American Thoracic Society Documents

Workshop on Lung Disease and the Environment

Where Do We Go from Here?

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A workshop was held May 6, 2000, in Toronto, Canada to evaluate the interactions of the lung and its environment. This workshop was organized to focus on three levels of knowledge and research: a population level, an organ/multicellular level, and a cellular level. At each level, interactions with the environment are currently being investigated for their contribution to the pathogenesis of chronic lung disease. Recommendations for specific future research directions were generated for each level of interaction. These recommendations are intended to identify major research needs in these areas of discussion and not to exclude the need for research in other general or closely related areas.

The respiratory system is one of the primary interfaces with the external environment and faces unique demands to handle and detoxify inhaled gases and particles. It must both control and express inflammatory pathways in ways that preserve the primary functions of the respiratory system while protecting it from invasion by foreign infective agents or antigens. The respiratory system has an extraordinary surface exposed to the external environment, with the lower respiratory system having a surface area of approximately 100 m^2 in the adult human (1). This large surface area serves as the basis for gas exchange with the tissue barrier separating the air surface from the underlying capillary vascular surface having an average thickness of 0.36 μm (2) and being as thin as 0.2 μm over substantial portions of the alveolar capillary bed. A balanced, uniform distribution of both gas and blood across the vast alveolar surface is a fundamental requirement of optimizing gas exchange. Inflammatory reactions in airways that alter gas distribution, inflammatory conditions in pulmonary vasculature that affect blood distribution, and inflammatory conditions along alveolar septa that disrupt the delicate alveolar–capillary membrane all have profound adverse effects on lung function. Inhaled air, even under relatively pristine conditions, contains large numbers of particles of diverse origins. Pollens, animal and plant proteins, inorganic dusts, and combustion materials from industry, transportation, and voluntary (active smoking) or involuntary (passive smoking) smoking create particulate counts in inhaled air ranging from thousands to even millions of particles per cm^3 when ultrafines are considered (3).

Some inhaled gases and particles are processed or cleared by the upper respiratory tract (4) where turbulent airflow facilitates gaseous reactions with the mucous interface and the deposition of particles on the thin mucus/serous coat lining the nasopharynx. Ciliary action brings the mucus with the deposited particulate material to the posterior pharynx, where it is commonly swallowed and excreted through the gastrointestinal tract. Reactive gases and particulate matter that reach the tracheobronchial tree also primarily react with or deposit on the mucous/serous coat on the tracheobronchial tree with turbulence at airway branch points causing high depositions in those regions (5). Mucociliary clearance action returns the majority of this mucus and the deposited particulate matter to the posterior pharynx where it is swallowed. Thus, the first defense against inhaled toxic gases, antigenic and chemically reactive materials, and infective agents is the highly efficient mucociliary clearance action of the upper and lower respiratory tracts, where both the composition of the fluid lining layers and the ciliary action to move it to the posterior pharynx accomplish a rapid bulk removal of these materials. Small concentrations of inhaled materials that penetrate the mucociliary layer to reach the underlying upper and lower respiratory tract epithelium require immune processing, as do the infective agents and antigens that reach the alveolar or gas exchange region.

Assuming a minute ventilation of 5–8 L, the average (nonexercising) adult human breathes in approximately 7–12,000 L per day, with each liter commonly containing in excess of 100,000 fine plus ultrafine particles per cubic centimeter (6). This yields a potential total particulate dose to the respiratory system that is greater than 10^{12} particles per day. Approximately 20–25% of this (7) or in excess of 2×10^{11} particles can be assumed to reach the alveolar gas exchange region, where they are distributed over a gas exchange surface composed of approximately 5×10^8 alveoli (8). Many particles that deposit past the mucociliary clearance mechanisms require some type of cellular detoxification or immunologic processing for clearance. The challenge to the lung is to accomplish that processing without inappropriate and potentially damaging inflammatory amplification. The respiratory system is inherently able to process this kind of constant bombardment by a wide range of inhaled antigenic material without activating an inflammatory cascade while at the same time remaining capable of mounting an appropriate inflammatory cascade in response to a serious infective challenge.

Disease or pulmonary dysfunction can occur when the normal pathways for control of inflammatory processes in the lung become disordered and the lung begins to mount an uncontrolled and injurious response to inhaled materials. The delicate balance between highly controlled inflammatory pathways and the amplified expression of those pathways in the lung thus is a critical element in the normal homeostasis of the lung and is potentially a part of the pathogenesis of a variety of forms of chronic lung diseases.

POPULATION LEVEL

Asthma Epidemiology and Disease Development

Asthma and allergic rhinitis coexist in the majority of affected patients and are triggered by reactions to many environmental

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agents, including common allergens. Allergic airway diseases are the result of interactions between as yet largely unknown genetic and environmental factors. The identification of these factors should offer the real possibility of disease modification and prevention. Events during early fetal life and childhood seem particularly important in the development of allergic airways diseases, which likely result from the interaction of genetic and environmental factors during this crucial time. In addition, these diseases are increasing in prevalence throughout the developed world at a time when other common problems, such as cardiovascular disease and cancer, are on the decline. This rise, given the stability of the genome, indicates a likely shift in the initiators of asthma.

Although numerous epidemiologic studies of asthma have been performed, a set of key questions remain only partly answered: (*1*) Who develops asthma? (*2*) What are risk factors for asthma disease onset? (*3*) How does the environment affects those with asthma? Asthma is undoubtedly a heterogeneous disease in terms of its pathogenesis. There are a substantial number of risk factors that contribute to that heterogeneity such as hygiene, diet, infections, development of the immune system, and environmental or occupational exposures. This heterogeneity of "asthma" creates substantial difficulty in satisfactorily answering the previously mentioned questions. As genes that determine asthma risk are identified and the genotype–phenotype relationships are characterized, our research focus will be sharpened by being directed at identifiable subpopulations of patients with asthma. A major problem in accomplishing this is that there is deficient funding for large cohort studies of respiratory disease. This is particularly true when compared with funding of large cohort studies in cardiovascular disease and cancer.

To address these questions better, prospective studies of birth cohorts of children that are designed to assess exposures beginning antenatally and continuing into adulthood are needed. The studies need to include collection of DNA for assessment of gene–environment interactions. Large cohorts will be needed to answer these difficult research questions with reasonable certainty and to cover the diversity of the U.S. population. If the changing picture of asthma over time is to be understood, studies of successive cohorts are needed so that comparisons can be made over time. Studies of asthma also need to target groups that are likely to be relatively homogenous, for example, early onset childhood asthma and asthma in the older population.

Concern also remains as to the general role of air pollution in causing and exacerbating asthma. In both indoor and outdoor environments, there are exposures to numerous gaseous and particulate pollutants. A few of these exposures are being linked to the causation of asthma. For example, soybean allergen was identified as a cause of epidemic asthma in Barcelona during the 1980s (9). Sensitive research strategies to determine which specific air pollutants can be linked to the causation of asthma are needed. Recent research in animal models and *in vitro* research suggest that diesel particles may contribute to causing some cases of allergic diseases (10, 11).

MULTICELLULAR/ORGAN LEVEL

Inhaled environmental agents can have profound impacts in driving the interrelationships between signaling molecules and their targets, thereby upsetting the homeostasis in the lung and leading to inflammation and to remodeling of the structure of the lung.

Signaling Molecules: Eicosanoids, Cytokines, Tachykinins, Reactive Species, and Surfactant Proteins

Eicosanoids have long been associated with lung disease (12). Although best known for their effects on smooth muscle and inflammatory processes, recent studies identifying eicosanoid biosynthetic enzymes (13) as well as receptors (14, 15) in the cell nucleus have led to recognition that these lipids can also function as autocrine mediators and regulators of gene expression. Environmental factors influence eicosanoid production and alter cellular responses to eicosanoids (16, 17). Important future questions about the role of eicosanoids in environmental lung disease include (*1*) investigating the role of various eicosanoids in mediating or protecting against development of environmental lung disease, (*2*) determining whether genetic or acquired (e.g., related to disease, aging, or diet) alterations in eicosanoid synthesis influence responses to environmental agents, and (*3*) evaluating the efficacy of pharmacologic modifiers of eicosanoid synthesis or action (e.g., nonsteroidal antiinflammatory agents and leukotriene modifiers) as therapeutics for environmental lung disease.

The respiratory tract is innervated by nociceptive sensory nerves, which are activated directly or indirectly by noxious environmental agents such as ozone, allergens, cigarette smoke, isocyanates, and volatile organic compounds (18). Activation of nociceptive airway sensory nerves triggers release of sensory peptides known as tachykinins, which include substance P, neurokinin A, and neurokinin B (19). Tachykinins bind to neurokinin receptors, thereby controlling microvascular leakage, airway smooth muscle tone, mucus secretion, and chemotaxis and activation of inflammatory cells. Observed effects apparently depend on the anatomic distribution of receptor subtypes, the ability of pulmonary toxicants to activate receptor subtypes, and signal transduction mechanisms that operate downstream from receptor activation. Currently, little is known about how environmental agents may differentially stimulate neurokinin receptor subtypes in the lung or what signal transduction mechanisms are activated by neurokinin receptors.

It is well established that numerous cytokines and growth factors are involved in lung diseases and that environmental agents are mediators of lung disease such as pulmonary fibrosis and asthma. However, relatively little is known about the specific effects of environmental agents on regulation of cytokine gene expression and the subsequent impact on cell proliferative events (20, 21). In addition, there is a need to develop genetically defined and genetically altered mouse models that can be used to elucidate the mechanisms by which environmental agents influence cytokine expression at the molecular, cellular, and tissue levels (22).

Reactive species are generally regarded as mediators of widespread and indiscriminate structural and metabolic injury to tissues. However, reactive species also play a crucial role in both normal and pathologic cell signaling processes, including calcium homeostasis, kinase activity, and gene regulation (23). The focus of free radical biology is thus shifting from trying to understand mechanisms of cell necrosis to investigations of more subtle adaptive, abnormal functional and apoptotic response of tissues to environmental stresses. Functional genomics and proteomics, as well as advances in imaging and mass spectroscopy, need to be used in detecting and defining the specific reactive species responsible for inducing chemical modification to DNA, lipid, and protein that ultimately affect differentiated cell function.

Although generally regarded as a surface tension-reducing agent, recent studies implicate surfactant as a key participant in pulmonary host defense. Two of the surfactant proteins, SP-A and SP-D, participate in innate immunity by regulating immune cell function by facilitating pathogen clearance and by modulating the inflammatory responses (24, 25). Recent studies also suggest that these proteins mediate cross-talk between innate immunity and adaptive (antibody-mediated) immunity. Although it has been shown that exposure of surfactant to oxidants impairs

its function, little is known about the effects of environmental agents on the functions of surfactant protein or the cells that they regulate (26, 27).

Cytokines in Asthma, Chronic Obstructive Pulmonary Disease, and Environmental Lung Disease

Multiple cytokines are involved in the orchestration of chronic inflammation in asthma and chronic obstructive pulmonary disease (COPD) (28, 29). Cytokines play a key role in determining the nature of the inflammatory process, its amplitude (severity), and its persistence. In asthma, some cytokines are characteristic of the allergic inflammatory response and are derived from Th2-like lymphocytes, including interleukin-5 (which is critical for eosinophilic inflammation) and interleukin-4 and interleukin-13, which are critical for IgE formation for B lymphocytes. Certain chemokines, including eotaxin, monocyte chemoattractant protein-4 (MCP-4), and RANTES (regulated upon activation, normal T cell expressed and secreted) selectively recruit eosinophils to the airway mucosa. Other cytokines amplify the inflammatory response, including tumor necrosis factor-α and interleukin-1β, both of which activate nuclear factor-κB, which then switches on a panel of inflammatory genes (30). COPD is characterized by a different type of inflammation and a different pattern of cytokines. Chemokines that attract neutrophils (CXC chemokines), such as interleukin-8 and growth-related oncogene-α (GRO-α) predominate, and there are high levels of tumor necrosis factor-α (31). In both asthma and COPD, growth factors, such as platelet-derived growth factor and transforming growth factor-α are believed to play an important role in airway remodeling. Environmental agents may release cytokines in the airways in patients with both asthma and COPD. Although the molecular pathways are not established, there is considerable evidence that inhaled oxidant pollutants (ozone and nitric oxide) and diesel particulates activate nuclear factor-κB in airway epithelial cells and thus switch on multiple inflammatory genes.

MATRIX PRODUCTION AND REMODELING

Alterations in connective tissue, either an excessive accumulation or a marked loss of structural proteins, are key characteristics of several forms of lung disease. Quite likely, changes in extracellular matrix metabolism are initiated by focal insult or injury. Indeed, a fibrotic response (scar) is an important component in the repair of all tissues, including the lung. Repeated day-to-day minor airway injuries, such as those caused by inhalation of environmental particulates, mediate a transient, controlled, focal, and necessary fibrotic response. However, for mostly unknown reasons, an excessive, chronic deposition of matrix may occur, such as in interstitial pulmonary fibrosis or bronchiolitis obliterans with organizing pneumonia. In other conditions, such as forms of COPD, key structural components may be destroyed and not repaired. Such aberrant changes in matrix are essentially always accompanied by inflammation.

In contrast to asthma where primary initiating causes are often unknown, COPD is most often attributable to smoking. Occupational and other environmental exposures may also contribute. The natural history is also well characterized. We lack an understanding, however, of those factors, likely genetic, that place individual smokers at risk. A great deal remains to be learned regarding the factors contributing to the pathogenetic sequences in COPD that determine its progression, severity, persistence, and causes of exacerbations. Although COPD in the United States is a largely preventable disease, its continued occurrence offers an opportunity to learn more about determinants of response to inhaled irritants. Cigarette smoke is an extraordinarily complex mixture of combustion products that injures the lung through several mechanisms, including producing oxidant–antioxidant and protease–antiprotease imbalances. There are undoubtedly multiple genes that determine risk in individual smokers. Smokers with airflow obstruction and COPD are at greater risk for lung cancer, even after taking account of smoking history. This association needs follow-up to better understand its basis.

The net accumulation of extracellular matrix is the sum of protein production and assembly minus turnover. In addition to these metabolic events, which involve a variety of assembly proteins and processing enzymes, the vast diversity and function of extracellular matrix proteins themselves add to the complexity of understanding the biology of the interstitial compartment.

CELLULAR LEVEL

The ultimate target of the environmental insult is the cell and its membrane. From the initial signal at the cell surface, the cell responds via signaling molecules and gene expression leading to functional and phenotypic changes. Whether these changes are transient or long lasting, or adaptive or not, may determine the ultimate response of the organ and the organism to the environmental stimulus.

Signaling Pathways

Signaling pathways orchestrate cellular responses to the initial signal at the cell membrane. Little knowledge exists regarding the effects of environmental toxicants on initial signaling molecules such as protein kinases or their phosphorylation targets (32, 33). Other areas for future emphasis include investigations of how these environmental agents initiate the cellular response, the relationship between signaling pathways and pathologic responses to environmental toxicants, and the mechanisms of cross-talk between signaling molecules (34–36).

Cell signaling and transactivation of genes governing phenotypic and functional outcomes may be critical to the initiation and development of many environmental lung diseases; however, little is known about these phenomena in lung biology. It is known that inhaled environmental agents such as asbestos, particulate matter, and oxidants in general stimulate a number of signaling cascades (37–39); the relationship of these events to consequent cell responses and the pathogenesis of lung injury and disease is unclear. Research is needed to understand these pathways in animal models of environmental lung disease and in human lungs.

Gene Expression

Acute and chronic responses of pulmonary cells to the environment undoubtedly involve many alterations in genetic expression. The genes involved in cell responses are understood to mediate both inflammation and remodeling. Important known genetic responses include those involving matrix production and cytokine elaboration. Unknown genetic responses may be revealed by microarray approaches to identify global cell expression in response to environmental agents (40).

Genetic Regulation of Disease Expression and Lung Remodeling

The pattern of gene expression may differ between asthma and COPD, as this will depend, in part, on both the cause and the effect of different patterns of expressed cytokines and transcription factors in these two diseases. In addition, these pollutants interact with allergens in patients with asthma. The cytokine response to environmental stimuli is likely to be influenced by genetic polymorphisms affecting genes (especially upstream promoter regions) encoding cytokines, their receptors, signal trans-

duction pathways, and transcription factors, resulting in different responses between individuals.

Conclusions and Recommendations

Understanding the development of environmental diseases will proceed from research into the interaction of an environmental agent at each level: the target cell(s), the lung, and the population. Important points will include the identity, toxicity, and dose of the environmental insult, the identity of target cells, the key pathologic responses of the cells and of the lung, and the genetic characteristics that determine the development of disease in some individuals within populations.

Key questions outlining areas for future investigation include the following:

1. How do environmental stimuli interact with the different components of the lung (cellular or noncellular) to create disease? The major environmental (non-neoplastic) lung diseases that require a bold effort to elucidate the fundamental mechanisms of disease are asthma, chronic obstructive lung disease, and interstitial lung disease. All of these involve complex signaling mechanisms that activate specific genes controlling cascades of cytokines, arachidonic acid metabolites, tachykinins, and reactive oxygen species.
2. What key signaling pathways transmit the injurious message in which key cells? Signaling pathways that are likely to yield important new information include the protein kinases, tyrosine kinases, mitogen-activated protein kinases, phospholipases, and their substrates. The cell surface, cytoplasmic and nuclear receptors that feed into these signaling pathways, and the "cross-talk" among these molecular pathways will be useful avenues for research.
3. Can cell-signaling pathways be manipulated to alter the course of disease, first in animal models of environmental disease and ultimately in humans suffering from lung disease? The elucidation and manipulation of the precise roles of individual cytokines, arachidonic acid metabolites, and oxygen radicals will require appropriate genetically modified animals as models of human disease. Cells isolated from such models should provide critical further insights into the molecular mechanisms of environmental lung disease.
4. What differing characteristics of the exposed human population (e.g., genetic polymorphisms) determine the pathologic response to environmental agents?
5. What is the role of the environment and its interaction with genetic factors in predisposing some individuals and in controlling the severity of asthma? Does the environment play a role in varying responses to asthma-specific therapy? Why does asthma remit in some individuals and recrudesce later in life? A large multicenter, long-term longitudinal, and maternal/birth cohort is needed to understand the environmental and genetic risk factors for asthma as well as the natural history of asthma. Understanding of the interaction of the environment and genetic risk factors for this specific disease should provide insights for other diseases such as COPD and pulmonary fibrosis.

This official Workshop Report was originated in the Research Advocacy Committee.

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