Microengineered Human Gut-on-a-Chip: From Organomimicry to Precision Medicine

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The human gut microbiome substantially orchestrates intestinal homeostasis, disease development, and metabolic functions of the human body. Indeed, dysbiosis of human intestinal microbiota develops diverse intestinal disorders that can potentially lead to inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, colorectal cancer (CRC), infectious diseases, or irritable bowel syndrome (IBS) that manifests a dysfunction in the gut-brain axis. However, a lack of robust models of the living human intestine that demonstrates longitudinal host-microbiome crosstalk remains a critical unmet need. Human intestinal organoids have emerged as an advanced tissue-engineered model, but an enclosed lumen embedded in static hydrogel considerably hampers to recapitulate host-microbiome crosstalk *in vitro*. My group has spearheaded to offer a human Gut-on-a-chip microphysiological model that demonstrates intestinal physiology, three-dimensional (3D) morphogenesis, accurate oxygen control, mechanodynamic bowel movement, and longitudinal host-microbiome co-cultures. The accessibility and modularity of a microengineered Gut-on-a-chip can identify a specific disease trigger by recoupling the uncoupled complex factors germane to disease development in a spatiotemporal manner. In a pathomimetic human intestinal inflammation-on-a-chip model, we discovered that the intact epithelial barrier is necessary and sufficient to maintain the homeostatic tolerance of the gut under complex host-microbiome crosstalks. Furthermore, an integrative culture of patient-derived organoid epithelium in a Gut-on-a-chip enables to simulate patient-specific host responses under various microbial stimulations in an IBD Chip and a CRC Chip. Finally, we highlight the breakthrough of our personalized disease models and discuss the future impact of investigating the etiology and therapeutic targets in multifactorial human gastrointestinal diseases.