Abstract

TYROSINE-PHOSPHORYLATED WBP2, A NOVEL CANCER TARGET AND BIOMARKER

WW-binding protein 2 (WBP2) has been demonstrated in different studies to be a tyrosine kinase substrate, to activate ERα/PR transcription and to play a role in breast cancer. However, the role of WBP2 tyrosine phosphorylation in regulating ER function and breast cancer biology is unknown. Here, we established WBP2 as a tyrosine phosphorylation target of estrogen signaling via EGFR crosstalk. Using dominant negative, constitutively active mutants, RNAi and pharmacological studies, we demonstrated that phosphorylation of WBP2 at Tyr192 and Tyr231 could be regulated by c-Src and c-Yes kinases. We further showed that abrogating WBP2 phosphorylation impaired >60% of ERα reporter activity putatively by blocking nuclear entry of WBP2 and its interaction with ERα. Compared to vector control, overexpression of WBP2 and its phospho-mimic mutant in MCF7 resulted in larger tumors in mice, induced loss of cell-cell adhesion, enhanced cell proliferation, anchorage-independent growth, migration and invasion in both estrogen-dependent and -independent manner, events of which could be substantially abolished by overexpression of phosphorylation-defective mutant. Wnt/β-catenin inhibitor FH535 blocked phospho-WBP2-mediated cancer cell growth more pronouncedly than tamoxifen and fulvestrant, in part by reducing the expression of ERα.

Figure 10