Concept Clearance

Branch: GEHB

Council Period: February 2017

Concept Title: The Role of the Microbiome in the Developmental Origins of Health and Disease (DOHaD)

Introduction

While there is quite a bit of evidence linking early life exposures to disease outcomes later in life, the mechanism by which this occurs is not completely clear. The field has focused largely on the potential role of epigenetic mechanisms, but as of yet, few examples have been identified that establish causal relationships between exposure induced epigenetic changes and later onset disease. Alternative, as yet undiscovered mechanisms might underlie the persistence of the effects of early life exposures, and must be considered.

With the help of the NIH Common Fund program, the Human Microbiome Project, we are beginning to understand the normal human microbiome and the important role it plays in health and wellness. The microbiome develops throughout infancy and early childhood, starting at birth. Many factors can affect the community structure of the developing microbiome, including birth route and method of feeding. An increased risk for several disease states has been associated with differences in birth route and early antibiotic use, suggesting that these early impacts on the microbiome may have persistent effects.

Several groups have looked at the effects of external or environmental perturbations on the community structure or function of the adult microbiome. The data from these studies seems to suggest that once established, the microbiome exists in a fairly stable state. In adults, both dietary changes and antibiotic use result in short term changes to the community structure of the microbiome, but once these perturbations are removed, the community structure reverts to something very close to the original structure.

Although the fully developed adult microbiome is largely stable, the developing microbiome may be more sensitive to the effects of external factors, and changes induced during this sensitive time may be more persistent. Two intriguing recent studies showed that in mice, exposure to antibiotics during the first few weeks of life lead to functional changes in the microbiome, and increased obesity as an adult. Although the community structure of the microbiome in the developmentally-treated adults did not appear to be significantly different from that of the untreated adults, transferring the microbiome of these treated animals to germ-free untreated mice resulted in the same metabolic changes, proving that alterations to the microbiome itself play a causal role in the observed obesity phenotype. In the acute exposure model, reduced microbial diversity persisted through adulthood, and the metagenome (i.e. the functional capacity of the microbiomes) was also changed.

Recent NIEHS investments in microbiome/environment research have resulted in increased interest in this area, and a growing number of funded grants. Several environmental chemical exposures have now been shown to impact the microbiome. However, few of these researchers are looking specifically at the effects of exposure within this sensitive developmental window. A funding announcement specifically focused on early life exposures, their effects on the microbiome, and how this relates to the DOHaD hypothesis is needed to fill this important knowledge gap, and ties together several areas of research of significant interest to NIEHS. Grants funded as part of this RFA will also add to the growing body of evidence linking environmental chemical exposures to changes in the microbiome, more generally.

Research Goals and Scope

This RFA would solicit applications that investigate the potential role of the microbiome in mediating the latent effects of early life exposures. The goal of the RFA is to address the following key knowledge gaps:

- Determine whether early life exposures to environmental chemicals impact the development and functional capacity of the microbiome
- Establish whether a causal relationship exists between exposure-induced changes in the microbiome and a disease associated with early life exposure
- Investigate persistence of exposure induced changes to the developing microbiome, and the factors that affect persistence
- Determine whether certain developmental windows are more susceptible to long-term changes in the microbiome
- Evaluate the role of the maternal microbiome in transmitting the effects of prenatal exposure to offspring.

Appropriate exposures include:

- Environmental chemicals for which early life exposures have been linked to later disease onset, either in animals or in epidemiological studies, even if these chemicals have not yet been linked to changes in the microbiome
- Environmental chemicals that have been shown to cause changes in the microbiome
- Diet, drugs of abuse, or smoking (including maternal smoking) in the absence of a relevant environmental chemical exposure are not allowable.

Mechanism and Justification

The RFA will use the R01 mechanism, although applicants may propose shorter, exploratory projects. The R01 mechanism provides the budget and years of funding that will be required to address these research gaps. The RFA will state that exploratory projects are welcomed, and reviewers will be oriented as such.

In order to achieve the primary goal of linking early exposures to later life disease outcomes, investigators will need to follow exposed individuals across the lifespan. In addition, specialized germ-free models will be needed to establish causality. For these reasons, applicants will be limited to the use of animal models, although they may propose experiments that use microbiota isolated from exposed human populations (for example, to generate humanized gnotobiotic mice).

The review is expected to be handled by a microbiome-centered Special Emphasis Panel that has been convened by the Center for Scientific Review, with ad hoc expertise in exposure science to be added. This panel has been reviewing applications from institute RFAs and program announcements that are focused on the microbiome.