It is a sobering thought that as we approach the 21st century, breast cancer remains one of the most prevalent of all carcinomas, with one in eight women in Western societies being expected to develop the disease at some point in her life. Research examining those factors affecting the development of breast cancer has identified that steroid hormones are of pivotal importance in directing the growth of these tumours. This knowledge has been exploited clinically, with endocrine treatments which seek to perturb the steroid hormone environment of the tumour cells often promoting extensive remissions in established tumours and furthermore providing significant survival benefits for patients (Nicholson et al, 1992). Unfortunately, the beneficial actions of existing endocrine measures are, in part, counteracted by the capacity of the tumour cells to eventually circumvent the need for steroid hormones, allowing them to continue to grow and progress despite such therapy (Gee et al, 1996; Nicholson et al, 1996). Thus, at presentation of breast cancer, current endocrine therapies are not effective in all patients (de novo endocrine resistance), while initially-responsive tumours will sooner or later progress despite such treatments (acquired resistance), inevitably resulting in patient relapse and, ultimately, death. Identification of the factors and pathways responsible for the development of these resistant conditions is therefore an important diagnostic and therapeutic goal in cancer research.

One proposed model for such loss of steroid hormone sensitivity in breast cancer in both the de novo and acquired setting suggests that aberrations advantageous to tumour cell growth occur specifically within important growth factor signalling pathways, allowing mitogenesis to proceed highly efficiently despite the challenge of endocrine therapy. A new paradigm is thus emerging where knowledge of the tumour expression of growth factor signalling elements may be prognostically relevant in identifying endocrine responsiveness, and where appropriate anti-growth factor signalling therapeutic regimens, in combination with antihormonal measures, would be expected to be beneficial to breast cancer patients (Nicholson et al, 1999a).

In this light, the present review seeks to outline the elaborate molecular biology of oestrogen and growth factor signalling pathway interactions which are likely to play a central role in hormone sensitive breast tumour growth. It subsequently examines how changes often occur in the breast cancer phenotype might severely perturb the balance of such signalling, thus providing a possible explanatory hypothesis for the tumour growth associated with the phenomena of de novo and acquired endocrine resistance. A discussion of how such data might be therapeutically-exploitable in breast cancer has been published elsewhere (Nicholson et al, 1999a, 1999b).

‘Cross-talk’ between steroid hormone and growth factor signalling pathways influences the growth of endocrine responsive disease

Many studies have now identified that breast tumours which exhibit an effective endocrine response (i.e. complete and partial response) are often histologically low grade, well-differentiated and notably oestrogen receptor (ER)-positive with a minimal level of proliferation at presentation (Williams et al, 1986; Bouzubar et al, 1989; Robertson et al, 1989; Nicholson et al, 1991, 1993; Locker et al, 1992; Cheung et al, 1997). The 40–50% of breast cancer patients bearing such tumours frequently enjoy a long duration of response and survival time (Nicholson et al, 1984). In such tumours, it is likely that ER signalling is central to mitogenesis, with steroid hormone occupancy of the receptor efficiently driving cell growth and survival together with expression of target genes bearing either oestrogen response elements (ERE) (Nicholson et al, 1999a, 1999b; Seery et al, in press) or composite response elements which bind receptors in addition to other transcription factors (Diamond et al, 1990). However, it is increasingly proposed that such events proceed most efficiently in an appropriate growth factor environment, with steroid hormone and growth factor signalling pathways ‘cross-talking’ to reinforce each others’ signalling. While many of the relevant growth factors and their receptors are expressed by the breast cancer epithelial cells themselves, thereby potentially working in an autocrine manner, additional paracrine factors may be liberated from the surrounding stroma. In each instance, several potential points of interaction between steroid hormone and growth factor signalling pathways have been identified. A number of these are detailed below and are illustrated in Figure 1.

The ER is a target for growth factor-induced kinase activity (Figure 1.1)

Numerous studies have now shown that the ER protein is subject to phosphorylation and activation by several peptide growth factors (e.g. IGF1 [Aronica and Katzelnellenbogen, 1993], EGF, transforming growth factor-α [TGF-α, Bunone et al, 1996] and heregulin [Pietras et al, 1995]), events which can subsequently initiate ERE-mediated gene expression (Ignar-Trowbridge et al, 1996; Lee et al, 1997). These events are believed to be effected by...
downstream signal transduction molecules such as MAP kinase, which has been shown to activate ER possibly by a direct phosphorylation of serine 118 located in the A/B region of the ER (Kato et al, 1995). Additional transduction molecules demonstrated to target the ER to date include casein kinase II, pp90rsk1, protein kinase C δ, cyclin A/cdk2, Rho pathway elements and p60c-src (Ali et al, 1993; Arnold et al, 1994, 1997; Le Goff et al, 1994; Casalini et al, 1997; Trowbridge et al, 1997; Zwijsen et al, 1997; Joel et al, 1998; Lahooti et al, 1998; Rubino et al, 1998; Tzahar and Yarden, 1998). Significantly, growth factors and downstream signal transduction pathways appear to differentially regulate the two transcriptional activator functions of the ER (i.e. AF-1 and AF-2), with the former becoming more responsive to EGF, TGF-α and mitogen activated protein (MAP) kinase signalling (Bunone et al, 1996). While activation by these factors occurs most efficiently in the presence of oestrogens, their promotion of AF-1 and AF-2 responses certainly appears adequate for initiating transcription in the absence of the steroid hormone. An increasing number of additional cell signalling pathways appear to also impact on the bioactivity of ER, including the pineal hormone melatonin (Ram et al, 1995), neurotransmitters such as dopamine (Gangolli et al, 1997), and second messengers including cAMP (Cho and Katzenellenbogen, 1993). An emerging concept for steroid hormone receptors is therefore that they function not only as direct transducers of steroid hormone effects but, as members of the cellular nuclear transcription factor pool, also serve as key points of convergence for multiple signal transduction pathways (McDonnell et al, 1995).

**Oestrogens stimulate positive elements of growth factor signalling pathways, including cell attachment factors which may facilitate growth factor-directed cell proliferation (Figure 1.2)**

Oestrogen sensitivity and endocrine response have been extensively investigated in experimental models of human breast cancer both in vitro and in vivo. Based on these studies (Gee et al, 1996; Nicholson et al, 1996), it is becoming increasingly evident that oestrogens can promote the autocrine expression of growth factor signalling pathway components (Figure 1.2a), notably TGF-α (Bates et al, 1988), IGF-II (Brunner et al, 1993) and growth factor receptors (e.g. epidermal growth factor receptor [EGFR; Berthois et al, 1989] and IGF-IR [Freiss et al, 1990]), in oestrogen-responsive (MCF-7 and T47-D) and oestrogen-dependent (ZR-75-1) human breast cancer cell lines. In the latter instance, the IGF-IR has also been shown to be activated by oestrogen (Richards et al, 1996; Guvakova and Surrmacz, 1997), subsequently recruiting downstream signalling components, notably including insulin receptor substrate-1 (IRS-1; Richards et al, 1996; Guvakova and Surrmacz, 1997), which in turn may be oestrogen-regulated (Westley et al, 1998). Such actions, which are often antagonized by anti-oestrogens (Gee et al, 1996; Nicholson et al, 1996), could significantly supplement the cellular growth responses directly primed by oestrogens (Cho and Katzenellenbogen, 1993; Smith et al, 1993). In addition, it appears that oestrogens directly stimulate (while anti-oestrogens inhibit) the tyrosine kinase activities both of the EGFR-related protein c-erbB-2 (Matsuda et al, 1993) and of c-src (Migliaccio et al, 1993), the activation of which can provide important mitogenic signals to epithelial cells (Figure 1.2b) through the recruitment of the p21ras/Raf/MAP kinase pathway (James et al, 1994; Troppmain et al, 1994).

Commonly, the frequency with which a cell divides in vitro is dependent upon its adherence, increasing as cells spread out over the extracellular matrix. This may not only facilitate increased nutrient uptake, but also the ability of the cell to capture growth factors, this being particularly evident at focal adhesion contacts which function as sites for priming of intracellular signals (Weisberg et al, 1997). In this light, oestrogens in addition to stimulating growth factor signalling pathways directly, can promote cell–cell and cell–matrix adhesion (Millon et al, 1989; De Pasquale, 1998), thereby facilitating growth factor directed cell proliferation. Oestrogens have thus been shown to induce laminin receptor, together with various extracellular matrix components and cell membrane adhesion proteins (Castronovo et al, 1989), events which may be blocked by anti-oestrogens (Millon et al, 1989). Indeed, the anti-oestrogen toremifene has been shown to inhibit the phorbol ester enhanced ß1, ß3 integrin-dependent adhesion of MCF-7 breast carcinoma cells (Maemura et al, 1995).

**Oestrogens inhibit negative elements of growth factor signalling pathways (Figure 1.3)**

As well as the positive influences exerted by oestrogens on growth factor signalling pathways detailed above, it is notable that in parallel they diminish (while anti-oestrogens induce) the expression of the growth inhibitory factor TGF-β (Knabbe et al, 1987) in several oestrogen-responsive human breast cancer cell lines. Oestrogens thus serve to inhibit the expression of a factor implicated in the induction of programmed cell death (Perry et al, 1995) and which acts through the p38/Jun kinase (JNK) pathway (Hill, 1996).

Additionally, however, it is of particular significance that oestrogens have been reported to inhibit expression of tyrosine phosphatases in ER-positive breast cancer cells to increase growth factor mitogenic activity, while both steroidal and non-steroidal anti-oestrogens increase phosphatase activity (Freiss and Vignon, 1994; Freiss et al, 1998). Tamoxifen, for example, inhibits the mitogenic activity of EGF by promoting significant dephosphorylation of EGFR, an effect believed to be ER-mediated (Freiss et al, 1990; Freiss and Vignon, 1989). It appears that such EGFR-dephosphorylation is accomplished via an increase in tyrosine phosphatase activity, as evidenced not only by an effective inhibition by sodium orthovandate (a broad-spectrum phosphatase inhibitor), but furthermore by a time- and dose-dependent increase in membrane phosphatase activity with the anti-oestrogen (Freiss and Vignon, 1998). In this light, two tyrosine phosphatases have been identified which appear to be regulated by oestrogens and anti-oestrogens, LAR and FAP-1 respectively (Freiss et al, 1998).
Significantly, antisense inhibition of FAP-1 expression abolishes the anti-oestrogen-mediated inhibition of growth factor mitogenic activity, although the ‘pure’ anti-oestrogen ICI 182,780 appears to retain inhibitory activity under these conditions suggesting that the effects of this compound are FAP-1-independent (Freiss et al., 1998).

The ER interacts with growth factor-induced nuclear transcription factors, co-activators/co-repressors and additional proteins to target a diversity of response elements (Figure 1.4)

An important feature of growth factor signalling is its potential to activate several profiles of nuclear transcription factors which subsequently serve to promote the expression of genes participating in a diversity of end points, including cell cycle progression. For example, in addition to its phosphorylation of the ER protein, growth factor-induced MAP kinase (ERK1/2) directly activates Elk-1/p62TCF (Gille et al., 1995). This latter transcription factor subsequently forms a ternary complex with p67SRF (serum response factor) and primes Fos expression via the c-fos transcription factor NF-kB (Nakshatri et al., 1997), which regulates expression of many cytokines (such as IL-6) and growth factors (Sharma and Narayan, 1996). cER-dependent inhibition of IL-6 again appears to be mediated via a direct protein–protein interaction with NF-κB (Ray et al., 1997).

Finally, it should be remembered that ER/ERE-mediated gene transcription is also significantly enhanced by the recruitment of several co-activators and/or by overcoming the effects of co-repressor proteins (McDonnell et al., 1992) that may feasibly be regulated by growth factor signal transduction pathways (Hanstein et al., 1996; Smith et al., 1996). Indeed, an increasing number of co-activators and co-repressors that can interact with the ER have been described (Parker, 1998), including the co-activators SRC-1, RIP-140 and AIB1 (Anzick et al., 1997; Smith et al., 1997; Parker, 1998), and the co-repressors Ssn6 and SMRT (McDonnell et al., 1992; Smith et al., 1997; Lavinsky et al., 1998). Of particular interest is the co-activator CREB-binding protein (CBP)/p300, which is believed to be a component of multiple signalling pathways including cAMP signal transduction (Hanstein et al., 1996; Smith et al., 1996). Additional proteins also under growth factor regulation have been shown to interact with the ER including the cell cycle protein cyclin D1 (Lavoie et al., 1996). This protein can activate ER by direct binding, as well as by recruiting co-activators of the SRC-1 family to the ER (Zurijsen et al., 1997, 1998).

Steroid hormone and growth factor signalling pathways influence common growth regulatory genes (Figure 1.5)

In order for cells to proliferate, they initially need to be recruited into the cell cycle and then be induced to progress through it. These outcomes are orchestrated by at least two series of events which can be jointly influenced by steroid hormone and growth factor signalling pathways (Musgrove et al., 1993; Prall et al., 1998): firstly, the induction of intermediate early response genes, such as c-fos (Morishita et al., 1995; Duan et al., 1998), c-jun (Morishita et al., 1995; Mohamood et al., 1997) and c-myc (Dubik and Shiu, 1992; Musgrove et al., 1993), and secondly, the regulation of G1 cyclins (e.g. cyclin D1) and their partner kinases and inhibitors which are involved in restriction point control (Musgrove et al., 1993; Lukas et al., 1996). Joint activation of these pathways by oestrogens and growth factors would at a minimum reinforce mitogenic signals to responsive cells, and might even result in synergistic interactions between overlapping elements. Additionally, it is likely that steroid hormones (Kyprianou et al., 1991) and many growth factors (Amundadottir et al., 1996; Werner et al., 1997; Wang et al., 1998) influence the expression of cell survival factors in endocrine responsive cells, such as the bel-2 protein (Huang et al., 1997; Wang et al., 1998).

Changes in the tumour cell phenotype potentially perturb ‘cross-talk’ between oestrogen and growth factor signalling pathways in endocrine unresponsive disease (Figure 2)

The above data generated largely from model systems provides compelling evidence that many points of convergence exist for oestrogen- and growth factor-mediated signalling pathways, and that it is likely that growth responses in endocrine responsive breast cancers hence proceed more efficiently in a mixed oestrogen and growth factor milieu. In such tumours, although reductions in input signals from steroid hormones appear sufficient to promote extensive tumour remissions, there is an increasing body of evidence to suggest that phenotypic changes which would severely perturb the balance of steroid hormone and growth factor
‘cross-talk’ may underlie the phenomenon of in vivo endocrine unresponsiveness in breast cancer.

**EGFR and other members of the erbB receptor tyrosine kinase family**

Clinical data emerging in the late 1980s and early 1990s has convincingly shown a significant inverse relationship between the expression of the EGFR (reviewed in Klijn et al, 1992; Nicholson et al, 1994) and endocrine sensitivity in breast cancer. Thus, while patients whose tumours express low levels of EGFR frequently benefit from antihormonal drugs such as tamoxifen, women whose tumours express unusually high numbers of binding sites for EGFR/TGF-α (Nicholson et al, 1989) or significant cell membrane-associated EGFR immunostaining (Nicholson et al, 1994) are largely de novo endocrine unresponsive. Although to some degree these associations may be simply explained by the inverse relationship known to exist between the oestrogen and EGFR, with ER negativity thus being commonly associated with EGFR positivity, nevertheless a direct involvement of the EGFR in growth responses in endocrine unresponsive disease has been suggested, with increased EGFR levels directly correlating both with elevated tumour proliferation and poor prognosis (Nicholson et al, 1997a, 1997b). Such a growth input would be likely to be pivotal to ER-negative/EGFR-positive tumours, since their lack of steroid hormone receptor expression would obviously preclude steroid hormone receptor mitogenic signalling. In addition, such an input might also be important to the proportion of de novo resistant ER-positive tumours maintaining elevated EGFR expression, since the absence of second-line responses in such patients similarly indicates a dislocation from steroid hormone receptor signalling.

Importantly, the inverse association between ER and EGFR also occurs at a cellular level (Sharma et al, 1994a, 1994c), where the long-term action of oestrogen is to suppress the expression of the EGFR (Berthois et al, 1989). In this light, it has been suggested that antihormonal measures which deprive breast cancer cells of oestrogens may consequently encourage increased cellular expression of the EGFR, a phenomenon perhaps culminating in the development of an acquired endocrine-resistant phenotype deriving an increased growth stimulus from EGFR signalling. Interestingly, this is a common phenotypic feature of endocrine-resistant breast cancer cells generated in vitro following either long-term exposure to anti-oestrogens or prolonged oestrogen deprivation (Gee et al, 1996; Nicholson and Gee, 1996), as exemplified by our own ‘in house’ acquired resistant MCF-7 sub-lines. Surprisingly, clinical and experimental data would suggest that such cells rarely lose all ER expression in parallel (Gee et al, 1996; Nicholson and Gee, 1996, Robertson, 1996), and as such the tumour re-growth hallmarking antihormonal relapse must be biologically distinct from the 20–30% of tumours displaying an ER-negative/EGFR-positive endocrine unresponsive phenotype at the time of clinical presentation (Nicholson et al, 1997a,b).

Tumour expression of an additional erbB family member, the c-erbB2 protein, has similarly been associated with endocrine unresponsiveness (Nicholson et al, 1993). Indeed, tumour co-expression of both EGFR and c-erbB2 appears to be associated with particularly aggressive phenotypes which lead to poor prognosis and resistance to endocrine treatment (Nicholson et al, 1997a, 1997b). This may be a direct result of the formation of heterodimeric receptor complexes which are highly efficient in their transmittance of mitogenic signals, conferring a cellular ability to escape the growth restraints exerted by hormonal therapy. In contrast, however, although interactions between either EGFR or c-erbB2 and an additional family member c-erbB3 synergistically enhance their mitogenic and transforming activity on 3T3 fibroblast cells in vitro (Alimandi et al, 1995; Wallasch et al, 1995; Tzahar et al, 1996), readily detectable levels of c-erbB3 (and c-erbB4) are surprisingly more frequent in well-differentiated ER-positive endocrine responsive clinical breast cancer, where EGFR (and often c-erbB2) expression is at its lowest (Knowlden et al, 1998). Patterns of expression (and therefore potentially the heterodimeric interactions) of the erbB family members thus appear to vary dramatically between hormone-sensitive and de novo insensitive disease. Given the increased expression of EGFR and the resultant overt sensitivity to an EGFR selective tyrosine kinase inhibitor, ZM 1839 exhibited by our MCF-7 cells emergent either following long-term antihormonal exposure or prolonged oestrogen deprivation, it is similarly likely that changes in these receptor patterns are a general feature of the acquired endocrine resistant state (McClelland and Nicholson, in preparation). Importantly, however, second-line endocrine responses occur in many acquired resistant breast cancer patients. Moreover, there is significant expression of the steroid hormone receptor at relapse, and in vitro inhibitory studies with the pure anti-oestrogen ICI 182780 confirm that ER is functional and actively contributory towards acquired tamoxifen- and oestrogen-resistant breast cancer growth. These data thus identify a maintained importance for ER (and hence potentially ‘cross-talk’) in acquired resistant growth that is also potentially EGFR-driven.

**TGF-α and other erbB receptor ligands**

Enhanced production of TGF-α has been observed in transformed rodent and human fibroblast and epithelial cells, where it may function as a downstream intermediary in the transformation pathway elicited by oncogenes (Salomon et al, 1990). It has been suggested that TGF-α may act to induce hyperplastic responses in transformed breast cells, and thereby act as a promotional agent in combination with a normal background of mutational events (Matsui et al, 1990; Sandgren et al, 1990). Certainly, TGF-α has been demonstrated to be present in readily detectable amounts in clinical breast cancer specimens (Ciadello et al, 199; Lundy et al, 1991; Uemekita et al, 1992), where its increased expression has been related to primary endocrine insensitivity in ER-positive disease (Nicholson et al, 1994), possibly through substantial ligand-independent activation of the ER as noted to occur experimentally. Furthermore, our recent examination of sequential clinical breast cancer biopsy specimens obtained during tamoxifen treatment is also supportive of elevated TGF-α protein expression being involved in acquired endocrine resistance in ER-positive disease, while diminished expression appears to be a therapeutic feature of those patients exhibiting a good quality and longer duration of initial response (Gee et al, in preparation). Although to date no direct associations have been reported between the cellular levels of TGF-α and ER/ERE-mediated events in vivo, ER-positive and ER-negative tumours with elevated cellular levels of TGF-α show an increased growth fraction, as monitored with the Ki-67 antibody (Nicholson et al, 1994, 1997a, 1997b). These data certainly suggest that elevated expression of this growth factor may comprise an integral part of the driving force behind the growth of many breast cancers, or may at least confer a significant growth or survival advantage upon such cells (Nicholson et al, 1994, 1999a, 1999b).
Although no published in vivo data exists which relates the cellular levels of other ligands for the erbB family of receptor tyrosine kinases and endocrine response, multiple studies have shown that breast tumours express variable amounts of EGF and amphiregulin (ligands for the EGFR), together with heregulin α, β and γ and betacellulin (ligands for c-erbB3/4 [Lupu et al, 1995, 1996]). In this light, our preliminary examination of relevant ligands for the erbB family has indicated that expression of the mRNA for heregulin β1 (reported to be the most potent ligand for the c-erbB3 receptor) is associated with ER and c-erbB3 positivity in well-differentiated tumour types and is inversely associated with EGFR (Knowlden et al, in preparation). ErbB signalling in well-differentiated tumour cells would appear, therefore, biased towards c-erbB3/4, while anomalous increased expression of TGF-α/EGFR/c-erbB-2 in endocrine-insensitive disease may direct tumour growth response pathways away from their strict reliance on oestrogens, possibly towards substantial ligand-independent activation of the ER.

**IGF family**

Many clinical breast carcinomas contain membrane-bound receptors for IGFs, and their ligands, IGF-I and IGF-II, are generally more potent mitogens for human breast cancer cells than either TGF-α or EGF (Gee et al, 1996, Nicholson et al, 1999a). Indeed, there is an increasing body of evidence demonstrating that IGF signalling plays a significant role in growth and survival of endocrine-responsive cells particularly under steroid-rich conditions (Arteaga et al, 1989), where synergistic interactions with oestrogens have been reported (Westley et al, 1989). Additionally, both IGF-I and IGF-II reputedly influence the in vitro expression of oestrogen-regulated genes such as PR (Cho et al, 1994, Giani et al, 1998), Fos (Wosikowski et al, 1992) and the novel oestrogen-regulated gene pLIVI (El-Tanani and Green, 1997b), a gene that may have a role in directing metastatic spread in ER-positive disease (Manning et al, 1993, 1995). Although little is directly known about the IGF receptor family and their influence on clinical responsiveness of breast cancer to endocrine treatments, a correlation has been reported between IGF-I expression and better clinical outcome (Papa et al, 1993). Potentially, therefore, such tumours exhibiting productive interactions between ER and IGF signalling may be particularly growth-sensitive to steroid hormone withdrawal.

Interestingly, acquired resistance to tamoxifen in vitro is reported to be accompanied by substantial increases in IGF-I binding in MCF-7 cells (Wiseman et al, 1993), while marked over-expression of IGFRI in vitro reduces oestrogen growth requirements (Guvakova and Surmacz, 1997). Given the synergism apparent between IGF and oestrogen signalling pathways, such increases in the IGF may serve to substantially enhance the partial oestrogenicity which is a feature of tamoxifen, ultimately allowing tumour cell re-growth during therapy. Similar changes occurring in vivo in elements of the IGF signalling pathway may feasibly contribute towards the acquired resistance phenomenon in the clinic. Additional elements which may similarly influence the relationship between endocrine response and IGFs include the presence or absence of specific binding proteins (IGFBPs) which are known to enhance or suppress IGF signalling. Breast cancer cells have been found to express several IGF-binding proteins, some of which are regulated by oestrogens and anti-oestrogens (Yee, 1998).

**Intracellular components of growth factor signalling pathways**

In clinical specimens, Sivaraman et al (1997) demonstrated that hyperexpression of MAP kinase is a feature of clinical breast cancer. In this light, our own recent studies using antibodies which detect fully-activated erk1/2 MAP kinase have shown a highly significant relationship between increased activation and a poorer quality and shorter duration of response to the anti-oestrogen tamoxifen, as well as with a reduced survival time in ER-positive patients, while substantial increases also occur at the time of disease relapse (Gee et al, submitted). As stated above, MAP kinase has been shown, in addition to its inherent capacity to influence AP-1 and Elk-1 signalling, to activate the ER possibly by direct phosphorylation on Ser-118 located in the A/B region of the ER (Kato et al, 1995). Since this region contains the ligand independent AF-1 domain (Tzukerman et al, 1994), it remains a possibility that increased levels of activated erk1/2 MAP kinase may contribute substantially to growth responses via AF-1 driven transcriptional events originating from unoccupied or indeed anti-oestrogen-occupied ER.

Elevated levels and/or activity of additional intracellular molecules comprising growth factor signalling pathways have also been noted in malignant breast, including pp60c-src (Lehrer et al, 1989), Grb2 (Daly et al, 1994), RHAMM (Wang et al, 1998), Ras (Dati et al, 1991; Archer et al, 1995), Raf (Callans et al, 1995) and protein kinase C (Gordge et al, 1996). Importantly, in a number of instances, overexpression of such components in ER-positive, hormone-sensitive breast cancer in vitro following transfection of appropriate vectors leads to an altered sensitivity to hormones and antihormonal agents (Van Roy et al, 1990; El-Ashry et al, 1997). Although the mechanisms underlying these artificially acquired changes in endocrine response have not been fully documented, it is notable that both PKCβ and c-src have, like MAP kinase, have been suggested to target the ER, phosphorylating Ser-122 (Lahooti et al, 1998) and Y-537 respectively (Arnold et al, 1997). Such interactions once again raise the possibility that growth factor-induced kinase activity, in addition to directly signalling onto specific nuclear transcription factor end points, may alter the behaviour of the ER protein under oestrogen-deprived or antihormone-occupied conditions, thereby generating resistance to endocrine measures. Antihormone resistance, therefore, may arise from altered ER phosphorylation patterns influencing its transcriptional activation.

**Nuclear transcription factors**

As previously stated, an important element in growth factor-induced cell proliferation is the induction and activation of the AP-1 complex (Davis, 1995) and elevated expression of AP-1 activity has been observed in some human breast tumours, as compared to normal adjacent tissue (Linardopoulos et al, 1990). The Jun component of AP-1 is thus reported to be elevated in breast cancer (Tinarakos et al, 1994), and importantly there is an increasing body of in vitro and in vivo evidence to implicate the nuclear transcription factor Fos in the control of many processes associated with the ER-positive neoplastic breast cell, most notably in its acquisition of endocrine independency and invasive capabilities (Gee et al, 1995). Thus, we have demonstrated significant associations between elevated Fos protein expression and increased proliferation, de novo endocrine insensitivity (Gee et al, 1995) and furthermore a worsened patient outlook in clinical breast cancer (Gee et
al., 1995), also noted by Bland et al (1995). Furthermore, our recent examination of sequential clinical breast cancer biopsy specimens obtained during tamoxifen treatment is also supportive of elevated Fos protein expression being involved in both primary and ER-positive acquired endocrine resistance (Gee et al., 1999), while diminished Fos expression appears to be a therapeutic feature of patients with a good quality and longer duration of response. Our clinical findings demonstrating therapeutic increases in the Fos component of the AP-1 complex associated with endocrine resistance are mirrored by limited in vitro studies. As such increased AP-1 DNA binding activity has been observed to be a feature of tamoxifen-resistant ER-positive breast cancer cells in vitro (Dumont et al., 1996), whilst prolonged tamoxifen exposure appears to render this anti-oestrogen agonistic in such cells via its augmentation of the phorbol ester-inducible expression of a chimeric AP-1 response (Astruc et al., 1995; Badia et al., 1995). These studies clearly reveal the importance of AP-1/ER signalling in directing long-term cellular responses to tamoxifen and its agonistic/antagonistic profile.

Sadly, little is known about the relationship between ER and additional nuclear transcription factors during the development of either endocrine insensitivity or acquired resistance. NF-kB/Rel is present in increased amounts in a proportion of clinical breast cancer specimens (Dejardin et al., 1995; Sovak et al., 1997) and has been linked to tumour progression in vitro (Nakshatri et al., 1997). Indeed, its increased expression in two human breast cancer cell lines has been suggested to lead to an inhibition of apoptosis (Sovak et al., 1997). Expression of Myb (a transcription factor that has been linked with cell cycle progression and appears to positively influence the expression of cyclin D1 [Sala and Calabretta, 1992; IGF-1 [Reiss et al., 1991] and bcl-2 [Thompson et al., 1998]) is commonly increased in ER-positive disease (Guerin et al., 1990; Gudas et al., 1995). Finally, the Ets-related transcription factor PEA3, a nuclear transcription factor primed by c-erbB2, appears increased in tumours overexpressing this receptor and moreover relates to progression in breast cancer (Benz et al., 1997). Growth factor-directed/constitutive expression of these factors may thus serve to influence endocrine response.

**Negative elements of growth factor signalling pathways**

TGF-β is the most potent known inhibitor of the progression of normal mammary epithelial cells through the cell cycle (Reiss and Barcellos-Hoff, 1997). In clinical breast cancer, TGF-β proteins (Walker and Deering, 1992) or mRNAs (MacCallum et al., 1994) are present in many samples examined, usually at significantly higher levels than observed in the normal breast, indicating that such cancers may often be growth-refractory to the inhibitory activity of this factor (Travers et al., 1988, Reiss and Barcellos-Hoff, 1997). It is notable, however, that the levels and patterns of expression of TGF-β1–3 are highly variable (MacCallum et al., 1994).

In keeping with the reported effects of this growth factor on the extracellular matrix (Reiss and Barcellos-Hoff, 1997), several studies have indicated a positive relationship between TGF-β1 and both disease progression (Gorsch et al., 1992) and lymph node metastasis (Walker and Deering, 1992; Reiss and Barcellos-Hoff, 1997), with TGF-β1 localizing to the advancing epithelial edge of primary tumours and lymph node metastases (Dalal et al., 1993). Similarly, the detection of all three isoforms of TGF-β mRNA in breast cancer specimens is associated with lymph node involve-

ment (MacCallum et al., 1994; Reiss and Barcellos-Hoff, 1997), with TGF-β1 mRNA levels being highest in ER-positive disease (Amoils and Bezwoda, 1997).

Although the relationship between TGF-β and endocrine sensitivity of breast cancer has not been been studied in great depth in clinical breast cancer, an early study was performed on 11 patients who had received tamoxifen for 3–6 months prior to surgery (Thompson et al., 1991). Unexpectedly high levels of TGF-β1 mRNA were found in patients whose tumours increased in size and were unresponsive to the anti-oestrogen. It is possible that progression during tamoxifen therapy may thus be due to a failure of the autocrine inhibitory functions of TGF-β1 either alone (as noted in in vitro [Herman and Katzenellenbogen, 1994]) or in combination with a paracrine stimulation of stromal cells or angiogenesis. Certainly, up-regulation of TGF-β1 mRNA in breast cancer cells in vitro following their transfection with either v-H-ras or TGF-β1 cDNA (Arteaga et al., 1993) leads to oestrogen growth-independence. Such cells, however, may also show parallel increases in TGF-α and IGF-1, together with a loss of growth response to insulin and bFGF (Daly et al., 1995). In contrast to the TGF-β1 clinical data, several studies have noted that the TGF-β2 isoform increases both in tumours and in plasma during tamoxifen therapy in responders, with no increases recorded in initial progressors (Knabbe et al., 1996; MacCallum et al., 1996). Interestingly, antibodies to TGF-β have been shown in a recent study to reverse tamoxifen resistance in LCC2 breast cancer cells (Arteaga et al., 1999), strongly implicating the pleiotrophic properties of TGF-β in the development of this condition.

**Genetic events in growth factor expression and cell cycle control**

Breast cancer cells, in common with other tumour types, are subject to genetic alterations, notably including those targeting growth factor-associated pathways and cell cycle control elements, and it is likely that such genetic changes would serve to markedly influence cellular response to their steroid hormone and anti-hormone environment (Dorssers and van Agthoven, 1996; Osin et al., 1998).

To date multiple activated oncogenes have been identified in breast cancer, together with the loss of several suppressor gene activities (Walker et al., 1997). These include an amplification of the c-erbB2 oncogene (Seshadri et al., 1993; Ross and Fletcher, 1998), which potentially directly alters the balance of growth factor signalling through the erbB family of receptor tyrosine kinases (see ‘The ER is a target for growth factor-induced kinase activity’), and elevated expression of the Ras oncogene (Dati et al., 1991; Watson et al., 1991), which in culture not only increases the cellular output of several autocrine growth factors, but also serves to activate the ras/raf/MAP kinase signalling cascade (Janes et al., 1994). Altered signal transduction in such cells would thus serve to promote an increased expression and activity of multiple nuclear transcription families (Gille et al., 1995; Whitmarsh et al., 1996; Wasylyk et al., 1998), potentially including the steroid hormone receptors themselves (Kato et al., 1995).

Significantly, c-myc is also overexpressed in many breast tumours, where it relates to an increased proliferative activity, elevated tumour grade and disease spread to unfavourable sites (Kreipe et al., 1993). In our own unpublished series, Myc expression is particularly prominent within ER-positive de novo progressive disease. Although the precise molecular mechanisms which
lead to such elevated expression of Myc remain to be established, it is certainly interesting that Myc expression in clinical material correlates with that of TGF-α and activated erk 1/2 MAP kinase. Indeed, both TGF-α and MAP kinase are signalling parameters which have been shown to impinge on and synergize with Myc in the control of proliferation in many cancers both in vivo and in vitro (Amundadottir et al, 1996; Gupta and Davis, 1994; Nass and Dickson, 1998; Santoni-Rugui et al, 1998). Additionally, TGF-α has also been reported to be a survival factor for mammary tumour cells that overexpress Myc, thereby potentially enabling increased Myc-directed cell proliferation to occur (Nass et al, 1996), while limiting any apoptosis-inducing activity known to be an additional feature of this nuclear transcription factor (Amundadottir et al, 1996). Since Myc has been shown to mimic the effects of oestradiol in promoting S phase entry (Prall et al, 1998), it is certainly feasible that Myc expression, together with other altered elements of growth factor signalling, may be of considerable importance in modifying endocrine response.

Additionally, our recent collaborative studies performed with Professor Robert Sutherland (Garvan Institute, Sydney) have demonstrated that the proportion of breast cancers overexpressing the key cell cycle protein cyclin D1 is much greater than had previously been appreciated from gene amplification studies of the chromosome 11q13 locus, suggesting that aberrant transcriptional/translational regulation is relatively common within such tumours (Hui et al, 1996). In this light, while many ER-positive tumours certainly overexpress the mRNA coding for the cell cycle protein cyclin D1 (Buckley et al, 1993; Hui et al, 1996; Kenny et al, submitted), interestingly its elevated expression marks a shortened disease-free interval, decreased time to local recurrence and metastasis, and poor patient survival characteristics. Growth factors signalling via erk 1/2 MAP kinase (Lavoie et al, 1996) and Myc (Santoni-Rugui et al, 1998) appear to contribute (together with steroid hormones [Sutherland et al, 1995]) to the regulation of cyclin D1. An important element in this event may be the eukaryotic initiation factor 4E (eIF4E), which is involved in regulation of cyclin D1 expression (Flynn and Proud, 1996 and is controlled by Ras/MAP kinase (Flynn and Proud, 1996; Sunenberg and Gingras, 1998) and Myc signalling (Jones et al, 1996). In this light, it is interesting that eIF4E is similarly overexpressed in breast carcinoma (Sorrells et al, 1998), where its expression again relates to poor patient prognosis (Kerekatte et al, 1995; Li et al, 1997, 1998). It is certainly feasible that the elevated erk 1/2 (and/or Myc) activity frequently observed in ER-positive, progressive disease may contribute to the marked proliferative capacity associated with resistance via increased positive influences on cyclin D1. Indeed, overexpression of cyclin D1 in ER-positive breast cancer cells in vitro has been shown in one study to subsequently allow unrestricted passage through the cell cycle, which can confer a resistance to growth inhibition by antiestrogenic agents (Wicklen et al, 1997b).

Interestingly, TGF-α has been observed to dramatically enhance c-myc-induced hepatocarcinogenesis in a transgenic mouse model, with the resultant hyperproliferative responses being not only associated with raised cellular expression of cyclin D1, but also with significant changes in additional components of cell cycle regulation (e.g. intense Rb hyperphosphorylation and increased E2F activity [Santoni-Rugui et al, 1998]). Clearly, aberrations in growth factor signalling are likely to impinge on several key growth/survival regulatory elements, thereby potentially influencing tumour growth and hence steroid hormone/antihormone response. Such positive effects on cell cycle progression may be further aided by the reduced expression of the downstream mediator of p53, p21/WAF-1, in many de novo endocrine-resistant patients (Nicholson et al, 1997c; McClelland et al, 1998).

Finally, BRCA1 expression may also play a role in influencing endocrine response in view of recent results that have shown that its mRNA levels are indirectly elevated in breast cancer cells in response to oestradiol (Spillman and Bowcocc, 1996; Marks et al, 1997), while familial mutation associates with an endocrine unresponsive phenotype (Osin et al, 1998). Indeed, we have recently shown that BRCA1 and ER gene expression are closely associated in clinical breast cancer, where low levels of BRCA1 expression mark a propensity of the tumours to metastasize to distant sites (Seery et al, 1999).

ER loss, receptor variants mutations and sub-types

ER negativity is a relatively common event comprising some 20–30% of breast tumours at presentation, and is predictably associated with de novo endocrine resistance (Campbell et al, 1981; Nicholson et al, 1986, 1995; Merkel and Osborne, 1989; Robertson et al, 1992). Although the origins of the steroid hormone receptor-negative phenotype at presentation are as yet unknown (Ferguson and Davidson, 1997), TGF-α/EGFR/c-erbB2 signalling, and the intracellular transduction elements MAP kinase, PKC and AP-1, all appear of significance in relation to growth responses (Nicholson et al, 1997a, 1997b). Relevant mutations in the ER gene resulting in an inability to transcribe ER are likely to be extremely rare in breast cancer (Ferguson et al, 1998). However, a number of potential mechanisms preventing the efficient transcription or translation of the ER gene resulting in a lack of ER protein expression may exist. These mechanisms include: (i) transcriptional inactivation by hypermethylation of the CpG island in the regulatory region of the ER gene (Falette et al, 1990; Ottaviano et al, 1994; Lapidus et al, 1996); (ii) altered expression of transacting factors responsible for ER transcription (deConinck et al, 1995); and (iii) abnormalities in ER translation or synthesis of an unstable receptor protein (Ferguson and Davidson, 1997). Alternatively, ER-negative tumours may feasibly arise from the selective outgrowth of a sub-population of steroid receptor-negative cells which are likely to exist in the normal breast epithelium (Walker et al, 1991, 1992), although such selective outgrowth is reported to be very infrequent in vivo (Dowsett, 1996).

Although recent studies have revealed the ER protein may be subject to several mutations, as well as the generation of several truncated or exon deleted variant forms (Dowsett et al, 1997; Murphy et al, 1997) which theoretically may alter its functionality and ability to interact with growth factor signalling elements (Murphy et al, 1997), in practice the ER mutations and variants that have been noted in vivo are unlikely to provide a general mechanism for resistance to tamoxifen therapy in ER-negative disease (Karnik et al, 1994; Daffada et al, 1995). However, there may be a role in breast cancer for the relatively recently-identified ER sub-type (Dotzlaw et al, 1997; Leygul et al, 1998), ERβ, and its variants (Lu et al, 1998; Vladusic et al, 1998). In contrast to ERα (previously referred to as ER in the current text), wild-type ERβ promotes AP-1 activity in the presence of anti-oestrogens (Paech et al, 1997), while showing differential effects on ER-mediated events (Watanabe et al, 1997; McNerney et al, 1998) and co-activator selectivity (Suen et al, 1998). Moreover, interactions

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between ERα/ERβ and other nuclear receptor interacting proteins which serve as co-activators and co-repressors of ER transcriptional activity may change during breast cancer progression and contribute to endocrine failure (Berns et al, 1998; Lavinsky et al, 1998). Unfortunately, although such proteins are often phosphorylated and thus potentially subject to growth factor-related kinase activation, virtually no clinical data is available in this subject area.

**Model of endocrine response and new therapeutic targets**

Increasing knowledge of the molecular biology of ER and growth factor signalling is providing new ideas regarding the mechanisms of action of hormones and antihormones, and moreover possible explanatory hypotheses for the tumour growth associated with the phenomena of de novo and acquired endocrine resistance. A simplified working model for the transition of endocrine-responsive breast cancer to endocrine insensitivity/resistance has been compiled in summary of the data presented in this review.

In hormone-sensitive breast cancer cells, it is likely that external signals generated by steroid hormones and stimulatory growth factors act to induce/activate several classes of nuclear transcription factors (e.g. steroid hormone receptor, Fos, Jun, Myc, Elk-1 etc.). These influence patterns of gene expression leading to the gain of positive influences on cell cycle regulation (e.g. cyclin D1) and the suppression of negative influences (e.g. TGF-β). In the presence of adequate steroid hormone and growth factor input signals, cells are perceived to be recruited into the cell cycle and successfully progress through it. Equivalent pathways maintain cell survival. Although it is likely that cross-talk between steroid and growth factor pathways enables efficient growth signalling, reductions in the input signals originating from steroid hormones appear sufficient to reduce proliferation and induce programmed cell death, thereby leading to tumour remissions. In this model, differences between endocrine responses exhibited by normal and cancerous cells would be expected to be minimal if oncogenic events occurred in those cellular pathways which either act to limit the extent of growth, but still require an input signal for growth (i.e. which normally maintain tissue size and architecture through negative feedback and homeostasis mechanisms), or facilitate a more efficient use of input signals from steroid hormones.

In cancers unresponsive to current endocrine measures (Figure 3), we postulate that further alterations have occurred in those elements of their response pathways which:

1. Have a positive influence on steroid hormone receptor signalling and which facilitate the biological functions of the receptor in a lowered endocrine environment (or indeed in the presence of antihormones which show oestrogen-like activity such as tamoxifen). Retention of the ER protein in such cells (as a continued orchestrator of growth responses) would facilitate additional responses to endocrine measures which act by different mechanisms (i.e. aromatase inhibitor/pure anti-oestrogen substituting for tamoxifen). Such second line responses certainly occur in over 50% of women with acquired resistant disease who have benefited from a first-line endocrine response.

2. Circumvent the cellular requirement for steroid hormones via by-passing those elements of their response pathways which impinge on cell proliferation and survival i.e. post-receptor mechanisms. Such phenotypic/genotypic changes may be severe enough to override the importance of ‘cross-talk’ and hence effectively dislocate growth from a reliance on the steroid hormone receptor. Importantly, the majority of patients who fail to respond to one form of endocrine therapy de novo rarely respond to another, suggesting that the influence of the ER in their tumour cells is entirely nullified or circumvented at the time of presentation. This mechanism may also account for the eventual development of acquired resistance to multiple endocrine measures.

3. Provide a mitogenic input for tumours lacking ER. ER negativity is predictably associated with de novo endocrine resistance, comprising ~20–30% of breast tumours at presentation. Although it is as yet unknown if such a phenotype arises from aberrant loss of the steroid hormone receptor or from selective outgrowth of steroid hormone receptor negative cells, the regulation of such tumours is severed from the steroid hormone environment and they appear wholly dependent on elements of growth factor signalling.

Based on the above model, it is clear that while the presence of ER within tumours obviously offers an opportunity for response to those antihormonal measures which directly target the ER, other elements of the complex breast cancer phenotype are likely to dictate the quality and duration of response and to be involved in relapse mechanisms. In the future, the identification of these elements is thus likely to be not only of great prognostic value in identifying those women likely to benefit from existing endocrine measures, but should promote the development of novel therapeutic strategies designed to delay the appearance of, treat, or even reverse endocrine resistance, thereby severely compromising the disease process (Nicholson et al, 1999a, 1999b). These might potentially include the targeting of:

i. Any continued use of steroid hormone receptor signalling
ii. Aberrant growth factor signalling
iii. Cross-talk between (i) and (ii)
iv. Genetic aberrations within additional growth regulatory components.

Although the fulfilment of these strategies will be a challenging goal for those involved in breast cancer research (Nicholson et al, 1999a, 1999b), success should significantly extend the value of endocrine measures and improve patient survival.

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The text on the image is a collection of scientific articles, reviews, and research papers related to the field of breast cancer research. The articles discuss various aspects such as signal transduction through MAP kinase cascades, altered estrogen receptor activities, and the expression and regulation of genes in breast cancer. The papers also explore the interaction between hormone and growth factor signaling, the role of estrogen receptor-beta mRNA variants, and the significance of heregulin in breast cancer tumor progression.
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