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New Computer Model Predicts Gut Metabolites to Better Understand Gastrointestinal Disease

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MEDFORD/SOMERVILLE, Mass-- Tufts University School of Engineering researchers and collaborators from Texas A&M University have published the first research to use computational modeling to predict and identify the metabolic products of gastrointestinal (GI) tract microorganisms. Understanding these metabolic products, or metabolites, could influence how clinicians diagnose and treat GI diseases, as well as many other metabolic and neurological diseases increasingly associated with compromised GI function. The research appears in the November 20 edition of *Nature Communications* (doi: 10.1038/ncomms6492).

The human GI tract is colonized by billions of bacteria and other microorganisms, belonging to hundreds of species that are collectively termed "microbiota." Disruptions in the microbiota composition, and subsequently the metabolites derived from the microbiota, are increasingly correlated not only to GI diseases such as inflammatory bowel disease (IBD) and colitis, but also to insulin resistance and Type 2 diabetes.

"There is increasing evidence that microbiota-derived metabolites play a significant role in modulating physiological functions of the gut," said Professor Kyongbum Lee, senior author on the paper and chair of the Department of Chemical and Biological Engineering in Tufts School of Engineering. "Emerging links between the GI tract microbiota and many other parts of the body, including the brain, suggest the tantalizing possibility to influence even cognition and behavior through relatively benign interventions involving diets or probiotics."

However, to date, only a handful of metabolites principally produced by microbiota—rather than the host organism itself—have been identified. Identifying microbiota-derived metabolites and understanding their effects on specific host functions could open up new avenues of basic and clinical research to develop safe, targeted therapies involving molecules that, by definition, constitute the natural chemical makeup of the host.

"Current methods of identifying and quantifying these metabolites are unable to distinguish whether the metabolites are produced by the host or the microbiota," said Lee.

The newly reported approach models the microbiome as a single, complex network of reactions. By using computational algorithms for network analysis, virtual pathways can be constructed to determine possible metabolic products. Then, these products can be parsed into host-derived or microbiota-derived metabolites.

The research team focused on aromatic amino acids (AAAs) because their metabolites are involved in many of the more than 2,400 distinct reactions expressed in the microbiota as a whole.

"In addition, we studied AAA-derived metabolites because AAAs can give rise to a variety of bioactive chemicals, such as salicylic acid, an anti-inflammatory compound, and serotonin, which is a neurotransmitter, obviously important in proper brain function," said Lee.

Work previously published in the Proceedings of the National Academy of Sciences (doi: 10.1073/pnas.0906112107) from Lee's collaborator Arul Jayaraman, professor in the Artie McFerrin Department of Chemical Engineering at Texas A&M University who holds a master's from Tufts School of Engineering, had already demonstrated that indole, a bacterial metabolite derived from the aromatic amino acid tryptophan, caused an anti-inflammatory response in the gut and increased resistance to pathogen colonization that could lead to infection

The algorithmic model in the research published today predicted 49 different metabolites would appear as exclusive to the microbiota. In vivo tests on mice then confirmed the presence of more than half of the predicted metabolites, including two novel metabolites, which play a role in the pathways that regulate microbiota metabolism as well as host immune function.

Next steps for the team include identifying microbiota metabolites whose levels are either significantly elevated or depleted during diseases such as IBD or cancer, to find disease-specific markers and explore possible roles for these metabolites in disease progression.

"Ultimately, the goal is to apply our models to arrive at a mechanistic understanding of the roles microbiota products may play in human physiology, and in turn, diagnose and treat disease," said Lee. "I think the potential for impact is immense."

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