Abstract citation ID: bvae163.1809

Steroid Hormones_Nuclear Receptors_ and Coregulators

7615

Genomic Consequences of GRHL2 Overexpression in ER+ Breast Cancer Cells

Kaelyn O. Allen, BS[1], Christy Zheng, BS[1], Natalia Solodin, BS[1], Mary S. Ozers, PhD[2], Christopher L. Warren, PhD[2], Paige E. Messa, BS[2], Noah R. Nicol, BS[2], Daniel T. Vogt, PhD[2], Mark B. Meyer[1], and Elaine T. Alarid, PhD[1]

[1]University of Wisconsin-Madison, Madison, WI, USA; [2]Proteovista LLC, Madison, WI, USA

Disclosure: K.O. Allen: None. **C. Zheng:** None. **N. Solodin:** None. **M.S. Ozers:** Owner/Co-Owner; Self; Proteovista, LLC. **C.L. Warren:** None. **P.E. Messa:** None. **D.T. Vogt:** None. **E.T. Alarid:** None.

Breast cancer progression is characterized by the presence and prevalence of metastatic disease. At a genomic level, metastasis can be facilitated via rearrangement of the chromatin landscape to expose oncogenic genes for transcription. Grainyhead like protein 2 (GRHL2) is a nuclear transcription factor implicated in epithelial cell differentiation. The GRHL2 motif has been found near activated estrogen receptor (ER) binding sites, and elevated levels of GRHL2 have been linked to worse prognosis in hormone receptor positive breast cancer patients. In its capacity to contribute to a more severe disease state when overexpressed, GRHL2 may function as either a transcription or pioneer factor to aid in the expression of metastasis-associated genes. Our lab previously showed that GRHL2 genomic binding precedes ER binding at co-regulated binding sites. Also, overexpression of GRHL2 in MCF7 cells for 24 hours did not appreciably alter gene expression by RNA-Seq. These data taken together indicate that GRHL2 may be exhibiting pioneer factor activity. However, the specific role of GRHL2 overexpression in hormone positive breast cancer progression remains unknown. In order to examine the mechanism of GRHL2 action, GRHL2 genomic binding was investigated using a tetracycline-inducible MCF7 model that allows controlled overexpression of GRHL2. ChIP studies were performed to determine GRHL2 binding intensity at specific and genome wide GRHL2 binding sites. Specific focus was given to established GRHL2 binding sites near oncogenic genes responsible for epithelial to mesenchymal transition (EMT), dormancy, and proto-oncogenic behavior. A similar analysis examined H3K27 acetylation to validate active gene transcription. An orthogonal technology, Specificity and Affinity for Protein (SNAP) microarrays, which characterizes direct GRHL2 binding to tiled genomic regions identified in ChIP-Seq analyses from multiple labs, was utilized to discriminate direct and indirect GRHL2 binding sites. The requirement for GRHL2 transactivation function in regulation of EMT related genes was

further interrogated using transactivation GRHL2 dominant negative mutants. This work aims to distinguish the transcriptional and non-transcriptional activities of GRHL2 in breast cancer cells on a genome wide level and thereby, provide a deeper understanding of how overexpressed GRHL2 contributes to hormone positive breast cancer.

Presentation: 6/3/2024