

ER- α 36, A Novel Biomarker for ER-Negative Breast Cancer

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Breast cancer is one of the most common cancers among women in the world. The expression level of estrogen receptor- α (ER- α) is an important diagnostic factors for breast cancer. ER- α is a 66 kDa, ligand-induced transcription factor [1]. Tamoxifen has been proven as a successful treatment for ER-positive breast cancer for decades; however some breast tumors are finally resistant to tamoxifen therapy. The molecular mechanisms underlying tamoxifen resistance is still largely unknown.

A novel variant of ER- α with molecular weight of 36 kDa was identified and cloned in Cav-1 insufficient human Mammalian epithelia by Dr. Wang, named ER- α 36. ER- α 36 is predicted to act as a dominant-negative effector of ER- α 66-mediated estrogen-responsive gene pathways [2]. ER- α 36 protein lacks ligand-dependent and -independent transactivation domains (AF-1 and AF-2), but it retains DNA-binding, partial dimerization and ligand-binding domains. ER- α 36 possesses a unique 27 amino acid domain at the C-terminal that replaces the last 138 amino acids encoded by exons 7 and 8 of ER- α 66 gene [3]. ER- α 36 mediated non-genomic estrogen signaling pathways has been proven by many studies.

Zhang et al. demonstrated that ER- α 36 mediated non-genomic estrogen signaling pathway through EGFR/Src/ERK and was expressed highly in ER-negative breast cancer cells. ER- α 36 interacted with EGFR/ Src/Shc complex through AP1 site in the ER- α 36 promoter region and mediated estrogen-induced phosphorylation of EGFR and Src [4]. They also found that cells with high ER- α 36 expression became more sensitive to estrogen, activating ERK phosphorylation [5,6].

Our previous study demonstrated that Caveolin-1 down-regulation activates the MEK/ERK and PI3K/AKT pathway, which in turn accelerates the growth of cells [7]. Deng et al. found that ER- α 36 mediated rapid estrogen signaling via AKT/GSK3 β pathway played an important role in the regulation of ER-positive breast cancer stem/progenitor cells [8]. Zhang et al. transfected an ER- α 36-specific microRNA hairpin vector into MDA-MB-231 cells and established ER- α 36 stable knockdown cell line. They found that these cells were more sensitive to paclitaxel; c-Jun N-terminal kinase pathway. Down regulation of ER- α 36 also resulted in decreasing of invasion and migration, which were estrogen independent [9].

Overexpression of HER2 in breast cancer cells has been proven responding poorly to tamoxifen therapy. Yin et al. found that increased ER- α 36 level by ER- α 36-EGFR/HER2 loops is one of the mechanisms by which ER-positive breast cancer cells resist tamoxifen therapy [10]. They also reported that high expression of ER- α 36 in breast cancer cells were resistant to tamoxifen and down regulation of ER- α 36 in tamoxifen resistant cells could restore tamoxifen sensitivity, indicating that regained ER- α 36 expression is one of the potential mechanisms of tamoxifen resistance. They suggested novel therapy for tamoxifen resistant patients may target the ER- α 36-EGFR/HER2 loops [11].

These findings revealed that ER- α 36 may be a novel target for treating ER-negative breast cancers. Thus, ER- α 36 may be a novel biomarker for diagnosis and prognosis of ER-negative breast cancer [12]. SNG-162 (Icaritin) is first-in-class small molecule specifically targeted at ER- α 36 for breast cancer and liver cancer treatment discovered by Shenogen Pharma Group. Icaritin got Investigational New Drug approval in 2009

and completed phase I clinical trial by Dr. Xu at Cancer Institute and Hospital, Chinese Academy of Medical Sciences in China. Icaritin had been approved for phase II/III clinical trials in 2013. Recently, Icaritin phase II clinical trial is progressing simultaneously in many hospitals by Dr. Sun.

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