TMEM16A inhibition represents a novel therapy for breast cancer with high EGFR expression

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Abstract

The Ca^{2+}-activated chloride channel TMEM16A is overexpressed in breast cancer. The mechanisms underlying TMEM16A overexpression and its carcinogenesis remain unclear. Here, we investigated the association between TMEM16A and EGFR/STAT3 expression using the TCGA dataset and 65 human breast cancer tissues. We found that TMEM16A expression positively correlated with EGFR and STAT3 expression in breast cancer tissues. Furthermore, we found that EGFR/STAT3 signaling activation promoted TMEM16A expression, and TMEM16A overexpression activated the EGFR/STAT3 signaling pathway in breast cancer MCF-7 and T47D cells. This mutual activation loop was critical for proliferation, migration, and tumor growth of breast cancer both *in vitro* and *in vivo*. In addition, high TMEM16A/EGFR expression was associated with good clinical outcomes in ER-positive breast cancer patients following the treatment of tamoxifen, an ER modulator that also inhibits TMEM16A. TMEM16A inhibitor T16Ainh-A01 and EGFR inhibitor gefitinib in combination more effectively inhibited breast cancer proliferation and migration than single treatment alone. Our findings suggest that a mutual activation loop between TMEM16A and EGFR/STAT3 signaling is important for breast cancer proliferation, migration, and growth. Combined inhibition of EGFR and TMEM16A represents a novel therapy for treating breast cancer with high EGFR and TMEM16A expression.