NIH Award from the National Institute of Environmental Health Sciences

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- Project: DNA Methylation Alterations in Response to Pesticides Exposure
- Start Date: September 27, 2009
- Total Award Amount: $499,982

How the results of this project will benefit society:
In the United States, exposure to pesticides is ubiquitous, and over one million people are subjected to high occupational exposure. Pesticides and their residues are pervasive in our environment and our dependence upon pesticides is increasing. Although all pesticides sold in the United States have passed Environmental Protection Agency (EPA) tests for carcinogenicity, exposure to pesticides has repeatedly been associated with increased human cancer incidence in epidemiologic studies. Our recent analysis of the Agricultural Health Study (AHS) cohort, the largest prospective study in the world of pesticide applicators from Iowa and North Carolina, also indicates that pesticide exposure increases risk for several cancers. The results from this study will address a critical gap in our knowledge of pesticides and their ability to cause cancer.

The problem the project is trying to solve:
The concern is that EPA’s evaluation of chemical carcinogenicity is primarily based on the detection of mutagenic events. Altered DNA methylation, an emerging hallmark of cancer, is not considered in the EPA testing system. Emerging evidence suggests that promoter DNA methylation is affected by environmental exposures. Prior studies have shown that epigenetic information, including DNA methylation, contained in blood cell DNA represents a valuable predictive marker of cancer risk. Blood is a conduit between the external environment and human tissues, and as such, constitutes a seminal target tissue to evaluate the effects of environmental toxicants on human health. Our preliminary data recently linked exposure to organophosphate pesticides (OPs), the most commonly used insecticides in the United States, to increased promoter methylation of several tumor suppressor genes in blood DNA. We further confirmed this finding in vitro, using human blood cells treated with OPs. Taken together, we hypothesize that exposure to pesticides can induce promoter DNA methylation changes in blood cell DNA, and that this will provide currently unknown mechanistic insights into the association between pesticide exposure and cancer risk.

How this project will work:
We propose to study whether OP exposure alters gene promoter DNA methylation patterns in human subjects, and in OP-treated cell lines. We will first conduct a genome-wide screening in a subset of the population with the highest and lowest OP exposure, and in cell lines. Findings will then be validated using a gene-specific approach in an independent replication population, and after treatment of cells with varying doses of OP. We will also examine whether methyl donor-related nutrients and related genetic polymorphisms, two major factors in DNA methylation process, modify the associations between OP exposure and promoter DNA methylation levels. The investigations proposed in the current study will take advantage of the population and resources included in an existing NIEHS-funded cross-sectional study nested in the AHS.

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