NEW FRONTIERS IN THE BIOLOGY OF LUNG CANCER: WHAT INFLUENCES DIAGNOSIS AND THERAPY?

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Steven M. Dubinett is Chief of the Division of Pulmonary and Critical Care Medicine and Director of the Lung Cancer Research Program. He is the Principal Investigator for the UCLA Clinical and Translational Science Institute (CTSI) and serves as UCLA Associate Vice Chancellor for Translational Research. Dr. Dubinett is jointly appointed as Professor in the Departments of Medicine, Pathology and Laboratory Medicine, and Molecular and Medical Pharmacology. He has extensive experience in translational investigation, academic administration, mentorship and peer review. Building on original discoveries relevant to inflammation in the pathogenesis of lung cancer, he has developed a translational research program which now utilizes these laboratory-based discoveries in the translational research and clinical environment. His studies focus on the microenvironment, inflammation and epithelial mesenchymal transition in the pathogenesis of lung cancer. As a member of NCI’s Translational Research Working Group, Dr. Dubinett participated in designing pathways to clinical goals.

He previously served as the Director for Biomarker Development for the American College of Surgeons Oncology Group and directed biospecimen utilization in the context of clinical trials. He serves as the Chair of the Research Evaluation Panel for biospecimen utilization for the American College of Radiology Imaging Network / National Lung Screening Trial (ACRIN / NLST). He previously chaired the FDA Cellular, Tissue & Gene Therapies Advisory Committee.

He currently serves on the NCI Thoracic Malignancy Steering Committee as a Translational Science Representative. He has served as a grant proposal reviewer for numerous government agencies and foundations including as a member of both the NIH Tumor Microenvironment and the Cancer Immunology and Immunotherapy study sections. Dr. Dubinett has trained more than 30 graduate students, post-doctoral fellows and junior faculty, nearly all of whom have continued in academic careers. In addition to his work, he enjoys wildlife photography while hiking in the Santa Monica Mountains.
OBJECTIVES:
Participants should be better able to:

1. To understand advances in lung cancer pathogenesis
2. To understand the importance of patient selection for targeted therapy
3. To understand the rationale for immunotherapy for lung cancer
New Frontiers in the Biology of Lung Cancer: What Influences Diagnosis and Therapy?

March 13, 2015
NAMDRC 38th Annual Meeting
and Educational Conference

Steve Dubinett, MD
www.ctsi.ucla.edu

LEARNING OBJECTIVES

• Understanding lung cancer pathogenesis

• Patient selection for targeted therapy and detection of resistance

• Understand rationale for immunotherapy
Questions

1. How can understanding lung cancer pathogenesis advance early diagnosis and therapy?

2. Why should patients’ tumors be tested for molecular abnormalities?

3. How can understanding the immune pathogenesis of lung cancer improve immunotherapy?

4. What is the nature of immune suppression at the tumor site in non-small cell lung cancer?

Lung Cancer

• Leading cause of cancer deaths in the United States
  – Estimated >170,000 deaths annually
  – 31% and 26% of all cancer deaths in men and women, respectively

• Poor prognosis
  – 5-year survival = 15%
  – Responsible for more deaths than prostate, colon, pancreas and breast cancers combined.
  – > 1.3 million deaths per year worldwide
48% of new patients with non-small cell lung cancer were diagnosed with advanced stage (IIIIB and IV) disease.

Biomarkers could be complementary to imaging:

- Imaging can increase early detection of lung cancer.
- The number of indeterminate lung nodules also increases.
- Biomarkers could potentially add biological information to imaging.
Circulating miRNA in plasma of high-risk control subjects and cancer patients

Changes in Bronchial Epithelium in Relation to Cigarette Smoking and in Relation to Lung Cancer

Oscar Auerbach, M.D., A. P. Stout, M.D., E. Cuyler Hammond, Sc.D., and Lawrence Garfinkel, M.A.

NEJM 1961; 265:253-267 August 10, 1961
Histopathological and molecular changes during the pathogenesis of squamous cell carcinoma

What promotes EMT in lung cancer?
Mutations and inflammation
Snail is expressed in premalignant lung lesions in situ

<table>
<thead>
<tr>
<th>Control Abs</th>
<th>Normal lung</th>
<th>AHH</th>
<th>Squamous metaplasia</th>
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Experimental evaluation of human bronchial epithelial cells for early transformation

![Image](image13.png)

Sato et al Cancer Res 2006
Human bronchial epithelial cells: High Migratory

Human bronchial epithelial cells

Heterogeneity in bronchial epithelial motility

Low velocity

High velocity
### Two Models of Cancer Development and Progression

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
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<tr>
<td>normal tissue</td>
<td>normal tissue (e.g., a stem cell expressing Snail)</td>
</tr>
<tr>
<td>in situ cancer</td>
<td>dissemination</td>
</tr>
<tr>
<td>disseminated cancer</td>
<td>in situ cancer</td>
</tr>
<tr>
<td>aggressive metastasis</td>
<td>disseminated cancer</td>
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</table>

**Adapted from Sánchez-García NEJM 2009**

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### Opportunities

- **Understanding lung cancer pathogenesis**
- **Patient selection for targeted therapy and detection of resistance**
- **Understand the rationale for immunotherapy**
Driver mutation:
An oncogenic mutation that induces and sustains tumorigenesis

Stephanie Cardarella, Dana-Farber Cancer Institute

Driver mutations 2015

Aria Vaishnavi
Several mutations in the TK domain of *EGFR* have been described.

*EGFR* mutations are common in NSCLC (approx 20%).

Mutations are limited to the first four exons of the TK domain.

Importantly, the presence of mutations in the TK domain correlates with tumor drug sensitivity to TKIs.

*EGFR* mutations: tend to occur in selected subpopulations: adenocarcinoma histology, never-smoker, East Asian, and female.

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**Overall Survival: Erlotinib vs. Best Supportive Care**

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<th>Erlotinib (n=488)</th>
<th>Placebo (n=243)</th>
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<tr>
<td>Median survival (mo)</td>
<td>6.7</td>
<td>4.7</td>
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<tr>
<td>1-year survival (%)</td>
<td>31.2</td>
<td>21.5</td>
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</table>

HR=0.73 (95% CI, 0.61-0.86)*

*P<0.001†

*From Cox regression model.
†From 2-sided log-rank test.
HR = hazard ratio.
Multiple components of each of the growth signaling pathways are involved in lung cancer but special focus has been on proteins that are frequently affected by genetic abnormalities.

These mutated proteins, while driving affected cells toward transformation, also “addict” the cells to their abnormal function.

“oncogene addiction” -- the continued presence of the abnormal function, although oncogenic, also becomes required for the tumor to survive.

Weinstein, Science, 2002 and Nature Clinical Practice Oncology, 2006

Epidermal Growth Factor Receptor (EGFR) Signaling Pathways

Drug resistance: What can we learn about the biology of lung cancer?

Reasons for resistance to EGFR TKI:
Secondary mutations in EGFR and/or amplification of the gene encoding the MET receptor tyrosine kinase appear to account for most cases of resistance.

Examples of additional potential causes of primary or acquired resistance include:

- NFkB activation (Sawyers Nature 2011)
- Enhanced IGFR signaling (Guix J Clin Invest 2008)
- Epithelial Mesenchymal Transition (Witta Cancer Res 2006)

Unfortunately, the vast majority of patients eventually develop acquired resistance to targeted agents.

Correlation between the Presence of T790M Mutations in Tumor-Biopsy Specimens and Decreased Progression-free Survival

CTCs in Lung Cancer: enumeration and mutation analysis

Objectives

• Understanding lung cancer pathogenesis

• Patient selection for targeted therapy and detection of resistance

• Understand rationale for immunotherapy

PD-1’s Role in Normal & Malignant Cells

- PD-1: a T-cell immunoreceptor and immune checkpoint that inhibits T cell activity

- PD-1 is expressed on activated T cells, restraining T-cell activity during chronic inflammation or infection

- PD-1 ligands, PD-L1 and PD-L2, hinder autoimmunity and protect peripheral tissues through inhibiting T-cell proliferation, cytokine production, and cytolytic function

- Interaction between PD-1 and its ligands can promote an immunosuppressive tumor microenvironment

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**Co-stimulation**
Enhances T-cell function

**Checkpoints**
Limits T-cell function

Numerous ligand-binding partners maintain immune system equilibrium
Two general mechanisms of expression of immune-checkpoint ligands on tumor cells

Mutational load: The prevalence of somatic mutations across human cancer types

LB Alexandrov et al. Nature 2013
Ground breaking studies reveal that lung cancer can be responsive to immune-based therapies

15-25% of patients are responding to antibodies that disrupt the immune checkpoint PD1 binding to PD-L1

**What may limit the response to immune-based therapies?**

- immune inhibitory mechanisms in the tumor microenvironment
- insufficient number /quality of effector T cells
- inadequate infiltration of T cells into the tumor

**Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients**


**Intratumoral DC CCL21 therapy**
Learning Objectives

- To understand advances in lung cancer pathogenesis
- To understand the importance of patient selection for targeted therapy
- To understand the rationale for immunotherapy for lung cancer

Question #1

**How can understanding lung cancer pathogenesis advance early diagnosis and therapy?**

A. Lung cancer pathogenesis can only help with therapies for advanced disease.

B. A more complete understanding of lung cancer pathogenesis is anticipated to identify new targets for early detection and treatment.

C. There is no known connection between pathogenesis and diagnosis.

D. Lung cancer pathogenesis is now thoroughly understood.
Question #2

Why should patients’ tumors be tested for molecular abnormalities?

A. It is not necessary to test for molecular abnormalities because therapy is dictated by tumor histology alone.
B. Testing for molecular abnormalities should not be performed because it's too expensive.
C. The definition of molecular targets in patient tumors cannot be defined by tumor histology alone.
D. Molecular profiling may be important in the future but it is not part of current therapy decisions.

Question #3

How can understanding the immune pathogenesis of lung cancer improve immunotherapy?

A. Lung cancer is non-immunogenic and therefore immune based therapies cannot be useful.
B. Immunotherapy is still too immature to be applicable in human cancer.
C. Understanding the nature of immune suppression at the tumor site can lead to future patient selection for specific immunotherapies.
D. Immunotherapy is only effective for melanoma.
Answer #4

Which statement best describes the nature of immune suppression at the tumor site in non-small cell lung cancer?

A. There is no evidence for immune suppression at the tumor site.

B. It is only mediated by the PD1 pathway.

C. It does not impact therapy.

D. There are multiple pathways by which the tumor subverts the immune response.