

GUEST EDITORIAL

The importance of gene–environment interactions and exposure assessment in understanding human diseases

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Introduction

Over 75% of direct medical costs in the US are for chronic conditions (Hoffman et al., 1996), a situation that we can reasonably presume to increase in the future. Despite the need for improvement, only limited advances in reducing the burden of chronic diseases can be made until we more fully understand the complex biological mechanisms from which these diseases arise. Currently our understanding is fragmented, although we have made significant progress in our study of certain aspects of the disease puzzle. One important aspect is that of the role that individual genetic susceptibilities play in disease development. Realization of a genetic underpinning to disease susceptibility led to the Human Genome Project, completed in 2003. Despite the undeniable advancements in genetic understanding and genetic research capacity that arose from the Human Genome Project, however, we still are no better off in our ability to treat and prevent disease than we were before the project's completion.

Gene–environment and environment–epigenome interactions

In fact, it is not surprising that the Human Genome Project alone would be unable to usher in an era of new disease treatments. It has been known for some time that genetics is not the sole determinant of health or disease. Some of the most compelling evidence comes from studies comparing disease risk between monozygotic and dizygotic twins. In one study evaluating risk for developing several types of cancer, genes accounted for less than 50% of disease risk; other, possibly environmental, factors played a role in the remaining cancer cases (Lichtenstein et al., 2000). In a review of autoimmune diseases, genetics appeared to account for less than 50% of disease risk and, in the case of systemic lupus erythematosus, only 25–40% of disease risk, with environment accounting for the remaining 60–75% of risk (Powell et al., 1999). In a study of Parkinson's disease, early-onset cases (before age 50 years) appeared to be controlled predominantly by genetic factors. In the more common late-onset cases, however, an environmental trigger was suspected of accounting for roughly 85% of the cases (Tanner et al., 1999). My own work group has been conducting meta-

analyses of a number of published twin studies on asthma, diabetes, Alzheimer's disease, and breast and prostate cancers. Although our work is still preliminary, the data so far validates the concept that both genetic and environmental factors are important components of these all-too-common diseases. Although none of these twin studies identified any specific environmental agents, they do serve to highlight the fact that genes and environment operate in tandem and that you cannot fully understand a disease until you have defined the critical gene–environment interactions leading to it.

There is another critical layer of complexity in defining gene–environment components of human disease, that of the epigenome. While we generally think of genetic studies in terms of the DNA sequence of genes, the activity of these genes can be influenced in ways that extend beyond the actual DNA sequence. These epigenetic mechanisms, which can alter gene activity without changing the DNA sequence, are being linked to multiple illnesses, including cancer, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral diseases. Moreover, the epigenome appears to be sensitive to environmental agents, providing a new level of study — that of environment–epigenome interactions.

Epigenetic processes are natural and essential to biological functions. They include DNA methylation, acetylation of the histone proteins in chromatin, imprinting, and post-translational modifications. These structural changes are transmitted to the daughter cells of an organism. Interestingly we now have evidence that these same epigenetic changes or “codes” can be transmitted through subsequent generations. In studies by Anway et al. (2005) of endocrine disrupting compounds, it was shown that spermatogenic capacity was reduced in male mice by *in utero* exposures to either vinclozolin or methoxychlor. These effects were passed through four generations of mice and, because they correlated with altered DNA methylation patterns in the germ line, are assumed to operate through the epigenome. Another environmental component, the diet, has also been shown to affect the epigenome. Jirtle's laboratory at Duke University used a heterozygous *Agouti* gene model (A^{vy}) to assess the effect of maternal diet on methylation in offspring. In this mouse model, coat color in pups, ranging from yellow to brown, provided a visual indication of DNA methylation. Dietary supplements found to affect methylation status were vitamin B₁₂, folic acid, choline, betaine (Waterland and Jirtle,

2003) and the soy component, genistein (Dolinoy et al., 2006). Moreover, the latter study showed that differences in methylation status persisted into adulthood and altered susceptibility to obesity.

Twin studies have also revealed important influences of the environment on the human epigenome. Fraga et al. (2005) examined the DNA methylation and histone acetylation patterns of monozygotic twin pairs who ranged in age from 3 years to 74 years of age. Interestingly, the younger twin pairs had very similar expression patterns, but older twin pairs had more divergent patterns. The more different the lifestyles or environments of a twin pair, the greater the difference in gene expression. Overall, this study found that there were four times as many differentially expressed genes between a pair of 50-year-old twins as were found between 3-year-old twins. Thus DNA methylation is a dynamic process, subject to a lifetime of environmental influences.

Study of environment–epigenome interactions is an important complement to our study of gene–environment interactions. Defining the epigenome is difficult, however, because it involves the study of a fluid system, as opposed to genetic studies of a defined DNA sequence. Nonetheless, attempts are being made to develop a Human Epigenome Project, with initial studies focusing on the better understood components of DNA methylation and histone acetylation. The Human Epigenome Consortium, a European alliance, is focusing on methylation sites in the human genome, as well as a comparative analysis of epigenomes across different organisms (Beck et al., 1999). In the US, the cancer research community has proposed a blueprint for a Human Epigenome Project that would “identify all the chemical changes and relationships among chromatin constituents that provide function to the DNA code, which will allow a *fuller understanding of normal development, aging, abnormal gene control in cancer, and other diseases as well as the role of the environment in human health*” (Jones and Martienssen, 2005; italics my own).

Exposure assessment

Individual variation in response to environmental exposures has been a major impediment to understanding the environmental contribution to disease. These variations in response have provided a high background noise that, in epidemiological studies, has served to obscure important environmental contributors to disease risk. As scientists are better able to assess the genetic components of this variability, they will be able to reduce this background noise in ways that improve our ability to decipher how exposures affect health.

Unfortunately, although, environmental health scientists will still face another impediment in their research efforts. This impediment is caused by the generally poor quality of current exposure assessment tools, which are unable to provide the same level of precision or sophistication that are now possible

with genomic technology. Lacking precise measures of exposure, particularly at the individual level, greatly complicates our ability to identify environmental risk factors for disease. To determine how our environment, diet, and physical activity contribute to disease, new technologies are clearly needed.

One major funding source to move the field forward is the Genes and Environment Initiative (GEI) recently created by the Secretary of Health and Human Services (HHS) and the Director of the National Institutes of Health (NIH). This initiative will focus on the role that both genetic variation and environmental exposures play in the development of complex human diseases and will be administered by the Directors of the National Institute of Environmental Health Sciences (NIEHS) and the National Human Genome Research Institute (NHGRI). GEI will have two components: a laboratory component that analyzes genetic variation in people with specific illnesses and a technology development component that devises new ways to monitor personal environmental exposures that interact with genetic variations to cause diseases. In the proposed FY 2007 budget for GEI, \$26 million will go to genetic analysis and \$14 million will support development of new tools to measure environmental exposures.

The exposure biology component will provide \$14 million annually for 5 years to develop new tools that measure environmental exposures and the relevant biological responses to these exposures. The technology development is not limited to environmental exposures, but ideally will also include measures of dietary intake and activity level; these risk factors would then be analyzed to see how they interact with specific genotypes to either maintain health or to potentiate disease processes.

The first workshop for the Exposure Biology Program was held May 16–17, 2006. Attendees were selected from a variety of fields, including engineering; care was taken to include scientists who were not from the traditional exposure assessment community, but who had technical skills that could be used in novel ways for assessment purposes. It was determined that technologies are currently available, or could be re-engineered, to provide information on point-of-contact exposures (environmental sensors), biological response indicators (biological sensors), and measures of diet and activity and psychosocial stress. For example, wireless technology could be adapted to allow simultaneous monitoring of physical activity, physiological responses (such as heart rate, respiratory rate, and oxygen exchange), and possibly geographic location and external environmental conditions (such as temperature, particulate levels).

A range of sensing capability that can provide information from the macro level (ambient environment) to the molecular or nanolevel (intracellular environment) are now possible for application to environmental health science. New molecular assays based on global changes in metabolites (metabolomics) or proteins (proteomics) are relatively high-throughput approaches to the analysis of biomarkers in samples of blood and urine. These “omic” approaches can be incorporated

into micro- or even nanoscale devices, such as chip-based and microfluidics platforms, effectively decreasing sequencing costs and enabling multiplexed analysis of minute samples. Combining new molecular and nanoscale technologies with imaging approaches can provide real-time data on molecular signaling, protein activity, and protein-protein interactions at a level not previously available.

A biosample repository is one possible outgrowth of this project, where shared specimens could be collected, analyzed, and distributed among multiple research centers. New computational and informatic capability will doubtless also be needed in order to meaningfully integrate genomic and exposure information generated from this ambitious project.

The NIEHS will be releasing RFAs and contracts soon for this project. It is the Institute's goal to develop, over the next 4–5 years, up to 25 new environmental sensors or biomarkers of response that could be applied in population studies to study the contribution of the environment to human disease. This exposure information, cross-referenced with information of relevant genes, will help identify the basic underpinnings of molecular response to exposures, as well as suggesting treatments and prevention strategies.

Conclusion

Ultimately our vision is to define how environmental exposures elicit pathological responses, culminating in disease. Recognizing that these exposures are only one part of a multifactorial process, we are investigating interactions along the gene-environment and environment-epigenome axes in order to gain a fuller understanding of the underlying processes in disease initiation and progression. One major impediment to our understanding of environmental components of disease is the paucity of reliable measures of exposure, both long-term and short-term. The HHS/NIH Exposure Biology Project of the Genes and Environment Initiative will help in this effort by enhancing exposure assessment technologies, particularly at the level of individual measures of exposure, diet, and physical activity. It is our goal to provide to the research community approximately 10–25 improved environmental sensors and biomarkers of response over the next 5 years and to integrate this knowledge with information on genetic susceptibilities. Outgrowths of this research could provide a way to determine very early pathophysiologic measures of disease initiation, thus allowing for better screening and intervention strategies.

Improved environmental assessment technology could also be harnessed to help clinicians discriminate among the different subtypes of a disease or symptom. My own research in asthma has shown how environmental exposures can be used to identify different pathophysiologic phenotypes, rendering the genetics and biology of this condition more amenable to study. Asthma is a complex disease, involving many exposures and linked to multiple loci throughout the

genome. By focusing on endotoxin-induced asthma, we were able to demonstrate that polymorphisms in the TLR4 gene, the primary receptor for endotoxin, were associated with a blunted response to endotoxin (Arbour et al., 2002). Moreover, this fundamental finding led to the observation that a blunted innate immune response affected the development of several diseases (Cook et al., 2004), including atherosclerosis, sepsis, and lung transplant rejection. Thus, specific environmental triggers can serve to narrow the pathophysiological phenotype of a complex human disease, leading to the understanding of the basic biological processes that not only cause that disease but apply to many different diseases.

Ultimately, the ability to develop, validate, and correlate exposure-response indicators with genetic variation will be critical to the medical community's success in reducing the burden of common diseases such as obesity, asthma, neurodegenerative diseases, and cancer. Technology arising from the GEI will enhance the ability of the environmental health research community to provide this type of information to the medical community, hopefully leading to strategies that reduce the prevalence of many chronic diseases.

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