

The Environment–Autoimmune Link

Autoimmune diseases are chronic, frequently life-threatening conditions that strike when the immune system goes awry and attacks the body's own tissues. Although some autoimmune diseases—such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus (SLE)—are relatively common, many of the more than 80 identified diseases are rare. However, overall, autoimmune diseases are the third most common group of diseases in the United States; they affect an estimated 14–22 million Americans and are responsible for significant morbidity, mortality, and health care expenditures. Many strike women and minority populations disproportionately. For example, 85% of SLE patients are female, and minorities have a two- to threefold greater risk of developing the disease.

Although genetic predispositions have been clearly implicated as major risk factors for many of these diseases, experts estimate that such factors account for only about one-third of the risk. Today, a great deal of research attention is focused on the highly complex and thus far poorly understood interactions between environmental exposures and genetic predisposition that appear to contribute to the onset of autoimmune diseases.

Over 4–5 February 2003, a diverse group of basic scientists, epidemiologists, clinicians, and other researchers gathered in Durham, North Carolina, for “Environmental Factors in Autoimmune Disease,” a workshop designed to assess the current state of the knowledge on autoimmune diseases, and to make recommendations on goals for future research initiatives. The workshop was sponsored by the American Autoimmune Related Diseases Association along with a variety of governmental agencies—the NIEHS, the NIH Offices of Rare Diseases and Research on Women’s Health, the National Health and Environmental Effects Research Laboratory of the U.S. Environmental Protection Agency, the National Institute of Allergy and Infectious Diseases, and the National

Institute of Arthritis and Musculoskeletal and Skin Diseases.

This workshop was a follow-up to the NIEHS’s initial meeting in the field, held in September 1998. The thrust of that session was to determine whether there was in fact an identifiable link between environmental exposures and autoimmune diseases. Now the search is on to discover which agents may play a role in which diseases, how gene–environment interactions result in the onset of autoimmune diseases, and ultimately how these devastating conditions might be prevented, ameliorated, and eventually cured.

Following the 1998 meeting, the NIEHS awarded seven grants to study the role of environmental factors in autoimmune diseases. This year’s workshop was

grantees and other leading experts in the field. According to Pat Mastin, an extramural program administrator with the NIEHS and the chief organizer of the conference, not all of the grant results were what researchers were expecting, “but sometimes what you find is more interesting than what you go looking for. Each of the grantees advanced the state of our knowledge in this critical area.”

NIEHS epidemiologist Glinda Cooper reported on the state of the science in the epidemiology of autoimmune diseases. After familiarizing the attendees with the latest information regarding the incidence, prevalence, demographics, and trends associated with autoimmune diseases, she identified several future epidemiologic research opportunities. Cooper particularly



originally intended to be a meeting of those grantees, whose projects were completed in late 2002. As interest in the workshop grew, it expanded into a more comprehensive opportunity to assess progress in the field and identify research goals across the disciplines involved.

Grants Grow Research Understanding

Day one of the workshop was devoted to scientific presentations from the NIEHS

emphasized the need for epidemiologic studies of the prevalence of autoantibodies, which, as possible markers of subclinical disease, could shed light on the pathways by which environmental exposures trigger abnormal immune responses.

Traditionally, autoimmune diseases have been identified as diseases that are systemic or those that are organ-specific. Fred Miller, head of the NIEHS Environmental Autoimmunity Group,

presented a thought-provoking case for a more refined paradigm that he termed “elemental disorders” to approach the study of these diseases. He suggested that many of the autoimmune diseases as they are understood today are actually composed of a variety of elemental disorders, each of which is a unique syndrome with a unique pathogenesis resulting from the interaction of certain genetic and environmental risk factors.

To illustrate his proposed approach, Miller cited the example of myositis. Depending on which of the myositis-specific autoantibodies is involved, myositis can clinically manifest in three distinct ways, each with its own identifiable symptoms, prognoses, and therapies. Miller considers these to be unique syndromes, or elemental disorders, and suggests that by not accounting for this characteristic of several of the autoimmune diseases, much of the research is being confounded.

Michael Pollard, an associate professor of molecular and experimental medicine at The Scripps Research Institute in La Jolla, California, presented his work investigating the immunology and genetics of murine mercury-induced autoimmunity. His studies in knockout mice have shown a clear dose–response relationship, with animals receiving the highest dose of mercury producing the most antibodies. This suggests that mercury accelerates disease in genetically susceptible populations. Pollard has identified several potential pathways of mercury-induced autoimmunity.

Noel Rose, director of the Johns Hopkins Center for Autoimmune Disease Research, discussed his work with mouse models of varying genetic susceptibility to myocarditis, an autoimmune disease that is a major cause of heart failure. His data suggest that although the disorder is induced by a viral infection, there are clearly environmental influences—in this case, lipopolysaccharides—that can exacerbate the disease or increase susceptibility. Rose believes that environmental exposures can modify the immune response, triggering autoimmune diseases in individuals with genetic susceptibility, often in concert with infectious agents.

Addressing the issue of imbalance in autoimmune disease prevalence between the sexes, Virginia Rider, an associate professor of biology at Pittsburg State University in Kansas, presented evidence that environmental factors could play a role in sexual dimorphism and autoimmunity. In *in vitro* studies, she has identified pathways by which estrogen metabolites could activate human lymphocytes from patients with SLE, causing an autoimmune response.

Exposure to environmental estrogens from sources such as food animals, pesticides, industrial by-products, and plants (some of which produce phytoestrogens, compounds similar to human estrogens) could also play a role in triggering an autoimmune response in susceptible people.

Denise Faustman, director of immunobiology at Boston’s Massachusetts General Hospital, presented a modified paradigm that suggests that environmental factors could be responsible for modifying the normal immune response mainly at the level of protein expression—that is, downstream of the genes themselves. Posttranscriptional modifications would account for the unexpectedly low concordance of autoimmune diseases among identical twins, suggesting that to a great extent there is a protein–environment interaction occurring, as opposed to a strictly gene–environment interaction. She also asserted that protein defects could represent a worthwhile target for treatment of autoimmune diseases.

Two grantees investigated the process of apoptosis in keeping the immune system in check. Michael McCabe, an assistant professor of environmental medicine at the University of Rochester, presented data suggesting that mercury exposure can interfere with the complex assemblage of molecules involved in apoptosis. Reduction or curtailment of apoptosis can lead to an autoimmune response. Shyr-Te Ju, a professor of internal medicine at the University of Virginia School of Medicine, has approached the question of apoptosis by developing transgenic mice that underproduce IL-2 (one of the most important activating factors in the immune response) and fas (a protein necessary for apoptosis). He found that lacking these compounds did in fact suppress apoptosis in his mice, and an autoimmune response followed.

Two other grantees investigated screening processes. Laurence Morel, an assistant professor of rheumatology at the University of Florida, worked with congenic mice having chromosomal regions that confer SLE susceptibility. She exposed these animals to estrogen and pristane. Her results suggested that several different genes could be involved in a gene–environment effect. M. Eric Gershwin, chief of the Division of Rheumatology, Allergy, and Clinical Immunology at the University of California, Davis, used the reverse approach. He bred mice prone to primary biliary cirrhosis, an autoimmune disease that leads to the destruction of the small bile ducts in the liver. He then exposed these animals to a spectrum of synthesized chemicals designed to mimic lipoic acid, a molecule implicated in the onset of the disease. The

idea was to determine whether the candidate compounds produced the highly disease-specific antimitochondrial antibodies characteristic of the disease. Identifying mimics of lipoic acid could shed light on compounds in the environment that trigger the disease.

Research by C. Lynne Burek, an assistant professor of molecular microbiology and immunology at The Johns Hopkins University, with a mouse model of thyroiditis—the third most common autoimmune disease—showed “proof positive of a gene–environment interaction,” according to Mastin. Iodine was added to salt in the 1920s to combat goiter resulting from a lack of dietary iodine. In the decades since, although goiter has all but disappeared, there has been a steady increase in the incidence of thyroiditis, which might stem from the ingestion of too much iodine. Burek’s work suggests that the protein thyroglobulin may be the culprit behind this association.

Eric Sobel, an associate professor of rheumatology and clinical immunology at the University of Florida, studied the effects of chlordecone, an organochlorine pesticide, on the development of SLE in a mouse model bred to be susceptible to the disease. Upon exposure to chlordecone, the mice showed autoimmune changes, as well as specific clinical end points, particularly renal damage, in dose–response fashion. It was significant that these effects were caused in a sensitive population not by a metal—one of the few fairly reliable “smoking guns” in this area of research and the topic of many studies—but by a weak exogenous estrogen.

Patricia Fraser, an assistant professor of medicine at Harvard Medical School, was the only grantee to focus on human populations. Her work on potential environmental associations with SLE, particularly in the African-American population, suggested that sunlight and organic solvents may be individual risk factors for SLE by interacting with glutathione *S*-transferase genetic polymorphisms. Although it is more difficult to show definitive gene–environment interactions with human subjects than with a controlled animal population, Fraser’s research shows that increased risk can be quantified in humans, suggesting a valuable methodology for studies of human populations.

Forward Focus

A report on the Autoimmune Diseases Coordinating Committee research plan (available at http://www.niaid.nih.gov/dait/pdf/ADCC_Report.pdf) was presented by Tom Esch, a program officer with the National Institute of Allergy and

Infectious Diseases. This landmark multi-agency effort was mandated by Congress to coordinate research and educational efforts in the area of autoimmune diseases. The plan, which was intended to bring together the various stakeholders in autoimmune disease research—patients, the public, and basic, preclinical, and clinical researchers—included several references to the importance of assessing the role of environmental factors in these diseases.

One important aspect of the workshop was the results of six breakout sessions on the topics of gene–environment interactions, altered antigens, immune modulations, signal transduction, and translational research in both systemic and organ-specific autoimmune diseases. Each breakout group offered a variety of recommendations within its subject, but broad areas of apparent consensus also emerged from the proceedings. Most consistently, the groups emphasized the need for improved collaboration. The general feeling was that multidisciplinary cross-institutional research initiatives would do three things: help synthesize existing data by better integrating animal and human studies, improve communication among investigators, and focus future research efforts more effectively as more information emerges about the role of environmental factors in autoimmune diseases.

The other major point of agreement among the groups was the need for translational research. As evidence that environmental factors can play a critical role in the onset or exacerbation of autoimmune diseases continues to accumulate, the research community needs to concentrate more effort on the human application of its findings. Specifically, the “bench-to-bedside” concept of translational research holds the potential to generate more and better biomarkers of susceptibility, improved risk assessment, preventive measures for susceptible populations, and, eventually, therapies designed to control or cure autoimmune diseases.

“There is good reason to think that environmental agents are involved in autoimmune diseases,” said Mastin. “Genetics clearly isn’t the whole answer, and infectious agents are clearly not the rest of the answer. So it has to be something else, and naturally, environmental exposures come to mind.” Mastin said that autoimmune diseases are an excellent area where translational research can take place: “We have many clinical people out there working on autoimmune diseases, and if we can help them become more cognizant of environmental factors, it will go a long way toward approaching the ultimate goal we all share—the treatment or prevention of these debilitating and often fatal diseases.” —Ernie Hood

Headliners

NIEHS-Supported Research

Gene–Environment Interaction



Effect of Polymorphisms on Biomarkers in Coal Miners

Nadif R, Jedlicka A, Mintz M, Bertrand J-P, Kleeberger S, Kauffmann F. 2003. Effect of *TNF* and *LTA* polymorphisms on biological markers of response to oxidative stimuli in coal miners: a model of gene-environment interaction. *J Med Genet* 40:96–103.

Genetic polymorphisms have been implicated in the difference in response to environmental agents, but interactions between genes and environmental oxidants involved in the development of human lung diseases have been largely unexplored. Oxidative stress arising from cigarette smoking and long-term exposure to dust and particles causes chronic airway inflammation, which is essential to the development of many lung diseases such as asthma, chronic obstructive pulmonary disease, and coal workers’ pneumoconiosis. In a study of 253 coal miners in France, NIEHS grantee Steven Kleeberger and colleagues investigated whether polymorphisms in two genes coding for the proinflammatory cytokines tumor necrosis factor α (*TNF*) and lymphotoxin- α (*LTA*) modify lung response to oxidants.

Specifically, the researchers measured intermediate biomarkers of response to oxidant exposure, including glutathione peroxidase (GSH-Px) and catalase activity in red blood cells among miners genotyped for the two polymorphisms. The researchers also gathered detailed information on the workers’ cumulative dust exposure and smoking habits.

For miners with a promoter polymorphism at the –308 position in the *TNF* gene, the researchers observed a significant association with red blood cell GSH-Px activity at high oxidant exposure. No association was observed among workers with this polymorphism who experienced low exposure. Regarding clinical outcomes, the results showed a positive association for coal workers’ pneumoconiosis among workers who had low catalase activity and an *NcoI* polymorphism in the *LTA* gene. No association was seen in those with high catalase activity, nor were any other significant associations observed.

These results provide the first demonstration of the involvement of genetic polymorphisms of two genes in the control of physiologic responses to exposure to oxidative stressors. The study suggests an interaction of genetic background with environmental exposure, and further suggests that intermediate responses are important in the development and progression of chronic pulmonary diseases such as coal workers’ pneumoconiosis. —Jerry Phelps