GREB1: An evolutionarily conserved protein with a glycosyltransferase domain links ERα glycosylation and stability to cancer

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Abstract

What covalent modifications control the temporal ubiquitination of ERα and hence the duration of its transcriptional activity remain poorly understood. We show that GREB1, an ERα inducible enzyme catalyzes O-GlcNAcylation of ERα at residues T553/S554, which stabilizes ERα protein by inhibiting association with the ubiquitin ligase ZNF598. Loss of GREB1-mediated glycosylation of ERα results in reduced cellular ERα levels and insensitivity to estrogen. Higher *GREB1* expression in ERα^{+ve} breast cancer is associated with greater survival in response to tamoxifen, an ERα agonist. Mice lacking *Greb1* exhibit growth and fertility defects reminiscent of phenotypes in ERα null mice. In summary, this study identifies GREB1, a protein with an evolutionarily conserved domain related to DNA-modifying glycosyltransferases of bacteriophages and kinetoplastids, as the first inducible and the only other (apart from OGT) O-GlcNAc glycosyltransferase in mammalian cytoplasm and ERα as its first substrate.

Graphical abstract:

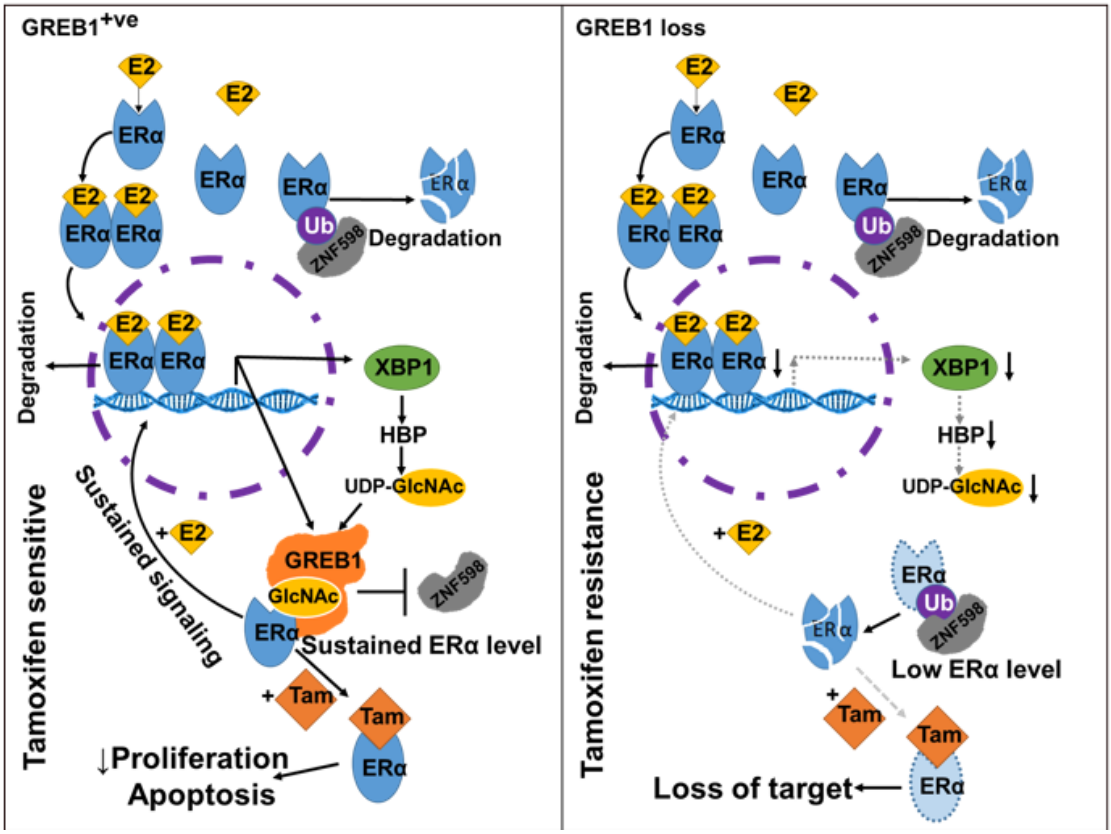

Figure legend: Graphical abstracts of GREB1 function in ERα^{+ve} breast cancer and drug response. When cells express GREB1, ERα is stabilized by glycosylation and imposes ERα signaling transcription signature, which is vulnerable to tamoxifen, an ERα agonist. For cells that transcriptionally repress GREB1, ERα protein and its transcriptional profile are lost. Because of this loss of target, these cells are resistance to tamoxifen.