Genomics and Idiopathic Pulmonary Fibrosis

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Central Dogma

DNA → *transcription* → RNA → *translation* → Protein

*replication*
What is the study of Genomics?

- A discipline for analyzing the structure of genomes (the totality of genetic material in an organism)
- Traditional genetics or molecular biology tends to investigate single genes
- Genomics can include interactions between many genes as well as modifications not covered by the central dogma
- Tends to be bioinformatics heavy and computationally intensive
2003 – The promise of the genomic revolution after the Human Genome Project

- Variant genomic content
  - Identify cause of all single gene diseases
  - Catalog normal variants leading to complex diseases
  - Identify normal variants that predict drug response
  - Understand gene environment interaction
- Gene expression patterns
  - Reverse engineer normal and abnormal response to stimuli
  - Identify pathways involved in disease
  - High fidelity tools for diagnosis and predictive medicine
  - Predict drug response and toxicity

Together:
- Identify new targets for therapeutic intervention
- Personalized treatment
- Predict and prevent of drug toxicities
- Detailed understanding of disease & health
Why is Genomics More Possible Now?

The falling price of memory over the years has made genomics more feasible. The diagram illustrates the decrease in price per gigabyte of storage from 1993 to 2013.
DNA Microarrays

- Microarrays are slides with DNA “spots” containing known sequences of genes.
- Fluorescently labeled cDNA from subjects’ RNA is hybridized to these spots, and the more similar the sequences, the tighter the bonds.
What about the lung?

- Pubmed search
  - Gene expression profiling cancer – 52,456 articles
  - Gene expression profiling asthma – 656 articles
  - Gene expression profiling COPD – 297 articles
  - Gene expression profiling IPF – 81 articles
Why the discrepancy?

- Proliferation of fragmented phenotypes and disease definitions
- Animal models do not necessarily represent human phenotypes
- Significant understanding of molecular mechanisms did not lead to unified model
- The lung is very complex and dynamic
- The lung is relatively inaccessible
- Difficult to obtain human “Normal Controls”
Robust genomic signature, which makes picking a direction to analyze difficult
Lung Genomics Research Consortium

- 5 Center study
- Collect lung tissue from subjects with IPF or COPD
- Performed microarray analysis on over 500 tissue samples, as well as sequencing, miRNA analysis, methylation patterns, and genotyping
IPF lungs are very different from other lungs

Differentially expressed genes across all three groups

Control | COPD | IPF

Yellow is increased
Purple is decreased

Individual subjects’ lung tissue
Gene expression profiles of IPF lung distinguish them from Controls

CTRL, Early ILD, UIP, AE, K-UIP, K-NSIP, K-COP, Other ILD, PAH, Silicosis
Gene expression can differentiate subjects with acute exacerbation

Konishi et al, AJRCCM 2009
A gene expression signature in peripheral blood could predict poor outcome in IPF subjects

Herazo et al, AJRCCM, 2013
52 gene signature predicts outcome in 6-center cohort

425 patients total

Profiles do not change with time unless treated with antifibrotic

Herazo et al, Lancet Respiratory Medicine, 2017
RXFP1 is an interesting gene for potential therapeutics.

Relaxin decreases collagen deposition in bleomycin model in vivo.

Tan et al, AJRCCM, 2016
With increased access to biological technology and computational power, we hope genomics will provide key insights into clinical course, mechanisms of IPF, as well as the next wave of therapeutics.
Thank you for your attention!