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BITS AND BYTES

Hedgehog: the key to maintaining adult lung repair and regeneration

Amruthansh Sriperumbudur[1] · **Mason Breitzig**[1] · **Richard Lockey**[1] · **Narasaiah Kolliputi**[1]

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Cells are the building blocks of life, and despite losing a myriad of them each day, we survive. In fact, we thrive, because not all tissues are created equally when it comes to their ability to regenerate. While nerve and heart cells regenerate slowly, if at all, skin and blood cells are constantly regenerating, resulting in a completely new generation every few days. Between these two extremes are cells that have low rates of regeneration, but can experience extensive periods of regeneration after an injury. These tissues are thought to be quiescent.

Previously, postnatal tissue quiescence was thought to be the default state of mature tissue when in the absence of a stimulus (Beers and Morrisey 2011, Herriges and Morrisey 2014, Hogan et al. 2014). Furthermore, it remained unclear how the default state was maintained in organs such as the lung and liver where the tissues exhibit low rates of regeneration in adults, but respond to injury with extensive regeneration (Blenkinsopp 1967, Breuer et al. 1990).

In a recent issue of Nature, Peng et al. have shed new light on the role of the hedgehog signaling pathway in maintaining adult lung quiescence (Peng et al. 2015). They have shown that the same pathway that is essential for proper embryonic development also regulates quiescence in adult lungs. Peng et al. found that epithelial-specific deletion of sonic hedgehog (shh) during postnatal homeostasis in adult murine lungs results in a rapid expansion of the adjacent lung mesenchyme. In the acute phase of epithelial injury, while the mesenchyme proliferates, hedgehog signaling is initially downregulated, but as quiescence is restored the signaling levels return to the baseline (Peng et al. 2015). If hedgehog is activated instead of being downregulated, tissue regeneration does not occur. On the other hand, if hedgehog signaling is completely eliminated, quiescence is not restored (Peng et al. 2015). In addition to maintaining adult lung quiescence, Peng et al. also found that hedgehog signaling regulates epithelial quiescence and regeneration in response to injury via a mesenchymal feedback mechanism.

To reach these results, Peng et al. facilitated a series of procedures stemming from previous research stating that the hedgehog signaling pathway coordinates tissue-tissue interactions in multiple organs during embryonic development via paracrine activation of smoothened (Smo)-mediated downstream signaling events and that Shh expressed by incipient lung endoderm ancestors coordinates cardiopulmonary mesoderm progenitor differentiation into various cardiac and lung mesenchymal cell lineages (McMahon et al. 2003, Lum and Beachy 2004, Peng et al. 2013).

To determine whether Hh signaling remains active in the adult lung, Peng et al. utilized Shh^{creGFP} in isolated Scgb1a11 club epithelial cells, ciliated epithelium, and Sftpc1 alveolar type II epithelial cells, and analyzed Shh expression by confocal microscopy. Further, Peng et al. examined the expression of Gli1, a target of hedgehog, as well as other markers including Ki67 (cell cycle), by microscopy and lineage tracing with $Gli1^{creERT2}$:$R26R^{mTmG}$. To determine the effects of deleting Shh in the airway, $Scgb1a1^{cre}$:$Shh^{flox/flox}$ adult lungs were examined for cell proliferation in the airway epithelium[5].

✉ Narasaiah Kolliputi
nkollipu@health.usf.edu

[1] Division of Allergy and Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL, USA

Additionally, Peng et al. deleted Smo within $Gli1^{1}$ Hh-responsive adult lung cells as well as within Pdgfrb1 mesenchyme, and analyzed cell proliferation to determine the cell-autonomous role of Hh signaling.

To identify the role of Hh signaling in modulation of acute mesenchymal response to epithelial injury (induced by naphthalene), $Gli1^{LacZ}$ activity, as well as Shh and Gli1 expression, and GFP expression in the Shh^{creGFP} reporter, were measured by qPCR (Peng et al. 2015). Stochastic multicolor clonal analysis was utilized in $Gli1^{creERT2}$:$R26R^{confetti}$ mice to show clonal expansion in $Gli1^{1}$ lung cells after injury (Peng et al. 2015). To determine the role of Hh signaling in the restoration of quiescence, Peng et al. measured Hh activation as well as Shh and Gli1 expression by qPCR, following naphthalene induced injury in $Gli1^{lacZ}$ lungs. The result of conditional Smo deletion was also analyzed in lineage-traced $Gli1^{1}$ lung cells to determine the effect on restoration of mesenchymal quiescence (Peng et al. 2015). Shh was deleted from the proximal secretory epithelium and also Smo within $Pdgfrb^{1}$ derived mesenchymal cells to determine the effects on $Scgb1a1^{1}$ club cell proliferation (Peng et al. 2015).

Taken together, the experiments Peng et al. conducted demonstrate that epithelial-mesenchymal interactions are coordinated by hedgehog signaling, which actively maintains postnatal tissue homeostasis. Deregulation of the hedgehog signaling pathway leads to abnormal repair and regeneration in the lung (Peng et al. 2015). Moreover, these results demonstrate that the functions of various pathways may change at any given time. This study provides a better understanding of the relation between the hedgehog signaling pathway and lung disease, a link that may very well lead to novel treatments for otherwise incurable and fatal lung diseases.

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References

Beers MF, Morrisey EE (2011) The three R's of lung health and disease: repair, remodeling, and regeneration. J Clin Invest 121:2065–2073

Blenkinsopp WK (1967) Proliferation of respiratory tract epithelium in the rat. Exp Cell Res 46:144–154

Breuer R, Zajicek G, Christensen TG, Lucey EC, Snider GL (1990) Cell kinetics of normal adult hamster bronchial epithelium in the steady state. Am J Respir Cell Mol Biol 2:51–58

Herriges M, Morrisey EE (2014) Lung development: orchestrating the generation and regeneration of a complex organ. Development 141: 502–513

Hogan BL, Barkauskas CE, Chapman HA, Epstein JA, Jain R, Hsia CC, Niklason L, Calle E, Le A, Randell SH, Rock J, Snitow M, Krummel M, Stripp BR, Vu T, White ES, Whitsett JA, Morrisey EE (2014) Repair and regeneration of the respiratory system: complexity, plasticity, and mechanisms of lung stem cell function. Cell Stem Cell 15:123–138

Lum L, Beachy PA (2004) The Hedgehog response network: sensors, switches, and routers. Science 304:1755–1759

McMahon AP, Ingham PW, Tabin CJ (2003) Developmental roles and clinical significance of hedgehog signaling. Curr Top Dev Biol 53: 1–114

Peng T, Frank DB, Kadzik RS, Morley MP, Rathi KS, Wang T, Zhou S, Cheng L, Lu MM, Morrisey EE (2015) Hedgehog actively maintains adult lung quiescence and regulates repair and regeneration. Nature 526:578–582

Peng T, Tian Y, Boogerd CJ, Lu MM, Kadzik RS, Stewart KM, Evans SM, Morrisey EE (2013) Coordination of heart and lung co-development by a multipotent cardiopulmonary progenitor. Nature 500:589–592