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"Investigating the role of estrogen receptor beta (ERβ) and estrogen-related receptor alpha (ERRα) in combinatorial drug treatment of triple-negative breast cancer cells"

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NHRF seminar room

Investigating the role of estrogen receptor beta (ERβ) and estrogen-related receptor alpha (ERRα) in combinatorial drug treatment of triple-negative breast cancer

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Triple-negative breast cancer (TNBC) lacks expression of estrogen receptor alpha (ERα), progesterone receptor (PgR) and HER2, accounts for ~15% of breast cancer cases, is treated with chemotherapy, has poor prognosis, and is considered non-responsive to targeted hormonal therapy with tamoxifen. Recent studies have shown, however, that TNBC expresses three isoforms of ERβ, the hormone-binding ERβ1 and the orphan ERβ2 and ERβ5 as well as estrogen-related receptor alpha (ERRα); and that tamoxifen treatment of ERβ1-expressing TNBC is associated with better disease outcome.[1] Tissue microarray IHC assessment of 306 invasive and 40 non-invasive TNBC cases along with 91 samples of normal breast for levels of expression of 5 biomarkers of potential therapeutic response, namely total ERβ, ERβ1, ERβ2, p65NFkB and pcJun, revealed association of ERβ2 with ERβ1 and pcJun in invasive TNBC on top of the normal association of ERβ1 with p65NFkB and pcJun. The therapeutic implications for ERβ1-positive TNBC are discussed.

TNBC-derived cell line MDA-MB-231 (ERα-/PgR-/HER2-/EGFR+) was found to express ERβ2, ERβ5 and ERRα but not ERβ1 and therefore is a model of ERβ1-negative TNBC. Hence, it was used to investigate the role of ERβ2/5 and ERRα in the ability of hydroxy-tamoxifen (OHT), potential low-affinity ligand of both ERβ2/5 and ERRα, to act synergistically with other targeted drugs in repressing cancer cell growth. Gefitinib (GEF), an EGFR inhibitor, Genistein (GEN) and Trichostatin A (TSA), HDAC inhibitors reportedly restorative of ERα expression, and XCT790, an ERRα inverse agonist, were tested for synergy with OHT against MDA-MB-231 cells. GEN and TSA failed to restore ERα or ERβ1 expression. Interestingly, GEF(10μM) and XCT790(10μM) displayed synergy with OHT(1μM). An ERβ2/5 knock-down mutant of MDA-MB-231 cells exhibited higher sensitivity to OHT alone or in combination with GEF compared to the mock knock-down mutant, suggesting that ERβ2/5 is not the target of OHT. Similarly, the ERRα shRNA knock-down mutant displayed higher sensitivity to GEF and OHT compared to the mock knock-down cells, suggesting that ERRα is also not the target of OHT. Effective synergy of OHT with either of GEF and XCT790 was observed at 7 μM OHT, consistent with off-target effect(s) of OHT. Microarray gene expression analysis of MDA-MB-231 cells treated with GEF(10μM) and/or OHT(1μM) provided an insight into the molecular determinants of sensitivity of MDA-MB-231 cells to OHT and GEF when acting alone and in combination.

[1] *Honma et al. (2008) J Clin Oncol 26: 3727-34*

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