Appendix A: Breakout Sessions

Biology and Cancer Breakout Session

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Overview

Two major barriers to research in lung cancer biology were identified: the diversity of biological processes that contribute to lung carcinogenesis, and the stigma associated with tobacco-related disease. Relevant research questions are often dismissed as too difficult to study, given the complexity of the exposure (since tobacco smoke is a complex mixture) and other factors (such as underlying lung disease and genetic variation in how tobacco carcinogens are metabolized) that contribute to lung cancer development. In addition, a sense that smokers are behaviorally responsible for their tobacco-related illnesses inhibits the allocation of sufficient resources to this field of study. Another barrier is that researchers in the tobacco field often do their research in isolation. Lack of multidisciplinary collaboration can increase research costs while limiting the understanding of tobacco injury from the cellular through the population levels.

Tobacco-induced cancers are late-onset diseases resulting from chronic long-term exposure to tobacco combustion products. The multitude of combustion products results in a complex set of possible initiation and promotion events that are also affected by individual variation. Neither the steps in cancer initiation nor those in cancer promotion are fully understood because they involve dynamic interplay between tobacco smoke constituents and the susceptible cells of the smoker.

Most of what we know about the effects of tobacco is based on extrapolations of single-agent carcinogen exposure studies. However, cigarette smoke is a mixture of more than 4,000 compounds, more than 60 of which are known carcinogens (1). Therefore, focusing on exposure to smoke as a mixture would allow investigators to determine what happens in the "real world," although single-agent research is still needed to confirm mechanistic insights beyond tobacco carcinogenesis. Continued studies on nicotine are especially useful now that smoking cessation efforts are moving toward nicotine replacement therapy. In addition, the presence of nicotinic receptors on lung tumor cells (2) suggests that nicotine can affect lung tumor biology directly.

Across all diseases, tobacco use has been postulated to modulate quality of life, comorbidities, response to treatment, and overall survivorship of patients with lung cancer. However, minimal prospective data are available (reviewed in 3), and at present, clinical trials do not routinely collect these types of data. A recent paper by Videtic and colleagues (4) has confirmed a previous study that found significantly better outcomes in patients with small-cell lung cancer who do not smoke during their combination chemo-/radiation therapy. Future studies should include prospective analyses that can determine outcome differences and treatment side effects related to sex and tobacco use, including tobacco-attributable comorbidities as mediating variables in treatment side effects and efficacy, and investigate the impact of smoking cessation on the physical health and quality of life of cancer survivors.

Recommendations

Research

***1. Support further research into cross-disciplinary interactions in tobacco-related disease mechanisms, especially gene-hormone-environment interactions.**

Estrogen status is recognized as a factor that affects lung cancer risk in women. Evidence also indicates a positive interaction between estrogen replacement therapy, smoking,

* Recommendations with an asterisk are those identified by the breakout groups as their top three recommendations.

and the development of adenocarcinoma of the lung (5). Estrogen or one of its metabolites may be a weak carcinogen, but this has not been studied in depth, particularly in relation to tobacco smoking. Estrogen metabolites can cause various types of DNA damage (6), and estrogens may induce lung tumors through these types of DNA alterations. Cigarette smoking alters the metabolism of endogenous estrogens, although possible interactions among estrogen metabolism, tobacco exposure, DNA adducts, and lung cells are unclear. Lung tumor cells express estrogen receptors and are induced to proliferate in response to estrogen exposure both *in vitro* and *in vivo* (7). Thus, once tumors are induced, estrogens may also drive proliferation of mutated cells. This raises the possibility that estrogen plays a role in both premalignant disease and malignant disease progression. An understanding of the role of estrogens in the pathogenesis of lung cancer should facilitate the selection and evaluation of antiestrogen therapies for the treatment of this disease.

Partners

- National Institute of Environmental Health Sciences (NIEHS)
- Environmental Protection Agency (EPA)
- Centers for Disease Control and Prevention (CDC)
- Breast, Lung, and Transdisciplinary Tobacco Use Research Centers (TTURCs)
- Specialized Programs of Research Excellence (SPOREs)
- American Lung Association
- American Thoracic Society
- Department of Defense Breast Cancer Research Program
- National Institutes of Health (NIH)
- Pharmaceutical industry
- Susan G. Komen Breast Cancer Foundation
- State health departments

Impact

This area of research can influence recommendations on tobacco cessation, chemoprevention, disease prevention, and issues of hormone replacement therapy and phytoestrogens. Researchers can also identify noncancer sex effects and obtain biological evidence relating environmental tobacco smoke to breast and other sex-related cancers. This research will affect multiple disease processes.

*2. Validate biologically relevant measures of tobacco smoke exposure, injury, and recovery.

This includes linking measures of exposure to those of injury in biological models and measures of injury to outcomes, examining modifying factors of injury from exposure, and investigating new tobacco products. At present, little or no data link molecular changes of intermediate biomarkers—which may be observed prior to the clinical appearance of disease and bear some relationship to its development (8)—to actual tobacco exposure and disease occurrence. Complex dose-response relationship phenomena point to a need to identify the intermediate markers between injury and disease. For example, chemoprevention data from a randomized Phase III trial of isotretinoin suggest that the therapy is effective in those who have never smoked and former smokers but not in current smokers (9). Pathways of disease progression associated with low-level exposures may differ from those associated with high-level exposures. Although several good models are available for study (reviewed in 10), identifying the effects of tobacco exposure in these models is time consuming. This points to a need for accelerated models, as well as for mixture and single-agent models.

Partners

- CDC
- National Cancer Institute (NCI) and Cancer Centers
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Child Health and Human Development (NICHD)
- National Institute on Drug Abuse (NIDA)
- TTURCs
- Society for Research on Nicotine and Tobacco
- Society of Toxicology
- EPA
- Flight Attendant Medical Research Institute
- Pharmaceutical industry
- Robert Wood Johnson Foundation
- American Lung Association
- American Heart Association
- American Cancer Society (ACS)
- California Tobacco-Related Disease Research Program

Impact

Research in this area will result in the identification of biomarkers that can be used to determine intermediate outcomes in long-term studies. This knowledge will provide a more specific and efficient tool to assess biological exposure and effect and, thus, to identify persons at risk. Ultimately, this knowledge will influence policy on exposure dosage and affect multiple disease processes.

*3. Support further research into cross-disciplinary interactions in tobacco-related disease mechanisms, specifically sex differences in carcinogenic and disease pathways.

This exploration of mechanisms should include the early premetastatic stage and chemoprevention so that pharmaceutical agents can be developed to treat these early stages of tobacco combustion exposure. Some epidemiologic evidence from case-control studies suggests that women are more susceptible than men to tobacco-induced carcinogenesis, after taking into account baseline exposure, body weight, body height, and body mass index (11), although cohort studies have not confirmed this. Nevertheless, women with lung cancer have been shown to have a higher level of smoking-induced pulmonary DNA adducts (12) and decreased DNA repair capacity (13) than men with lung cancer. DNA adduct levels are determined, in part, by the relative activity of phase I and phase II detoxifying enzymes. Phase I enzymes, such as cytochrome P4501A1 (CYP1A1), activate the carcinogens in cigarette smoke, whereas phase II enzymes, such as glutathione-S-transferase M1 (GSTM1), convert tobacco carcinogens to inactive conjugates. The CYP1A1 mutant/GSTM1 null genotype has been found to be more common in women with lung cancer than in controls, suggesting that alteration in the activity of these enzymes contributes to lung cancer risk (14). Clinical studies are required to show that such differences are important. Further insight into sex-specific pathways for lung carcinogenesis may be gained through the use of proteomic and genomic approaches in the analysis of established tumors and early lesions collected from both men and women.

Partners

- Society of Toxicology
- Molecular Epidemiology Group, American Association for Cancer Research
- Breast cancer, lung cancer, and TTURC SPOREs
- NCI
- NIDA
- NIEHS
- Society for Research on Nicotine and Tobacco
- ACS
- Office of Research on Women's Health

Impact

Research in this area will uncover real differences and potentially identify new targets for interventions. This research will affect multiple disease processes.

4. Support further research into cross-disciplinary interactions in tobacco-related disease mechanisms, especially inflammation.

Common pathways may exist between inflammation and tobacco-related disease. In addition to the carcinogen exposure inherent in tobacco use, chronic injury and inflammation may contribute to cancer risk. Consistent with this hypothesis, it has been shown that among male smokers, airway obstruction is a better indicator of lung cancer risk than either age or level of smoking (15). History of prior lung disease (asthma, chronic bronchitis) is associated with a significantly increased risk of lung cancer in nonsmoking women (16). To date, relatively little research has focused on the interplay between inflammation and the development of lung cancer. In mouse models, a positive correlation has been found between inflammation and susceptibility to lung tumors (17). However, subsequent studies showed that agents that reduce pulmonary inflammation do not necessarily suppress lung tumorigenesis (18). Thus, the relationship between these two processes requires further clarification. Inflammatory cells that migrate into the lungs of cigarette smokers may increase the oxidative stress produced by inhaling cigarette smoke. Consequently, further understanding of the effects of oxidative stress on lung biology and the mechanisms controlling the expression and release of proinflammatory mediators in the lung may lead to the development of new therapies to prevent inflammation and, thus, potentially have an impact on lung tumorigenesis.

5. Support further research into cross-disciplinary interactions in tobacco-related disease mechanisms, especially promotional mechanisms.

Tobacco smoke contains many constituents, such as nicotine, that may not be directly carcinogenic but may influence

disease pathways. Nicotine may protect normal human airway epithelial cells and tumor cells from apoptosis (19, 20) and stimulate blood flow to tumors (21). Understanding the variety of cellular processes regulated by nicotine and other tobacco smoke constituents may provide new therapeutic targets for intervention in tobacco-related diseases. Further understanding of the mechanisms by which nicotine alters cell growth will also be important in evaluating nicotine supplementation for smoking cessation. Given that such approaches can result in serum concentrations of nicotine close to those achieved in active smokers (22), determining the impact of chronic nicotine supplementation on disease processes is required. Since the effects of nicotine alone on epithelial and endothelial cells may be different than the effect of cigarette smoke, future studies will also be required to determine whether single-agent exposure and exposure to mixtures will have similar consequences.

6. Encourage transdisciplinary investigations into common pathways of tobacco-related cancer, heart disease, and lung disease.

Smoking is a well-known risk factor for vascular disease (23-25). Although progress is being made in understanding its pathogenesis, the precise mechanisms by which smoking affects vascular disease have not yet been fully elucidated. Epidemiologic data support the notion that common mechanisms may exist for cigarette smoke-induced carcinogenesis and cardiovascular disease. For example, the *MspI* polymorphism in the cytochrome P450 enzyme CYP1A1 increases both lung cancer risk and the risk of cardiovascular disease in light smokers (26, 27). Recent studies have defined common biological pathways that may be important to the pathogenesis of tobacco-related diseases (reviewed in 28); one notable example is nicotine stimulation of endothelial cell proliferation in the setting of both tumor growth and atherosclerosis (21). Further characterization of these common pathways, combined with the use of mouse models that have disruptions in genes that confer disease susceptibility, may allow for the development of targeted intervention and treatment strategies for all tobacco-related diseases.

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