Inflammatory bowel disease (IBD) is associated with dysfunction of the intestinal epithelial barrier. The creative pathway, which involves the reversible interconversion of creatine to phosphocreatine, functions as an important energy shuttle system in many cells; disruption of this pathway in the intestinal epithelium results in reduced barrier function. Creatine kinase (CK), which catalyzes this interconversion, is reduced in intestinal biopsies from patients with IBD, though the effect of CK loss in the intestinal epithelium remains poorly understood.

We hypothesize that that loss of CK in intestinal epithelial cells results in altered energetics and, thus, reduced epithelial barrier function.

**RESULTS**

Figure 1. Epithelial barrier formation is reduced in CK-deficient cells

Figure 2. CK-deficient cells proliferate more slowly

Figure 3. ATP levels were measured in T84 cells in various growth conditions. Under typical growth conditions, CKB-knockdown T84 cells had 51% as much ATP as control (p<0.05). When grown exclusively in substrates used for oxidation (butyrate or glutamine), ATP level in knockdown cells was further reduced to 20% (p=0.05) or 37% (p=0.01), respectively. When grown in a substrate used for glycolysis or oxidation (glucose), ATP level in knockdown cells was not significantly different from control.

Figure 4. Mitochondrial content is reduced in CK-deficient cells

**CONCLUSIONS**

Loss of creatine kinase in intestinal epithelial cells results in an energy deficit, characterized by reduced ATP levels, reduced ability to utilize oxidation substrates. ATP production, and decreased mitochondrial content. These cells also perform more poorly in high energy cellular processes, such as barrier formation and proliferation. As intestinal biopsies from patients with inflammatory bowel disease have been shown to have decreased expression of CK, this alteration in energetics may contribute to pathogenesis in IBD.

**IMPLICATIONS**

Inflammatory bowel disease is associated with decreased intestinal epithelial barrier function and decreased creatine kinase expression. Using in vitro models of creatine kinase-deficient intestinal epithelial cells, we have found that loss of creatine kinase is sufficient to produce a barrier defect, and have found these cells to be energy deficient with reduced capacity for oxidation. Gaining further understanding of the regulatory pathways in creatine kinase-deficient cells that lead to this energy deficit may guide future therapeutic targets for the treatment of inflammatory bowel disease.