c-erbB2 expression predicts tamoxifen efficacy in breast cancer patients

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Summary

c-erbB2 is a proto-oncogene that encodes the trans-membrane protein p185. This protein shares considerable sequence and structure homology with members of the epidermal growth factor receptor family and it is believed to cooperate with these receptors in the signal transduction process in order to control cell proliferation. Overexpression of c-erbB2, with or without gene amplification, is frequently found in breast cancer, and a body of evidence suggests it is implicated in the development of resistance to the anti-estrogen tamoxifen. Scientific evidence strongly supports a correlation between c-erbB2 overexpression and lack of efficacy of tamoxifen in both advanced and adjuvant settings. However, given the important therapeutic repercussion of this topic, further studies are required before c-erbB2 evaluation can be routinely used to select patients who are likely to benefit from tamoxifen administration.

Introduction

In 1981, Shih et al [1] transfected mouse 3T3 fibroblasts with genetic material obtained from rat neuroblastoma cells and identified a novel DNA-transforming sequence. This oncogene, which was designated “neu” (i.e. neuroblastoma), was mapped on chromosome 17. A few years later, the human equivalent of the rat neu gene was independently cloned from a complementary DNA (cDNA) library [2]. This was first called “HER-2”, and after genomic DNA cloning, it became known as “c-erbB2”. c-erbB2 encodes the trans-membrane p185 protein which has a molecular weight of 185 kDa. The p185 protein shares considerable sequence and structure homology with a family of proteins that includes the epidermal growth factor receptor (EGFR or c-erbB1) and two other related growth factor receptors, c-erbB3 and c-erbB4. The proteins of the trans-membrane growth factor receptors have intracellular tyrosine kinase activity that is activated after ligand binding to the extracellular domain. In contrast to erbB1, erbB3, and erbB4, a direct ligand has yet to be identified for erbB2. However, erbB2 seems to be involved in cell signaling after ligand binding of the other members of the erbB family [3]. In this respect, c-erbB2 can form heterodimers with ligand-activated c-erbB1, c-erbB3, and c-erbB4, which are able to transduce the mitogenic signals through the phospholipase-Cγ and the ras/raf pathways [4-6]. In particular,
the c-erbB2 pathway is activated by forming heterodimers with c-erbB3 or c-erbB4 bound by a family of growth factors named “heregulins” or “neuregulins”. Heregulins, formerly believed to be specific ligands for c-erbB2, have thus been used to induce in vitro activation of the c-erbB2 pathway. Interestingly, overexpression of c-erbB2 induces spontaneous homodimerization of this receptor, thereby leading to activation of the tyrosine kinase moiety of the intracytoplasmic domain in the absence of ligand binding [7].

The function and regulation of the normal c-erbB2 gene are not well understood. The gene is widely expressed in epithelial cells of human fetal and adult tissues including the mammary gland [8,9]. Overexpression of c-erbB2, with or without gene amplification, occurs in 20-30% of human breast cancers, and it has been implicated in the pathogenesis of the disease and its clinical behaviour [10,11]. The many studies conducted to establish whether or not a prognostic value could be attributed to c-erbB2 overexpression, have been inconclusive [12]. Instances of conflicting results may be related to flawed experimental design and to the lack of a standardized methodology for c-erbB2 analysis. In fact, although the majority of investigators have employed immunohistochemical determination of the p185 protein, various procedures have been used for staining and scoring. Therefore, present data do not support the routine use of c-erbB2 determination for the prediction of the clinical outcome of untreated breast cancer patients.

More interestingly, a body of studies suggests that c-erbB2 expression may have value as a predictive factor: its level of expression by the tumor may be a useful marker of responsiveness or, conversely, resistance of the disease to specific treatment including chemotherapy and hormone therapy. Data on c-erbB2 expression as a predictive marker of chemotherapy efficacy are discussed elsewhere in this issue. Here we shall review the evidence that high levels of this oncoprotein could help to predict resistance to treatment with the antiestrogen tamoxifen.

Laboratory evidence of interaction between c-erbB2 expression and the effect of tamoxifen on tumor growth

Breast cell proliferation is dependent on the regulatory action of steroid hormones and growth factors. The signal transduction pathways of steroid hormones and growth factors are often altered in breast cancer, which suggests that they may be implicated in the development of dysregulated cell growth [13]. The mechanism by which alterations in each pathway contribute to cancer cell growth is still unclear. Many laboratory data suggest the presence of complex cross-talk and interactions between the c-erbB2/tyrosine kinase pathway and the estrogen receptor pathway. Thus, dysregulation of one pathway may be reflected in altered signal transduction in the alternative regulatory pathway. Upon binding to the estrogen receptor, estrogen induces phosphorylation of its receptor on tyrosine and/or serine [14]. Phosphorylation of the estrogen receptor seems to be essential for downstream actions which include: a) dimerization of the complex estrogen/estrogen receptor; b) binding of the estrogen receptor to its specific estrogen-response elements (ERE) in DNA; and c) promotion of the transcription of specific genes. Phosphorylation of the estrogen receptor may be an important link to the kinase-mediated c-erbB2 pathway by which growth factors may modulate estrogen receptor-dependent growth control. Blockade of estrogen-induced growth of breast cancer cells by tyrosine kinase inhibitors is further evidence of this modulation [15]. Modulation appears to be bidirectional because p185 expression undergoes transcriptional down-regulation by the estrogen receptor-mediated action of estradiol [16].

The antiestrogen tamoxifen exerts its inhibitory effect on breast cancer cell proliferation through interaction with estrogen receptor. This has prompted scientists to investigate whether modulation of the effect of tamoxifen occurs via the c-erbB2/tyrosine kinase pathway and whether it contributes to the development of resistance to the drug.