Lung Biology Research & Trainee Day
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Category: Predoc
Name: Erin Gibbons
PI: Stephen Hammes
Title: Glycoprotein-NMB (GPNMB) is Pro-Tumorigenic in Lymphangioleiomyomatosis (LAM)
Abstract: Lymphangioleiomyomatosis (LAM) is an estrogen-sensitive lung disease found almost exclusively in women. LAM is characterized by the hyperproliferation of smooth muscle cells creating small tumors throughout the lungs, resulting in the formation of large cysts that replace normal alveolar space. Growth of these tumors and progression of the cyst development leads to loss of pulmonary function, and sometimes subsequent lung transplantation. LAM tumor cells contain mutations in one of the tuberous sclerosis genes (TSC1 or TSC2), leading to activation of the mTORC1 pathway. In fact, mTOR inhibitors are commonly used to treat LAM; however, these drugs are not always effective and have significant side effects, suggesting the need for new therapeutic targets. Additionally, tumors recur even after lung transplantation and LAM cells are found in circulating body fluids, suggesting a metastatic nature of LAM, and a question of the origin of the LAM cell. Due to LAM's estrogen sensitivity, female specificity, and metastatic nature, we previously proposed that LAM cells originate from the uterine myometrium. We therefore designed a uterine-specific TSC2-null mouse model where all the mice generate uterine tumors characteristic of LAM and half develop lung metastases. Using RNASeq analysis of uterine tissue from this mouse model, when focusing on genes regulated by estrogen and TSC2, we discovered increased expression of melanocytic markers, including Glycoprotein Non-Metastatic Melanoma Protein B (GPNMB). GPNMB is known to be oncogenic in other cancers and has been shown to be expressed intracellularly in benign cells, but both intracellularly and on the cell surface of tumor cells. This melanocytic marker was not only highly expressed in our mouse model, it was also expressed in TSC2-null cell lines, as well as in human LAM patient lung and uteri samples. In our hands, knocking down GPNMB expression by siRNA directed against GPNMB mRNA decreased proliferation, migration, and invasion in TSC2-null cells. We also found that GPNMB's large ectodomain is shed by TSC2-null cells. Further, knocking out GPNMB in TSC2-null cells using CRISPR/Cas9 decreased xenograft tumor growth in mice. Importantly, the GPNMB ectodomain is a potential biomarker of human LAM, as we detect a significant difference in GPNMB ectodomain levels in patient blood as compared with healthy controls.