Modulation of host immune responses by gut microbiota-derived metabolites

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A major focus of Visekruna's laboratory is gaining a better understanding of the mutual interactions between the gut microbiota and the host immune system. The gut microbiota comprises a highly diverse and densely populated microbial ecosystem that plays a critical role in regulating host physiology. Intestinal homeostasis requires a stable gut microbiome that resides exclusively in the outer mucus layer. Loss of intestinal barrier integrity during gut dysbiosis allows pathogens and commensals to invade deeper intestinal layers and disseminate through the vasculature, frequently resulting in chronic inflammation and systemic infections.
Gut microbiota-derived metabolites have been shown to play an important role in regulating the metabolic activity and epigenetic status of immune cells. However, the exact regulatory mechanisms remain to be fully elucidated. Visekruna's work focuses primarily on the impact of bacterial metabolites, such as short-chain fatty acids (SCFAs) and microbial tryptophan catabolites, on T cell-mediated immunity. Anaerobic bacteria express diverse enzymes that participate in the generation of SCFAs through the saccharolytic fermentation of dietary fiber. The most abundant SCFAs - acetate, propionate, and butyrate - modulate cellular processes in T lymphocytes that govern gene expression, differentiation, proliferation, and cytolytic activity. In the context of cancer, certain SCFAs, particularly pentanoate and butyrate, have emerged as promising modulators of cancer immunotherapy, with accumulating evidence from our laboratory indicating their potential to enhance therapeutic efficacy.
Tryptophan, an essential amino acid, serves as a substrate for several enzymes widely distributed among gut microbiota. Recently, we found that tryptophan catabolites generated by the commensal bacterium *Clostridium sporogenes* modulate the function of the intestinal epithelium and mucosal T cells. In particular, the tryptophan metabolite indole-3-propionic acid (IPA), derived from *C. sporogenes*, protected mice against intestinal inflammation.
In summary, numerous gut microbiome-derived metabolites can modulate immune cell function. Microbial SCFAs are key mediators of communication between microorganisms and their host. Through their effects on immune regulation, inflammation, and intestinal homeostasis, SCFAs and other microbial metabolites play important roles in maintaining host health and influencing disease outcomes.