

National Institute of Environmental Health Sciences
Division of Extramural Research and Training

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

September 1-2, 2010

Concept Clearance

Environmental Influences on Transcriptional Regulation

Overview:

It is becoming increasingly apparent that exposure to environmental toxicants can be associated with epigenetic changes, such as altered patterns of DNA methylation. These changes can affect gene expression patterns and likely contribute to disease or other phenotypes associated with exposure. DNA methylation is thought to be one of the last steps of epigenetic gene regulation – a read-out of chromatin states established by other proteins. In order to understand the mechanism by which toxicants impact gene expression, we must look at how exposure affects the proteins and processes upstream of DNA methylation and other epigenetic marks. While NIEHS has a significant investment in research aimed at identifying epigenetic signatures of exposure, such mechanistic studies are under-represented in our portfolio. The purpose of this proposed PAR is to move the field from descriptive and correlative studies to an enhanced mechanistic understanding of how environmental exposures affect the proteins and other elements involved in establishing and maintaining gene expression patterns and chromatin states.

Background:

Every cell in an organism has the exact same set of instructions encoded within the DNA sequence. In order to perform cell type or tissue-specific functions, a cell must read a specific subset of these instructions. One way in which this is accomplished is through epigenetic gene regulation. Epigenetic modifications, such as DNA methylation or post-translational modifications to histone tails, change the DNA or the way it is packaged into chromatin to make certain genes either more or less accessible to trans-acting elements, such as transcription factors. However, these epigenetic marks are only one player in this complex process. Other proteins or protein complexes act as “readers” or “writers” of the epigenetic code, depositing epigenetic marks or binding to them and recruiting other proteins. In addition, other factors such as non-coding RNAs, chromatin remodeling complexes, inter- and intra-chromosomal interactions and functional genomic elements play important roles in this process. Thus to understand the mechanisms involved in the environmental control of gene regulation and the central role of epigenetics in the process, it is critical to understand all the interacting pathways.

The NIEHS investment in environmental epigenetics has grown considerably over the last decade. Our current portfolio addresses a wide range of projects, including but not limited to: arsenic and its impacts

on epigenetic gene regulation; epigenetics, environmental exposures and autoimmune disorders; airborne particulates and metals impact on epigenetic processes and cardiovascular disease; identification of epigenetically labile genes; the effects of fetal or perinatal exposure to xenoestrogens and organophosphates on epigenetic processes in neurodevelopmental disorders; discordant exposures on monozygotic twins; the impact of nickel exposure on epigenetic processes and carcinogenesis; dietary influences on epigenetic processes; fetal and perinatal exposure to tobacco smoke, imprinted genes and birth outcomes. However, the current portfolio does not adequately address the mechanism by which these changes occur and how they lead to adverse health outcomes. This proposal is intended to stimulate environmental health scientists to pursue mechanistic studies aimed at understanding the environmental control of epigenetic mechanisms, as well as to encourage researchers focused on more basic aspects of epigenetic regulation to consider the impact of environmental toxicants in this process.

Objectives:

This PAR proposal is intended to stimulate environmental health scientists to pursue mechanistic studies aimed at understanding the environmental control of epigenetic mechanisms, as well as to encourage researchers focused on more basic aspects of epigenetic regulation to consider the impact of environmental toxicants in this process. These studies could be carried out using *in vivo* or *in vitro* systems.

Examples of studies that could be considered under this PAR include:

- Investigation of how co-activator or co-repressor complexes respond to environmental toxicants and how exposure impacts recruitment to target genomic loci.
- Investigation of how chromatin remodeling complexes respond to environmental toxins, including but not limited to endocrine disruptors, metals, organophosphates to Determination of how exposures affect functional genomic elements, such as retrotransposons/mobile elements, DNase I hypersensitive sites, repetitive elements (LINE1, Alu, LTRs), imprinting regulatory domains, centromeres, telomeres, or pericentric/subtelomeric regions.
- Studies that explore the role of non-coding RNAs in the mechanism of gene regulation by environmental exposure.

Mechanism and justification:

This PAR will solicit R01 applications. The rationale for developing a PAR is to stimulate/realize an increase in the number of research grants that explore how environmental exposures impact mechanisms of epigenetic regulation submitted, reviewed and supported by the NIEHS during the next three years.