Abstract Title

COPS5 Amplification and Overexpression Confers Endocrine Resistance in ERα-positive Breast Cancer by Degradation of NCoR Protein

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BACKGROUND: Tamoxifen and other estrogen receptor □ (ER□) antagonists are widely used in endocrine therapies for ER□-positive (ER□+) breast cancer patients. Unfortunately the clinical benefit is limited due to intrinsic and acquired drug resistance, leading to development of incurable metastatic cancer. Only a subset of endocrine-resistant breast cancers are associated with known mechanisms including ESR1 (the ER□-encoding gene) mutations, growth-promoting kinase activation, dysregulation of coregulators and apoptosis-related genes.

HYPOTHESIS: Uncovering novel mechanisms is of importance to develop new therapeutic strategies for the treatment of endocrine-resistant patients. Here, using integrated genomic and functional studies, we report that amplification and/or overexpression of COPS5 (CSN5/JAB1) confers resistance to tamoxifen in breast cancer.

METHODS: Amplification and overexpression of COPS5, a catalytic subunit of the COP9 complex, is presented in about 10% of the ER+ primary breast cancer and more frequently in tamoxifen-refractory tumors. Overexpression of COPS5 leads to an ubiquitination and proteasomal-mediated degradation of NCoR protein, which is a key corepressor for ER□ and tamoxifen-mediated suppression of ER target genes, through its isopeptidase activity. Importantly, COPS5 overexpression causes tamoxifen-resistance in preclinical breast cancer models in vitro and in vivo.

RESULTS: We also demonstrate that genetic inhibition of the isopeptidase activity of COPS5 is sufficient to re-sensitize the resistant breast cancer cells to tamoxifen treatment, offering a potential therapeutic approach for endocrine resistant breast cancer patients.