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**Department of Biological Regulation and Dwek Institute for Cancer Therapy Research**

CANCER RESEARCH CLUB

# Hyperactive FOXA1 Signaling in Breast Cancer Endocrine Resistance and Metastasis - When Genomics Meet Epigenomics


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**14:00**

Candiotty Auditorium


Forkhead box A1 (FOXA1) is a pioneer factor that facilitates chromatin binding and function of lineage-specific and oncogenic transcription factors. Hyperactive FOXA1 (high FOXA1) signaling due to gene amplification and/or overexpression has been reported in estrogen receptor (ER)-positive endocrine-resistant metastatic experimental and clinical breast cancer. However, the molecular mechanisms by which FOXA1 upregulation promotes these processes and the key downstream targets of the FOXA1 oncogenic network remain elusive. We now demonstrate that FOXA1 hyperactivation in ER-positive breast cancer cells drives genome-wide enhancer reprogramming to activate pro-metastatic transcriptional programs. Upregulated FOXA1 employs super-enhancers to synchronize transcriptional reprogramming in endocrine-resistant breast cancer cells, reflecting an early embryonic development process. We identify the hypoxia-inducible transcription factor EPAS1/HIF-2α and the AP-1 components FRA1/FOSL1 and ATF4 among the top high FOXA1-induced super-enhancers targets, mediating partly the impact of high FOXA1 in activating pro-metastatic gene sets and pathways associated with poor clinical outcome. Using clinical ER-positive/HER2-negative metastatic breast cancer datasets, we show that FOXA1 genomic aberrations and the aberrant FOXA1/HIF-2α transcriptional axis is largely non-concurrent with the ESR1 mutations, suggesting different mechanisms of endocrine resistance and treatment strategies. We further demonstrate the selective efficacy of a HIF-2α antagonist, currently in clinical trials for advanced kidney cancer and recurrent glioblastoma, in reducing the clonogenicity, migration, and invasion of endocrine-resistant breast cancer cells expressing high FOXA1. Our study has uncovered high FOXA1-induced enhancer reprogramming and HIF-2α- and AP-1-dependent transcriptional programs as vulnerable targets for treating endocrine-resistant and metastatic breast cancer.


**Host**

**Prof. Yosef Yarden**
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