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Integrative multi-omics approach for analyzing gut ecosystem

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Gut microbiota interact each other to establish their unique metabolic system, and the host-microbial interaction creates a unique gut ecosystem. Symbiotic gut ecosystem is normally robust and maintains physiological homeostasis; however, once its homeostasis is disrupted, the resulting “dysbiosis” often leads to various disease states. Despite its importance, studies of gut ecosystem has hampered until recently because of the lack in good analytical methodologies, especially those suitable for analysis at the level of organisms. We have proposed the application of integrative multi-omics approach, combining multiple exhaustive analyses such as genomics, transcriptomics and metabolomics, with gnotobiote mice, for understanding gut ecosystem.

To verify the approach, we employed a simplified model of lethal infection with enterohemorrhagic *Escherichia coli* O157:H7 (O157) in germfree mice associated with several bifidobacterial strains. Our integrative omics approach has revealed that acetate produced by *Bifidobacterium* confer intestinal epithelial cells the protective ability against O157-induced cell death. We have also revealed that *Bifidobacterium* possessing the genes encoding ATP-binding-cassette-type carbohydrate transporters for fructose can produce more acetate with the consumption of fructose, and thereby preventing the translocation of the O157 Shiga toxin from the gut lumen into the blood and protecting mice from O157-infectious death.

Gut microbes belonging to order *Clostridiales* has been reported to efficiently induce colonic regulatory T cells (Tregs). The integrated omics approach was able to show that butyrate produced by these bacteria can promote differentiation of Tregs from naïve T cells via epigenetic regulation through its histone deacetylase inhibition ability. Furthermore, butyrate-induced colonic Tregs produce an anti-inflammatory cytokine IL-10 and ameliorate experimental colitis in mice. These observations suggest that gut microbiota induces colonic Tregs to suppress excessive inflammatory responses against themselves and maintain homeostasis of the gut environment.

These studies indicate that integrative multi-omics approach is a promising methodology to evaluate complicated host-gut microbiota interaction and to understand gut ecosystem.