MECHANISMS OF TAMOXIFEN RESISTANCE IN THE TREATMENT OF ADVANCED BREAST CANCER

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Multiple mechanisms may render breast cancer cells resistant to treatment with the antiestrogen tamoxifen. This review describes changes in the estrogen receptor (ER) signaling pathway which may lead to tamoxifen resistance: change in uptake or metabolism of tamoxifen, loss of expression of ER, decreased expression of ER, expression of mutant or variant forms of ER, intact ER but loss of cofactors, ligand-independent ER activation, modification of the estrogen response element, altered post-receptor events. Non-ER related alterations are also mentioned.

About one-third of breast cancer patients with advanced disease respond to treatment with the antiestrogen tamoxifen (1) and most of them are patients with an estrogen receptor positive primary tumor (2, 3). The growth inhibitory effect of tamoxifen is mainly due to binding of tamoxifen to the estrogen receptor (ER). Non-receptor mediated responses to tamoxifen treatment may also be beneficial for breast cancer patients with advanced disease, e.g. tamoxifen suppression of the circulatory and microenvironmental insulin-like growth factor-I levels (4). Most patients who exhibit an initial response to tamoxifen will eventually develop resistance to treatment. However, many of these patients respond to both second and third line endocrine therapy, indicating that resistance is not necessarily due to a complete loss of hormone responsiveness. Since the main effect of tamoxifen is mediated via the estrogen receptor signaling pathway, change in any step in this pathway may render the cells resistant. Such changes include (1) change in uptake or metabolism of tamoxifen, (2) loss of expression of ER, (3) decreased expression of ER, (4) expression of mutant or variant forms of ER, (5) intact ER but loss of cofactors, (6) ligand-independent ER activation, (7) modification of the estrogen response element (ERE), (8) altered post-receptor events. Many non-ER related changes may also lead to antiestrogen resistance, e.g. increased expression of autocrine growth factors. Multiple mechanisms may thus confer tamoxifen resistance. Some of these mechanisms are specific for the antiestrogen tamoxifen and will not result in cross-resistance to other types of antiestrogens or other endocrine therapies, whereas some may result in complete hormone unresponsiveness and cross-resistance to other types of endocrine therapy.

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Change in uptake or metabolism of tamoxifen

Tamoxifen has both antagonistic and agonistic activities and in breast cancer cells the agonistic activity is mainly observed when the intracellular tamoxifen level is low. This has been shown for the progesterone receptor (PgR) which, in the human breast cancer cell line MCF-7, is stimulated by low tamoxifen concentrations, whereas high concentrations of tamoxifen inhibit PgR synthesis (5). The mechanism for this dual response to tamoxifen could be that homodimers of tamoxifen-bound ERs are required to exert an antagonistic effect on PgR synthesis, whereas heterodimers of tamoxifen-bound and estradiol-bound ERs may have an agonistic effect. Treatment of patients with 20 mg tamoxifen twice daily results in a plasma level of tamoxifen in the order of 1 μM (6), a concentration which usually inhibits growth of breast cancer cells in vitro. Two clinical studies have demonstrated a reduced intratumoral level of tamoxifen in patients with acquired tamoxifen resistance (7, 8), indicating that resistance may occur from e.g. reduced uptake of tamoxifen or increased efflux of tamoxifen from the cells. In a recent report an increase has been shown in expression of P-glycoprotein in non-responders to tamoxifen treatment (9), and since P-glycoprotein is involved in efflux of chemotherapeutic agents from cancer cells, a similar P-glycoprotein-mediated efflux pump mechanism may account for the low levels of

tamoxifen in resistant tumors. Increase in the expression of the specific antiestrogen binding sites (AEBS) which bind tamoxifen with a similar high affinity as the ER (10) may reduce the intracellular level of tamoxifen and thereby render the cells resistant to tamoxifen therapy. Determination of AEBS activity in 128 breast carcinomas revealed that AEBS activity was present in most tumors and could exceed the level of ER (11). These data and the observation that the antiestrogen-resistant human breast cancer cell line LY2 expresses increased levels of AEBS compared to the parent MCF-7 cell line indicate that increased expression of AEBS may be a mechanism which can result in antiestrogen resistance (11).

In some breast cancer patients a withdrawal response is observed after tamoxifen therapy (12) indicating that tamoxifen in these patients acts as an agonist. A nude mouse model has shown similar tamoxifen-stimulated tumor growth (13, 14) and it has been suggested that tamoxifen may be metabolized to compounds with estrogenic activities. However, recent studies have shown that metabolism and isomerization of tamoxifen is not the mechanism of tamoxifen-stimulated growth in this animal model (15, 16).

Loss of expression of ER

About 20–40% of the patients with ER positive primary tumors have ER negative tumors at the time of recurrence (17, 18, 19), and it may be primarily these patients who do not respond to tamoxifen therapy (de novo resistance). In vitro investigations have shown that only 1 out of 13 human breast cancer cell lines having developed acquired antiestrogen resistance has lost ER expression (Table 1), and 28% of the patients lose ER expression during development of acquired tamoxifen resistance (8). These data indicate that acquired antiestrogen resistance is most often associated with maintained expression of ER.

Decreased expression of ER

In patients with advanced breast cancer the highest response rates to tamoxifen therapy are achieved in those with the highest levels of ER (3), and adjuvant tamoxifen treatment is also most beneficial for patients with levels of ER above 100 fmol/mg cytosol protein (34). A reduction in the expression of ER may lead to changes in some of the ER functions, since different threshold levels may be required for the activation of specific gene transcription (35) and thus render breast cancer cells antiestrogen resistant. A significant reduction in the quantitative level of ER was found in patients who developed acquired tamoxifen resistance (8). These data concur with the in vitro studies in which 7 of 13 breast cancer cell lines with acquired antiestrogen resistance express a decreased level of ER (Table 1). It is of interest that one of the tamoxifen-resistant cell lines expressing about half the ER level of the parent cell line was found to be sensitive to the more potent pure steroidal antiestrogens ICI 164,780 and ICI 182,780 (27), and treatment with ICI 182.780 is also effective in breast cancer patients resistant to tamoxifen (36).

Expression of mutant or variant forms of ER

ER gene analysis in human breast cancers has disclosed no deletions or insertions in the gene and point mutation in only 1% of the primary breast cancers (37). In tamoxifen-resistant breast cancer, expression of mutant ERs is a similarly rare phenomenon (38). However, several papers have shown that breast tumors express ER mRNA splice

Table 1

Gene expression in cell lines with acquired antiestrogen resistance

Cell line	Antiestrogen treatment	ER	PgR	52 kDa protein	pS2	Specific change	Ref. no.
R27	TAM	wt	wt	change	wt		(20, 21)
R3	TAM	wt	red				(22)
RT × 6	TAM	wt	wt	change	wt		(21, 23)
LY2	LY117018	red	lost	wt	wt		(24, 25)
MCF-7/TAM^R-1	TAM	red	lost	red	change	lost tamoxifen induction of 42 kDa protein	(26, 27)
ZR-75-9a1	TAM	lost	lost				(28)
RL-3	TAM	wt		red	wt	increased sensitivity to IGF-I	(29)
MC7/LCC2	OH-TAM	wt	red	wt	wt		(30, 31)
MCF-7/TOT	OH-TAM	red	change		change	resistant to TGF-β	(32)
MCF-7/164^R-1	ICI 164,384	red	lost				(33)
MCF-7/182^R-1	ICI 182,780	red	red				(33)
MCF-7/182^R-6	ICI 182,780	red	red				(33)
MCF-7/182^R-7	ICI 182,780	red	red				(33)

TAM = tamoxifen, OH-TAM = trans-4OH-tamoxifen, wt = wildtype content or regulation, red = reduced content or regulation, change = change in content or in regulation

variants, and some of these variant mRNAs may give rise to ER proteins with altered function, e.g. the exon 5 deletion ER mRNA variant which may be translated to a protein capable of activating transcription without ligand binding (39). Breast cancer cells stably transfected with a mammalian expression vector for the exon 5 deletion variant and expressing the expected truncated ER protein without most of the hormone-binding area lost the tamoxifen sensitive phenotype and displayed tamoxifen-resistant cell proliferation, indicating that in this in vitro system expression of the variant protein renders the cells tamoxifen resistant (40). Seventy tamoxifen-resistant and 50 primary breast carcinomas have been investigated for expression of wild type and exon 5 deletion ER mRNA variants and both types of ER mRNAs were expressed in most of the tumors. No significant difference in the ratio of exon 5 deletion variant and wild type ER was observed between tamoxifen-resistant and primary tumors and the authors conclude that the exon 5 deletion ER variant is unlikely to be responsible for tamoxifen-resistance in most breast cancers (41). Analysis of variant ER mRNA expression in a tamoxifen-resistant human breast cancer cell line, the MCF-7/TAM^R-1 cell line, showed differential expression of the ER splice variants compared with the tamoxifen-sensitive parent MCF-7 cell line but gave no support for the exon 5 deletion variant being involved in the tamoxifen-resistant phenotype of this cell line (42). As mentioned in the paper by Daffada et al. (41), the relevance of the ER mRNA splice variants depends on the demonstration of significant levels of translated variant ER protein, and in our work we could not detect ER proteins corresponding to the ER mRNA splice variants observed although the sensitivity of the assay was high enough to detect protein, provided the protein expression level is correlated to the mRNA expression level (42).

The exon 3 deletion ER mRNA variant which encodes a protein lacking 40 amino acids in the DNA-binding domain appears to inhibit estrogen-dependent transcription activation in a dominant negative fashion (43). Two clinical studies have shown that a significant fraction of the ER positive breast tumors contains ERs which are unable to bind to ERE, indicating a modification of the DNA-binding domain (44, 45). Receptors lacking the DNA-binding domain may form dimers with wild type ER and these dimers are unfunctional, thereby also unable to elicit a growth inhibition when bound to tamoxifen.

Intact ER but loss of cofactors

As illustrated in Fig. 1, the function of the ERs depends on several cofactors (associated proteins = AP) which associate with the activated conformation of the ER (46, 47, 48). Data are not yet available from tamoxifen-resistant tumors but change in or loss of expression of these factors may render breast cancer cells antiestrogen resistant.

Ligand-independent ER activation

Ligand-dependent phosphorylation of the ER has been shown to be important for the transcription activation function AF-1 of the ER (49). Phosphorylation of the ER via routes other than ligand binding (50, 51) may give rise to ligand-independent transcription activation as shown in Fig. 1, in which cross-talk between a growth factor signaling pathway and the ER pathway is presented (52). Changes in phosphorylation of the ER so that tamoxifen is ineffective or acts as an agonist may result in tamoxifen-resistant tumors (53).

Modification of the ERE

The activated ER dimer binds to specific DNA sequences, ERE, usually located in the 5'-flanking region of estrogen-regulated genes. The ERE consensus sequence consists of a 13 base pair palindromic sequence but great variation in sequence of the various EREs exists. Recent data have disclosed an ERE element which is more sensitive to the partial agonistic activity of tamoxifen (54) and these data support the suggestion that modification of the ERE may manifest the tamoxifen-resistant phenotype (55).

Altered post-receptor events

To elicit a biological response, the activated, DNA-bound ER dimer has to interact with the general transcription apparatus (GTA) consisting of RNA polymerase II and associated transcription factors. As indicated in Fig. 1, adaptor molecules seem to be involved in this process (56) and lack of or modification of these factors may result in tamoxifen resistance. Alteration in other post-receptor events can also be constitutive synthesis of, e.g., estrogen-regulated growth factors, as seen in tumors unresponsive to endocrine therapy and expressing increased levels of the growth factor TGF-α (57).

Non-ER related changes

The control of cell proliferation is a complex process involving a multitude of factors, and uncontrolled cell proliferation and also tamoxifen resistance may occur as a result of disturbance of the balance between these factors. Increased oncogene expression, decreased suppressor gene expression, up-regulation of factors functioning as mitogens and down-regulation of factors participating in growth inhibition may all, despite a normally functioning ER mechanism, lead to tamoxifen resistance. Examples of these suggestions are the loss of endocrine sensitivity in tumors with high expression of the oncogene-encoded growth factor receptors EGF-R and erbB2 (58, 59), and shorter disease-free and overall survival in patients with breast tumors expressing mutated P53 suppressor gene (60).

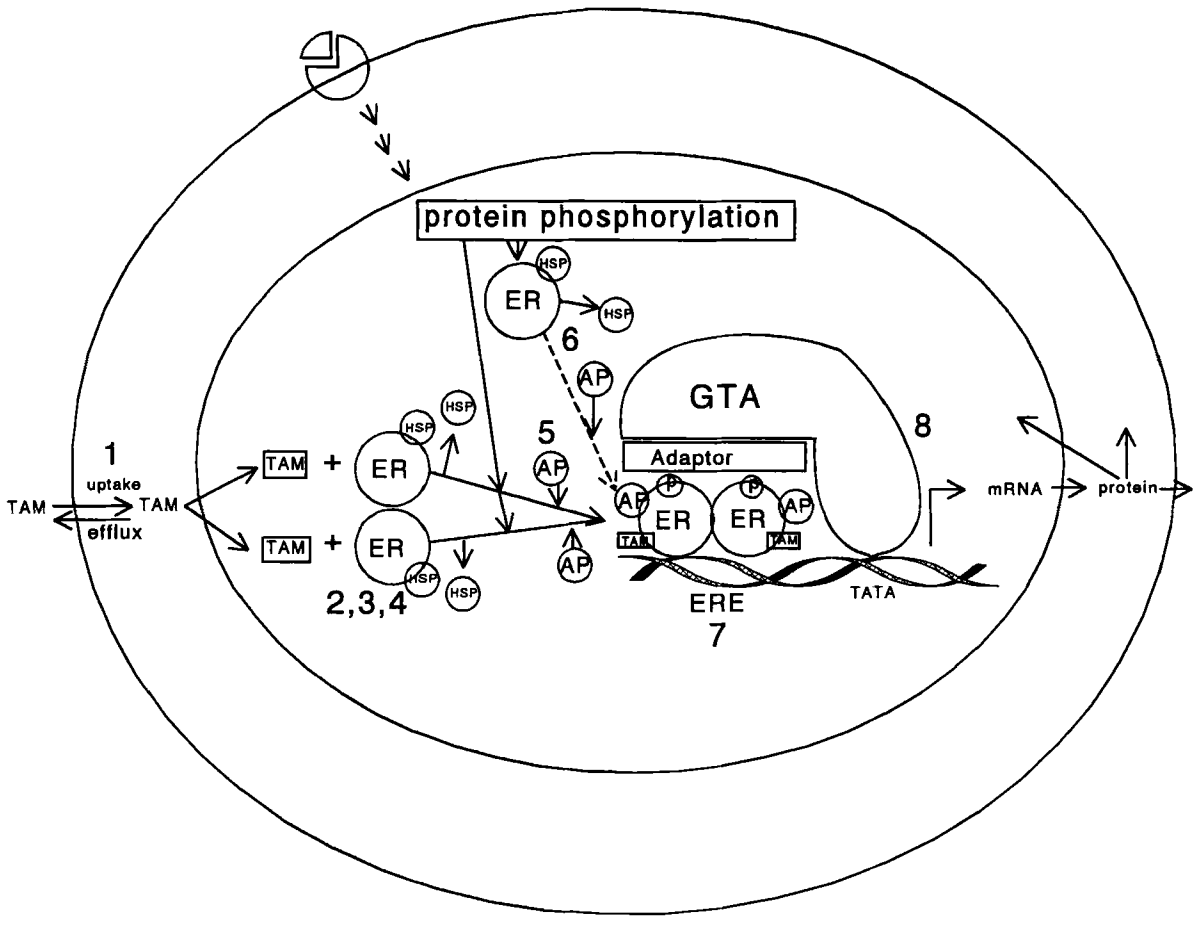

Fig. 1. The estrogen receptor signaling pathway. TAM: tamoxifen, ER: estrogen receptor, HSP: heat shock proteins, AP: associated proteins, P: phosphate, ERE: estrogen response element, GTA: general transcription apparatus. Details are described in the text.

Conclusion

Multiple mechanisms may render breast cancer cells resistant to tamoxifen therapy. Some of the mechanisms described in this review are at present hypothetical, whereas mechanisms such as decreased intratumoral tamoxifen level, loss of or decreased ER expression, constitutive synthesis of an originally ER-regulated growth factor and non-ER related changes, such as up-regulation of growth factor receptors and expression of mutated suppressor protein, have been supported by clinical data. Since many patients respond to second and third line endocrine therapy, development of methods to determine the mechanisms involved in tamoxifen resistance in the individual patient will give a rational basis for further treatment. Research to achieve this goal is in progress.

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