LIST ALL AUTHORS and AFFILIATIONS – underline presenting author

Ashley Zuniga¹, Jonathan Cho¹, Upasana Parthasarathy¹, Theodore Drashansky¹, Kyle Lorentsen¹, Zhen He PhD², Christian Jobin PhD², Dorina Avram PhD¹
1. Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, College of Medicine, University of Florida, Gainesville, FL 32610 USA
2. Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Florida, Gainesville, Florida 32610 USA
3. Department of Infectious Diseases and Pathology, University of Florida, Gainesville, Florida 32611 USA

TITLE
E3 Ubiquitin Ligase HECTD3 Protects Against DSS Colitis and Colon Cancer

HYPOTHESIS:
We hypothesize that Hectd3 restricts inflammation associated with ulcerative colitis and blocks development of colorectal cancer by inhibiting STAT3 phosphorylation.

BACKGROUND/AIMS:
Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that results in chronic inflammation in the colon, and is considered a significant risk factor for the development of colorectal cancer. Data from public databases showed that the ubiquitin ligase Hectd3 has reduced mRNA levels in colorectal cancer (CRC) versus normal colon and in inflamed tissue from UC versus non-inflamed tissue. Hectd3 represents a member of the largely understudied HECT family of E3 ubiquitin ligases. As the last step of the ubiquitination pathway, E3 ligases determine the specificity of the substrate being ubiquitinated and targeted for degradation or signaling. Identification of targets for HECTD3 specific ubiquitination provide means to develop therapeutic tools to modulate disease progression in a highly precise and effective manner.

METHODS:
We used a chemically induced murine model of UC and CRC (AOM/DSS colitis), to investigate the role of Hectd3 in the development of colitis and CRC.

RESULTS & CONCLUSIONS
Our results show that the absence of Hectd3 results in elevated DSS-induced colitis severity, mediated by both hematopoietic and non-hematopoietic components, and increased colonic tumors. Our preliminary data identified STAT3 as a target for Hectd3 non-degradative ubiquitination in HCT116 colon cancer cells. Also during colitis, western blot analysis showed decreased ubiquitination and increased phosphorylation of STAT3 in the absence of Hectd3. Collectively, these data demonstrate a protective role of Hectd3 in the development of UC and colon cancer. By ubiquitinating STAT3 in a non-degradative manner, Hectd3 prevents its phosphorylation, which blocks inflammation and damage in the colon. However, because of the critical role of pSTAT3 signaling in inflammation, it remains a crucial question as to the specific immune cell populations facilitating this disease phenotype and the mechanism by which these cells are manipulating the balance between repair after inflammatory damage and tumor suppression.