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Mutations in the Estrogen Receptor Alpha Hormone Binding Domain Promote Stem Cell Phenotype through Notch Activation in Breast Cancer Cell Lines

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Abstract

The detection of recurrent mutations affecting the hormone binding domain (HBD) of estrogen receptor alpha (ER α /*ESR1*) in endocrine therapy-resistant and metastatic breast cancers has prompted interest in functional characterization of these genetic alterations. Here, we explored the role of HBD-*ESR1* mutations in influencing the behaviour of breast cancer stem cells (BCSCs), using various BC cell lines stably expressing wild-type or mutant (Y537N, Y537S, D538G) ER α . Compared to WT-ER α clones, mutant cells showed increased CD44⁺/CD24⁻ ratio, mRNA levels of stemness genes, Mammosphere Forming Efficiency (MFE), Self-Renewal and migratory capabilities. Mutant clones exhibited high expression of NOTCH receptors/ligands/target genes and blockade of NOTCH signaling reduced MFE and migratory potential. Mutant BCSC activity was dependent on ER α phosphorylation at serine 118, since its inhibition decreased MFE and NOTCH4 activation only in mutant cells. Collectively, we demonstrate that the expression of HBD-*ESR1* mutations may drive BC cells to acquire stem cell traits through ER/NOTCH4 interplay. We propose the early detection of HBD-*ESR1* mutations as a challenge in precision medicine strategy, suggesting the development of tailored-approaches (i.e. NOTCH inhibitors) to prevent disease development and metastatic spread in BC mutant-positive patients.

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