Tumor Biology

EMERGING MECHANISMS AND THERAPIES IN ENDOCRINE-RELATED TUMOR BIOLOGY

Identification of Genes and Pathways Differentially Expressed in Progestin Responsive Endometrial Cancer and Hyperplasia

Jay Gertz, PhD, Craig Rush, PhD, Jeffery Vahrenkamp, PhD, Kathryn Szczotka, MPH, Mark Dodson, MD, Elke Jarboe, MD, Andrew Soisson, MD.
University of Utah, SALT LAKE CITY, UT, USA.

One of the oldest and most common therapies for endometrial complex atypical hyperplasia (CAH) and low-stage, low-grade endometrioid endometrial carcinoma (EEC) is the use of progestins. Importantly, the use of progestins remains the only fertility-sparing treatment available. Despite frequent initial response to progestins, relapse rates are high (35-50%). Currently, there are no biomarkers available for predicting a woman's likelihood of successful progestin therapy.

Primary samples (n = 63) were obtained from a total of 31 patients with either CAH or EEC who underwent progestin therapy and were acquired pre- and post-treatment with progestins. Pathological review of the FFPE samples was performed to identify regions of high hyperplastic or neoplastic content for core punches and RNA extraction. RNA-seq was then performed on the FFPE RNA using the TruSeq RNA Exome approach, a method that uses targeted capture to improve sequencing from fragmented samples. Differential expression analysis was performed using two **methods:** DESeq2 a parametric method and Noiseq a non-parametric method. Both methods were used to obtain an overlapping subset of genes to reduce spurious results due to samples with outlier expression.

Analysis of all samples identified 137 genes significantly associated with outcome. These 137 genes were largely increased in post-treatment samples from progestin responders and were highly enriched for progestogen and estrogen responsive genes, indicating a strong hormonal gene expression response to progestin therapy. Importantly, post-treatment samples from non-responding patients did not show this expression pattern, demonstrating that this set of genes may indicate successful hormone response in post-treatment samples. We also identified a 61 gene signature that remains high in non-responders after treatment compared to responders. Overall, we find that responders show a coordinated change in expression during progestin therapy that is missing from non-responders and this signature could be used in the early evaluation of progestin treatment success.

Focusing solely on pre-treatment samples, we identified more variable expression differences across tumors, suggesting multiple reasons for progestin success/failure. We found that the combined expression of estrogen receptor alpha and progesterone receptor was predictive of progestin therapy success. In addition, non-responding tumors had increased expression of several immune-related genes that we are currently exploring. Overall, these results show that progestin therapy response could be predicted using gene expression signatures and that multiple factors may underlie progestin success/failure.

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Pro-Tumorigenic Role of Neutrophil Elastase in Lymphangioleiomyomatosis (LAM)

Erin Gibbons, MS, Manisha Taya, PhD, Briaunna Minor, MS, Christina Seger, MS, Stephen R. Hammes, PhD,MD.
UNIVERSITY OF ROCHESTER, Rochester, NY, USA.

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 significant upregulation of inflammatory proteases such as Neutrophil Elastase (NE). NE is secreted by myeloid cells such as polymorphonuclear cells (PMNs) and has been reported to promote invasion, migration, and proliferation in various cancers. We found this to be true in LAM as well, as depleting myeloid cells with an antibody directed against PMNs, or inhibiting NE with the NE inhibitor, sivelestat, markedly decreased TSC2-null uterine tumor growth. NE is released when PMNs undergo Neutrophil Extracellular Trap release, or NETosis. NETosis has been shown to have a protumorigenic role in various cancers and we are investigating the effects of NETosis in LAM. We have also generated a novel uterine-specific TSC2-null mouse in the background of no NE to determine whether uterine tumor burden and lung metastases are reduced in NE-null mice and if these mice have PMNs capable of undergoing NETosis in the absence of NE. Overall, our results suggest that NE release from PMNs is critical for LAM tumor development and may be a novel target for its treatment.

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Thyroid Hormone and Estrogen Promote Endocrine Resistance, Proliferation, Dedifferentiation, and Cancer Stem Cells in Steroid Receptor-Positive Breast Cancers