Opportunity

Lung injury, through both disease and trauma, affects many people worldwide. Elucidation of novel mechanisms through which lung regeneration may be induced has the potential to save lives and transform patient outcomes. While there are many who would benefit from a breakthrough in lung regeneration research, there are no definitive regenerative therapies for patients. The axolotl salamander, Ambystoma mexicanum, has long been studied as a model organism of vertebrate regeneration, particularly in limbs. It is thought that axolotls regenerate all of their tissues, but exploration of lung regeneration has not been performed until now.

Goal: To understand how axolotl salamanders regenerate their lungs, and one day harness this knowledge to cure human lung disease.

Method

Lung regeneration was investigated using histology and qPCR. Left lungs were injured while the right contralateral lung was untouched. Animals were housed in water containing the ErbB2 inhibitor from days 12 through 21 post-lung amputation. Control levels of proliferation were measured without injury to the lung. Dividing cells were counted to measure proliferation.

Uninjured animals were injected with 100 ng/g body weight of recombinant neuregulin IP. Tissue was collected for processing three days after injection and stained to measure proliferation.

Inhibition of ErbB2, a receptor partner for other Erb family receptors, was sufficient to reduce proliferation seen in untreated animals four fold. Additionally, we injected neuregulin, a ligand for ErbB4 receptors, and induced the formation of new lung tissue. We have found that activation of ErbB8 receptors induces proliferation in lung tissue.

Selected Results


Impact

Through our experiments we have determined:

Epidermal growth factor family signaling is crucial for regeneration to take place, specifically through the ErbB2:ErbB4 receptors.

Neuregulin-1 can induce proliferation in the lung, and is a likely candidate to exert molecular control over lung regeneration.

HoxA1 is upregulated during regeneration, and is a downstream product of Yap activation by ErbB4 nuclear localization. ErbB4 could hold therapeutic value for future research.

Future Implications of our Research Include:

Neuregulin and ErbB4 activation could serve as a therapeutic intervention for human lung disease.

We have performed the first exploration of a new model species in the field of lung regeneration.