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Phosphoinositide 3-Kinase-Dependent CREB Activation is Required for the Induction of Aromatase in Tamoxifen-Resistant Breast Cancer

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Abstract : Estrogens are important for the development and growth of estrogen receptor (ER)-positive breast cancer, for which anti-estrogen therapy is one of the most effective treatments. However, its efficacy can be limited by either de novo or acquired resistance. Aromatase is a key enzyme for the biosynthesis of estrogens, and inhibition of this enzyme leads to profound hypoestrogenism. Here, we found that the basal expression and activity of aromatase were significantly increased in tamoxifen (TAM)-resistant human breast cancer (TAMR-MCF-7) cells compared to control MCF-7 cells. We further revealed that aromatase immunoreactivity in tumor tissues was increased in recurrence group after TAM therapy compared to non-recurrence group after TAM therapy. Phosphorylation of Akt, extracellular signal-regulated kinase (ERK), and p38 kinase were all increased in TAMR-MCF-7 cells. Inhibition of phosphoinositide 3-kinase (PI3K) suppressed the transactivation of the aromatase gene and its enzyme activity. Furthermore, we have also shown that PI3K/Akt-dependent cAMP-response element binding protein (CREB) activation was required for the enhanced expression of aromatase in TAMR-MCF-7 cells. Our findings suggest that aromatase expression is up-regulated in TAM-resistant breast cancer via PI3K/Akt-dependent CREB activation.

Keywords : TAMR-MCF-7, CREB, estrogen receptor, aromatase
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