Macronutrients, Mitochondria and Blood Metabolome/Proteome Disease Risk Profiles

Bruce S. Kristal

Department of Neurosurgery, Brigham and Women's Hospital

Links between diet and human disease, and between reactive species and disease, are so commonly considered they lie in the realm of textbooks and the popular press.

Links between a component of cells called mitochondria and energy production are generally appreciated by junior high school.

Links between mitochondria and calcium (a key component in both normal cell function and in disease), free radicals, or cell death may be less known to the general public, but each has in excess of 10,000 PubMed citations, and is thus well known to the general scientific community.

However, despite broad and strong theoretical considerations supporting casual connections between diet effects on mitochondria and diet effects on disease – and some specific experimental support – there are, to our knowledge, no systematic studies that bridge this fundamental gap.

Bridging this gap is central to understanding environment-gene interactions, as suboptimal dietary macronutrient choices are arguably the major environmental stressor in individuals living in Western societies. We therefore propose to bridge this gap using an interdisciplinary, product-development approach to discover and confirm innovative plasma metabolomic and proteomic biomarkers for dietary intake of subclasses of fats and carbohydrates, and for their effects on mitochondrial (dys)function. Thus, we propose to measure blood constituents with a long range goal of using them to better assess both the body's function and an individual's risk of disease. We will then validate these markers by using them to test the hypothesis that diet-associated effects on mitochondria are linked to diet-associated changes in disease risk. We will approach this study in five pieces:

Aim 1: *To determine the effects of dietary changes in fatty acid and carbohydrate composition on mitochondrial physiology*

Here we focus on creating a series of diets that vary in fat and carbohydrates. The fat component of the diets range from those enriched in unhealthy fats (eg, trans-fats, saturated fats) to those enriched in healthy fats (eg, monounsaturated fats and omega-3 fats such as fish oil). The carbohydrate components of the diets range from those enriched in simple sugar (like table sugar) to those enriched in complex, slowly metabolized sugars, such as complex starches. We will then systematically determine how each affects the ability of the body to produce energy and to produce, and detoxify, free radicals.

Aim 1: *To determine the effects of dietary changes in fatty acid and carbohydrate composition on the plasma metabolome and proteome*

Here we focus on creating a series of blood tests that allow us to recognize both the combined diets (ie, the fat and the carbohydrate together), and each of the individual components. This sets the stage to develop blood tests to study the effects of diet on disease risk – and for creating personalized risk analysis.

Aims 3 and 4: To determine the extent to which adherence to/presence of each diet, dietary constituent, and mitochondrial property predict type II diabetes (Aim 3) and breast cancer (Aim 4) in previously profiled case control studies nested within the Nurses' Health Study

At the conceptual level, we will now use the data determined above to determine whether individuals who fit each of these profiles have higher or lower risk of developing type II diabetes and breast cancer over an approximately 10-year time frame. In addition, we will begin to use these data in conjunction with other available dietary data from Nurses' Health Study to provide objective validation of an individual's biologic response to specific diets, and how these responses track with questionnaire data.

Aim 5: To provide an electronic archive of the metabolomic and proteomic constituents of the blood of participants that could be repeatedly mined for future testing of new hypotheses.

The study that we are performing is expected to provide baseline data and understanding on several fronts, nutritional influence on biochemistry all the way through disease risk prediction and personalized medicine. Thus, a final aspect of our work will be to put this data in a format that can be generally used by other investigators asking questions in the future. This includes studies linking the genome to both nutritional input and disease risk.

In contrast to many of the studies within the GEI (Gene's and Environment Initiative), we study environmental effectors that everyone is exposed to, and which are expected to exert relatively subtle, long term effects, where the critical effects may exist buried in the noise of an individual's other, more severe and potentially transient environmental influences, such as cigarette smoke, daily medication, or exposure to polluted city air. Thus, our study has the potential to contribute to understanding of many of the other studies in GEI, in which our differences are the noise in their studies. We thus seek to link the existing wealth of data in nutritional epidemiology datasets with defined dietary regimens and the other studies present in GEI. Our goal is to further general NIH goals of focusing on health and early interventions rather than late stage disease.