Emerging Concepts in Mechanobiology of Lung Disease

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Lung Structure-Function

...“engineered” for efficient gas-exchange
Cellular Homeostasis in the Adult Lung

Burns AR, Smith CW, Walker DC. *Physiol Rev* 83: 309, 2003
Cellular Signaling – Control of Cell Phenotypes

- Cell-Cell Adhesions
- Soluble Factors
- Diffusible Factors

Factors:
- Matrix Factors
  - Composition
  - Rigidity
  - Dimensionality
What more do we need from our model systems?

• Lung-specific stiffness

Fibrosis: What, How & Why?

• Definition – loss of cellular homeostasis

• Mechanisms – activated effector cells

• Teleology – adaptive response (good)
  - evolutionary “tradeoff”
  - natural selection may favor fibrosis

“Imagine not being able to distinguish the real cause from that without which the cause would not be able to act as a cause. It is what the majority appear to do, like people groping in the dark; they call it a cause, thus giving it a name that does not belong to it…” - Plato

“We do not have knowledge of a thing until we have grasped its why” - Aristotle
Why might natural selection favor fibrosis?

- Wound healing
  - barrier re-constitution (wound closure, prevent pathogen entry)

- Infection
  - scarring to limit pathogen invasion
Peripheral distribution

Reticulation/septal thickening

Honeycombing

Traction bronchiectasis

honeycombing

Basilar distribution

honeycombing

Marked fibrosis and microscopic honeycombing

Area of normal lung

subpleural, paraseptal distribution

Transforming Growth Factor (TGF)-β: a potent fibrogenic cytokine

Shi et al. Nature 2011
Effects of ECM Stiffness on Tension-Induced TGF-β Activation

- Cell contraction transmits tensile force through actin-myosin filaments to a surface bound integrin

- Latent TGF-β bound to the integrins are physically pulled apart, freeing the non-covalently associated active TGFβ

Model of Intrinsic Mechanotransduction in the Regulation of Matrix Stiffening-Induced Myofibroblast Differentiation

Yong Zhou, Ph.D.

Latent TGF-β1 activation → αβ

Stiff/Fibrotic ECM

Myosin II

Cytoplasm

Contraction

F-actin

G-actin

MKL1

Nuclear

SRP

CARG

αSMA

Myofibroblast

RhoA/ROCK activation

Y-27632

Huang X, et al., AJRCMB, Sept, 2012
Matrix stiffening changes actin dynamics in favor of α-SMA-containing filamentous actin formation and promotes nuclear translocation of MKL1
Mechanosensitive Signaling as a Target for Anti-Fibrotic Therapy

The ROCK inhibitor, Fasudil, induces apoptosis of myofibroblasts > fibroblasts
Fasudil induces apoptosis of myofibroblasts in-vivo following fibrogenic lung injury.
Fasudil induces activation of the intrinsic (mitochondrial) apoptosis pathway in IPF-FBs
Fasudil downregulates Bcl-2 gene expression by inhibiting MKL1-SRF binding to an upstream CArgG box.
ROCK activity in IPF and experimental lung fibrosis
ROCK activity is increased in FBs isolated from lungs of human IPF and murine experimental lung fibrosis.
Fasudil administered in the post-inflammatory phase of lung injury protects from fibrosis.
Mkl1-deficient mice are protected from bleomycin-induced pulmonary fibrosis
Mechanosensitive Signaling as a Target for Anti-Fibrotic Therapy

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PMCs: Pleural Mesothelial Cells
Fbs: Resident Fibroblasts

PMCs

Myofibroblast

ROS

Matrix
Stiffness

Active TGF-β

Latent TGF-β

NOX4*

SMAD2/3

RhoA

α5 Integrin

Wt1

miR-31*

Pro-fibrotic

Anti-fibrotic

* Therapeutic targets
Acknowledgements

Thannickal Lab
Louise Hecker, Ph.D.
Yan Sanders, Ph.D.
Ragini Vittal, Ph.D.
Jeffrey C. Horowitz, M.D.
Tommy Hock, Ph.D.
Karen Bernard, Ph.D.

Collaborators
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