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Acquisition of estrogen independence induces TOB1-related mechanisms supporting breast cancer cell proliferation

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Abstract

© 2016 Macmillan Publishers Limited.Resistance to therapies targeting the estrogen pathway remains a challenge in the treatment of estrogen receptor-positive breast cancer. To address this challenge, a systems biology approach was used. A library of small interfering RNAs targeting an estrogen receptor (ER)-and aromatase-centered network identified 46 genes that are dispensable in estrogen-dependent MCF7 cells, but are selectively required for the survival of estrogen-independent MCF7-derived cells and multiple additional estrogen-independent breast cancer cell lines. Integration of this information identified a tumor suppressor gene TOB1 as a critical determinant of estrogen-independent ER-positive breast cell survival. Depletion of TOB1 selectively promoted G1 phase arrest and sensitivity to AKT and mammalian target of rapmycin (mTOR) inhibitors in estrogen-independent cells but not in estrogen-dependent cells. Phosphoproteomic profiles from reverse-phase protein array analysis supported by mRNA profiling identified a significant signaling network reprogramming by TOB1 that differed in estrogen-sensitive and estrogen-resistant cell lines. These data support a novel function for TOB1 in mediating survival of estrogen-independent breast cancers. These studies also provide evidence for combining TOB1 inhibition and AKT/mTOR inhibition as a therapeutic strategy, with potential translational significance for the management of patients with ER-positive breast cancers.

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