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The Role of the Creatine Kinase Energy System in Intestinal Inflammation

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Inflammatory bowel disease (IBD) is a chronic inflammation of the intestine affecting more than 1 million people in the United States. Intestinal epithelia facilitate nutrient transport as well as protect against luminal bacteria and disruption of the intestinal epithelial barrier is a hallmark of IBD. The regulation of intestinal epithelial barrier is made possible by junctional complexes including tight junctions and adherens junctions that are supported by the actin cytoskeleton. Maintenance of the actin cytoskeleton is an energy demanding process and intestinal epithelial cells shuttle energy to the locations of the cellular junctions through the creatine energy circuit. Within the cell, creatine and its associated enzyme creatine kinase (CK) facilitate the shuttling of high energy phosphates in the form of phosphocreatine between sites of ATP generation. Previous work in our lab has shown that CK contributes to apical junction assembly in vitro and that supplementation of creatine in murine colitis models has a protective effect. Further studies have shown that mice lacking the brain and mitochondrial isoforms of CK have worse outcomes in a DSS model of colitis. In addition to impaired barrier function, this may be due in part to exacerbated intestinal bleeding observed in these mice. To that end, we measured platelet counts and aggregation and found that platelet counts are lower in CK double knockout mice compared to wild-type mice. The platelets from the knockout mice also showed a hyporesponsive phenotype in a collagen adhesion assay. Together, these results provide evidence that the CK energy circuit is essential in maintaining intestinal epithelial barrier function as well as supporting proper platelet function.