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SPECIAL FEATURE

Breast cancer research from bench to bedside

Prediction of hormone sensitivity for breast cancers

Yasuo Miyoshi · Keiko Murase · Masaru Saito · Koushi Oh

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Abstract The classic action that leads to transcriptional activation of estrogen response genes mediated through estrogen receptors (ER) and the estrogen complex plays a pivotal role in the development of ER-positive breast cancers. In addition to this pathway, non-classic action and non-genomic action, both estrogen-dependent and estrogen-independent genomic actions have also been found to contribute to ER-positive tumor growth. Although the details of these mechanisms are not well known, participation of the growth factor signaling pathway is likely to be the most significant factor for acquisition of resistance to hormonal therapy. This resistance is mediated not only directly through cell growth promotion by growth factor signaling, but also through enhancement of alternative ER signaling pathways in addition to classic action. The reason why tamoxifen-insensitive ER-positive breast cancers respond to aromatase inhibitors may be explained, at least in part, by the different estrogen-related signaling pathways in which aromatase inhibitors may block estrogen signaling. In this paper we discuss the molecular mechanisms for resistance to hormonal therapy based on an understanding of estrogen signaling pathways.

Keywords Breast cancer · Signaling pathway · Hormonal therapy · Growth factor

Y. Miyoshi (✉) · K. Murase · M. Saito · K. Oh
Division of Breast and Endocrine Surgery,
Department of Surgery,
Hyogo College of Medicine,
1-1 Mukogawa-cho, Nishinomiya,
Hyogo 663-8501, Japan
e-mail: ymiyoshi@hyo-med.ac.jp

Introduction

Endocrine therapy that blocks estrogen signals is reportedly the most effective treatment strategy for patients with estrogen receptor (ER)-positive breast cancers both in metastatic and adjuvant settings. However, the effectiveness of this treatment is often restricted by the occurrence of resistance. As for hormonal agents, tamoxifen and aromatase inhibitors including anastrozole, letrozole, and exemestane are clinically available, and fulvestrant is likely to be introduced in the clinical setting in the near future. A phase III trial by Ellis et al. [1], in which the time-to-progression (TTP) curves for letrozole and tamoxifen in the first-line therapy for postmenopausal women with advanced breast cancer were compared, demonstrated the different phases of treatment failure. It is noteworthy that the first curve, which represents rapid progression within 3 months, was observed in both the group treated with letrozole and with tamoxifen. In this phase, tumors are speculated to be of the pan-endocrine resistance phenotype. Between 3 and 6 months, the TTP curves differentiated, and the breast cancers that were sensitive to letrozole but intrinsically resistant to tamoxifen were identified. After 6 months, the TTP curves of both groups decreased gradually at a slower pace. In this third phase, tumors initially respond but subsequently progress, which means acquisition of secondary resistance can be assumed. Since the difference between the two curves remains separate by about the same degree even after prolonged follow-up, second resistance to both letrozole and tamoxifen is likely to occur at the same rate. Thus, in advanced breast cancers, the existence of three different responses to endocrine therapy, i.e., pan-endocrine resistance, agent-selective resistance, and secondary acquired resistance, can be assumed. Similar resistance mechanisms are also evident in

adjuvant settings since endocrine therapy is not effective for all ER-positive breast cancers. In order to overcome resistance to endocrine therapy, the mechanisms that initiate initial and secondary hormone insensitivity must be identified. In this review, we first describe the estrogen signaling pathways related to drug sensitivity and then discuss the prognostic factors for endocrine therapy.

Estrogen signaling pathway

Estrogen is essential for the development of ER-positive breast cancer cells. Its action can be achieved through different pathways mediated by ER as shown in Fig. 1. In the "classical" action, which depends on ligand-activated transcription, estrogen binds to ER and dimerizes with another ER in the nucleus (Fig. 1a). These estrogen-bound ER dimers then recruit co-activator proteins, such as amplified in breast cancer-1 (AIB1), nuclear-receptor-coactivator-1 (NCoA-1/SRC1) and p300/CBP-associated factor (PCAF), which results in their activated form binding to DNA promoter regions, which are known as estrogen-response elements (EREs) [2]. This transcriptional activation is achieved through activation function 2 (AF-2) existing in the ligand binding domain in the *ERα* gene and leads to induction of genes involved in cell proliferation, angiogenesis, invasion and inhibition of apoptosis, eventually leading to progression of breast cancers. In addition to this classic action, genes not mediated through EREs are also transcriptionally activated by the estrogen–ER complex. In this estrogen-dependent non-classic action, the estrogen–ER complex binds AP-1, cycline AMP-response elements (CREs) and SP1 sites through fos and jun, which regulate the expression of a variety of proteins involved in cell proliferation such as insulin-like growth factor 1 (IGF-1), myc, cyclin D1 and Bcl-2 [2] (Fig. 1b). Since it has been reported that one-third of estrogen regulated genes do not contain ERE sequences in the promoter region [3], a distinct number of these genes may be induced through this non-classic action and contribute to tumor growth in ER-positive breast cancers.

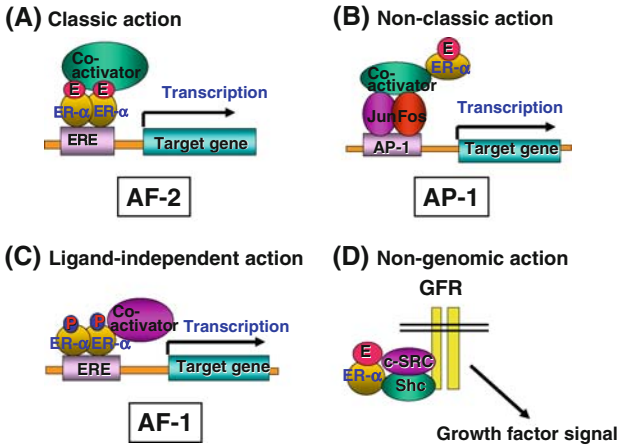

Fig. 1 **a** In the classic action, estrogen and estrogen receptor (*ER*) dimmers recruit co-activator proteins and bind to DNA promoter regions, which are known as estrogen-response elements (*EREs*), and transcriptional activation is achieved through activation function 2 (*AF-2*). **b** In the non-classic action, transcriptional activation occurs at through AP-1 sites. **c** The ER signaling can be activated in an estrogen-independent manner mediated by phosphorylation at specific ER sites. **d** In the cytoplasm, estrogen–ER complex possibly induces activation of membrane-bound growth factor receptors without transcription (non-genomic action)

In contrast to this estrogen-dependent transcriptional activation, estrogen–ER signaling can be activated in an estrogen-independent manner (Fig. 1c). ER-α contains several phosphorylation sites targeted by kinases including mitogen-activated kinases, Akt, p90 ribosomal S6 kinase (Rsk), protein kinase A (PKA) and c-Src [4]. These kinases can directly phosphorylate several sites such as S104/106, S118, S167, S236, T311 and Y537 of ER-α [5]. Of these sites, serine 118 and serine 167 located within the AF-1 region and phosphorylated by mitogen-activated protein kinase (MAPK) and Akt, respectively, are thought to be the most important components of this pathway. Notably, phosphorylation of these sites introduces activation of ER function in an estrogen-independent manner and promotes transcription through EREs also in an estrogen-dependent manner [6] (Fig. 1c). In addition, ERK1/2 enhances the ability of AIB-1, a co-activator, to recruit p300/CBP to the transcriptional complex, leading to transcriptional activation.

In addition to localization of ER to the nucleus, ER has been recognized as performing a function in the cytoplasm associated with the cell membrane through interaction with molecules including IRS-1, Shc and PI3K [4]. It is further known that ER physically interacts with c-Src and phosphorylates at Y537, after which estrogen-bound ER induces further binding to Shc, PELP1/MNAR or p85α, followed by anchoring to the cytoplasmic domain of membrane-bound growth factor receptors, such as IGF-1R, EGFR and HER2. The ER/c–Src complex subsequently phosphorylates tyrosine kinase receptors, which leads to activation of its downstream signaling through MAPK and Akt (Fig. 1d). This non-genomic action is also known as the membrane-initiated steroid signaling (MISS) pathway. It is noteworthy that in addition to non-genomic action, the enhanced MAPK and Akt pathways also induce phosphorylation of nuclear ER, resulting in transcriptional activation of the estrogen signaling pathway through genomic action mediated in an estrogen-independent manner.

Signaling pathway and sensitivity to hormonal therapy

In clinical settings, it has been found that breast cancers with intrinsic or acquired resistance to tamoxifen will

nevertheless respond to further hormonal therapy using aromatase inhibitors or fulvestrant to form a distinct subset and demonstrating that estrogen signaling still continues to play a critical role in such tumor growth. In the classic action mediated through AF-2 site, tamoxifen, aromatase inhibitors and fulvestrant are thought to be effective. Tamoxifen seems to behave as an agonist for estrogen-dependent non-classic action mediated through the AP-1 site in a specific condition, but in such a condition, both aromatase inhibitors and fulvestrant may still be effective, considering the estrogen- and ER-dependency of this pathway. As for the ligand-independent pathway, antagonistic effects are sometimes unlikely to be attained with tamoxifen or aromatase inhibitors, which lead to resistance to these agents. On the contrary, fulvestrant can theoretically inhibit this signaling through ER downregulation. It is further believed that tamoxifen acts as an agonist on the non-genomic ER pathway [7], while it is speculated that aromatase inhibitors and fulvestrant are effective for blocking this signaling pathway. As mentioned above, it has been suggested that specific correlations exist between signaling pathways and hormonal effectiveness, although clinical data supporting this speculation have rarely been reported except those for the classic action.

Mechanisms of endocrine resistance

In a great majority of ER-positive breast cancers, classic action is definitely the predominant estrogen signaling pathway that contributes to proliferation and progression of tumor cells. However, activation of other pathways, such as estrogen-dependent non-classic, estrogen-independent and non-genomic actions, may constitute parts of the mechanisms of resistance to hormonal therapy. These alternative pathways can be induced through changes in the expression of co-activators, co-repressors, tyrosine kinase receptors or other molecules involved in growth signaling. Although these altered estrogen signaling pathways appear to contribute to endocrine resistance, details of their mechanisms in clinical settings have yet to be identified.

Under conditions of prolonged hormonal blockade, breast cancer cells have been shown to be hypersensitive to estrogen in cultured cell models of long-term estrogen deprivation (LTED) [8]. Both ER and growth factor receptors such as IGF-1R and HER2, which induce activation of MAPK and Akt signals, are upregulated in these cells, which seems to suggest that there is crosstalk between ER and growth factor signaling in the process of acquisition of estrogen hypersensitivity. Interestingly, since enhanced localization of ER to the cell membrane is prominent in hypersensitive LTED cells, the MISS pathway may play, at least in part, an essential role in this phenomenon, in which ERE-regulated genes are transcribed mediating through ER phosphorylation in spite of low levels of estrogen. Similar to this estrogen depletion, long-term treatment with tamoxifen has been shown to induce estrogen hypersensitivity in cultured cells [9]. The findings of these in vitro studies raise the possibility that hormonal therapy may fail after induction of growth factor signaling, including the MAPK and Akt pathways, a hypothesis supported in part by the observation of increased expression of HER2 and MAPK activity associated with tamoxifen failure in breast cancers [10]. Chung et al. [11] used an immunohistochemical staining technique to demonstrate that HER2 directly interacts with ER at the cell membrane and that relief of tamoxifen resistance is associated with HER2 downregulation. Furthermore, increased activation of co-activators such as AIB1, which is phosphorylated by p42/44MAPK, may also lead to tamoxifen failure [12]. These findings strongly suggest that overexpression of HER2 may influence hormone sensitivity in ER-positive breast cancers treated with tamoxifen.

It is well established that a reduction in the expression of progesterone receptor (PR) induced by ER signaling is associated with overexpression of EGFR, HER2 and IGF-1 [13, 14]. Furthermore, reduced expression of phosphatase and tensin homolog (PTEN), which negatively regulates PI3K/Akt pathway, also correlates with diminished expression of PR [15]. Since IGF-1 is known to downregulate PR expression through Akt-mediated signaling, which inhibits transcriptional activation of PR induced by ER in the promoter region [13], downregulation of PR may indicate the potential activation, at least in part, of the growth factor signaling pathway.

Preclinical data suggest that activation of growth factor signaling in ER-positive cancer cells initially remains estrogen-dependent, but after prolonged exposure to growth factor signaling develops into an estrogen-independent phenotype. For example, exogenous administration of EGF and IGF-1 leads to downregulation of ER expression [16, 17]. Similarly, LTED leads to induction of growth factor signaling, resulting in an ER-negative phenotype [18]. Details of the mechanisms of hormone insensitivity in breast cancers are poorly understood, although it is strongly suggested that activation of growth factor signaling is implicated as described above. In such mechanisms, activation of membrane-associated non-genomic action, ligand-independent action as well as functional activation of co-factors in classic action are likely to be involved. In addition to such activated estrogen signaling, signaling pathways directly induced by growth factors might also contribute to the growth and progression of ER-positive breast cancers. These speculations prompted us to try and overcome resistance to hormonal therapy by inhibiting such activated growth factor signaling.

Predictive factors for endocrine therapy

As described above, many mechanisms are thought to be implicated in the development of endocrine resistance including altered expression of ER, co-activators, co-repressors and factors involved in growth factor signaling. It is well established that ER is the strongest predictor for endocrine response; all patients with ER-positive tumors do not necessarily respond to hormonal therapy. Although the PR-negative phenotype may reflect activation of growth factor signaling and possibly that AIs is more beneficial than tamoxifen, this issue remains controversial.

HER2 status and endocrine sensitivity

It is speculated that overexpression of HER2 confers endocrine resistance mediated through activation of the PI3K/Akt pathway and is less independent of estrogen signaling. Especially when both ER and HER2 are expressed, the MISS pathway, in which tamoxifen acts as an agonist, may also enhance HER2 signaling, at least in part. Consistent with these speculations, it has been reported that HER2-positive patients derive less benefit from tamoxifen than HER2-negative patients [19], but contradictory results have also been obtained [20]. Unlike tamoxifen, AIs are thought to effectively inhibit MISS signaling, and HER2-positive tumors have been reported to show higher response rates to AIs than to tamoxifen as compared with the response rates of HER2-negative tumors in the neoadjuvant setting [20]. However, inferior prognosis has been reported for HER2-positive tumors than for HER2-negative tumors treated with anastrozole or letrozole in the adjuvant setting [21, 22]. Although they initially respond well to AIs, it is speculated some HER2-positive tumors may acquire resistance to AIs.

Ki-67 expression level and endocrine sensitivity

Immunohistochemical examination of Ki-67 staining, which is a reflection of proliferating cells, is used for its predictive value in endocrine therapy. In an IMPACT trial, which compared the efficacy of preoperative treatment with anastrozole, tamoxifen or combined for hormone receptor-positive tumors, recurrence-free survival among patients with a high Ki-67 expression level at baseline was worse than for others when treated with anastrozole, although the difference was not statistically significant [23]. Interestingly, however, a low Ki-67 expression level after 2 weeks of anastrozole treatment proved to be significantly associated with patients' favorable prognosis [23]. In the adjuvant setting, it has been reported that the expression level of Ki-67 serves as a prognostic factor, and the benefits of treatment with letrozole were greater than of treatment with tamoxifen for patients with high Ki-67 expression (HR 0.53, 95% CI 0.39–0.72 for Ki67-high; HR 0.81, 95% CI 0.57–1.15 for Ki67-low) [24]. It is thus speculated that patients with a relatively high Ki-67 expression level may especially benefit from initial adjuvant therapy with letrozole rather than with tamoxifen, although no conclusive evidence has been presented.

Gene expression profiling and endocrine sensitivity

Recently developed high-throughput genomic technologies have facilitated the development of gene expression profiles that provide prognostic or predictive information more accurately than conventional biomarkers. These multigene assays, even though they were originally developed for prognosis of breast cancers, may also prove to be useful for predicting response to endocrine therapy. The Oncotype DX assay (Genomic Health, Redwood City, CA) evaluates prognosis of ER-positive patients using 16 genes and 5 reference genes based on the reverse transcription-PCR method [25]. Women with a high recurrence score (RS) showed a worse prognosis when treated with tamoxifen alone, which may indicate a poor response to tamoxifen in the high-RS group. However, since this assay is derived from the prognostic data for treatment with tamoxifen, Oncotype DX may not necessarily be useful for selection of hormonal therapy. Similarly, the MammaPrint assay (Agendia BV, Amsterdam, The Netherlands), which yields prognosis of patients regardless of ER status on the basis of a microarray-based multigene assay [26], has not yet been evaluated for predicting endocrine responsiveness.

However, gene expression profiling has been used to identify genes that are directly associated with response to tamoxifen treatment. Jansen et al. [27] examined 112 ER-positive advanced breast cancers treated with tamoxifen by means of microarrays and identified 44 genes that were significantly associated with response to tamoxifen. The ratio of two estrogen-regulated genes, *HOXB13* and *IL17BR*, has been shown in multivariate analysis to be the strongest predictor for a poor response to tamoxifen therapy in recurrent tumors [28]. In addition, Kok et al. [29] demonstrated the efficacy of a 78-gene tamoxifen response profile for analysis of tumors treated with first-line tamoxifen for metastatic disease. Interestingly, Oncotype DX and the *HOXB13-IL17BR* ratio have been significantly associated not only with relapse of disease, but also tumor progression. On the other hand, the 78-gene assay showed a significant correlation with tumor progression, but not with relapse of disease, which appears to indicate the utility of this assay for predicting response to tamoxifen but not for prognosis.

Genetic polymorphisms and endocrine sensitivity

4-Hydroxy-*N*-desmethyl-tamoxifen (endoxifen), an important active metabolite, is mainly generated from *N*-desmethyl tamoxifen, one of the metabolites of tamoxifen, catalyzed by CYP2D6 (Fig. 2). Many genetic polymorphisms of *CYP2D6* have been identified and classified into high, intermediate and low/absent enzyme activities. Homozygous carriers of the most common non-functional variant of *CYP2D6*, *CTP2D6*4*(1934G>A), which constitutes the major component of a poor metabolizer phenotype, have been reported to be associated with lower endoxifen concentrations compared with wild-type carriers [30]. Interestingly, women carrying the *CYP2D6*4/*4* genotype showed worse relapse-free and disease-free survival excepting severe hot flashes than did women who were heterozygous or homozygous for the wild-type alleles. These observations suggest that low or no activity of *CYP2D6* genotypes is associated with higher risk of disease relapse when treated with tamoxifen mediated through lower production of endoxifen.

The *CYP19* gene encoding aromatase, a target molecule, has many polymorphisms involving both coding and non-coding regions. Using functional in vitro analyses, Ma et al. found that the Cys^{264}, Thr^{364}, and double variant $Arg^{39}Cys^{264}$ allozymes showed decreased activity as compared with wild type [31]. Interestingly, the double mutant ($Arg^{39}Cys^{264}$) displayed a significant change from the WT enzyme in inhibitor kinetics for letrozole, suggesting patients carrying such variants may be different sensitivity to letrozole. Recently, a polymorphism present in the 3′ non-coding region of the *CYP19* gene (rs4646) has been reported to be associated with improved time to progression in patients with hormone receptor-positive metastatic breast cancers treated with letrozole [32]. In addition to variants involved in drug metabolization of aromatase inhibitors, genetic polymorphisms in the *CYP19* gene could thus affect the efficacy of AIs.

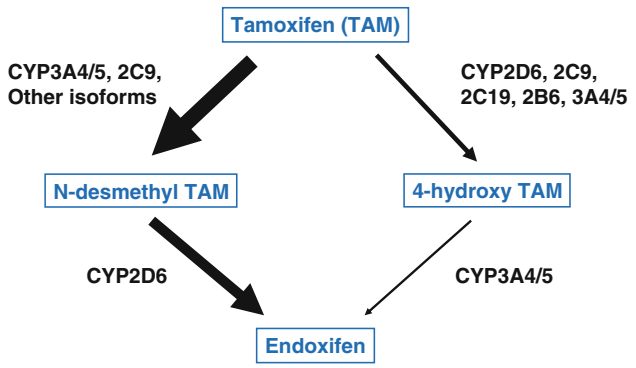

Fig. 2 Pathway for tamoxifen metabolism. Tamoxifen (*TAM*) is mainly metabolized to *N*-desmethyl TAM mediated through CYP3A4/5 and other isoforms, then metabolized to endoxifen (4-hydroxy-*N*-desmethyl-tamoxifen) mediated by CYP2D6. In addition, 4-hydroxy-tamoxifen, a minor metabolite of tamoxifen, synthesized by several enzymes including CYP2D6, further metabolized to endoxifen mediated through CYP3A4/5. The relative contribution of each metabolic pathway is indicated by the *arrow thickness*

Conclusion

Although classic action is the essential major component of the estrogen signaling pathway, other estrogen pathways could be activated in the process of developing resistance to hormonal therapy in ER-positive breast cancers. Currently, it is not known which pathway(s) is activated in individual breast cancers. Nevertheless, activation of growth factor signaling, which may promote not only estrogen-independent action, but also membrane-initiated or classic actions, seems to be the most important process for acquisition of hormone-independent phenomena. A recent study reported that appearance of new vasomotor symptoms or joint symptoms initiated by endocrine therapy suggested a better response to treatment than the absence of such symptoms [33]. These symptoms are possibly generated through higher concentrations of active forms of tamoxifen or stronger estrogen depletion induced by aromatase inhibition, which may indicate that some factors related to a patient's background also play an essential role in endocrine sensitivity. It is therefore necessary to evaluate both types of factors, that is, tumor characteristics and host responsiveness, for accurate prediction of the efficacy of endocrine treatments.

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