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Microbiota-Derived Indole Metabolites Provide a Novel Pathway for Regulation of Intestinal Homeostasis

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Inflammatory bowel disease (IBD) is a multifactorial chronic condition that results in numerous perturbations in the gastrointestinal mucosa. IBD is characterized by the continual breakdown of the intestinal epithelial barrier leading to an inappropriate immune response towards intestinal microbiota. This exposure promotes inflammation and continued mucosal injury, though the pathogenesis of the disease remains unknown. There is currently significant interest in understanding the role of gut microbiota in IBD. Loss of commensal bacteria and their metabolites may play a role in homeostasis of the intestinal epithelia. Microbes benefit the host through the local synthesis of numerous metabolites. One such metabolite is indole. Indoles are gut microbiota-derived tryptophan metabolites that are abundant in the healthy mammalian gut and positively influence intestinal health. Using an unbiased metabolomics profiling approach, we identified a selective reduction in microbiota-derived indole metabolites in active murine colitis. We have developed HPLC-based technologies to validate these results and quantify indole and indole-derived metabolites within murine and human colitis samples. We show that exposure of intestinal epithelial cells to indole metabolites induces genes important in formation and maintenance of intestinal barrier. For instance, IL-10 is an anti-inflammatory cytokine that inhibits production of numerous pro-inflammatory mediators in various cell types. This cytokine functions through binding to the IL-10 receptor alpha subunit (IL-10R1) and colitis is strongly associated with the induction of the epithelial IL-10R. Our results have revealed a prominent induction of IL-10R1 mRNA and protein expression following treatment of intestinal epithelial cells with indole metabolites. Ongoing work has shown a potential role for selective indole metabolites, particularly indole-3-propionic acid (IPA), to alleviate disease severity and decrease inflammatory mediators in models of murine colitis. Together, these data suggest that microbial-derived indoles play a central role in mucosal homeostasis. Based on these findings and ongoing studies, we show that microbial-derived indole metabolites inhibit inflammation-induced damage and promote mucosal homeostasis. These studies elucidate a novel role for microbial metabolites in innate immune responses during intestinal inflammation using *in vitro* and *in vivo* models. This work will provide new insight to improved therapeutic approaches for treating IBD.

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