

The IBD Metabolome Project: NMR Metabolomic Analysis To Identify IBD And The Microbe-Genotype Relationship

Summary of Research Proposal

Hypothesis

NMR metabolomic analysis will reveal a metabolic fingerprint specific for IBD and will demonstrate the relationship of the very earliest metabolic alterations associated with enteric microbial flora responsible for the initiation and perpetuation of intestinal inflammation in IBD.

Objective

The purpose of this grant is to employ innovative metabolomic techniques to characterize the disease state in an animal model of IBD and to explore the relationships between luminal microbes and the intestine and the animal genotype. Metabolic "fingerprints" will establish a pattern that can be used to identify and classify IBD. Furthermore we will apply these metabolic fingerprint techniques to develop the relationships and identify the metabolites associated with IBD-causing bacteria and non-IBD-causing bacteria.

Research Plan

We will employ NMR spectroscopy to build a metabolic profile of bio-fluid and tissue samples that can be used to distinguish IBD from non-IBD in the IL-10 gene-deficient mouse model of IBD. We will analyze the metabolic fingerprint of disease pathogenesis, including kinetics of disease development, gender differences, and disease development in the presence altered intestinal flora. Furthermore we will derive metabolic fingerprints of selected bacteria that do or do not cause IBD in mono-associated experimentation and from these establish common metabolic patterns that will provide insight into the factors initiating and perpetuating IBD.

First we will investigate the metabolic fingerprint in bio-fluids and intestinal tissue of IL-10 gene-deficient mice with IBD and compare it to the fingerprint from samples of healthy control mice. Second, in a kinetic approach we will obtain metabolic fingerprints at various time points before and during the onset of disease to identify the metabolic inflection point at which intestinal and systemic inflammation is initiated. This is likely to yield important information relative to putative initiating events. Third, changes in metabolic fingerprints will be compared to changes in cytokine release and systemic response and to account for gender differences we will analyze male and female mice separately. We and others have employed mono-association studies in IL-10 gene-deficient mice to investigate whether individual bacteria of the endogenous flora can initiate sustained intestinal inflammation. From these studies, we have learned that some bacteria can initiate a disease whereas others cannot. The difference between disease-causing and non-disease causing bacteria remains elusive. This background experimentation in our lab will provide the foundation for the fourth step. We will investigate metabolic fingerprints of bacteria we know cause IBD in this model and those that don't, and then examine the unique metabolic fingerprints when these bacteria are mono-associated into the axenic IL10-gene deficient mouse. Subsequent subtraction analysis will provide description of the precise time and the associated metabolic changes occurring at the moment intestinal and systemic inflammation initiates. These findings will allow us to significantly advance our understanding of the microbe-epithelial-genotype relationships