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Title:

The role of Tab2 as a regulator of repression and reactivation of ERα target genes

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ABSTRACT

ERα interacts with coactivators or corepressors at target genes; the balance between coregulators, which establishes the transcriptional results, is primarily directed by the nature of the ligand bound to the LBD. Many signaling pathways impinge upon this balance by variously regulating the localization, stability and activity of components of coactivator and corepressor complexes.

Tab2 was firstly identified as an adaptor protein that links TAK1 and TRAF6 in TGF-β and IL-1β signaling, involved in the activation of JNK and NF-κB (Takaesu et al., 2000). Moreover, studying antiandrogen-resistant prostate cancer cells, it was reported that Tab2 is a facultative component of the NCoR corepressor complex. Tab2 acts as a sensor of inflammatory pathway and induces NCoR dismissal from target genes, causing resistance to endocrine therapy (Zhu et al., 2006).

Detailed knowledge of the mechanism by which Tab2 acts in derepressing a subset of estrogen-dependent genes may lead to the identification of a more general scheme of cross-talks between signaling pathways in transcriptional control as well as in pharmacological resistance in cancer.

In this study, we present evidence that some E_2 repressed genes utilizes an LXXLL motif-containing orphan nuclear receptor, SHP, which is required for ERα-dependent NCoR/Tab2 recruitment to their promoters. We show that inflammatory signals cause TRAF6 translocation to the nucleus and interaction with a conserved motif in NCoR, leading to Tab2 ubiquitination, MEKK1 recruitment, and ultimately NCoR dismissal and gene derepression. Finally, we report that a TRAF6/Tab2-dependent mechanism is required for derepression of a number of other breast cancer associated genes, which are components of the ERα gene repression program.

Moreover, since it was reported that Tab2 mediated a switch in function of selective androgen receptor antagonists from repression to activation, causing drug resistance in prostate cancer cells, we investigate the possible role of Tab2 in breast cancer cell line that are spontaneously resistant to tamoxifen. To address this question, we set out to interfere with Tab2 action in MCF7 derivatives that were rendered resistant to tamoxifen by continuous drug exposure. The data presented here demonstrate a role for Tab2 in the pharmacological resistance to tamoxifen, since interfering with Tab2 expression with siRNA or with Tab2 interaction with ER alpha using a mimic peptide leads to recovered inhibition of cell growth in the presence of tamoxifen. Downregulation of Tab2 in tamoxifen resistant cells also resulted in changes in gene expression, as verified by microarray analysis. Gene ontology and pathway analysis demonstrated that Tab2 is involved in the regulation of cell cycle related genes and DNA replication, repair and recombination, with major implication of BRCA1-linked gene network, in tamoxifen resistant breast cancer cells. In conclusion we have showed that Tab2 can modulate gene expression through cofactors complexes exchange in breast cancer models.