National Cancer Institute

Common Pathogenetic Mechanisms of Lung Cancer and COPD

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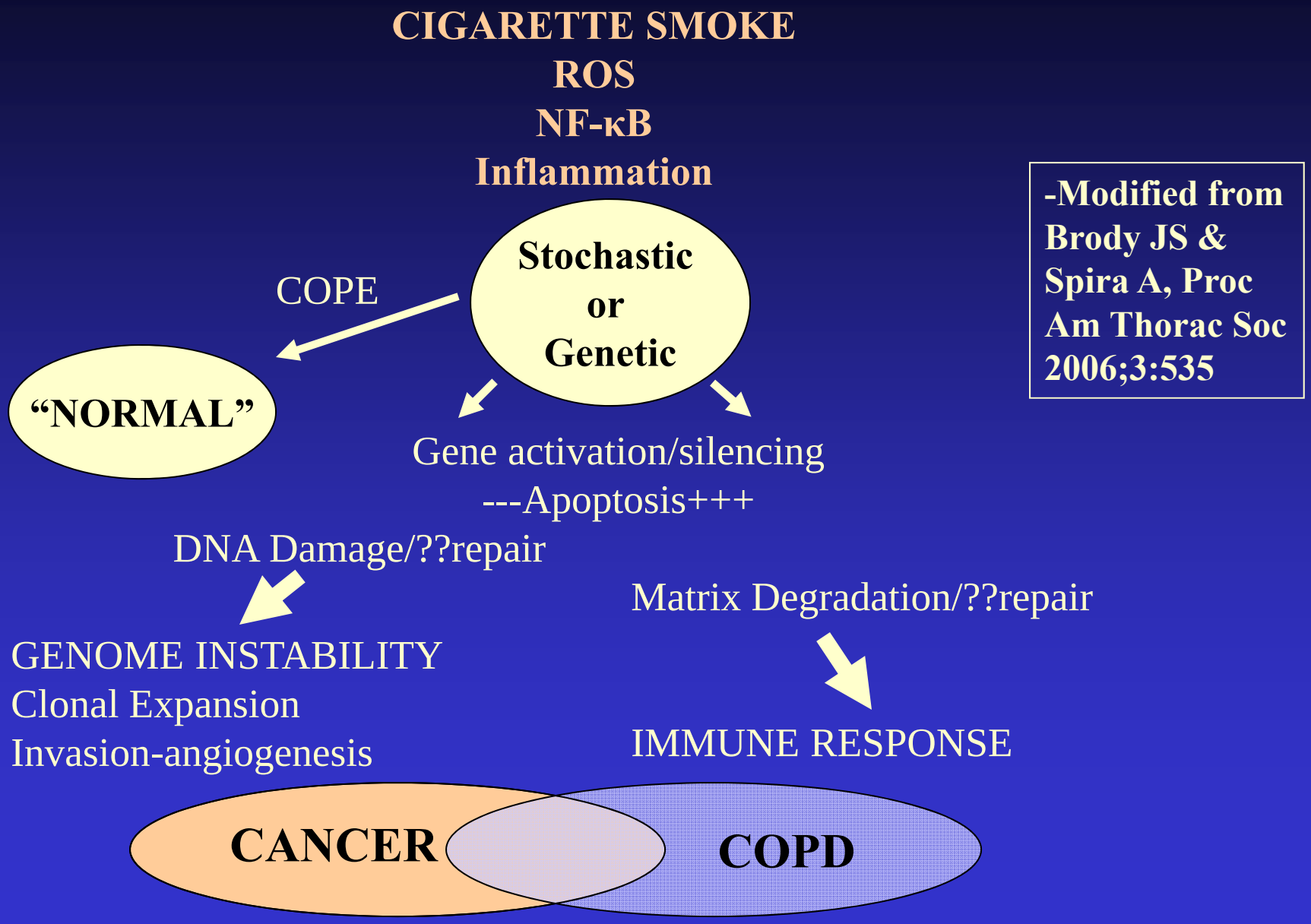
National Institutes of Health

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



-Modified from Brody JS & Spira A, Proc Am Thorac Soc 2006;3:535

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

Lung Cancer-COPD Initiative

Funding mechanism:	**R01**
Length of Awards:	**4 years**
Anticipated Award Date:	**FY2011**
NCI Amount Set Aside 01 Year:	**$3M***
Total NCI Amount for 4 Years:	**$12M**
Anticipated # Awards:	**6-8**
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: ✂1-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