



EGF Receptor Signaling is Critical for Compensatory Lung Growth

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Abstract

Rationale. In experimental animals, pneumonectomy (PNX) induces rapid, hyperplastic compensatory lung growth (CLG) of the remaining lung. Angiogenesis likely plays a critical role in CLG since angiogenic growth factors can induce CLG while anti-angiogenic drugs can disrupt this process. We thus tested the hypothesis that epidermal growth factor (EGF) signaling is necessary for post-PNX CLG.

Methods. A sham thoracotomy or left PNX was performed in the following groups (n=4-6/group): a) C57BL6 mice treated with recombinant mouse EGF (200 mg/kg, q72h), b) C57BL6 mice treated with EGF receptor inhibitor (AG1478, 200 mg/kg daily), and c) SPC-EGFR-M transgenic mice which express a mutant, dominant negative EGF receptor in alveolar type II epithelial cells. Mice which received saline (for EGF) or DMSO (for AG1478) were used as vehicle control groups. Two weeks after surgery, right lung weight index was measured to determine CLG.

Results. PNX resulted in CLG as demonstrated by increased right lung weight index (4.77±0.15 vs. 3.07±0.03 mg/g in sham, p=0.001), which was further, significantly augmented after recombinant EGF treatment (5.43±0.12 mg/g, p=0.032). In contrast, AG1478 prevented post-PNX increase in lung weight index (3.79±0.29 mg/g in sham+DMSO, 3.93±0.20 mg/g in PNX+AG1478, and 4.83±0.16 mg/g in PNX+DMSO, p=0.02). Finally, CLG after PNX was unaffected in the SPC-EGFR-M transgenic mice.

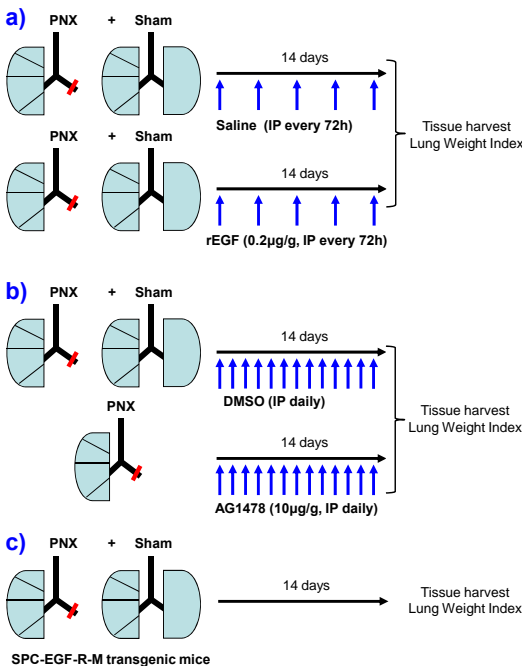
Conclusions. CLG was augmented by EGF and prevented by AG1478, indicating that EGF receptor activity, via EGF, is a critical signaling mechanism for CLG. EGF receptor activity on type II epithelial cells is not required for CLG since CLG was unaffected in the SPC-EGFR-M transgenic mice.

Materials and Methods

Surgery: A sham thoracotomy or left PNX was performed in the following groups (n=4-6/group): a) C57BL6 mice treated with recombinant mouse EGF (200 mg/kg, q72h), b) C57BL6 mice treated with EGF receptor inhibitor (AG1478, 200 mg/kg daily), and c) SPC-EGFR-M transgenic mice which express a mutant, dominant negative EGF receptor in alveolar type II epithelial cells⁴. Mice which received saline (for EGF) or DMSO (for AG1478) were used as vehicle control groups.

Lung Harvest and Lung Weight Index: At 14 days after surgery, mice were anesthetized, and lungs were blotted dry and weighed. The right lung weight/total body weight index was then calculated as lung weight index (LWI).

Outline of Experiments:



Results

Figure 1. PNX resulted in CLG as demonstrated by increased right lung weight index (*p=0.001 vs. Sham) which was significantly augmented after recombinant EGF treatment (*p=0.032 vs. PNX+saline). EGF had no effect on lung weight in sham animals.

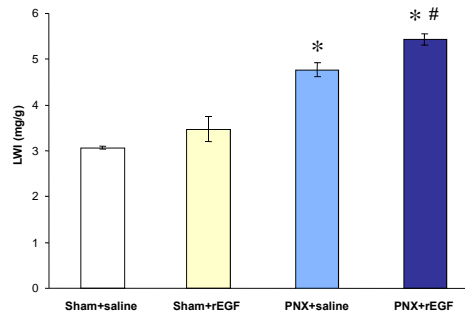
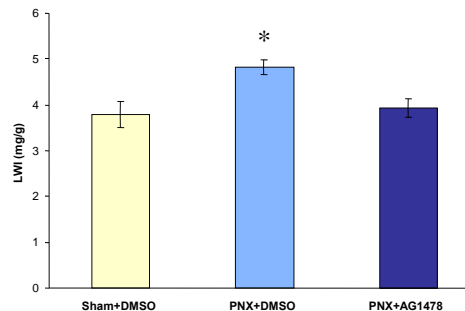
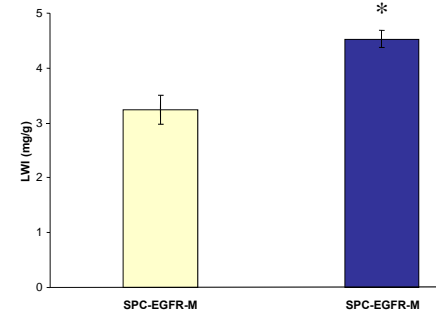


Figure 2. Specific Inhibition of EGF receptor signaling by AG1478 prevented post-PNX CLG. (*p=0.02)



Results

Figure 3. PNX resulted in normal CLG in the SPC-EGFR-M transgenic mice as demonstrated by increased right lung weight index (*p=0.01).



Background

Pneumonectomy (PNX) is often the last option for treatment in patients that otherwise cannot be cured such as patients with lung cancer or congenital lobar emphysema. In experimental animals PNX induces rapid compensatory lung growth (CLG) of the remaining lung where lung weight, volume, DNA, and protein are restored to control levels by 2-3 weeks.

This CLG occurs to maintain the lung's vital function of providing O₂/CO₂ exchange. Although CLG has been documented in children, it has not been reported in adult patients. Our ultimate goal is to be able to manipulate those mechanisms that regulate and induce CLG (alveolarization) to benefit patients with end-stage lung disease or injury, or to induce healthy lung maturation in severely premature infants.

The molecular mechanisms that regulate this regenerative growth are not well known. An understanding of the role of different signaling pathways in this process could lead to therapies for lung injury, pulmonary hypertension, respiratory failure, transplantation for end stage lung disease, and even stimulation of regenerative growth in patients with minimal pulmonary tissues left after lung resection.

Our laboratory has shown that CLG entails angiogenesis and vascular remodeling^{1,2}, and we have shown that inhibition of angiogenesis prevents CLG. Thus we believe that CLG and angiogenesis are tightly linked, with angiogenesis being a major driving force required for alveolar regeneration.

One potent angiogenic factor, epidermal growth factor (EGF) may be important in CLG since we have shown that EGF receptor is induced after PNX³. We thus tested the hypothesis that EGF receptor signaling is necessary for post-PNX CLG.

Conclusions

- EGF receptor signaling is critical for compensatory lung growth.
- CLG is augmented by exogenous EGF and prevented by inhibition of EGF receptor activity.
- EGF receptor activity on type II epithelial cells is not required for CLG, since CLG was unaffected in the SPC-EGFR-M transgenic mice. Perhaps the endothelial cell receptor is most important.

References

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