SPRING 2022

Biochemistry and Molecular Biology Brown Bag Series

Krushangi Nirav Shah

Ph.D. Student

"FBXL16 promotes breast cancer cell growth and diminishes fulvestrant responsiveness by stabilizing ERα protein"

Tuesday, January 18, 2022

11:00 AM

135 Oelman Hall

Lab: Weiwen Long, Ph.D.

Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

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https://science-math.wright.edu/biochemistry-and-molecular-biology

Abstract

FBXL16 promotes breast cancer cell growth and diminishes fulvestrant responsiveness by stabilizing ERα protein

Endocrine therapy (ET) resistance and metastasis are major obstacles for curing patients with advanced ERα$^+$ breast cancer (ER$^+$ BC). Upregulated oncogenic ERα activity plays a critical role in progression of ER$^+$ BC. One essential mechanism of regulating ERα signaling is the ubiquitination-dependent proteasomal degradation of ERα. In the current study, we have identified F-Box and Leucine-Rich Repeat Protein 16 (FBXL16) as a novel positive regulator of oncogenic ERα signaling. F-box proteins are major components of the SCF (SKP1-CUL1-F-box) E3 ubiquitin ligases that mediate protein ubiquitination. FBXL16 does not show detectable interaction with cullin 1 (CUL1) and is a poorly studied F-box protein. Our lab has recently discovered that FBXL16 upregulates the levels of oncoproteins targeted by SCF-E3 ligases, including c-myc and β-catenin. However, little is known about the roles of FBXL16 in human cancers. By data mining of cancer-related databases and immunohistological analysis of BC tissue microarrays, we found that FBXL16 is preferentially upregulated in ER$^+$ breast tumors and correlates with ERα protein expression in breast cancer cell lines and tumors. We identified that FBXL16 stabilizes ERα and decreases ERα ubiquitination thereby promoting ERα-mediated transcription and breast cancer cell proliferation. Our study reveals that FBXL16 decreases estradiol-induced ERα degradation by antagonizing an E3-ubiquitin ligase, FBXO45. Moreover, FBXL16 silencing downregulates the stability of a constitutively active mutant ERα-Y537S and restricts proliferation and metastatic growth of cells expressing this mutant. Silencing of FBXL16 accelerates fulvestrant (an FDA-approved ET that degrades ERα) mediated ERα degradation and increases fulvestrant efficacy in inhibiting cell growth. In conclusion, our findings identify FBXL16 as a novel regulator of ERα signaling and a potential therapeutic target for treating advanced ER$^+$ BC.