Review

UHN Microarray Centre

Microarray analysis reveals IGF-IR regulates expression of cyclin D1 in novel primary mammary tumour cell line

Review of: Jones RA, Campbell CI, Petrik JJ, Moorehead RA. Characterization of a Novel Primary Mammary Tumor Cell Line Reveals that Cyclin D1 Is Regulated by the Type I Insulin-Like Growth Factor Receptor. Mol Cancer Res, 2008, 6(5):819-828

Type I insulin-like growth factor receptor (IGF-IR) plays a role in a number of cancers and the effects of this receptor are mediated through many signalling pathways (1-4). In human breast cancer, IGF-IR is expressed on the surface of malignant epithelial cells and levels have been found to be elevated as high as 14-fold (4,5). Transgenic murine models of IGF-IR overexpression in mammary epithelial cells have been developed to study the role of IGF-IR. Carboni *et al*. developed mammary-specific IGF-IR transgenic mice known as CD8-IGF-IR that express a fusion protein containing the cytoplasmic portion of human IGF-IR and the extracellular and transmembrane portions of the human T-cell antigen CD8α (6). Jones *et al*. developed the transgenic mouse model MTB-IGFIR which overexpresses full length human IGF-IR cDNA in a doxycycline (Dox)-inducible manner (7).

To complement transgenic models, primary cell lines derived from the malignant tumours developed by these animals are often established (4,8,9). This article characterises the first primary murine mammary tumour cell line with Dox-inducible IGR-IR expression. The primary mammary tumour cell line, RM11A, was generated from a MTB-IGRIR transgenic mouse. This cell line expresses high levels of IGF-IR, phosphorylated Akt (protein kinase B), and phosphorylated extracellular signal-regulated kinase 1/2 in the presence of Dox. RM11A cells expressing high levels of IGF-IR also enhanced their proliferative capacity in the absence of exogenous growth factors. The overexpression of IGF-IR in RM11A cells also accelerates tumour formation *in vivo* upon injection into the mammary fat pad of wild-type mice. Wild-type mice injected with RM11A cells developed palpable tumours in 15.8 days when the mice were administered Dox, compared with 57.8 days in the absence of Dox.

To assess the alterations induced by IGF-IR overexpression, DNA microarray analysis of this cell line expressing high or basal levels of IGF-IR was carried out at the UHNMAC using the Affymetrix GeneChip Mouse Genome 430 2.0. The results showed that IGF-IR overexpression induced the expression of *cyclin D1* and that suppression of IGF-IR expression *in vitro* and *in vivo* led to a decrease in cyclin D1 protein levels.

Although IGF-IR is touted as a potential therapeutic target for breast cancer (10), the exact function of IGF-IR in human breast cancer is unclear. Overexpression of IGF-IR not only induces proliferation and inhibits apoptosis, but also enhances drug and radiation resistance in breast, prostate and lung cancer (3). Specifically, IGF-IR appears to play a role in the resistance to tamoxifen and trastuzumab (Herceptin®)(3,11). Most recently, the IGF-IR inhibitor BMS-536924 has been found to cause a reversion of an IGF-IR-mediated transformed phenotype in a several human breast cancer cell lines (12). Despite the pharmaceutical progress, scientists continue to investigate whether a molecule downstream of the IGF-IR would be a more effective therapeutic target (4).

This article describes the characterisation of the RM11A cell line and the importance of RM11A and the MTB-IGRIR transgenic mouse model in determining the role of IGF-IR in mammary tumourigenesis.

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