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Environment and Disease Risks

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Abstract

A new paradigm is needed to assess how a lifetime of exposure to environmental factors affects the risk of developing chronic diseases.

Although the risks of developing chronic diseases are attributed to both genetic and environmental factors, 70 to 90% of disease risks are probably due to differences in environments (1–3). Yet, epidemiologists increasingly use genome-wide association studies (GWAS) to investigate diseases, while relying on questionnaires to characterize "environmental exposures." This is because GWAS represent the only approach for exploring the totality of any risk factor (genes, in this case) associated with disease prevalence. Moreover, the value of costly genetic information is diminished when inaccurate and imprecise environmental data lead to biased inferences regarding gene-environment interactions (4). A more comprehensive and quantitative view of environmental exposure is needed if epidemiologists are to discover the major causes of chronic diseases.

An obstacle to identifying the most important environmental exposures is the fragmentation of epidemiological research along lines defined by different factors. When epidemiologists investigate environmental risks, they tend to concentrate on a particular category of exposures involving air and water pollution, occupation, diet and obesity, stress and behavior, or types of infection. This slicing of the disease pie along parochial lines leads to scientific separation and confuses the definition of "environmental exposures." In fact, all of these exposure categories can contribute to chronic diseases and should be investigated collectively rather than separately.

To develop a more cohesive view of environmental exposure, it is important to recognize that toxic effects are mediated through chemicals that alter critical molecules, cells, and physiological processes inside the body. Thus, it would be reasonable to consider the "environment" as the body's internal chemical environment and "exposures" as the amounts of biologically active chemicals in this internal environment. Under this view, exposures are not restricted to chemicals (toxicants) entering the body from air, water, or food, for example, but also include chemicals produced by inflammation, oxidative stress, lipid peroxidation, infections, gut flora, and other natural processes (5, 6) (see the figure). This internal chemical environment continually fluctuates during life due to changes in external and internal sources, aging, infections, life-style, stress, psychosocial factors, and preexisting diseases.

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The term “exposome” refers to the totality of environmental exposures from conception onwards, and has been proposed to be a critical entity for disease etiology (7). Recent discussion has focused on whether and how to implement this vision (8). Although fully characterizing human exposomes is daunting, strategies can be developed for getting “snapshots” of critical portions of a person’s exposome during different stages of life. At one extreme is a “bottom-up” strategy in which all chemicals in each external source of a subject’s exposome are measured at each time point. Although this approach would have the advantage of relating important exposures to the air, water, or diet, it would require enormous effort and would miss essential components of the internal chemical environment due to such factors as gender, obesity, inflammation, and stress. By contrast, a “top-down” strategy would measure all chemicals (or products of their downstream processing or effects, so-called read-outs or signatures) in a subject’s blood. This would require only a single blood specimen at each time point and would relate directly to the person’s internal chemical environment. Once important exposures have been identified in blood samples, additional testing could determine their sources and methods to reduce them.

To make the top-down approach feasible, the exposome would comprise a profile of the most prominent classes of toxicants that are known to cause disease, namely, reactive electrophiles, endocrine (hormone) disruptors, modulators of immune responses, agents that bind to cellular receptors, and metals. Exposures to these agents can be monitored in the blood either by direct measurement or by looking for their effects on physiological processes (such as metabolism). These processes generate products that serve as signatures and biomarkers in the blood. For example, reactive electrophiles, which constitute the largest class of toxic chemicals (6), cannot generally be measured in the blood. However, metabolites of electrophiles are detectable in serum (9), and products of their reactions with blood nucleophiles, like serum albumin, offer possible signatures (10). Estrogenic activity could be used to monitor the effect of endocrine disruptors and can be measured through serum biomarkers. Immune modulators trigger the production of cytokines and chemokines that also can be measured in serum. Chemicals that bind to cellular receptors stimulate the production of serum biomarkers that can be detected with high-throughput screens (11). Metals are readily measured in blood (12), as are hormones, antibodies to pathogens, and proteins released by cells in response to stress. The accumulation of biologically important exposures may also be detected as changes to lymphocyte gene expression or in chemical modifications of DNA (such as methylation) (13).

The environmental equivalent of a GWAS is possible when signatures and biomarkers of the exposome are characterized in humans with known health outcomes. Indeed, a relevant prototype for such a study examined associations between type 2 diabetes and 266 candidate chemicals measured in blood or urine (14). It determined that exposure to certain chemicals produced strong associations with the risk of type 2 diabetes, with effect sizes comparable to the strongest genetic loci reported in GWAS. In another study, chromosome (telomere) length in peripheral blood mononuclear cells responded to chronic psychological stress, possibly mediated by the production of reactive oxygen species (15).

Characterizing the exposome represents a technological challenge like that of the human genome project, which began when DNA sequencing was in its infancy (16). Analytical

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systems are needed to process small amounts of blood from thousands of subjects. Assays should be multiplexed for measuring many chemicals in each class of interest. Tandem mass spectrometry, gene and protein chips, and microfluidic systems offer the means to do this. Platforms for high-throughput assays should lead to economies of scale, again like those experienced by the human genome project. And because exposome technologies would provide feedback for therapeutic interventions and personalized medicine, they should motivate the development of commercial devices for screening important environmental exposures in blood samples.

With successful characterization of both exposomes and genomes, environmental and genetic determinants of chronic diseases can be united in high-resolution studies that examine gene-environment interactions. Such a union might even push the nature-versus-nurture debate toward resolution.

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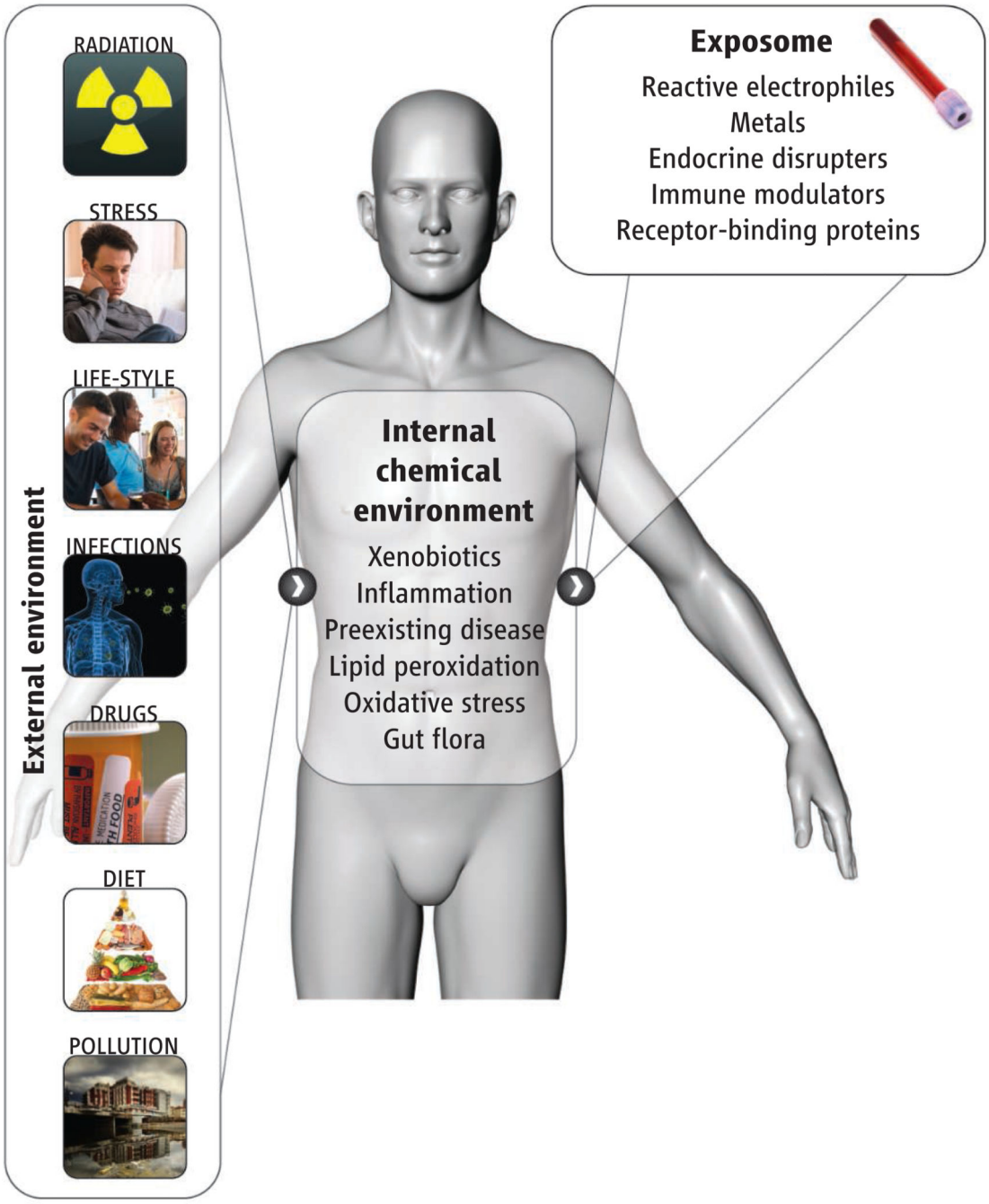

Figure 1. Characterizing the exposome

The exposome represents the combined exposures from all sources that reach the internal chemical environment. Toxicologically important classes of exposome chemicals are shown. Signatures and biomarkers can detect these agents in blood or serum.