Molecular mechanisms regulating the hormone sensitivity of breast cancer

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Breast cancer is a heterogeneous disease. Approximately 70% of breast cancers are estrogen receptor (ER) positive. Endocrine therapy has dramatically improved the prognosis of ER-positive breast cancer; however, many tumors exhibit de novo or acquired resistance to endocrine therapy. A thorough understanding of the molecular mechanisms regulating hormone sensitivity or resistance is important to improve the efficacy of and overcome the resistance to endocrine therapy. The growth factor receptor signaling pathways, particularly the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway can mediate resistance to all forms of endocrine therapy. In contrast, FOXA1 transcription factor is a key determinant of ER function and endocrine response. Intriguingly, a link between hormone resistance induced by the PI3K/Akt/mTOR pathway and the function of FOXA1 has been suggested. In this review, we focus on the PI3K/Akt/mTOR pathway and functions of FOXA1 in terms of the molecular mechanisms regulating the hormone sensitivity of breast cancer.

ER Signaling

There are two different forms of ER encoded by distinct genes, ERα and ERβ.[11] ERα is responsible for estrogen-induced mitogenic signaling in epithelial cells in the breast, uterus and ovaries and plays a crucial role in breast cancer initiation and progression. In the present review, “ER” refers to ERα unless stated otherwise.

When estradiol (E2) binds to ER, ER undergoes conformational changes and forms dimers. The ER dimers bind to the...
The PI3K/Akt/mTOR Pathway

Activation of the PI3K/Akt/mTOR pathway. The PI3K/Akt/mTOR pathway is frequently activated in various malignancies and plays key roles in the development, progression and therapeutic resistance of cancer. The PI3K/Akt/mTOR pathway is now considered to be an attractive and promising target for cancer therapy and many agents targeting this pathway have been developed.\(^{(13,14)}\)

One of the major mechanisms underlying the activation of the PI3K/Akt/mTOR pathway is the activation of the membrane RTK. Among them, HER2-containing heterodimers, especially HER2-HER3 heterodimers strongly activate the PI3K/Akt pathway.\(^{(15)}\) Akt activation is positively associated with HER2 overexpression in breast carcinomas obtained from human materials.\(^{(16-18)}\)

Cellular activation of Akt is dependent on the generation of inositol-containing membrane lipids phosphorylated by Class I PI3K composed of a catalytic subunit (p110) and an adaptor/regulatory subunit (p85). Mutations of \(PIK3CA\), which encodes p110, are the most common genetic alterations of this pathway in breast cancer.\(^{(19)}\) Akt is activated by the phosphorylation at Thr\(^{308}\) and Ser\(^{473}\) and it then phosphorylates its substrates.\(^{(20)}\) This pathway is negatively regulated by phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and inositol polyphosphate-4-phosphate, type II.\(^{(21)}\)

Akt is critical for cell survival, cell cycle regulation and protein synthesis via its phosphorylation of many kinds of proteins, including FOXOs, glycogen synthase kinase-3β (GSK3β) and mTOR.\(^{(22-25)}\) mTOR forms the mTORC1 complex with raptor, which controls protein synthesis and cell growth by activating ribosomal protein S6 kinase (p70S6K) and inhibiting the elongation-initiation factor 4E-binding protein (4E-BP). p70S6K can also phosphorylate ER (Figs 1,2).\(^{(26)}\) mTOR also forms the mTORC2 complex with rictor, which phosphorylates and activates Akt at Ser\(^{473}\), whereas Akt is phosphorylated at Thr\(^{308}\) by PDK1.\(^{(27)}\)

The PI3K/Akt/mTOR pathway and endocrine resistance. The PI3K/Akt/mTOR pathways activated by RTK signaling interact with ER both directly and indirectly. The phosphorylated ER by Akt or p70S6K promotes the transcription of genes encoding growth factors (GF), RTK and other target genes. (Fig. 1). This crosstalk between ER and the PI3K/Akt/mTOR pathway increases estrogen-induced, tamoxifen-induced and ligand-independent ER transcriptional activity, which confers resistance to tamoxifen, fulvestrant and estrogen deprivation in ER-positive breast cancer cells.\(^{(2)}\)

The ER-positive/progesterone receptor (PR)-negative breast cancers do not respond as well to tamoxifen compared with ER-positive/PR-positive tumors.\(^{(28)}\) The predictive value of PR expression has long been attributed to the dependence of PR expression on ER activity, with the absence of the PR reflecting a non-functional ER. However, a recent study revealed that PR expression is inhibited in breast cancer cells via the PI3K/Akt/mTOR pathway, not via a reduction in ER levels or activity.\(^{(29)}\) Therefore, a low PR status may serve as an indicator of activated GF signaling and resistance to endocrine therapy. We also reported that HER2 overexpression and loss of heterozygosity at the PTEN gene locus was associ-
activated with Akt activation and a lack of PR expression in breast cancer.\(^3\) Recent research using reverse-phase protein arrays and a gene-expression array revealed that tumors with low PI3K activation have high ER levels and vice versa.\(^4\) Thus, RTK and their downstream pathways can also reduce estrogen dependence by downregulating the expression of ER and PR.

So far, the only mechanism of resistance to endocrine therapy for which clinical data exist is HER2 positivity, with HER2-positive metastatic breast cancer found to be less responsive to all types of endocrine treatment by a meta-analysis.\(^3\) However, because fewer than 10% of hormone receptor-positive breast cancers are HER2 positive,\(^4\) the mechanism(s) underlying endocrine resistance remain to be elucidated for the majority of ER-positive breast cancers. Therefore, various factors related to activation of the PI3K/Akt/mTOR pathway are considered to be potential causes of endocrine resistance. A recent study showed that treatment with fulvestrant resulted in increased HER3 expression and PI3K/mTOR signaling, while the depletion of HER3 in fulvestrant-treated tumor cells reduced PI3K/mTOR signaling, tumor cell survival and tumor growth, suggesting that upregulation of HER3 causes resistance to fulvestrant.\(^5\) Miller et al.\(^6\) also reported that long-term estrogen-deprived (LTE D) ER-positive breast cancer cells exhibited increased PI3K/Akt/mTOR signaling, with hyperactivation of IGF-1R and/or the insulin receptor.

Clinically, the activation of Akt has been shown to be associated with worse outcomes in endocrine-treated patients with breast cancer.\(^7\) We also reported that Akt activation was associated with resistance to endocrine therapy in metastatic breast cancer.\(^8\)

The prognostic and predictive value regarding endocrine resistance of PIK3CA mutations in ER-positive breast cancer remains unclear. PIK3CA mutations have been shown to result in in vitro activation of the PI3K/AKT/mTOR pathway.\(^9\) However, in luminal tumors there are no significant relationships between PIK3CA mutations and pAkt, p70S6K and 4E-BP1, which indicate activation of the PI3K/Akt pathway.\(^10\) In addition, PIK3CA mutations did not have a significant effect on outcome after adjuvant tamoxifen therapy in hormone receptor-positive breast cancer patients.\(^11\)

**Targeting the PI3K/Akt pathway to overcome endocrine resistance.** The combination of endocrine therapy and targeted therapy directed against the PI3K/Akt pathway has been developed to overcome endocrine resistance. The combination treatment of ER-positive/HER2-positive breast cancer cells with trastuzumab and tamoxifen significantly inhibited their growth and treatment of Akt-activated breast cancer cells with mTORC1 inhibitors, rapamycin and temsirolimus led to similar growth inhibition.\(^12\) The growth of LTE D cell lines in the absence of estrogen was inhibited by treatment with the PI3K/mTOR dual inhibitor, BEZ235, or with the TORC1 inhibitor, everolimus.\(^13\) Intriguingly, ER is required for acquired hormone-independent breast cancer cell growth in some LTE D cell lines and therefore combined downregulation of ER and inhibition of PI3K induces a regression of tumors comprising these cells.\(^14\)

Clinically, some large studies have shown the efficacy of inhibiting the PI3K/Akt/mTOR pathway to overcome endocrine resistance. For ER-positive/HER2-positive breast cancers, the utility of the combined use of trastuzumab or latatinib with AI has been shown.\(^15\) In both trials, progression-free survival and the clinical benefit rate were superior in the combination arms. The efficacy of mTORC1 inhibitors was investigated in patients with ER-positive/HER2-negative tumors relapsed following previous treatment with AI. In the BOLERO-2 trial, patients were randomized to groups receiving everolimus or placebo, combined with exemestane.\(^16\) In the TAMRAD (GINECO) study, patients were randomized to tamoxifen combined with everolimus or tamoxifen alone.\(^17\) Statistically significant increases in progression-free survival were revealed following the addition of everolimus to the endocrine agents in both trials. In the TAMRAD study, only the secondary endocrine-resistant tumors received a benefit from everolimus.\(^18\) In contrast, adding temsirolimus to letrozole did not improve progression-free survival as first-line therapy in patients with AI-naive advanced breast cancer.\(^19\) These results suggest that the strategy of co-targeting the PI3K and ER pathways may work particularly well in patients...
whose tumors have acquired resistance to previous endocrine therapy. The key results of these studies are shown in Table 1.

An important finding of the previous trials of combination therapy was the observation that there was an increase in Akt activation in everolimus-treated tumors.\(^{(13)}\) p70S6K, a molecule downstream of mTORC1, suppresses IGF-IR signaling via suppression of IRS1. The blockade of mTORC1 and the resulting inhibition of p70S6K reduce the negative feedback loop effect and the IGF-IR becomes activated, which results in increased PI3K/Akt/mTOR activation. The activation of this compensatory pathway could be, at least in part, responsible for the limited activity of this class of agents. Inhibiting or preventing activation of this compensatory pathway might improve the response to treatment.\(^{(13)}\)

**FOXA1**

The functions of FOXA1. The network of the transcription factors, ER, GATA-binding protein 3 (GATA-3) and FOXA1 had attracted increasing attention, because the normal function of this network has been suggested to be required for hormone sensitivity in breast cancer.\(^{(50)}\) FOXA1 mRNA is expressed in luminal subtype tumors, along with several other discriminatory genes, including ER and GATA-3.\(^{(51)}\) GATA-3 regulates the lineage determination and differentiation of many cell types,\(^{(52)}\) as well as playing a crucial role during mammary gland development.\(^{(53)}\)

FOXA1, a member of the forkhead family of transcription factors, is expressed in many organs and plays a key role in development, chiefly in the lung and liver.\(^{(54)}\) FOXA1 is also

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**Table 1. Major published clinical trials of the combination of endocrine agents with RTK-targeting therapies for metastatic breast cancer**

| RTK-targeting therapy | Study design | Patients | Key results | Reference |
|-----------------------|-------------|----------|-------------|-----------|
| **Anti-HER2 therapy** |             |          |             |           |
| Trastuzumab           | ANA vs ANA + TRAS randomized phase III (TAnDEM study) | n = 207 | PFS: ANA + TRAS 4.8 month; ANA 2.4 month; HR, 0.63; 95% CI, 0.47–0.84; P = 0.016 | Kaufman et al.\(^{(45)}\) |
|                       |             |          | OS: ANA + TRAS 28.5 month; ANA 23.9 month; P = 0.325 |           |
|                       |             |          | 70% of patients in the ANA arm crossed over to TRAS after progression |           |
|                       |             |          | OS: without crossover usage of TRAS |           |
|                       |             |          | ANA + TRAS 28.5 month; ANA 17.2 month; P = 0.048 |           |
|                       |             |          | CBR: ANA + TRAS 42.7%; 95% CI, 33.0–52.9%; ANA 27.9%; 95% CI, 19.5–37.5%; P = 0.026 |           |
| Lapatinib             | LET vs LET + LAP randomized phase III | Overall, n = 1286 | HER2 positive, n = 219 | Johnston et al.\(^{(46)}\) |
|                       |             |          | PFS: LET + LAP 8.2 month; LET + placebo 3.0 month; HR, 0.71; 95% CI, 0.53–0.96; P = 0.019 |           |
|                       |             |          | OS: LET + LAP 33.3 month; LET + placebo 32.3 month; HR, 0.74; 95% CI, 0.5–1.1; P = 0.113 |           |
|                       |             |          | CBR: LET + LAP 48%; LET + placebo 29%; OR, 0.4; 95% CI, 0.2–0.8; P = 0.003 |           |
| mTOR inhibitors       |             |          |             |           |
| Everolimus            | TAM vs TAM + EVE randomized phase II (GINECO study) | After prior AI, n = 111 | CBR: TAM + EVE 61%; TAM 42%; P = 0.045 | Bachelot et al.\(^{(48)}\) |
|                       |             |          | TTP: TAM + EVE 8.6 month; TAM 4.5 month; HR, 0.54; 95% CI, 0.36–0.81; P = 0.0002 |           |
|                       |             |          | Exploratory subgroup analysis in patients with secondary hormone resistance |           |
|                       |             |          | CBR: TAM + EVE 74%; TAM 48% |           |
|                       |             |          | TTP: TAM + EVE 14.8 month; TAM 5.5 month; HR, 0.46; 95% CI, 0.26–0.83; P = 0.0087 |           |
| Temsirolimus          | LET vs LET + TEM randomized phase III | Previously treated with NSAI in the adjuvant setting or for advanced disease (or both), n = 724 Asian patients, n = 143 | Median PFS: Local assessment: EXE + EVE 6.9 months; EXE + placebo 2.8 month; HR, 0.43; 95% CI, 0.35–0.54; P < 0.001 | Wolff et al.\(^{(49)}\) |
|                       |             |          | Central assessment: EXE + EVE 10.6 months; EXE + placebo 4.1 month; HR, 0.36; 95% CI, 0.27–0.47; P < 0.001 |           |
|                       |             |          | Asian patients: EXE + EVE 8.48 month; EXE + placebo 4.14 month; HR, 0.62; 95% CI, 0.41–0.94; P < 0.001 |           |

Where available, P-values are indicated. AI, aromatase inhibitors; ANA, anastrozole; CBR, clinical benefit rate; CI, confidence interval; EVE, everolimus; HR, hazard ratio; LAP, lapatinib; LET, letrozole; mTOR, mammalian target of rapamycin; NE, not estimable; NSAI, non-steroidal aromatase inhibitor; OR, odds ratio; OS, overall survival; EXE, exemestane; PFS, progression-free survival; RTK, receptor tyrosine kinase; TAM, tamoxifen; TEM, temsirolimus; TRAS, trastuzumab; TTP, time-to-progression.
Fig. 3. Estrogen receptor (ER)-mediated transcription involving FOXA1. FOXA1 interacts with cis-regulatory regions in heterochromatin and in combination with adjacent DNA binding elements, such as estrogen response elements, to facilitate the interaction of ER with chromatin. Subsequent to the association with ER, the recruitment of co-factors occurs at these distal enhancer sites and the transcription of the target gene is initiated.

necessary in the postnatal development of the mammary gland and prostate.\(^{(53,56)}\) The expression levels of FOXA1 and GATA-3 showed a significant positive correlation. A ChIP study suggested that GATA-3 may function upstream of FOXA1.\(^{(53)}\)

Although FOXA1 and GATA-3 seem to interact, they have distinct functions. A deficiency of FOXA1 causes a defect in hormone-induced mammary ductal invasion associated with a loss of terminal end bud formation and ER expression.\(^{(5,57)}\)

**FOXA1 and ER signaling.** The mechanisms responsible for ER-mediated transcription are very complex.\(^{(58)}\) Recent studies using ChIP with ChIP-seq has identified a complex network composed of ER and its coregulators and, on activation by estrogen, ER is recruited to thousands of sites across the genome of human breast cancer cells, defining its cistrome.\(^{(5)}\) The ER frequently binds distal enhancers and FOXA1 is necessary for ER-chromatin interactions (Fig. 3).\(^{(8,9,59,60)}\) FOXA1 works as an important pioneer factor for the interactions between ER and androgen receptor (AR) and chromatin.\(^{(8,9,55,59-61)}\) Pioneering factors have the capacity to associate with condensed chromatin independently of other factors and can directly modulate chromatin accessibility.\(^{(62)}\) FOXA1 interacts with the cis-regulatory regions of heterochromatin and enhances the interaction between ER and chromatin.\(^{(8,63)}\)

These studies also revealed that GFR signaling results in the redirection of ER binding. The GF-stimulated ER cistrome is different from that induced by estrogen. Interestingly, the GF-dependent, ligand-independent ER cistrome regulates a set of genes found to be overexpressed in HER2-positive tumors.\(^{(64)}\) This GF-stimulated ER cistrome might be related to endocrine resistance.

**Association of FOXA1 and endocrine response.** FOXA1 can influence various interactions between ER and chromatin and is required for almost all ER binding events and ER transcription activity in breast cancer cells. As such, FOXA1 is a major determinant of the endocrine response in breast cancer cells.\(^{(9)}\) Tamoxifen functions by inhibiting estrogen-ER activity in breast cancer cells, where tamoxifen-ER is recruited to chromatin.\(^{(65)}\) Intriguingly, FOXA1 is required for the action of tamoxifen; in tamoxifen-resistant cells, ER binding was independent of the ligand but depended on FOXA1.\(^{(9)}\) Ross-Innes and colleagues reported important findings using clinical breast cancer samples.\(^{(10)}\) They analyzed the ER ChIP-seq data from primary ER-positive breast tumors with a good prognosis (ER positive/PR positive/HER2 negative) and a poor prognosis (ER positive/PR positive/HER2 positive or ER positive/PR negative/HER2 negative) and samples from distant metastases. Interestingly, the signal of ER binding was lowest in the patients with a good prognosis and highest in the metastatic samples, suggesting that ER-binding intensity might correspond to disease progression of ER-positive breast cancer. The tamoxifen-resistant cancers still recruited ER to chromatin, with the acquisition of unique ER-binding regions. The increased ER binding in tamoxifen-resistant cell lines, which have the same motifs observed in the poor outcome ER-binding events in primary tumors, are probably due to the FOXA1-mediated reprogramming of ER binding.

The distinctive ER cistrome reveals gene signatures that can
predict the clinical outcome in ER-positive breast cancers. The different types of ER binding at distinct cis-regulatory elements is functionally and biologically relevant, resulting in altered gene expression profiles that contribute to differences in the endocrine response and outcome (Fig. 4). (10) Importantly, the majority of metastases that arise from an ER-positive breast cancer retain ER and FOXA1 expression, regardless of the sites of metastasis, which suggests the parallel redistribution of ER and FOXA1 binding events in drug-resistant cells. (10) These data indicate that FOXA1 plays a key role in hormone-resistant cancers; therefore, a specific FOXA1 inhibitor might provide a useful clinical tool for the treatment of ER-positive, hormone-resistant breast cancer. (62)

Interestingly, MCF-7 cells overexpressing Akt exhibit a unique ER cistrome related to the Akt-dependent expression profile. (66) FOXA1 could contribute alteration of the ER cistrome induced by GFR signaling, which occurs in ER-positive breast cancers with acquired endocrine resistance.

Clinical impact of FOXA1 expression in breast cancer. In breast cancer, FOXA1 expression positively correlates with that of ER and another transcription factor, GATA-3. (67, 68) The expression of both GATA-3 and FOXA1 is associated with luminal subtypes and a good prognosis in patients with ER-positive breast cancers. Of note, FOXA1 is an independent prognostic factor for ER-positive breast cancer, probably because the presence of FOXA1 indicates the presence of a functional ER complex, which will respond well to endocrine therapy. (67, 69-71)

A high expression of FOXA1 in the primary site could predict a good prognosis of ER-positive breast cancer after adjuvant therapy. However, the expression of ER and FOXA1 is retained in the metastatic sites. (10) This is an interesting and important finding, although the mechanism underlying this finding is still unclear. It would be meaningful to evaluate the relationships between FOXA1 expression in the primary and metastatic sites and the levels of downstream proteins, such as the PR and cyclin D1, in future studies.

Conclusions

Endocrine therapy is essential for ER-positive breast cancer. In the adjuvant setting, it is difficult to determine the necessity of chemotherapy or the duration of adjuvant endocrine therapy. In the metastatic setting, the indications for chemotherapy are dependent on how the endocrine resistance is judged. In order to resolve these problems, a better understanding of the mechanisms defining the sensitivity or resistance to endocrine therapy is important. Recent research has been unveiling these factors step by step. The combination of endocrine therapy with agents that overcome the resistance or improve the sensitivity to endocrine therapy could be expected to maximize the effects of treatment.

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