Common Pathogenetic Mechanisms of Lung Cancer and COPD

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Lung Cancer and Chronic Obstructive Pulmonary Disease (COPD): Two Sides of the Same Coin?

• Leading causes of morbidity and mortality
  – Deaths in 2005: 159,415 (lung ca.), 127,100 (COPD)

• Shared environmental risk factor (tobacco)
  – 10-15% of smokers lifetime incidence

• COPD increases lung cancer risk up to 4.5-fold (independent of tobacco exposure)
  – COPD in non-smokers also increases lung ca risk

• Commonalities
  – Inflammation
    • ↓ lung cancer risk in COPD patients using inhaled steroids
  – Somatic mutations and histologic changes in exposed field
    • MSI in sputum cells from smokers with COPD, but not without COPD
Pathogenesis of Lung Cancer and COPD

CIGARETTE SMOKE
ROS
NF-κB
Inflammation

Stochastic or Genetic

Gene activation/silencing
---Apoptosis+++ 

DNA Damage/repair

GENOME INSTABILITY
Clonal Expansion
Invasion-angiogenesis

Matrix Degradation/repair

IMMUNE RESPONSE

“NORMAL”

COPE

CANCER

COPD

Objectives

- To identify fundamental pathogenetic commonalities between lung cancer and COPD in order to characterize:
  - Genotypic and phenotypic characteristics that identify individual susceptibility
  - Shared biochemical, molecular, and immunologic pathways involved in the origin and progression of both diseases

- Translational initiative focusing on human studies, ultimate goal to identify populations and molecular targets for clinical trials for prevention of lung cancer & COPD
Examples of Applications

• Clarify co-epidemiology of lung cancer and COPD
  – clinical characteristics and molecular phenotypes
  – shared genetic and epigenetic risk factors
    – gene-environment interactions
  – attention to early molecular events, timing, subsequent course of each
Examples of Applications

• Investigate common and disparate mechanisms involved in the pathogenesis of COPD and lung cancer
  – role of innate and adaptive immunity, redox balance, proteinases, injury repair, stem cell proliferation, epigenetic changes, somatic mutations, microenvironment, and epithelial-mesenchymal transition
Examples of Applications

• Identify and validate biomarkers, molecular signatures, and imaging measures of risk, presence, severity, and progression of COPD and lung cancer and of responses to therapy

Specific example:
– COPDGene, a 10,500 person COPD GWAS trial with high resolution CTs – opportunity to study natural history of ground glass opacities (AAH, putative precursor to lung ca.) and lung cancer risk across varying degrees of COPD
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Total NCI+NHLBI Amount, 4 Yrs: $24M

*NHLBI approved same concept for $3M/yr x 4 yrs, contingent on NCI funding
Unique Aspects of Initiative

• Full partnership between NCI and NHLBI
• Double PI governance, one from cancer and one from pulmonary community strongly encouraged
  – Historically separate research communities
• Annual meeting of all PIs in Bethesda (set aside funds)
  – Encourage collaboration, specimen/data sharing
• Secure web-site (set aside funds) for potential collaborative avenues, specimen/methodology sharing, etc.
Current Portfolio Analysis: Lung Cancer and COPD

• 2008 $3.8M NCI
  – One R01: Z1-antitrypsin genotypes and lung cancer risk
  – One U01: phase IIb clinical trial, green tea polyphenols in former smokers with COPD
  – 4 studies on lung cancer risk and genetic/epigenetic abnormalities (do not address COPD specifically)

• Other institutes
  – NHLBI: One R01 on neutrophil elastase in COPD and lung cancer
  – NIA: One R01 on COPD as a co-morbid condition in older cancer pts.
Rationale for RFA

• Area of high importance not well represented in RPG pool, “falls between the cracks”

• Stimulate new collaborative research between cancer and COPD communities (historical organizational barriers)
  – Leverage scientific knowledge and clinical expertise from 2 distinct research communities

• Review panel with specialized expertise

• Integration with other research infrastructures (e.g., EDRN, SPOREs, NHLBI LTRC and SPIROMICS programs)
NHLBI-NCI Working Group
Punturieri A et al., Lung Cancer and COPD: Needs and Opportunities for Integrated Research, JNCI, in press

Workshop June 26/27, 2007 Bethesda, MD

– Chairs
  • Stephen D. Shapiro, MD and Steven M. Dubinett, MD

– NHLBI (Division of Lung Diseases)
  • Antonello Punturieri, MD, PhD
  • Thomas L. Croxton, MD, PhD
  • Gail Weinman, MD

– NCI (Division of Cancer Prevention)
  • Eva Szabo, MD