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| Microbial metabolites in host health and disease |
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Increasing evidence indicates that interactions between the gut microbiota, diet, and the host contribute to the development of metabolic diseases such as type 2 diabetes. Many studies investigating the role of microbiota in metabolic diseases have identified associations between metabolic status and microbiota composition at the genera and/or species level. However, associations between individual bacterial species and disease can be positive or negative depending on the disease or treatment context, making it difficult to determine whether particular bacteria are beneficial or detrimental. Despite this issue, the gut microbiome has been shown to be functionally similar even in samples from geographically different regions and between human and mice. Thus, investigating microbial metabolites that reflect disease-associated changes of microbial function would overcome the limitations of current microbiome research.

This seminar will focus on the microbially produced metabolite imidazole propionate and how it potentially contributes to the pathogenesis of type 2 diabetes. In brief, I showed that imidazole propionate is present at higher concentrations in subjects with type 2 diabetes than in controls and is produced from histidine in a gut simulator at higher concentrations when using fecal microbiota from subjects with type 2 diabetes than from controls. I also identified bacteria that could produce imidazole propionate and showed that this metabolite impairs glucose tolerance when administered to mice. I further showed that imidazole propionate impairs insulin signaling at the level of insulin receptor substrate through the activation of p38γ MAPK, which promotes p62 phosphorylation and, subsequently, activation of mechanistic target of rapamycin complex 1 (mTORC1). I also demonstrated increased activation of p62/mTORC1 in liver from subjects with type 2 diabetes. These findings highlight the potential of identifying drugs that inhibit the production of imidazole propionate as a treatment for type 2 diabetes. I will also describe my ongoing work into investigating potential role of imidazole propionate on anti-diabetic drug response.