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Hypoxanthine as a Checkpoint Metabolite in Epithelial Energy Modulation and Barrier Function

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A primary function of intestinal epithelial cells (IECs) is to provide a selectively permeable barrier to protect the host from luminal microbiota and antigens, and to mediate the flux of nutrients, fluid, and waste across that barrier. Loss of intestinal barrier function is a hallmark of inflammatory bowel disease (IBD). Dysregulation of IEC barrier in IBD coincides with profound shifts in metabolic energy, especially in the colon, which exists in an energetically-vulnerable state of physiologic hypoxia. The precise mechanism(s) by which metabolic pathways contribute to and control inflammation have yet to be elucidated. To delineate barrier-related energy flux, an HPLC-based profiling method was developed to track changes in energy and adenylate metabolites during intestinal epithelial barrier development and restitution. Cultured epithelia demonstrated a remarkable capacity to maintain ATP and phosphocreatine during barrier development. Further epithelial cell profiling identified a significant capacity for cultured human IECs to salvage hypoxanthine (Hpx) and shift their metabolic equilibrium toward the production of ATP and phosphocreatine. In a consistent manner, we have demonstrated that Hpx-mediated shifts in metabolism result in enhanced epithelial barrier formation, increased epithelial restitution, and improved wound healing. Modulation of cellular energetics by Hpx were recapitulated with *in vivo* murine models, where orally-delivered Hpx increased colonic ATP levels. Guided by an unbiased microarray analysis of Hpx treated human IECs, we identified a number of target genes important in mucosal differentiation, energy metabolism, and reactive oxygen species mediation. As the ATP consumed by IECs under energetic stress is shuttled to and pooled as Hpx, it appears not only as a central energy metabolite, but also as a regulator of gene expression. Taken together, our ongoing studies provide strong evidence that Hpx functions as a central, checkpoint energy metabolite in IEC function.

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