

Endometrial Cancer Exploits Myosin 5B to Support Nutrient Uptake and Metabolism

Pramita Suresh¹, Anna M. Tingler¹, David Mysona², Amy Engevik¹, Mindy Engevik^{1,3}

¹Department of Regenerative Medicine & Cell Biology, Medical University of South Carolina, Charleston SC 29425

²Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston SC 29425

³Department of Pharmacology & Immunology, Medical University of South Carolina, Charleston SC 29425

Background: Uterine corpus endometrial carcinoma (UCEC) is the most common gynecologic malignancy in the United States, with approximately 68,000 new cases and 14,000 deaths annually. Although most UCEC cases are diagnosed early, advanced tumors have high rates of recurrence and limited treatment options. Cancer cells reprogram their metabolism and increase nutrient acquisition to support continued growth. Myosin 5b (MYO5B) is an actin-based molecular motor that transports cargo, including nutrient transporters, to the apical membrane of epithelial cells. Our group has previously demonstrated that MYO5B is critical for trafficking nutrient transporters in the intestine, but its role in other tissues and tumors, specifically in UCEC, is unknown. We hypothesized that UCEC cells exploit MYO5B-dependent trafficking to increase glucose transporter localization, nutrient uptake, and tumor metabolism. **Methods & Results:** Analysis of UCEC tumor biopsies and control tissue revealed that MYO5B was significantly upregulated at both the mRNA and protein levels across all stages of UCEC. Immunostaining confirmed increased apical MYO5B localization in UCEC tumors compared with adjacent normal tissue. Unfortunately, elevated MYO5B expression was associated with reduced patient survival. Increased MYO5B expression correlated with elevated levels of the glucose transporters GLUT1 and GLUT3. Metabolic pathway analysis identified significant enrichment of metabolic pathways in UCEC, and expression of key metabolic genes positively correlated with MYO5B. To identify the specific role MYO5B plays in UCEC, we generated MYO5B-deficient HEC1A uterine cancer cells. We found that the MYO5B-deficient cancer cells had reduced metabolism and lowered glucose uptake compared to parental cells. RNA-sequencing further revealed large-scale shifts in gene expression in MYO5B-deficient cells. MYO5B-deficient cells had reduced expression of amino acid transporters and genes involved in lipid synthesis and fatty-acid metabolism. We also observed decreased levels of several mitochondrial genes, and by Resipher, we found that MYO5B-deficient cells had decreased OCR. Finally, we found MYO5B-deficient cells had reduced proliferation and migration compared to the parental HEC-1A cell line. **Conclusions:** These findings suggest that MYO5B regulates nutrient transporter trafficking and metabolism in UCEC. As a result, targeting MYO5B could be a promising therapeutic avenue for UCEC.