

National Institute of Environmental Health Sciences
Division of Extramural Research and Training
Cellular Organs and Systems Pathobiology Branch

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

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Concept Clearance

Role of the Environment in the Development of Autoimmune Disease

Introduction

Autoimmune diseases result from an immune response directed against the body's own tissues. There are over 80 different autoimmune diseases, and though many individual autoimmune diseases are rare, autoimmune diseases collectively afflict approximately 24.5 million Americans, with women disproportionately affected. The cause(s) of autoimmune disorders remain largely unknown. Genetics can account for only a portion of autoimmune disorders, with concordance studies in identical twins generally in the 25 – 40% range. Animal model, *in vitro* research and epidemiological studies have demonstrated links between environmental exposures and the development of autoimmunity, lending support to an etiology of autoimmune disease involving both genetic and environmental factors.

Over the past 14 years, the NIEHS has participated in trans-NIH committees and co-sponsored a number of workshops examining the role of the environment and the development of autoimmune disease. Despite the recommendations for research initiatives and the ongoing but slow accumulation of research data, knowledge gaps persist in this field.

Recently, the NIEHS sponsored a workshop that brought together an interdisciplinary group of experts to evaluate the state of the science regarding the role of the environment and the development of autoimmunity and autoimmune disease. Experts were selected for membership on four specific panels examining in detail the role of the environment and autoimmune disease, including: 1) molecular mechanism(s) and receptor dynamics; 2) animal models; 3) epidemiology/human studies; and 4) and exposure assessment. Panels defined the areas for review and have reported their findings in to be published reviews.

While reports from this workshop will highlight areas in which we are confident environmental exposures are associated with the development of autoimmunity and/or autoimmune disease, it will also highlight areas in which data are lacking. The need exists to increase our efforts towards discovering these links and understanding their mechanisms, to expand our knowledge base and scientific foundation so that ultimately

steps can be taken to improve the public health by reducing and/or preventing the exposures linked to autoimmunity and autoimmune disease.

Research Goals and Scope

A funding announcement will be designed to support innovative basic, epidemiological, and interdisciplinary research to understand the role and mechanisms by which environmental exposures influence the development and/or the exacerbation of autoimmune disease. Relevant topics of research to be emphasized in the FOAs will be based on the published recommendations from the NIEHS autoimmune workshop and timed for release with the release of the publications. The following are research areas highlighted by the expert panels as areas of interest:

Mechanisms

Research efforts are needed to further clarify and/or elucidate the role of specific mechanisms in the development of environmentally induced autoimmunity and autoimmune disease. These can include but are not limited to studies of the functional effects *in vivo* of DNA methylation changes under different environmental and genomic conditions; sex-specific changes in immune function; the contributions of the various B cells subtypes in autoimmune disease and the role environmental factors have in biasing the activation of B cell subsets; examinations of specific chemical or physical agents capable to modulate Tregs and Th17 cells.

Animal Models

Specific improvements to animal studies are needed, including use of disease markers from easily obtained biological fluids (e.g., blood) to enhance comparisons with human studies. As single mouse strains cannot encompass the genetic heterogeneity in human populations, studies should not be limited to identification or use of “gold standard” animal models but should include multiple models reflecting human genetic heterogeneity. In spontaneous disease models, studies should consider whether environmental exposures exacerbate or accelerate idiopathic autoimmunity, or reflect specific “environmentally-associated” forms of autoimmunity. Screening for environment associated effects should be conducted in both autoimmune prone and non-autoimmune prone models.

Epidemiology/Human Studies

There exists a continuing need to identify single causal agents associated with the development of autoimmunity and autoimmune disease (e.g., specific solvents or pesticides contributing to increased risk for the group), as well as the need to address the role of multiple exposures. Studies of environmental exposure risks within specific autoimmune phenotypes are needed to elucidate associations which may be specific to that phenotype, such as the apparent differing smoking risks for rheumatoid arthritis according to Rheumatoid Factor (RF) or Anti-neutrophil cytoplasmic antibody (ANCA)

positivity. Defining critical windows in the timing of exposures and latencies relating to age, developmental state and hormonal changes, understanding dose-response relationships, and elucidating mechanisms for disease development are additional critical data gaps needing investigation.

Mechanism and Budget

Funding announcement(s) will utilize R21 and R01 grant mechanisms enabling both exploratory and more fully developed research projects. The program is estimated at \$2.5M annually to support 6 – 8 projects.

Conclusions

Funding announcements for research proposals examining environmental exposures and autoimmune outcomes represent one of a coordinated series of activities designed to enhance the visibility of NIEHS interests and to stimulate research efforts in this field. Additional activities to be undertaken include the sponsorship of scientific symposia at society annual meetings and the development of interagency-sponsored workshops, publications and webinars.