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EJC Supplements Vol 2 No. 9 (2004) 41–42

EJC Supplements

www.ejconline.com

E11. Endocrine resistance in breast cancer – how to overcome it?

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In breast cancers that become resistant to endocrine therapy, oestrogen receptor (ER) signalling still plays a crucial role in many tumours. Evidence has started to emerge that the various signalling pathways "cross-talk" at several levels with the ER pathway, and that this interaction becomes the dominant pathway when tumours become resistant to endocrine therapy [1]. Peptide growth factor pathways (such as HER2 or epidermal growth factor receptor (EGFR)) can directly/indirectly interact with ER and its transcription machinery, in particular by phosphorylation and activation of the ER protein at specific sites, or by activation of one of ERs major co-activator proteins [2–5]. Both the mitogen activated protein kinase (MAPK)/ERK pathway, which may be activated by upstream growth factors, such as HER-2 and EGFR, the AKT/PI-3 kinase pathway, which may be activated by the insulin-like growth factor pathway, and the p38 MAPK pathway, activated by stress or various cytokines, can all phosphorylate ER at key positions in the AF-1 and other domains of the receptor. Growth factor signalling may activate ER via phosphorylation and activation of the co-activator AIB1, and evidence from clinical studies has suggested that co-expression of AIB1 with HER2 predicted for a worse outcome in patients treated with tamoxifen after surgery [5].

Data are also accumulating that suggest that changes in these growth factor receptor pathways may occur in tumours that develop acquired resistance to tamoxifen over time. In the laboratory, enhanced expression of EGFR and subsequent downstream MAPK activation has been found in MCF-7 breast cancer cells that become resistant over time to tamoxifen, with evidence that co-treatment with the EGFR receptor tyrosine kinase inhibitor ZD1839 (gefitinib) may prevent or delay this resistance by blocking this signalling pathway [2,3]. More recently, changes in intra-cellular signalling in clinical samples from breast cancer patients taken before and at the time of relapse on adjuvant tamoxifen several years later were reported [6]. In tumours with retained ER expression, there was enhanced expression of HER-2 in some patients, with evidence in these tumours that the stress-activated kinase p38 MAPK was enhanced.

Because tamoxifen can still bind and partially activate ER, in cells that co-express ER and HER2/EGFR, an enhanced 'agonist' response to tamoxifen may occur via cross-talking pathways. In contrast, complete oestrogen deprivation in these cells would prevent ER activation (membrane or nuclear DNA bound), thus effectively abrogating any cross-talk activation of ER signalling with peptide growth factor pathways [7]. As such, this may explain the differences observed in efficacy between tamoxifen and aromatase inhibitors in a neo-adjuvant clinical trial of 4 months of letrozole versus tamoxifen, especially in the subset of ER-positive tumours that over-expressed HER2/EGFR (tumour regression rates 88% letrozole vs 9% tamoxifen) [8]. These clinical data support the concept that HER2 overexpression in ER+ve breast cancer may account for resistance to tamoxifen.

While oestrogen deprivation with aromatase inhibitors may be more effective than tamoxifen and circumvent some of the resistance pathways described above by removing all available ligand for ER, it is known that hormone-sensitive breast carcinomas treated with aromatase inhibitors will in-time also acquire endocrine resistance and start to re-grow [7]. In part, this is caused by an adaptive increase in ER expression and function, but there is similar evidence for increased "cross-talk" between various growth factor receptor signalling pathways and ER at the time of relapse, with ER becoming activated and super-sensitised by a number of different intracellular kinases, including MAPK and the insulin-like growth factor (IGF)/AKT pathway [9–12]. Increased expression of HER2/HER3, MAPK,

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1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2004.08.010

and IGFR signalling in cells that become resistance to oestrogen deprivation may activate residual and enhanced levels of ER in a manner similar to that observed in acquired tamoxifen-resistant cells. 'Proof of principle' has then been provided by evidence that ER-mediated gene transcription (which is enhanced 10-fold in these cells) can be abrogated by a number of different approaches to interrupt upstream signalling, including gefitinib, the MEK inhibitor UO126, and the ER downregulator fulvestrant which degrades the receptor [12]. Thus, once again, it would appear that the ER remains an integral part of signalling, even following failure of oestrogen deprivation.

These clinical and laboratory data support a concept that, over time, breast cancer cells utilise alternative intra-cellular signalling pathways to enhance and activate the ER, and, in particular, that this allows cells to escape from their initial endocrine therapy. Strategies to block these signalling pathways from the outset by co-treatment with gefitinib, in addition to tamoxifen, have been shown *in vitro* and *in vivo* to delay resistance to tamoxifen [13], and this approach is now being tested prospectively in a randomised controlled trial in the clinic.

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