLG in a rat model (Kaza, et al., 2001). At 10 and 21 days after pneumonectomy, lung weight, lung volume and cellular proliferation indices were all significantly augmented in rats that received exogenous retinoic acid versus vehicle controls. Interestingly, we also found that pulmonary expression of EGFR was upregulated in lungs after retinoic acid treatment, uncovering a possible relationship between these two important growth factors in CLG. Another similarly designed study corroborated our results several years later (Karapolat, et al., 2008); however, these effects did not translate into functional recovery according to studies developed using the dog model (Dane, et al., 2004).

### 5.2.9 Vascular endothelial growth factor (VEGF)

Angiogenesis, the formation of new blood vessels, is a critical step in normal organ development and in abnormal processes such as tumor growth and metastasis. In the lung, alveolar growth and angiogenesis should occur concurrently in order to result in normal organ development or regeneration. One of the most important angiogenic growth factors, VEGF has been studied in CLG, revealing its importance in this regenerative process. Researchers described the effects of exogenous VEGF in the mouse model, showing that exogenous VEGF therapy accelerated the CLG response, which was completed in only 4 days compared to 10 days in control animals. However, these effects could not be blocked by the use of either VEGF receptor inhibitors or neutralizing antibodies (Sakurai, et al., 2007). Another study associated lung expansion and other signaling pathways to VEGF. The acute deflation of prosthesis in the chest cavity of pneumonectomized dogs triggered the increase of HIF-1 $\alpha$  and its targets EPOR and VEGF compared to non-deflated animals, showing the interaction between these signals in the regulation of CLG (Zhang, et al., 2007). A recent paper studied the modulation of different VEGF isoforms along with its receptor during CLG, where VEGF 188 mRNA expression was decreased compared to sham animals and VEGF 164 and VEGF 120 mRNAs increased during days 1 and 3 respectively, describing what they believe is the recapitulation of the pattern of expression for these isoforms in the fetal lung (Jancelewicz, et al., 2010). A brief summary of evidence for the role of growth factors in CLG is shown in Table 1.

Growth Factor	Evidence	Species
<b>EGF</b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased EGFR lung expression.</li> <li>• Exogenous EGF enhances CLG.</li> </ul>	Rat, pig Rat
<b>EPOR</b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased EPOR lung expression.</li> </ul>	Dog
<b>HGF</b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased serum HGF, along with expression of HGF and its receptor (c-Met) in lung.</li> <li>• Exogenous HGF enhances CLG.</li> <li>• Neutralizing antibody against HGF attenuate CLG.</li> </ul>	Mouse Mouse, rat Mouse
<b>HIMF</b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased lung HIMF mRNA and protein expression.</li> <li>• Exogenous HIMF enhances proliferation.</li> </ul>	Mouse
<b>HIF-1<math>\alpha</math></b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased lung HIF-1<math>\alpha</math> mRNA and protein expression.</li> <li>• Lung expansion modulates HIF-1<math>\alpha</math> expression.</li> </ul>	Dog
<b>IGF-1</b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased lung IGF-1 mRNA and protein expression.</li> <li>• Neutralizing antibody against IGF-1 attenuate mitogenic <i>in vitro</i> effects.</li> </ul>	Lamb, rat Rat
<b>KGF</b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased lung KGF mRNA.</li> <li>• Exogenous KGF enhances CLG.</li> </ul>	Rat
<b>Retinoic Acid</b>	<ul style="list-style-type: none"> <li>• Exogenous retinoic acid enhances CLG.</li> <li>• Exogenous retinoic acid induces EGFR.</li> </ul>	Rat
<b>VEGF</b>	<ul style="list-style-type: none"> <li>• Pneumonectomy increased lung VEGF 164 and 120 mRNA expressions.</li> <li>• Exogenous VEGF accelerates CLG.</li> </ul>	Mouse

Table 1. Summary of potential roles of growth factors in CLG.

### 5.3 Transcription factors

Pneumonectomy induces shear stress in the lung, and several key transcription factors provide links between shear-mediated signaling and CLG. Mitogen-activated protein kinases (MAPKs), composed of extracellular signal-regulated kinases (ERKs), c-jun NH2-terminal kinases (JNKs), and p38 MAPKs, play a critical role in cell differentiation, growth and apoptosis and the regulation of various transcription factors and gene expression. One of the first reports about stretch-induced early gene expression demonstrated that in as early as 30 minutes post-pneumonectomy in rats, c-fos and JunB are significantly increased. These results were also reproduced when *in vitro* ventilation-perfusion was used (Gilbert & Rannels, 1998). Using array technology, researchers have also shown significant increases in six different transcription factors as early as 6 hours after pneumonectomy in mice including Erg-1 and Nur77, all of which have important roles in vascular biology, development and stress response (Landesberg, et al., 2001). In addition, a more recent paper found an important role for thyroid transcription factor 1 (TTF-1) in CLG (Takahashi, et al., 2010). These investigators detected a significant increase of TTF-1 expression 12 hours after pneumonectomy with TTF-1 expression primarily observed in cells of the alveolar ducts. When TTF-1 was repressed using small inhibitory RNAs (siRNAs), the CLG response was also temporally delayed.

#### 5.4 Telomerase

Telomerase is an important enzyme for DNA repair and contributes to cell maintenance. Telomerase prevents the excess shortening of telomeres, and it has been demonstrated that telomerase is active in proliferating cells in a number of organs, including the lung. In humans, mutations of the telomerase gene results in a pathological condition known as idiopathic pulmonary fibrosis (IPF). Its role in preserving lung epithelial integrity was demonstrated in an experimental model in mice, where telomerase deficiency resulted in a reduction in the number and integrity of type 2 alveolar epithelial cells (AEC2) (Lee, et al., 2009). It is important to know that this defect may not be apparent in early generations, but after progressive inbreeding, it was possible to establish the deficiency in AEC2s as well as in bronchoalveolar stem cell (BASC) populations in the lung, due to shortening of the telomeres. In a recent study, the importance of telomerase was demonstrated for CLG after pneumonectomy using telomerase deficient mice from second (F2), third (F3) and fourth (F4) generation animals (Jackson, et al., 2011). In wild-type mice, the activity of telomerase was found to increase in isolated AEC2s up to 3.5-fold during post-pneumonectomy days 3 and 7. In addition, the total number of AEC2s and BASCs also increased at day 3 after pneumonectomy. However, pneumonectomy resulted in diminished CLG in F3 telomerase null animals, expressed as failure to induce an increase in lung mass by day 7 after pneumonectomy. In addition, the number of AEC2s and BASCs did not increase during the initial period after pneumonectomy when compared to wild-type mice. The normal CLG, both in lung mass and AEC2 numbers, in wild-type mice was also accompanied by an elevation in the proliferation marker Ki-67, early growth response gene (Egr-1) and repair transcription factors such as ERK 1/2, which were not observed in telomerase null mice. The authors concluded that telomerase deletion produces an attenuated CLG response after pneumonectomy by arresting cell growth and inducing DNA damage.

#### 6. Conclusion

The extent of CLG in humans following pneumonectomy or lobectomy is incompletely investigated, but a number of long-term physiological studies suggest, however, that some degree of CLG may occur, especially in children (Nakajima, et al., 1998; Nonoyama, et al., 1986). The ability to manipulate the gain/loss of function for a particular gene in experimental animals has begun to provide a more detailed understanding of the molecular mediators and the pathologic consequences of CLG. Also, recent developments in cell therapy of diseased lungs with the use of adipose stem cells are indeed promising (Shigemura, et al., 2006). An important long-term goal of research into mechanisms of CLG is to generate knowledge that will allow the induction of alveolar regeneration or that rescues failed alveologenesis in humans. Such understanding will facilitate the development of therapies for the management of end-stage lung disease, lung volume reduction surgery, and transplantation. The potential clinical applications of this research are great. Specific examples of patients who would clearly benefit from lung regenerative therapies include chronic obstructive pulmonary disease (COPD), emphysema, pulmonary hypertension, bronchopulmonary dysplasia (BPD), as well as premature infants whose lungs are too underdeveloped to support life.

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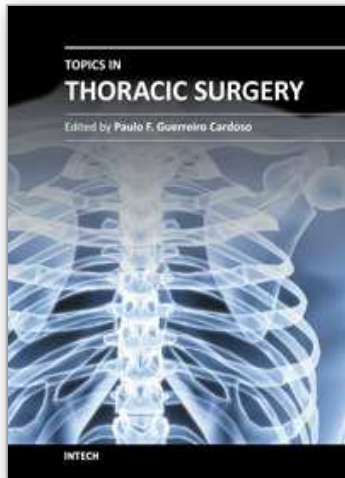
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