

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

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Concept Clearance

Microbiome/Environment Interactions

Introduction

The current dogma suggests that disease originates primarily from defects in our own cells along with cues from the environment. We are now beginning to appreciate the role of the microbiome – the collection of microbes living on and inside us – in triggering disease, as well as in promoting wellness. The critical role of the microbiome is not surprising when one considers that microbes outnumber human cells by 10 fold; indeed, many refer to the microbiome as the “11th organ system.” The core microbiome is established over the first year of life and its composition is known to be affected by external factors, including birth route (vaginal vs. caesarian), diet (breast milk vs. formula, introduction of solid foods), and antibiotic use. Several studies have demonstrated that differences in the diversity or composition of the gut microbiota can be associated with disease states, including environmentally relevant diseases such as obesity and autism.

Our microbiome is our first point of contact with the environment, and a number of studies indicate that it can directly impact the way that we are exposed to some environmental chemicals. The gut microbiota affects our exposure to certain toxicants in two ways: increasing their bioavailability by breaking down the non-digestible components of foods, and through presystemic transformation. The most well-studied example of this phenomenon is arsenic, which has been shown in both human and rodents to be presystemically transformed by gut microbes into more toxic forms. Although many examples of presystemic transformation involve metals and metalloids, similar studies have demonstrated similar effects for other toxicants, such as polycyclic aromatic hydrocarbons, which are transformed into estrogenic metabolites.

The fact that the microbiome is so readily affected by external factors suggests that it may also be susceptible to a number of other environmental insults, including exposure to environmental chemicals. This idea, coupled with the known role of the microbiota in presystemic transformation of certain environmental toxicants, suggests a number of intriguing possibilities relevant to environmental health, including: a) perturbation of the microbiome by environmental chemicals, particularly during the first year of life, could result in permanent functional changes that lead to disease later in life, b) differences in

composition of microbiota among individuals could contribute to population variation in susceptibility to environmental chemicals, and c) the microbiome may contribute to presystemic metabolism of many more compounds, having a significant impact on the ultimate internal dose received. Gaining a better understanding of the complex relationship between microbiota and environment may explain why some individuals are more susceptible to environmental exposures than others, and could completely revolutionize the way we currently think about toxicity testing.

The purpose of this proposal is to establish a comprehensive program aimed at investigating the interaction between the microbiome and the environment, how functional changes in the microbiome may contribute to the development of environmentally induced disease, and how such changes might affect individual susceptibility to exposure.

Research Goals and Scope

The overarching goal of this program is to bring the concept of the microbiome to the forefront in the environmental health sciences, as well as to encourage researchers already actively studying the microbiome and how it responds to more traditional “exposures” such as diet and antibiotic use to also consider exposures to environmental chemicals. This program will specifically exclude dietary or pharmacological exposures, which do not fall under the purview of NIEHS. The proposed program would begin with two initiatives intended to stimulate this field:

- a. Environmental Influences on the Microbiome (R21): The goals of this initiative are to solicit research aimed at investigating how environmental exposures impact the composition and/or function of the microbiome. This initiative would support investigators using wild-type or humanized gnotobiotic model organisms to investigate how exposure to environmental chemicals affects the microbiome in both the short and the long term. Early life exposures are of particular interest, as these occur during the initial colonization of the microbiota and may permanently affect its potential.
- b. Metabolism of Environmental Toxicants by the Microbiome (R21/R01): The goals of this initiative are to solicit research aimed at investigating how environmental toxicants undergo presystemic metabolism by the microbiome and/or how presystemic metabolism by the microbiome impacts internal dose. These studies may use microbiota isolated from wild-type or humanized gnotobiotic model organisms, or from humans.
- c. Microbiome/Environment Interactions in Disease (future): The long term goal of the program is to understand the role of the microbiome in environmentally-induced disease. This may include studies investigating how the microbiome contributes to the Developmental Origins of Health and Disease paradigm, studies aiming to correlate functional differences in the microbiome with disease status in exposed human populations, and work attempting to understand how



host genetics and microbiome interact in the development of disease after exposure. This initiative may involve partnerships with other Institutes and Centers with research programs focused on microbiome and disease, such as NICHD, NIDDK, and NHLBI.

Studies funded under the first two proposed PARs will help establish research teams and generate preliminary data necessary for future studies aimed at understanding how the environment and microbiome interact to cause disease, how changes in the microbiome may affect disease susceptibility after exposure, and to develop intervention strategies (such as dietary interventions) to reduce exposure in affected populations.

Mechanism and Justification

The initial initiatives will be PARs, released once a year for three consecutive years, with a focused review. Both will use the R21 mechanism, though the initiative investigating presystemic metabolism of environmental toxicants will also accept R01s, as this field is somewhat more developed.