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FOXC1 is a critical mediator of EGFR function in cancer cells

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Abstract

Basal-like breast cancer (BLBC) is associated with aggressive clinical behavior and poor prognosis. Currently, chemotherapy is the only systemic therapy for BLBC. We found that the forkhead box C1 (FOXC1) transcription factor is a critical maker for BLBC and predicts poor clinical outcome in breast cancer. FOXC1 induces BLBC cell growth, invasion, epithelial-mesenchymal transition, and chemoresistance. In this study, we show that EGF treatment upregulates FOXC1 expression in BLBC cells at the transcription level through MEKK1/ERK and PI3K/AKT pathways. FOXC1 expression was positively, significantly correlated with EGFR expression in BLBC tumors. Overexpression of EGFRvIII, a truncated constitutively active form of EGFR, also induced FOXC1 expression. Pharmacologic inhibition of EGFR suppressed FOXC1 expression in BLBC cells. Moreover, the nuclear factor κB (NF-□B) transcription factor was identified as a pivotal regulator of EGF-induced FOXC1 expression, downstream of AKT and ERK. NF-□B directly activates FOXC1 transcription through binding to the FOXC1 promoter. Deletion or mutation of the NF-□B binding sites in the FOXC1 promoter abolished the EGF induction of FOXC1 expression. Knockdown of FOXC1 levels in BLBC cells markedly attenuated EGF-elicited cell proliferation, migration and invasion, suggesting that FOXC1 mediates the effects of EGF on BLBC cell functions. Taken together, our findings shed light on the role of EGFR-NF-□B-FOXC1 signaling in BLBC pathogenesis. Intervention of this signaling pathway would provide potential modalities for BLBC treatment. FOXC1 levels may serve as readout of EGFR activity and a marker for selecting breast cancer patients who may benefit from anti-EGFR therapy.

Biography

Cui obtained a Ph.D. from the University of Texas at Austin. He received his postdoctoral training at Baylor College of Medicine's Breast Cancer Center. In 2007, he joined the John Wayne Cancer Institute as assistant professor, and directed the institute's translational breast cancer research program. He is now associate professor at Cedars-Sinai Medical Center. His current research focuses on basal-like breast cancer development, brain metastasis, targeted therapy resistance, and cancer stem cells.