Developing Interactions Between Basic Scientists and Surgeons

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Developing interactions between basic scientists and surgeons

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• What kinds of studies can basic scientists and surgeons collaborate on?

• How can we set up proper collaborations with surgeons to advance science?
Hdac1 and Hdac2 play important roles in development

- HDACs regulate gene expression by deacetylating both histones and TFs
- 3 classes of HDACs; HDAC1 and -2 are class 1 HDACs
- HDAC1/2 play redundant roles in heart, neural and epidermal development
- Our lab has shown that HDAC1/2 interacts with Foxp1/2/4 which are critical regulators of lung development

<table>
<thead>
<tr>
<th>Class</th>
<th>Protein domains</th>
<th>Time of lethality</th>
<th>Phenotype</th>
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</thead>
<tbody>
<tr>
<td>Class I</td>
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<tr>
<td>HDAC1</td>
<td><img src="image" alt="Hdac1 Protein Domain" /></td>
<td>482</td>
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<td>HDAC2</td>
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COPD is a devastating and common lung disease
- Smoking is a major cause
- Possibly caused by cycles of airway epithelial injury and inappropriate repair
- Associated with decreased HDAC activity, especially HDAC2

Loss of Hdac1/2 leads to defective lung airway branching

Wang et. al Dev Cell 2013
Loss of Hdac1/2 leads to decreased Sox2 expression

Array filtered for transcription factors

- **Blue**: down-regulated
- **Beige**: up-regulated

**Legend**
- **Green**: Sox2+
- **Red**: Sox9+

**Diagram**
- Secretory epithelium
- Ciliated epithelium
- After E13.5: alveolar epithelium
Loss of Hdac1/2 in lung endoderm leads to a selective loss of Sox2+ endoderm progenitors

- Sox2 marks proximal lung endoderm progenitors
- Sox9 marks distal lung endoderm progenitors
Hdac1/2 regulate lung endoderm proliferation through de-repression of p16, p21, and Rb1
Hdac1/2 are required for proper secretory epithelial regeneration

-Bmp4 expression is NOT altered in the Hdac1/2 deficient postnatal lung

Wang et. al Dev Cell 2013
Histone acetylation pathways and lung development/regeneration

- histone modifications, notably acetylation are reversible...balance between HATs and HDACs
HDAC-RB pathway in human COPD lungs

Collaboration with Ed Cantu
Lung transplant surgeon
“Molecular and Clinical Analysis of Syndromic and Isolated Anomalies of the Foregut”

CHOP IRB Protocol

Collaboration with Bill Peranteau (surgeon) and Dan Swarr (fellow)
Example Diagnoses

**Airways**
- Laryngeal atresia, webs, stenosis
- Laryngotracheoesophageal clefts
- Tracheal stenosis/atresia

**Esophagus**
- Esophageal stenosis or atresia
- Tracheo-esophageal fistula (TEF)

**Lungs**
- Congenital Cystic adenomatoid malformation (CCAM)
- Congenital lobar emphysema
- Bronchial atresia
- Pulmonary sequestration
- Primary pulmonary hypoplasia, agenesis, or aplasia
- Alveolar capillary dysplasia
CCAM

- Multiple types
- Etiology poorly understood
- Often detected prenatally
- Essentially all children with this lesion undergo surgical resection
- Immediate applications Wnt signaling pathway (via Fzd2 KO model)
Loss of Fzd2 in lung epithelium causes a CCAM-like phenotype
Trachoesophageal Fistula (TEF/EA)

- Relatively common (at least at CHOP)
- Isolated and syndromic forms
- Portion of esophageal pouch often resected (we can get tissue!)
- Applications to multiple projects including Foxp1/2/4, Wnt signaling, Shh signaling etc.
VACTERL Syndrome

- Etiology unknown (likely heterogeneous diagnosis)
- TEF/EA common feature
- Vertebral defects
- Cardiac defects (VSD, TOF etc.)
- Renal/GU anomalies
Many, Many Others...
Approach/Methods

- Clinical Data Collection
  - Will include detailed “phenotyping” using a structured nomenclature system (Human Phenotype Ontology) that may be amenable to future bioinformatic approaches

- Sample collection
  - Blood – DNA extraction, lymphoblastoid cells lines
  - Tissue
    - Lung
    - Esophagus
    - Anything else left over from procedure or biopsy

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