

Project Title

Investigating the role of the maternal microbiome in fetal neurodevelopment

Statement of Purpose

The goal of this proposal is to determine the effects of maternal microbiota on fetal microglia maturation and mechanistically define the impact of altered microglia on nearby neural progenitor programs.

Investigators

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Project Summary

A growing body of evidence implicates the maternal gut microbiota in the development and function of fetal physiological systems, including the central nervous system (CNS). Alterations in the composition of maternal microbiota are associated with neurodevelopmental disorders and deficits in social and cognitive performance in offspring children. Importantly, only a subset of these neurological and behavioral abnormalities can be improved by restoring the microbiome postnatally, suggesting that the maternal microbiota influences neural changes during embryonic development. However, the mechanistic link between the maternal microbiota and changes in neurodevelopmental programs remains poorly characterized.

Microglia are resident immune cells of the CNS whose maturation is strongly influenced by the host's microbiome. At the same time, these maturing microglia can interact with nearby neural progenitors and influence ongoing neurodevelopmental programs. Thus, microglia are uniquely positioned in the embryonic brain to sense alterations in the maternal microbiota and then translate those cues into changes in ongoing neurodevelopment. To date, most projects have focused on either half of this scenario: either the effects of the maternal microbiota on microglia or how maturing microglial influence neural development. Here, we combine our expertise in gut microbiota and neural development to study the entire pathway from maternal gut to neurodevelopment with a goal of defining the mechanistic events that link adverse changes in the maternal gut to neurodevelopmental disorders in the offspring. Across three aims we test the hypothesis that metabolites from the maternal microbiome are sensed by fetal microglia, which respond to impact normal neural development. Conversely, a dysbiotic or absent maternal microbiome will disrupt developmental program(s), causing altered behaviors later in life.

Aim 1: To determine the effects of the maternal microbiome on embryonic and early postnatal microglial maturation and priming. In GF pregnant dams, embryonic microglia display sex-specific defects in transcription and chromatin accessibility, suggesting that the microbiome contributes to maturation of fetal microglia. Here we will use a diverse

set of immunological approaches, transcriptomic and chromatin accessibility analyses, and high resolution microscopy to evaluate changes in embryonic microglial maturation.

Aim 2: To determine how alterations in microglial maturation perturb hypothalamic neural development. Using our colonized GF pregnant mice models, we will use immunohistochemistry, time-lapse imaging, and neurogenic assay to determine the neural developmental process perturbed by immature microglia.

Aim 3: To identify putative maternal microbial metabolites that convey educational signals to microglial cells in utero. Here, we will screen for critical maternal microbiome metabolites and ask if they rescue microglial maturation and behavioral phenotypes observed in adult offspring reared by our GF dam models.

Combined, identifying the mechanisms by which maternal gut-bacteria modulate microglial development and influence prenatal neurodevelopment presents a clear potential pathway for the development of clinical interventions to reverse the onset of neurodevelopmental disorders.