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Chapter

Challenges in Treating Estrogen Receptor-Positive Breast Cancer

Shang-Hung Chen and Chun Hei Antonio Cheung

Abstract

Despite hormone therapy is widely used (as both adjuvant and neoadjuvant therapy) for the treatment of estrogen receptor-positive (ER\(^+\)) breast cancer and patients receiving hormone therapy often show satisfactory initial response, resistance to selective estrogen modulators and aromatase inhibitors is frequently found in patients after prolonged treatment. In this chapter, we will discuss the molecular mechanisms of action of various hormone therapy agents and the biology behind the induction of hormone therapy resistance in ER\(^+\) breast cancer cells. Recent development of novel agents that can be used to treat ER\(^+\) hormone therapy-resistant breast cancer will also be discussed in this chapter.

Keywords: aromatase inhibitors, breast cancer, estrogen receptor, hormone therapy resistance, tamoxifen

1. Introduction

Breast cancer is the most common malignant disease and leading cause of cancer-related death for women worldwide. Among all subtypes, estrogen receptor-positive (ER\(^+\), i.e. expressing estrogen receptors endogenously) breast cancer is the most prevalent type, accounting for approximately 75\% of all patients. In clinical situations, hormone therapy targeting the estrogen (ER)-estrogen response element (ERE)-regulated cell survival-signaling pathway is commonly used for the management of ER\(^+\) breast cancer. The goals of applying systemic hormone therapy in patients with breast cancers are different in separate disease stages and generally hormone therapy can be given to patients with early disease prior to surgery (i.e. neoadjuvant therapy) or after surgery (i.e. adjuvant treatment), and patients with metastatic disease. There are four major classes of hormone therapy agents currently used for the management of ER\(^+\) breast cancer and they are: selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), selective estrogen receptor down-regulators (SERDs), and luteinizing hormone-releasing hormone analogs (LHRH analogs). Even though these agents are all functioned in interfering with the hormone-dependent cell survival-signaling pathways in breast cancer cells, their mechanisms of action are completely different (Figure 1).
2. Human breast cancer

2.1 Clinical classifications of human breast cancer

Breast cancer is now recognized as a group of diseases with distinct histopathological and biological characteristics. In the last decade, there is accumulating evidence indicating that individualized therapeutic strategies should be applied to treat breast cancers with different expression levels of histopathological biomarkers which own their unique biological behaviors and treatment responses [1–3]. Currently, the most determinant and commonly used molecular markers in clinical classifications of breast cancers are ER, progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67. The prognoses and most beneficial treatments of patients would be best evaluated after comprehensive examinations on the expression levels of these molecular markers in tumor cells. In addition to conventional risk factors such as tumor size, numbers of lymph node metastasis, surgical margin with tumor involvement, and tumor differentiation grade, the abovementioned molecular biomarkers have to be included in a modern pathological report of breast cancer. Breast cancer classification based on expression levels of these four biomarkers are summarized in **Table 1**.

Immunohistochemical (IHC) staining is the most accepted and widely used method to determine the expression levels of these biomarkers (i.e. ER, PR, HER2, and Ki67) clinically. Based on St. Gallen Consensus 2009 [4], ER⁺ and PR⁺ tumors were defined as if 1% or more immuno-reactive cells were identified. Noticeably, the definite percentage of breast cancer cells displaying nuclear immuno-reactivity for ER and PR must be reported, because the higher numbers of positive cells indicates the larger anticipated benefit of hormone treatment.
2.2 Current treatment options for ER+ breast cancer

2.2.1 Surgery

In general, surgery is the only way to cure most malignancies originated from solid organs. After diagnosis, patients with breast cancer in early stage should undertake surgery with or without radiotherapy, irrespective to the subtypes of breast cancer. There are two major surgical approaches for breast cancers—mastectomy (removal of the whole breast) and lumpectomy (breast-conserving therapy). The appealing advantage of lumpectomy enables patients to preserve their breast without compromising survival outcome. With the addition of radiotherapy following lumpectomy, survival outcomes have been reported to be equivalent to those after mastectomy as primary disease control in breast cancers with early stage [5–7].

Besides primary tumor resection, axillary lymph node (ALN) dissection or sentinel lymph node (SLN) biopsy and resection is also essentially performed on breast cancer patients to determine possible spread of cancer cells to lymph nodes from the original breast tumor. If the SLN examination reveals no evidence of malignant cell involvement, any other area of the body without cancer cell metastases would be highly postulated. Notably, the effectiveness of the SLN procedure to determine the presence of lymph node metastases is demonstrated to be identical to that of ALN dissection in various clinical studies.

2.2.2 Selective estrogen receptor modulators (SERMs)

The anti-breast cancer function of SERMs is mainly contributed by the competition with estrogen on ER, and modulations on ER-ERE (i.e. a type of gene promoter recognized by the activated ER) activity by altering the cooperated transcription factors in breast cancer cells (Figure 1) [8]. For both premenopausal and postmenopausal patients, the most commonly used SERM with established benefit in adjuvant setting is tamoxifen. Interestingly, although tamoxifen exhibits anti-estrogenic properties in the breast including the breast cancer cells; it exhibits estrogenic properties in bones and endometrial tissues. In ER+ breast cancers, the use of tamoxifen after surgery could decrease the risk of recurrence as well as death [9–11].

In general, if both chemotherapy and hormone therapy are indicated for patients after surgery, the recommended sequence of management is initial chemotherapy following with the use of tamoxifen. Traditionally, tamoxifen is given to patients with early breast cancer for 5 years after primary surgery. In fact, the NCCN guidelines recommend patients to receive at least 5 years of treatment, if tamoxifen is considered to be used after surgery. However, results from the recent randomized Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) study have supported 10 years of tamoxifen treatment in the adjuvant setting. The risks of disease recurrence

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Molecular profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ and/or PR+, HER2+, and low Ki67 (&lt;14%)</td>
</tr>
<tr>
<td>Luminal B</td>
<td>ER+ and/or PR+, HER2+, and high Ki67 (≥14%)</td>
</tr>
<tr>
<td></td>
<td>ER+ and/or PR+ and HER2+ (luminal-HER2 group)</td>
</tr>
<tr>
<td>HER2</td>
<td>ER+, PR+, and HER2+</td>
</tr>
<tr>
<td>Triple negative</td>
<td>ER+, PR+, HER2+</td>
</tr>
</tbody>
</table>

Table 1. Molecular profiles of different breast cancer subtypes.
and death were shown to be decreased in patients completing 10 years of tamoxifen treatment, as compared with those for 5 years of treatment, despite the increased risks of getting endometrial cancer and pulmonary embolism [9]. Based on these findings, adjuvant tamoxifen treatment for 10 years is now considered for patients with early breast cancer. The NCCN guidelines also recommend tamoxifen treatment for ER+ metastatic breast cancer patients.

Toremifene is another SERM which has demonstrated its clinical efficacy in ER+ breast cancers. Several studies have shown equivalent efficacy of toremifene in disease control of metastatic breast cancers, as compared with tamoxifen [12, 13]. Therefore, similar to tamoxifen, toremifene is also recommended in NCCN guidelines for disease control in patients with ER+ metastatic breast cancers.

2.2.3 Aromatase inhibitors (AIs)

Aromatase is an enzyme that belongs to the family of cytochrome P-450 and it is responsible for the conversion of androgens to estrogens in peripheral tissues. Given that this peripheral conversion by the aromatase is the main origin of estrogen production in postmenopausal women, inhibition of this particular enzyme could lead to the significant reduction of estrogens (Figure 1). AIs are now suggested to be the standard of care for postmenopausal patients with ER+ breast cancer in NCCN guidelines. Current AIs could be grouped into two different subtypes—steroidal and non-steroidal AIs. Steroidal AIs, also termed as type I inhibitors, have steroid-like structure similar to the substrate of aromatase. This similarity confers these AIs the ability to interact with the substrate-binding site of aromatase and subsequent inactivation of this enzyme. Non-steroidal AIs or type II inhibitors could bind to the heme moiety of the aromatase non-covalently, and therefore prevent binding of androgens. Unlike type I inhibitor, the inhibition of androgen by this type of AIs is reversible by competitive binding of androgens. There are currently one type I inhibitor (i.e. exemestane) and two type II inhibitors (i.e. letrozole and anastrozole) approved by the US Food and Drug Administration (FDA). They are all indicated in both the adjuvant and metastatic setting for postmenopausal patients with ER+ breast cancer (Table 2).

Several studies have been carried out to evaluate the effects of different therapeutic strategies of AIs in the treatment of postmenopausal patients with early stage ER+ breast cancer. Different therapeutic strategies including (1) initial treatment with AIs, (2) sequential therapy with AIs after 2–3 years of tamoxifen, and (3) extended therapy with AIs after the completion of tamoxifen for 5 years have been extensively studied. Two phase III pivotal studies, named ATAC [14] and BIG 1-98 [15], have demonstrated the clinical efficacy of 5 years of adjuvant AIs (i.e. initial treatment with AIs). However, the hazard ratio (HR) for disease-free survival (DFS) comparing 5 years of tamoxifen of these studies, ranging from 0.81 to 0.91, indicates minimal improvement of the use of AIs to prevent disease recurrence after surgery. Several clinical studies, such as ARNO 95 [16], ITA [17], and IES [18] have shown the clinical benefit of sequential treatment of AI after 2–3 years of tamoxifen. In patients receiving sequential therapy comparing with 5 years of tamoxifen, HR for DFS ranges from 0.57 to 0.76. In extended therapy of AIs beyond 5 years of tamoxifen, its clinical efficacy in the reduction of HR for DFS, ranging from 0.58 to 0.68, has also been reported in randomized studies [19, 20]. According to the NCCN guidelines, the abovementioned AIs related strategies (i.e. AIs as initial adjuvant therapy for 5 years; 2–3 years of tamoxifen followed by AIs to complete 5 years of adjuvant therapy; and 5 years of tamoxifen followed by 5 years of AIs) are all recommended for postmenopausal breast cancer patients who are required for receiving adjuvant hormone therapy.
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In metastatic disease, improved survival outcomes of applying AIs as the first-line hormone therapy as compared with using tamoxifen in postmenopausal patients have also been revealed in studies conducted by Arimidex Study Group, International Letrozole Breast Cancer Group, and the EORTC Breast Group [21–23]. Although this advantage is small, AIs are still recommended by NCCN for use in treating ER\(^+\) metastatic breast cancer in postmenopausal patients.

2.2.4 Selective estrogen receptor degrader (SERD)

Unlike SERMs that function as partial competitive antagonists of ER, SERDs are antiestrogens designed to destabilize ER of tumor cells (Figure 1). After binding to ERs, SERDs could induce the degradation of these receptors, and thereby lead to the inhibition of estrogen associated signaling pathway [24]. Fulvestrant is the only SERD approved by FDA for clinical use in the management of ER\(^+\) breast cancers. Equivalent effect of fulvestrant on tumor response rate and time to progression, as compared with AIs, have been reported in postmenopausal patients with progressive metastatic ER\(^+\) breast cancer following prior hormone therapy [25, 26]. In NCCN guidelines, fulvestrant is suggested in clinical use of postmenopausal metastatic ER\(^+\) breast cancers.

2.2.5 Luteinizing hormone-releasing hormone (LHRH) analogs

Ovary is the major organ responsible for estrogen production. Therefore, oophorectomy has been recognized as one of the effective treatments for premenopausal patients with metastatic ER\(^+\) breast cancers. Besides oophorectomy, medical treatments with LHRH analogs have also been used clinically to ablate ovary function for over 30 years [27]. Through desensitizing gonadotropin-releasing hormone (GnRH) receptors, LHRH analogs suppress the secretion of gonadotropin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in reduced estrogen levels in the body (Figure 1). Although a combination of LHRH analogs and SERMs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease setting</th>
<th>Study group</th>
<th>Control group</th>
<th>Significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC [14]</td>
<td>Adjuvant</td>
<td>Anastrozole for 5 years</td>
<td>Tamoxifen for 5 years</td>
<td>HR for DFS: 0.91</td>
</tr>
<tr>
<td>BIGI-98 [15]</td>
<td>Adjuvant</td>
<td>Letrozole for 5 years</td>
<td>Tamoxifen for 5 years</td>
<td>HR for DFS: 0.81</td>
</tr>
<tr>
<td>ARNO95 [16]</td>
<td>Adjuvant</td>
<td>2 years of tamoxifen + 3 years of anastrozole</td>
<td>Tamoxifen for 5 years</td>
<td>HR for DFS: 0.66</td>
</tr>
<tr>
<td>ITA [17]</td>
<td>Adjuvant</td>
<td>2-3 years of tamoxifen followed by anastrozole to complete total 5 years of HT</td>
<td>Tamoxifen for 5 years</td>
<td>HR for DFS: 0.56</td>
</tr>
<tr>
<td>IES [18]</td>
<td>Adjuvant</td>
<td>2-3 years of tamoxifen followed by exemestane to complete total 5 years of HT</td>
<td>Tamoxifen for 5 years</td>
<td>HR for DFS: 0.76</td>
</tr>
<tr>
<td>MA17 [19]</td>
<td>Adjuvant</td>
<td>4.5-6 years of tamoxifen + 5 years of letrozole</td>
<td>Tamoxifen for 5 years</td>
<td>HR for DFS: 0.58</td>
</tr>
<tr>
<td>B33 [20]</td>
<td>Adjuvant</td>
<td>5 years of tamoxifen + 5 years of exemestane</td>
<td>Tamoxifen for 5 years</td>
<td>HR for DFS: 0.68</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; HT, hormone therapy; HR, hazard ratio.

Table 2. Clinical benefits of using aromatase inhibitors in ER\(^+\) breast cancers.
Estrogen has been demonstrated to improve survivals significantly as compared to chemotherapy alone [28], further studies indicate that in premenopausal patients with ER’ early breast cancer, adjuvant treatment with LHRH analogs combined with SERMs (tamoxifen) does not carry any clinical benefits [29]. However, the combination of LHRH analogs and AIs (i.e. exemestane) as an adjuvant therapy significantly reduces the risk of recurrence in premenopausal patients with early disease [30]. In metastatic diseases, both the combinations of LHRH analogs and SERMs or AIs have shown the benefit of survivals in premenopausal patients [31–33]. In NCCN guidelines, LHRH analogs are recommended to use in combination with AIs or SERMs in premenopausal patients with ER’ breast cancer, both in adjuvant or metastatic setting.

2.3. Mechanisms of hormone therapy resistance in ER’ breast cancer

Despite various hormone therapy agents have been developed and proven to be effective in treating ER’ early stage breast cancer, intrinsic and acquired resistance to hormone therapy are frequently observed in breast cancer patients. In the following sections, we will discuss the biology behind the induction of hormone therapy resistance in ER’ breast cancer in details.

2.3.1 Dysregulation and conformation alteration of ERα

Under normal physiological conditions, the binding of estrogen to ER will trigger ER conformation changes and ER dimerization (e.g. ERαβ heterodimer formations). Then, the activated ER dimers will bind onto the estrogen response elements (EREs; promotor regions specifically recognized by the activated ER dimers) and drive the expression of the ERE-regulated cell survival- and growth-related genes. Decreased ERα expression (and aberrant ERα protein conformation) and reduced survival dependence on the estrogen-ER signaling pathway are both known to promote hormone therapy resistance in ER’ breast cancer. For example, upregulation of the zinc-finger-homeodomain transcription factor, zinc-finger E-box binding homeobox 1 (ZEB1), has been shown to downregulate ERα expression epigenetically through formation of a ZEB1/DNA methyltransferase 3B (DNMT3B)/histone deacetylase 1 (HDAC1) complex on the promoter of ERα and to induce tamoxifen resistance in breast cancer cells. High ZEB1 expressions also correlate with ERα promoter hypermethylation and reduced ERα expression in breast cancer patients [34].

As described in the above sections, tamoxifen is a SERM that exhibits differential effects on ER conformation and ER-signaling pathways. Despite tamoxifen inhibits the ER-ERE-related survival-signaling pathways in ER’ breast cancer cells and this drug is widely used to treat ER’ breast cancer; tamoxifen is known to increase the risk of having endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas in the treated breast cancer patients, possibly through activation of the ER-signaling pathways in endometrial cells. Phosphorylation of the amino acid residue serine-305 in the hinge region of ERα by protein kinase A (PKA) has been demonstrated to change the resulting conformation of ERα upon tamoxifen interactions, turning the tamoxifen-bound ERα from an inactive form into an active form (i.e. tamoxifen acts as an ER-agonist), leading to the activation of ER-ERE signaling pathways in ER’ breast cancer cells (Figure 2) [35].

2.3.2 Dysregulation of cell survival-related signaling pathways and pro-/anti-apoptotic molecules

It is widely demonstrated that aberrant downregulation of p53, upregulation of human epidermal growth factor receptor 2 (HER2/neu), the phosphatidylinositol
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3-kinase/protein kinase B/mammalian target of rapamycin [PI3K/PKB(Akt)/mTOR]-signaling pathway, and the extracellular signal-regulated kinases (ERK, also called MAPK)-signaling pathway can promote the survival and metastasis of cancer cells. In fact, dysregulation of these molecules and signaling pathways has also been found in the ER$^+$ hormone therapy resistance breast cancer cells (Figure 2). For example, a study by Liang et al. revealed that melanoma cell adhesion molecule (MCAM, also called CD146 or MUC18) negatively regulates ER$^+$ expression, but positively regulates the Akt-signaling pathway, in breast cancer cells. Moreover, increased expression of MCAM was found to induce epithelial-mesenchymal transition (EMT) and tamoxifen resistance via Akt-signaling pathway activation in the tamoxifen-resistance breast cancer cells in the same study [36].

Survivin is a well-known anti-apoptotic and pro-tumorigenic molecule. It contains a single baculovirus inhibitor of apoptosis protein repeat (BIR) domain and it is believed that survivin binds to caspases through its BIR domain and subsequently inhibits the activity of caspases. On the other hand, survivin forms chromosomal passenger complex (CPC) with aurora B kinase, borealin, and inner centromere protein (INCENP) and successful formation of CPC plays an important role in chromosome segregation during mitosis [37, 38]. Survivin protein translation is known to be positively regulated by the Akt/mTOR-signaling pathway and dysregulation of the Akt/mTOR/survivin pathway is known to be a factor of estrogen-independence and tamoxifen-resistance causation in the MCF7-derived ER$^+$ breast cancer cells [39]. Of note, hyper-phosphorylation of the survivin-binding partner, aurora B kinase, has also been demonstrated to be capable of causing fulvestrant resistance in ER$^+$ T47D breast cancer cells [40].

Besides dysregulation of the Akt/mTOR-signaling pathway, Yin et al. revealed that upregulation of G protein-coupled estrogen receptor (GPER) triggers Erk-signaling pathway activation, leading to the expression reduction of the BH3-only pro-apoptotic molecule, Bim, and induction of tamoxifen resistance in ER$^+$ breast cancer [41]. Myeloid cell leukemia-1 (Mcl-1) is a suppressor of Bim and overexpression of this anti-apoptotic molecule has also been found in MCF7-derived antiestrogen-resistant cancer cell lines [42]. Other molecules/pathways that have been found to play a role in the induction of hormone therapy resistance in ER$^+$ breast cancer are listed in Table 3.
2.3.3 Dysregulation of microRNAs (miRNAs)

MiRNAs are a class of small (20–22 nucleotides) non-coding RNA molecules that function in the regulation of gene expression. At the molecular level, miRNAs bind unto mRNAs at specific locations (putative binding sites) through complementary base-pairing and subsequently inhibit the translation of the targeted genes. Given that the expression of various tumor suppressors and oncoproteins is known to be regulated by miRNAs; dysregulation of miRNAs is believed as one of the causes of tumorigenesis, tumor metastasis, and tumor drug resistance in human.

Aberrant expression of different miRNAs has been shown to contribute to the induction of hormone therapy resistance through downstream modulations of different cell survival or division-related signaling molecules in ER+ breast cancer (Figure 2). For example, we found in a previous study that the MCF7-derived, ER+ hormone therapy-resistant (i.e. estrogen independent and tamoxifen resistant) breast cancer cells, which were generated in our laboratory, exhibits reduced expression of miR-125a-5p but increased expression of survivin as compared to the parental hormone therapy sensitive MCF7 cells. We also found that miR-125a-5p is an expression suppressor of survivin and dysregulation of the HDAC2/5-miR-125a-5p-survivin pathway in part contributes to the induction of estrogen independence and tamoxifen resistance in the same breast cancer cell line [39]. The role of miR-125a-5p downregulation in hormone therapy resistance induction is further supported by clinical data analysis showing that low miR-125a-5p expression levels correlate with poor overall survival in tamoxifen-treated ER+ breast cancer patients [39]. Induction of tamoxifen resistance has also been shown in ER+ breast cancer cells with dysregulation of miR-125a-3p, a molecule which is closely related to miR-125a-5p. A study by Zheng et al. revealed that miR-125a-3p is an inhibitor of cyclin-dependent kinase 3 (cdk3), which is an ER transcriptional activity enhancer, in ER+ breast cancer cells. In addition, reduced expression of miR-125a-3p and increased expression of cdk3 was found in the ER+ tamoxifen-resistant breast cancer cells and ectopic overexpression of miR-125a-3p was shown to decrease the expression of cdk3 and restore the sensitivity to tamoxifen in the same cell line in vitro [47].

Metabolic reprogramming is believed as one of the mechanisms that can promote drug resistance in cancer cells. Interestingly, aberrant upregulation of miR-155 has been found to drive metabolic reprogramming via miR-143 downregulation and hexokinase-2 (HK2; a glycolysis-priming enzyme and a known target of miR-143) upregulation, promoting the survival of ER+ breast cancer cells under estrogen-deprived conditions (mimics aromatase inhibitors treatment) [48]. Other miRNAs that have been found to play a role in the induction of hormone therapy resistance in ER+ breast cancer are listed in Table 4.

<table>
<thead>
<tr>
<th>Name of the molecule or signaling pathway</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTDH-PTEN-Akt</td>
<td>Xu et al. [43]</td>
</tr>
<tr>
<td>Plk1-Cdc25c</td>
<td>Jeong et al. [44]</td>
</tr>
<tr>
<td>RUNX2-ER-SOX9</td>
<td>Jeselsohn et al. [45]</td>
</tr>
<tr>
<td>Rac1-PAK1</td>
<td>Gonzalez et al. [46]</td>
</tr>
</tbody>
</table>

Table 3. List of molecules/pathways known to contribute to the induction of hormone therapy resistance in ER+ breast cancer during dysregulated situations.
2.3.4 Tumor microenvironment

Emerging evidences suggest that altered tumor microenvironment promotes drug resistance induction and malignant progression of cancer. As a tumor grows, tumor cells located at a distal distance from blood vessels will experience a hypoxic environment and eventually some of the severe hypoxia-experienced tumor cell will undergo necrosis or apoptosis. However, tumor cells are known to be capable of carrying a series of cellular and molecular changes in order to maintain their survival and also to promote tumor progression under hypoxic conditions. For example, it has been reported that hypoxia induces downregulation of ERα, upregulation of hypoxia-inducible factor 1α (HIF-1α; a transcription factor known promote the expression of various cell survival-related proteins) and vascular endothelial growth factor (VEGF; a growth factor known to promote angiogenesis) expressions, and promotes the development of estrogen independence in ER+ breast cancer cells in vitro.

Cancer-associated fibroblasts (CAFs) have been implicated in the development of hormone therapy resistance in ER+ breast cancer [54, 55]. It has been demonstrated that CD146-negative CAFs suppress ER expression in ER+ breast cancer cells, decrease tumor cell sensitivity to estrogen, and increase tumor cell resistance to tamoxifen therapy [55]. As mentioned in the previous section, GPER upregulation triggers Erk-signaling pathway activation and Bim downregulation in ER+ breast cancer cells. A study by Yuan et al. demonstrated that GPER also positively regulates the expression of an adhesion molecule, β1-integrin, and the downstream molecules of β1-integrin, FAK, and Scr, in the MCF7-derived tamoxifen-resistant breast cancer cells. Importantly, they further showed that the product of CAFs, fibronectin, interacts with β1-integrin and promotes epithelial-mesenchymal transition (EMT) in breast cancer cells [56].

3. Combating ER+ hormone therapy-resistant breast cancer

As described in the above sections, overexpression of survivin, aurora B kinase, and Mcl-1 has been found in different ER+ hormone therapy-resistant breast cancer models. In fact, survivin, aurora B kinase, and Mcl-1 are all known to play important roles in maintaining cancer cells survival and metastasis in ER+ breast cancer, HER2+ breast cancer, and the triple-negative breast cancer. Therefore, it is not surprising to see that the effectiveness of a group of survivin, aurora B kinase, and Mcl-1 inhibitors in targeting ER+ hormone therapy-resistant breast cancer has
been investigated extensively in different pre-clinical studies. For example, a small molecule inhibitor of survivin, YM155 (sepantronium bromide), has previously been demonstrated to exhibit similar potency in MCF7 and MCF7-derived ER\(^+\) tamoxifen-resistant breast cancer cells regardless to the expression of p53 [57]. Interestingly, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and the anti-cholesteremic agent, lovastatin (mevacor), has been shown to decrease survivin expression and increase the therapeutic effect of tamoxifen in tamoxifen-resistant breast cancer cells [58]. Targeting aurora B kinase by small molecule inhibitor, AZD1152 (barasertib), has also been shown to potentiate the effects of fulvestrant in patient-derived estrogen-independent ER\(^+\) breast cancer cells [40]. Moreover, a dual aurora kinase and cyclin-dependent kinase inhibitor, JNJ-7706621, and a deubiquitinase inhibitor (i.e. capable of destabilizing Mcl-1), WP1130, have both been demonstrated to be functional in promoting the death of tamoxifen-resistant breast cancer cells [42].

SAHA (vorinostat) is an epigenetic modulator [histone deacetylase inhibitor (HDACi)] that was approved by the US FDA for the treatment of cutaneous T cell lymphoma on 2006. A study by Lee et al. revealed that SAHA preferentially inhibits HDAC3, HDAC6 and their downstream targets, survivin and XIAP, in MCF7 and MDA-MB-231 breast cancer cells \textit{in vitro} [59]. Notably, a phase II clinical study revealed that the combination of SAHA and tamoxifen exhibited encouraging activity in reversing hormone resistance in patients with hormone therapy-resistant breast cancer [60]. Besides epigenetic modulators, the possibility of using Akt/mTOR-signaling pathway inhibitors in treating ER\(^+\) hormone therapy-resistant breast cancer has also been evaluated in different pre-clinical and clinical studies. For example, the orally bioavailable ATP-competitive mTOR inhibitor, AZD8055, was found to be more potent against the proliferation of the MCF7-derived tamoxifen-resistant breast cancer cells than that of parent cells [61]. In addition, co-treatment with the mTOR inhibitor, rapamycin (sirolimus), was shown to be capable of restoring tamoxifen sensitivity in ER\(^+\) tamoxifen-resistant breast cancer cells [62]. AZD5363 is a pan-Akt kinase catalytic inhibitor and it is currently in phase I clinical trials for various cancers. A study by Ribas et al. demonstrated that AZD5363 was capable of inhibiting the growth of the ER\(^+\) estrogen-independent MCF7-LTED, T47D-LTED, and ZR75-LTED breast cancer cells at the low-to-middle nanomolar range \textit{in vitro}. In addition, combination of AZD5363 with fulvestrant was shown to exhibit synergestic anticancer effects in a patient-derived luminal breast cancer xenograft HBCx220vaR model [63]. The pan-class I PI3K inhibitor, BKM120 (buparlisib), is currently in a phase III study in combination with fulvestrant in postmenopausal patients with ER\(^+\), HER2\(^-\) breast cancer refractory to non-steroidal aromatase inhibitors (ClinicalTrials.gov Identifier: NCT01610284).

4. Conclusion

Since hormone therapy is the mainstay of treatment in early ER\(^+\) breast cancer, hormone therapy resistance represents the major challenge in the management of this disease. Dysregulation of various cell survival-signaling pathways (such as Akt/mTOR and PI3K) and molecules (like HDACs, survivin, and miR-125a-5p) in breast cancer cells and CAFs in tumor microenvironment is now known to contribute to the induction of hormone therapy resistance in ER\(^+\) breast cancer. Therefore, co-treatments of mTOR inhibitors like rapamycin or HDACi like SAHA with SERMs/Als may give better therapeutic (i.e. clinical) outcomes in patients with advanced/hormone therapy-resistant ER\(^+\) breast cancer in the future. Furthermore, even though the effectiveness of hormone therapy in patients with ER\(^+\) breast cancer
can be predicted based on their breast cancer subtypes classified according to the results of the pre-treatment pathological examinations using IHC and PAM50 (Prosigna®); however, there is still room for the improvement of the current breast cancer pathological classification system as intrinsic resistance to hormone therapy is frequently found in patients with breast cancer predicted to be hormone therapy sensitive. A better breast cancer pathological classification system is needed for the development of personalized breast cancer treatments in the future.

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Conflict of interest

Authors declared no conflict of interest.

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Estrogen

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