Human Lung Cancer Pathology and Cellular Biology

Mouse Lung Tumor Workshop

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Brigitte Gomperts, MD

University of California, Los Angeles
Lung Structure and Function
Airway Epithelial Cell Types

Key Differences Between Mouse and Human Lungs

• Submucosal gland ducts extend throughout cartilaginous airways in humans

• Goblet cells are present in the airway epithelium in humans

• Mouse stem cell turnover is very slow in uninjured/unexposed mice (7 days for basal cell, 365 days for type II cell)

• Humans do not develop lung adenomas that progress to adenocarcinoma
## Lung Cancer Histopathology – WHO Classification

<table>
<thead>
<tr>
<th>CLASS</th>
<th>PREVALENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma</td>
<td>20</td>
</tr>
<tr>
<td>Non small cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>40</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>25</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>10</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>
Histopathology of Non Small Cell Lung Cancer

Lung Adenocarcinoma

Squamous Lung Cancer

Large Cell Lung Cancer
2011 IASLC/ATS/ERS Classification of Adenocarcinoma

- Histology of preneoplastic lesions (adenocarcinoma in situ and minimally invasive lung adenocarcinoma) (complete resection – near 100% survival)
- Refines the classification for application to lung cancer diagnosis in small biopsies and cytology specimens
- Stresses importance of distinguishing between adenocarcinoma and squamous cell carcinoma for prognosis and treatment
Biology of Lung Carcinogenesis

• Injury (from e.g. toxins in the environment) leads to aberrant repair by stem/progenitor cells, which undergo self-renewal to form a group of indefinitely self-renewing daughter cells.

• Additional genetic and epigenetic alterations prevent normal differentiation of these cells but instead result in proliferation of these cells.

• This “field cancerization” expands gradually displacing the normal epithelium.
Evidence for “Field Cancerization”

• Definition - Histologically normal adjacent airway epithelium has molecular changes, some of which are found in the cancer

• Avi Spira- airway gene expression signature that accurately distinguishes smokers with and without lung cancer

• MicroRNAs in the field – Huang et al 2012

• Ignacio Wistuba – temperospatial changes in the field

Kadara et al 2013
Stepwise Progression to Lung Cancer

- Premalignancy in Squamous Lung Cancer

  Histologically normal airway epithelium  
  Premalignant lesion (squamous metaplasia and dysplasia)  
  Squamous cell carcinoma

- Premalignancy in Adenocarcinoma
Tumor Initiating Cells in Lung Cancer

• Stem cells that develop uncontrolled self-renewal and block in differentiation that ultimately leads to tumor formation. Identified in other malignancies e.g. AML, breast cancer
• First suggested - Carla Kim – Cell 2005 – BASCs in the KrasG12D mouse model
• Carla Kim – Cell Stem Cell – 2010 – genotype alters tumor initiating potential
• Mark Onaitis – PNAS – 2012 – BASC controversy
Bronchi/Bronchioles: No phenotype
BADJ: CC10+ hyperplasia, CC10+Foxj1+
hyperplasia, CC10+Sftpc+ hyperplasia
Alveoli: Sftpc-positive adenoma/adenocarcinoma

Bronchi/Bronchioles: No phenotype
BADJ: No phenotype or very rarely small hyperplasia at late stage
Alveoli: Sftpc-positive adenoma/adenocarcinoma
Inflammation and Lung Cancer

• Pro-tumor vs anti-tumor effect?
  – PD1/PDL1 as new therapeutic targets
• Promote proliferation and cell survival
• Genomic instability – ROS, cytokines, epigenetics
• Inflammatory cells:
  – tumor-associated macrophages (TAM), mast cells, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils and lymphocytes
• Cytotoxic mediators:
  – ROS, proteases, MMPs, tumor necrosis factor α (TNFα), interleukins (IL-1, IL-6, IL-8), interferons (IFNs) and enzymes, as cyclooxygenase-2 (COX-2), lipooxygenase-5 (LOX-5) and phospholipase A2 (PLA2)
Inflammation and Cell Proliferation and Survival Signaling
Molecular Biology of Lung Cancer

• Activation of growth promoting proteins e.g., v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), epidermal growth factor receptor (EGFR), BRAF, MEK-1, HER2 (mutations), MET (amplification), ALK and rearranged during transfection (RET) (structural rearrangements)

• Inactivation of tumor suppressor genes e.g., P53, phosphatase with tensin homology (PTEN), LKB-1 (STK11)
Molecular Changes in Lung Adenocarcinoma

- **EGFR**: activating mutations lead to activation of PI3K/AKT/mTOR, RAS/RAF/MEK/MAPK and JAK/STAT signaling pathways. More common in females, non-smokers, younger age, 10-15% Western, 30-40% Asian

- **RAS**: activating mutations lead to activation of RAS/RAF/MEK/MAPK signaling pathways. Western populations, male, smokers

- **ALK**: rearrangements of receptor tyrosine kinase, most commonly EML4-ALK fusion, leads to RAS/RAF/MAPK1, PI3K/AKT and JAK3-STAT3 signaling pathway activation. Younger patients, never/light smokers
Are the Chemicals of Interest Involved in Lung Carcinogenesis?

• Naphthalene – toxic to Clara Cells – could this result in injury with aberrant repair?

• Styrene, Ethylbenzene - reactive metabolites – could this result in DNA damage, inflammation, ROS?

• Are there underlying genetic/epigenetic susceptibilities that promote lung carcinogenesis with these exposures?