

A036 Microbiota-sourced Purines Promote Gut Mucosal Wound Healing and Barrier Function

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Introduction: The gut epithelium relies upon microbiota-derived metabolites (MDMs) for nutrients and energy procurement. Dysbiosis of the composition and metabolism of the microbiota and resultant loss of MDMs contribute to diverse mucosal pathology, including inflammatory bowel disease (IBD). IBD coincides with profound shifts in mucosal energy balance, presenting an energetic deficit to the impediment of mucosal wound healing and barrier reformation. In published work we identified the purine nucleobase hypoxanthine as a metabolite that is readily salvaged by intestinal epithelial cells for nucleotide biosynthesis and energy balance. In the present work, we demonstrate that large quantities of purines are made and released by the gut microbiota and these microbiota-sourced purines (MSPs) are essential for intestinal wound healing, identifying a new therapeutic approach for intestinal disease. **Methods:** MSP production by the murine microbiota was depleted by antibiotic treatment, and the purines reconstituted by oral supplementation and colonization with antibiotic-resistant purine-producing bacteria. Mice were then subjected to dextran sodium sulfate (DSS)-induced colitis and colon tissue collected for HPLC-based energy metabolite, immunofluorescent, and histochemical analyses. **Results:** Microbiota-sourced and orally supplemented purines incorporated into the murine colonic purine metabolite pool and were utilized as substrate for nucleotide biosynthesis. DSS-insulted colon tissue lacking purine substrates showed limited proliferative capacity, increased energetic and endoplasmic reticulum (ER) stress, and lacked mucin production to the detriment of mucus barrier integrity. Upon purine reconstitution, the energetic state of the tissue was improved and ER stress alleviated, with concomitant reclamation of proliferative capacity and mucus barrier sterility. In extended experiments, mice colonized with a mutant bacterium enriched in purine production were conferred enhanced protection during DSS-colitis relative to a non-mutant control. **Conclusions:** The colonic mucosa relies upon MSP as an essential substrate for nucleotide biosynthesis. Without this exogenous purine supply, the colonic epithelium lacks the purine substrate necessary to support energy balance and nucleotide-demanding processes such as proliferation and mucin barrier construction. Enriched microbial purine delivery shows potential as a next-generation probiotic for intestinal disease.