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The emerging relevance of the gut microbiome in cardiometabolic health

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Humans are super-organisms or “holobionts” [1] composed of 10% human cells and 90% microbial cells [2], and the health and survival of both have co-evolved to become inextricably intertwined. Thus, vital host metabolic pathways and physiological responses, including lipid and bile acid metabolism and inflammatory response, are regulated by “cross-talk” between the host and the gut microbial community, or “microbiota” [3]. Perhaps not surprisingly, the gut microbiota is increasingly recognized as an agent of sickness, with dysregulation in the gut microbiota, or “dysbiosis,” emerging as both a feature and potential cause of cardiometabolic disease. The pace and scope of discovery in this arena reflects our increasing ability to incorporate powerful ‘omics’ technologies – in particular genomics, metagenomics and metabolomics – into preclinical and clinical studies.

It is well-established that cardiovascular complications are the leading causes of morbidity and mortality in individuals with obesity, insulin resistance and type 2 diabetes mellitus (T2DM). This association reflects in large part the deleterious impacts of systemic inflammation, lipotoxicity and oxidative stress on endothelial function that accompany these conditions [4–5]. Studies over the last decade have demonstrated that gut microbial dysbiosis can, by altering the balance between circulating and stored lipids and by promoting systemic inflammation (metabolic endotoxemia), promote obesity, insulin resistance and T2DM, thereby significantly increasing risk for CVD [3, 6–11].

Importantly, however, the microbiome prevails upon cardiovascular health in non-obese individuals, as well. A case-control study of lean individuals demonstrated that characteristic changes in the gut metagenome (shotgun sequencing across the genomes of all organisms in a fecal sample) were associated with inflammatory status and symptomatic atherosclerosis (i.e., stenotic atherosclerotic plaques in the carotid artery leading to cerebrovascular events) [12]. Peptidoglycan pathway genes were enriched in the gut metagenomes of patients, whereas metagenomes of controls were enriched for genes regulating synthesis of anti-inflammatory molecules and antioxidants. These results implicate the gut metagenome in the development of symptomatic atherosclerosis through regulation of host inflammatory pathways.

Metabolic byproducts of intestinal bacteria can have potent health consequences via cross-talk with human genes and signaling pathways, notably beyond the gut itself. For example, human omnivores were shown to produce higher levels of trimethylamine N-oxide (TMAO) than vegetarians via microbiome-dependent metabolism of L-carnitine [13]. Plasma TMAO,

Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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derived from dietary phosphatidylcholine and hepatic expression of FMO3 (a flavin monooxygenase), the enzyme that catalyzes synthesis of TMAO, has been linked to CVD risk [14–15]. Further, gut microbial metabolism of the bile acid cholic acid to deoxycholic acid has been demonstrated to promote hepatocellular carcinoma in mice and likely facilitates this cancer induced by a high-fat diet [16]. Recent studies of the microbiome in human subjects either with T2DM or impaired glucose homeostasis indicate that age, ethnicity, gender and geography are key factors in interpreting a subject's metagenome with regard to cardiometabolic risk. This has been revealed by a comparison of T2DM-associated microbiomes from middle-aged Chinese adults [9] with those from elderly Sweden women [10]. Although some functional gene groups were similar, different bacterial species were correlated with T2DM status in the two cohorts. Nonetheless, uncovering links between bacterial metabolic potential and human metabolic dysfunction has begun and will be exported from the research lab to find a place in clinical settings.

A key question then is, “How can clinicians and physicians in collaboration with research scientists translate our current understanding of the gut microbiome's role in health and disease into healthcare initiatives to reduce CVD burden?” According to Dr. Alex J. Rai Director, Special Chemistry Laboratory, and Chief Scientific Officer of the Center for Advanced Laboratory Medicine at Columbia University Medical Center, who recognizes the rapid growth and potential for diagnostics in this area, knowledge gained from the research settings have “not yet been directly translated to the clinical laboratory.” However, it is almost a certainty that microbiome-based clinical diagnostics and treatments will be available in the near future to identify patients who are at risk for developing CVD. The practicality and utility of such diagnostics is illustrated by a recent microbiome-based identification of individuals at increased risk for obesity co-morbidities, including insulin resistance, dyslipidemia and systemic inflammation [11]. Importantly, the authors of that study point out that this discrimination of at risk individuals was “achieved with very few bacterial species,” suggesting that simple microbiome-based tests can be developed. Microbiome-informed treatments are exemplified by the finding that levels of bacterially-derived bile acids predict LDL-C lowering by simvastatin and that this is at least partially attributable to alleles at marker rs4149056 in gene *SLCO1B1* encoding a statin and bile acid transporter [17]. Furthermore, the tools and technologies both to generate the data that identify microorganisms present in the gut and to accurately assess activity of the gut microbiome in terms of metabolic potential and inflammation are becoming increasingly available and affordable. Costs for basic 16S taxonomic profiling are currently around \$30 per sample. This all means that analysis of the gut microbiome will become an essential component of a patient's medical history and suggests that the gut microbiome and our ability to manipulate gut microbiome composition and metabolic activities will emerge as useful therapeutic approaches in the armamentarium against CVD.

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