

Reduced Myosin 5b Expression is Associated with Increased Epithelial Proliferation in Ulcerative Colitis and Colorectal Cancer

Casper J. van Altena¹, Ana Pettijohn¹, Kristen A. Engevik¹, Melinda A. Engevik¹, Amy C. Engevik¹

¹Department of Regenerative Medicine & Cell Biology, Medical University of South Carolina, Charleston SC USA.

Introduction: Inflammatory Bowel Disease (IBD) is a chronic condition that causes extensive intestinal inflammation and is currently without a cure. IBD is divided into two subtypes: Crohn's disease and ulcerative colitis. Ulcerative colitis is characterized by persistent inflammation and ulcers in the large intestine (colon). Individuals with IBD, including those with ulcerative colitis, have an increased risk of developing colorectal cancer (CRC) due to the presence of widespread inflammation. Myosin 5b is a motor protein that is highly expressed throughout the colonic epithelium and mutations in Myosin 5b have recently been identified in IBD cohorts. **Objective:** We aimed to investigate alterations in Myosin 5b expression during colonic inflammation in ulcerative colitis patients and colorectal cancer. **Methods & Results:** We analyzed human bulk and single cell RNA sequencing datasets to identify the distribution of Myosin 5b expression in human tissue and the colon. We found that Myosin 5b is broadly expressed across all major colonic epithelial cells and is uniformly expressed throughout the different anatomical regions of the human colon. We also observed that Myosin 5b expression was markedly decreased in both inflamed ulcerative colitis tissue and in CRC. Immunofluorescent staining and imaging of human colonic tissue confirmed decreased levels of Myosin 5b in ulcerative colitis samples, in dysplasia and in CRC tissue. In a tamoxifen inducible-intestinal specific Myosin 5b knockout mouse model we found that loss of Myosin 5b resulted in increased colonic proliferation *in vivo* and *in vitro* using colonic organoids. We identified that tissue from ulcerative colitis patients and CRC samples, which had low levels of Myosin 5b compared to healthy tissue, also exhibited increased proliferation. **Conclusions:** Collectively, these findings identify decreased Myosin 5b expression in active colonic inflammation in individuals with ulcerative colitis and in CRC. We also demonstrate that loss of Myosin 5b in the colonic epithelium is associated with a significant increase in proliferation within colonic crypts both *in vivo* and *in vitro*. These data suggest that decreased Myosin 5b may be a feature of colonic inflammation and could increase proliferation thereby impacting pathological states.