

## Controlling Inflammation and Atherogenesis through Exercise and the Gut Microbiome

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The gut microbiome may be a new target for modulating atherogenesis, an inflammatory process leading to plaque formation in the arterial intima. A subclinical state of inflammation occurs in most but not all obese individuals, and this inflammation plays a mechanistic role in atherogenesis. The human gut is an ecosystem comprised of human cells and a diverse assemblage of interacting microorganisms, called the microbiome. While it is established that the gut microbiome ecosystem can influence whether an individual has a low or high inflammation phenotype, no study has determined whether that phenotype and the resulting atherosclerosis potential can be transferred with the gut microbiome. Further, it is not clear how an anti-inflammatory stimulus, such as physical activity, affects the gut microbiome. The **specific objectives of this application** are to determine whether the gut microbiome dictates inflammation phenotype and to clarify whether the anti-inflammatory effects of exercise are dependent or independent of the gut microbiome. To achieve these objectives, we propose to investigate the following 3 specific aims: 1) assemble a cohort of obese individuals (n=30) with lower (Low-INF) versus higher (High-INF) inflammation phenotypes and characterize their gut microbiomes; 2) establish the gut microbiome of Low-INF and High-INF obese individuals in germ free mice and quantify changes in inflammation phenotypes; and 3) control the physical activity of humanized mice and test for differences in inflammation phenotypes and gut microbiome between low and high activity groups. While some researchers have identified components of the microbial profile that associate with functional outcomes, we expect the net function of a diverse ecosystem to be the most important determinant of inflammation phenotype. Associations between humans and humanized mice will be made to determine whether inflammation phenotype is transferred through the gut microbiome. If so, we will have identified a significant target for disease risk reduction. Coronary artery intima thicknesses (CIMT) will be measured and a finding of greater CIMT in mice humanized with the high inflammation microbiome will position us for highly significant follow up studies to pinpoint the bacteria most influential in this outcome. The comparison of low and high physical activity is important in determining the extent to which the gut microbiome may be shifted from high to low inflammation phenotype.