

A novel feedback loop with therapeutic implications in estrogen receptor-negative breast cancer

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Estrogen receptor-negative (ER-) breast cancer is a heterogeneous disease with limited therapeutic options. Molecular apocrine subtype constitutes 50% of ER- breast tumors and is characterized by a steroid-response signature including androgen receptor (AR) and a high rate of ErbB2 amplification. We have identified a positive feedback loop between the AR and ERK signaling pathways in molecular apocrine breast cancer. In this process, AR regulates ERK phosphorylation and kinase activity. In addition, AR inhibition results in the down-regulation of ERK target proteins including phospho-RSK1. Furthermore, AR-mediated induction of ERK requires ErbB2 and AR activity, in turn, regulates ErbB2 expression as an AR-target gene. These findings suggest that ErbB2 is an upstream connector between the AR and ERK signaling pathways. Another feature of this feedback loop is an ERK-mediated regulation of AR. In this respect, the inhibition of ERK phosphorylation reduces AR expression and CREB1-mediated transcriptional regulation of AR acts as a down-stream connector between the AR and ERK signaling pathways.

Importantly, this feedback loop has therapeutic implications in molecular apocrine breast cancer. There is an *in vitro* synergy between AR and MEK inhibitors in reducing cell viability and inducing apoptosis in molecular apocrine cells. In addition, we have demonstrated an *in vivo* synergy between AR and MEK inhibitors using a xenograft molecular apocrine model. Moreover, the combination therapy with these inhibitors can overcome trastuzumab resistance in molecular apocrine cells. Therefore, a combination therapy strategy with AR and MEK inhibitors may provide an attractive therapeutic option for ER-/AR+ subtype of breast cancer.

Biography

Ali Naderi is a clinician-scientist in oncology with a special interest in breast cancer research. He carried out his medical oncology fellowship at Mayo clinic, Minnesota and a post-doctoral research fellowship at Hutchison/MRC Research Center, University of Cambridge UK. He currently has a faculty position as a clinician-scientist at the University of Queensland, Australia. He has an American board certification in Medical Oncology and more than 25 publications in cancer research field.