PUBLIC ABSTRACT

IDENTIFICATION OF SURVIVAL MARKER CXXC5 AND METASTATIC MODELING OF ENDOMETRIAL CANCER.

By

Alyssa Michelle Fedorko

Endometrial cancer originates from the innermost lining of the uterus. Despite being the fourth most common cancer in women and the most prevalent gynecologic malignancy in the United States, there has been no improvement in treatment strategies for endometrial cancer over the past two decades due to lack of relevant models and inadequate prognostic markers. Problems in dealing with this disease will become more imminent in the future as the incidence and prevalence of this disease is increasing overall. Determination of therapeutic modality still relies heavily on two subjective measures: surgical staging and pathological classification. We have used three independent human endometrial cancer datasets to identify a gene, *CXXC5*, that when upregulated on an RNA or protein level correlates with poor outcomes for patients. This study identified an objective genetic fingerprint of endometrial tumors to pinpoint patients who are more likely to experience a poor outcome due to their disease and also resulted in the development of an immune-competent mouse model that develops distant metastatic disease in the lungs. Presently, there are no markers available that reliably predict either disease recurrence or poor survival. Thus, it is crucial that we identify targets for prevention of disease, markers that predict disease outcome, and targets for new therapies.

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Endometrial cancer is the most common gynecologic malignancy in the U.S. with metastatic disease remaining the major cause of patient death. Therapeutic strategies have remained essentially unchanged for decades. A significant barrier to progression in treatment modalities stems from a lack of clinically applicable *in vivo* models to accurately mimic endometrial cancer; specifically, ones that form distant metastases and maintain an intact immune system. To address this problem, we have established the first immune competent orthotopic tumor model for metastatic endometrial cancer by creating a green fluorescent protein (GFP) labeled cell line from an endometrial cancer that developed in a $Pgr^{cre/+}Pten^{f/f-}Kras^{G12D}$ genetically engineered mouse. These cancer cells (Mouse Endometrial Cancer PTEN deleted K-ras activated; MECPK) were grafted into the mechanically abraded uterine lumen of ovariectomized recipient mice treated with estrogen and subsequently developed local and metastatic endometrial tumors. We noted primary tumor formation in 59% and 86% of mixed background and C57BL/6 animals respectively at 4 weeks and distant lung metastases in 78% of mixed background mice after 2 months. Importantly this model is driven by PTEN and KRAS mutations, which are commonly found in human endometrial cancer. Immunohistochemical analysis indicates that tumors from this model are similar to human endometrial cancers with activated AKT and ERK pathways. This orthotopic tumor model is the first immunocompetent animal model that closely resembles human

metastatic endometrial cancer, modeling both local metastasis and hematogenous spread to lung and has significant potential to advance the study of endometrial cancer and its metastasis.

Additionally, there is a need to identify and classify new potential diagnostic and therapeutic targets in the genesis of endometrial cancer in order to more accurately tailor an individualized treatment regime. Thus, it is necessary to identify markers that predict more aggressive cancers. We have conducted a transcriptome analysis of 136 endometrial cancers from women who either experienced an event, meaning they died from their disease or had a recurrence of disease, or from women with cancer that did not experience such an event from their disease. In these samples, we found a clustering of upregulated genes in the women who experienced an event. Next, we used The Cancer Genome Atlas (TCGA) to validate the genes that appeared as significant in our dataset with their dataset. From comparison of the two datasets, we narrowed in on a particular gene, CXXC5 which, when overexpressed in an endometrial tumor, is highly predictive of negative outcome (recurrence or death of the patient). Using a third independent human dataset, we confirmed yet again that high transcript levels of CXXC5 correlates with detrimental outcomes. Current literature contains little information on how the protein coded by this gene functions in the endometrium and what possible role CXXC5 could have in contributing to a more aggressive cancer phenotype.