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Review Article

A review of the endocrine resistance in hormone-positive breast cancer

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Abstract: Hormone-positive breast cancer (BC) is a unique heterogeneous disease with a favorable prognosis compared to other types of breast cancer. As tumor biology influences the prognosis and clinical treatment, a deep understanding of how the molecular mechanisms regulate hormone sensitivity or resistance is critical in improving the efficacy and overcoming the endocrine resistance. This article comprehensively reviews the endocrine resistance in hormone-positive BC from a molecular and genetic perspective, encompassing the updated treatment and developing direction. This review includes the mechanisms of hormone resistance, which vary from epigenetic changes, crosstalk between signaling networks, cell cycle aberrance, and even change in the tumor microenvironment (TME) or stem cell. These mechanisms may contribute to treatment resistance. Current targeted therapy for hormone-resistant tumors includes PI3K/AKT/mTOR and cdk4/6 inhibitors. Several relevant pathways, biomarkers, and predictor genes have also been identified. Immunotherapy so far has a relatively less crucial role in hormone-positive than in triple-negative BC. Furthermore, the methodology to identify the PDL1 is not standardized. In a molecule and gene study, next-generation sequencing with circulating tumor DNA (ctDNA) has recently appeared as a sensitive and minimally invasive tool worth investigating.

Keywords: Breast cancer, endocrine resistance, hormone-positive, estrogen, signaling pathway, ESR1, tumor microenvironment, next-generation sequencing

Introduction

Breast cancer (BC) is one of the most relevant causes of death among women worldwide [1]. It is a heterogeneous disease with multiple intrinsic tumors, categorized into various subgroups presenting diverse biological and clinical behaviors [2].

There are four subtypes of BC based on the presentation of estrogen or progesterone receptors (PR) and human epidermal growth factor 2 (HER2). Luminal A is hormone-responsive BC (estrogen-receptor or progesterone-receptor positive, HER2 negative, and has low protein Ki-67), with a favorable prognosis that can be treated with endocrine therapies. Luminal B (estrogen-receptor or progesterone-receptor positive, and either HER2 positive or HER2 negative with high levels of Ki-67) generally grow slightly faster than luminal A cancers, and their prognosis is worse when compared with luminal A. Luminal B subtype can be treated with hormone regimen or antiHER2 targeted therapy if it is HER2 positive. The other two types are HER2 enrich type, which response to anti-HER2 regimen such as Trastuzumab or Pertuzumab [3], and triple-negative BC, which can be treated with an immune checkpoint inhibitor. As tumor biology influences the prognosis and clinical treatment, and 70% of BCs are estrogen receptor (ER) positive, a deep understanding of how the molecular mechanisms regulate hormone sensitivity or resistance is critical in improving the efficacy and overcoming the resistance to endocrine therapy [4]. Furthermore, many gene expressions determine the prognosis and affect the treatment strategy; that is why multigene assays, such as Oncotype Dx, Mammaprint, and EndoPredict, are currently available

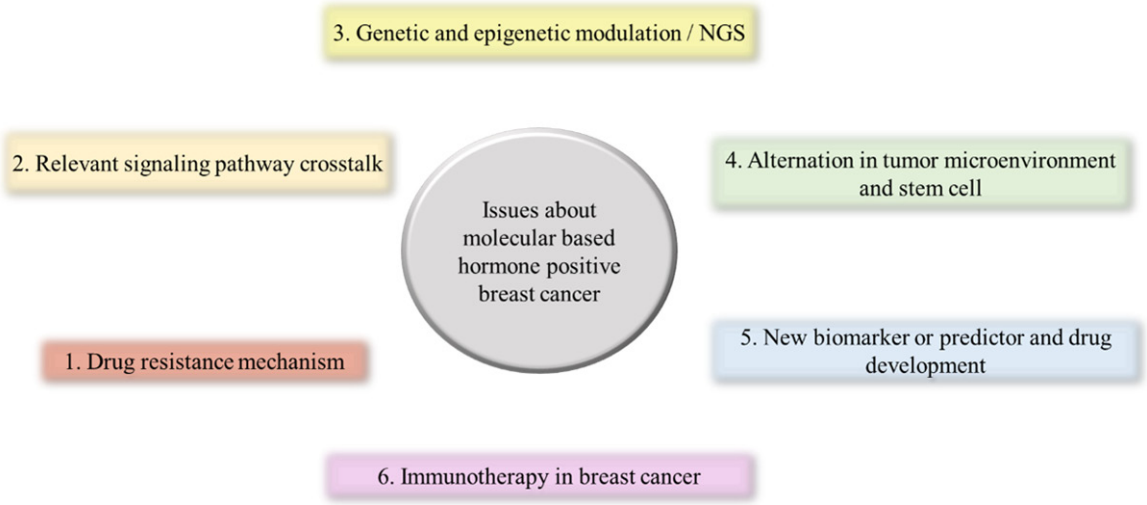

Figure 1. Issues about molecular based Hormone-positive breast cancer.

[5]. Whether other estrogen-response genes could be identified will be an issue in predicting prognosis and guiding treatment [6].

This article reviews the endocrine resistance in hormone-response BC from the perspective of signaling pathways, anti-endocrine resistance, potential or predictive biomarkers for the treatment to contribute a novel insight for the BC microenvironment (**Figure 1**).

The characteristics of hormone-positive BC and current therapy

The presentation of ER and PR are two crucial molecules that determine the heterogeneity of BC and prognosis, as ER/PR double positive has better survival than ER or PR single positive BC [7]. Studies have shown that the characteristics of single or double hormone receptor-positive subtypes are very different and warranted varied treatments for further investigation [8]. The two subtypes of ER are alpha (ERα) and beta (ERβ). ERα is the primary form of ER in BC and presents both protein and mRNA levels. ERα activation is considered responsible for the enhanced proliferation of breast epithelial cells, whereas ERβ exerts an antiproliferative effect [9].

Estrogen Receptor α (ERα) targets the treatment with antiestrogens, steroidal or non-steroidal molecules [10]. Nevertheless, scholars do not completely understand the mechanisms of the expression of ERα. Gene amplification was thought to be one of the most important factors regulating protein expression. However, around 40% of ERα-positive tumors showed an absence of response to endocrine therapy, and the majority of those with response eventually become resistant [11, 12].

The current therapies for Hormone-positive BC contain drugs that suppress estrogen presentation (aromatase inhibitors, GnRH agonists) and direct inhibitors of the ER (selective estrogen receptor modulators (SERM)) or selective estrogen receptor degraders (SERD), the uses of which vary among premenopausal and menopausal women [13] (**Table 1**). It is well that levels of the two ER subtypes change during BC progression, so the independent measurement of both ERs might help predict the disease prognosis and response to endocrine therapies. Selective activation of ERα or ERβ depends not only on binding affinity to the selective receptor but also on various activation of each receptor subtype [14].

Fulvestrant, which lowers both ER and PR levels, referring to a selective ER down regulators, is not inferior to tamoxifen and similar or superior to aromatase inhibitors in metastatic disease in the FALCON trial [15, 16] and sub-group analysis [16, 17]. Other ovarian suppression medication includes leuprorelin or goserelin, which can be used for premenopausal patients [18].

Furthermore, the updated therapy for hormone response BC in metastatic setting includes hormone therapy, chemotherapy, or target therapy

Table 1. Current hormone and target therapy for HR positive Breast cancer (BC)

Drug character	Drug	mechanism	Indication	Others
Hormone therapy selective estrogen receptor modulator (SERM)	Tamoxifen	Block ERs on BC cells	1. HR+ invasive BC treated with surgery, or breast-conserving surgery in ductal carcinoma in situ (DCIS) 2. mBC with HR+	associated with increased endometrial cancer risk
selective estrogen receptor degrader (SERD)	Fulvestrant (Faslodex)	Block and damages ERs	Alone to treat advanced BC not or underwent other hormone drugs combined with a CDK4/6 inhibitor or PI3K inhibitor to treat metastatic BC	CONFIRM trial FALCON trial FACT trial
Aromatase Inhibitor	steroidal (exemestane) non-steroidal AIs (letrozole/ anastrozole)	Block the aromatase activity, thus inhibiting estrogen biosynthesis	Post-menopausal women, either alone or after tamoxifen	Better than taking just tamoxifen for 5 years
LHRH analogs	goserelin (Zoladex) and leuprolide	Lower estrogen levels	Used alone or combined with other hormone drugs such as tamoxifen, aromatase inhibitors, or fulvestrant as hormone therapy in pre-menopausal women	Mechanism: inhibition of pituitary and gonadal function
PI3K Inhibitors	Pictillisib Buparilisib	Inhibiting PI3K signaling	Resistance to endocrine therapy in HR-positive BC	BELLE-2/SOLAR-1/ SANDPIPER Trial
MTOR inhibitors	Everolimus temsirolimus	Inhibit the intracellular protein FKB12, interacting with mTORC1 and inhibiting mTOR signaling	Resistance to endocrine therapy in HR-positive BC	BOLERO-2/HORIZON/ BALLET Trial
Cyclin-dependent Kinase (CDK) inhibitor	Ribociclib Palbociclib Abemaciclib	Prevents the cell cycle from proceeding G1 to S phase, then inhibiting cell proliferation	Alone or combine endocrine therapy for post-menopausal women	PALOMA/MONALEESA trial

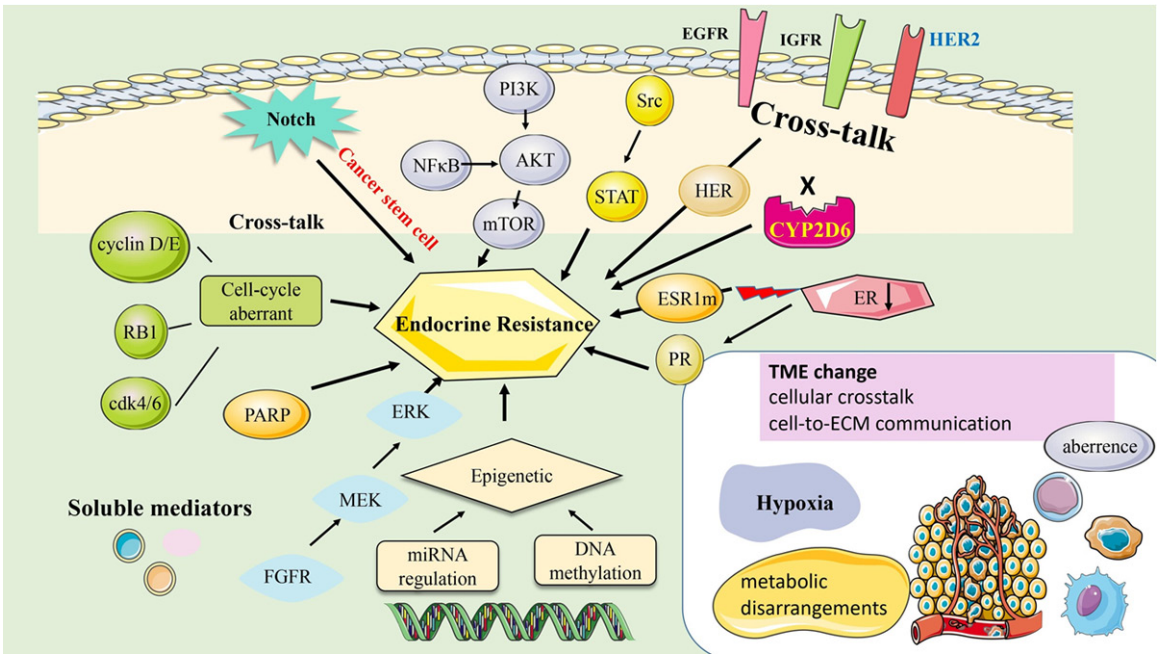

Figure 2. The mechanism of endocrine resistance in Hormone-positive breast cancer. A. ER down regulation (such as CYP2D6 variants; lack of ERα expression). B. The profiles of DNA methylation or miRNA regulation with differential adaptation of breast cancer cells to the hormone therapy, and hence could be cause of hormone resistance. C. Tumors harboring mutations of ESR1. D. Cross-talk between ER and other signaling networks, such as HER2/IFGR/EGFR/MAPK/mTOR). Acquired resistance to endocrine therapy involves alterations in translation signals through increasing the expression and activity of tyrosine kinase receptor family proteins (HER2, EGFR, and IGFR). These events result in aberrant activation of cAMP/PKA, MAPK/ERK, and PI3K/AKT signaling pathways. E. Aberrance of cell cycle regulators (c-myc; cyclin D1/E; CDK4/6). F. Resistance from Cancer stem cell: breast cancer stem cells to generate resistant BCs containing part of BCSCs; the other is via the dedifferentiation of BCs will gnerate tumors resistant to endocrine therapy and leading to the acquisition of BCSCs. G. Resistance from tumor microenvironment (cellular crosstalk and cell-to-ECM communication, inducing the release of soluble factors in charge of immune evasion and ECM remodeling, which further promote therapy resistance. Abbreviations: ER, Estrogen receptor; ECM, Extracellular Matrix; ESR1, Estrogen Receptor 1; EGFR, epidermal growth factor receptor; FGF2, fibroblast growth factor 2; FGFR, fibroblast growth factor receptor; GFR, growth factor receptor; HER2, human epidermal growth factor receptor 2; IGF, insulin-like growth factor; IGFR, insulin-like growth factor 1 receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3 kinase; PR, Progesterone receptor; TME, tumor microenvironment.

such as CDK4/6 inhibitors [19], PI3K/AKT/mTOR inhibitors (Everolimus), and PI3K inhibitor (Alpelisib) [20]. The novel topic in developing a new drug or enhancing efficacy will also focus on the cross-talk between various signal transduction and endocrine receptor pathways, which will be discussed later.

The mechanism of the endocrine resistance in hormone-positive BC

Drug resistance refers to both hormone resistance and multidrug resistance in Hormone-positive BC. The progression to drug resistance is considered a gradual, step-wise process. Several mechanisms have been proposed, but the resistance phenomenon still cannot be entirely explained by only one [21]. Regarding endocrine resistance, tumors with the biological character of hormone resistance formed de novo before therapy is referred to as primary resistance. At the same time, tumors that lost sensitivity to the effects of antiestrogens during endocrine therapy are referred to as secondary resistance [22]. Investigators have proposed several mechanisms such as downregulation of ER; ER gene mutation or epigenetic changes; overexpression of positive cell cycle regulators by activating CDKs; cross-talk between ER and other signaling networks; and change in the tumor microenvironment (TME) [23]. A brief review of these resistance mechanisms will be presented as follows (**Figure 2**).

ER down-regulation and epigenetic change

Lack of ERα expression is recognized as a primary mechanism for de novo endocrine resistance. Phosphorylation of specific serines on ERα is also related to tamoxifen resistance in BC [24]. The presence of active CYP2D6, the enzyme responsible for tamoxifen activation, decreases the response to tamoxifen therapy [25]. Endocrine resistance is also indicated due to DNA methylation and non-coding RNAs [26, 27]. DNA methylation in the promoter region of genes is predictive biomarkers to different modalities of endocrine therapies [28]. In the strategy of miRNA, post-transcriptional regulation of miRNAs, including overexpression of miR-221/222; miRNA-519a, which co-regulates a network of TSGs, have been related to hotmone resistance [29, 30].

Furthermore, downregulation of microRNA-27b-3p strengthens tamoxifen resistance through increasing NR5A2 and CREB1 expression [31]. Therefore, manipulating these miRNA expressions or using inhibitors of such miRNAs may serve as a novel therapeutic approach to combat hormone resistance in BC [32]. Furthermore, the quantitative measurement of circulating cell-free DNA (ccf DNA) from liquid biopsies is also a promising tool in detecting aberrant DNA methylation [33, 34]. Recently, epigenetic modifications, such as DNA methylation, acetylation of histone proteins, and miRNA expression alteration all influence protein synthesis patterns [35].

Other epigenetic change includes silencing Spalt-like transcription factor 2 (SALL2) induced downregulation of ERα and PTEN and activated Akt/mTOR signaling, rendering estrogen-independent growth and tamoxifen resistance ERα-positive BC [36]. Prostaglandin E2 receptor 4 (PTGER4) is essential for estrogen-independent growth, and it contributes resistance to endocrine therapy for BC on activation [37]. The expression of MTA1, relating to cancer progression, is also correlated to poor prognosis. The activation of AMPK and subsequent autophagy contributes to tamoxifen resistance in BC [38]. Some alterations in other pathways and related genes, such as MAPK, EGFR, KRAS, etc. or ER transcriptional regulators (MYC, CTCF, FOXA1, and TBX3) were also lead to endocrine resistance in BC.

Altogether, these data suggest that diverse gene expression, DNA methylation, or miRNA regulation profiles in BC cells correlate with differential adaptation to hormone therapy, and they could be the targets of hormone resistance [26]. We summarize the genomic alternation in Hormone-positive BC in **Table 2**.

Tumors harboring mutations of estrogen receptor 1 (ESR1)

Recently, a mechanism for acquired endocrine resistance noted as mutations in the gene encoding ERα, ESR1, have drawn attention in metastatic BC more than in primary BC [39]. In the BC population, nearly 20% of metastatic tumors evolve ESR1 mutations during hormone therapy [40]; furthermore, ESR1 and TP53 were the most mutually exclusive gene pair in Hormone-positive mBCs [41]. Patients with an ESR1 mutation had decreased progression-free survival (PFS) and worse overall survival (OS) than patients with WT ESR1, and a clear association between ESR1 mutation and AI resistance was noted [42]. The missense mutations have been recognized in more than 50 other residues; most occur within the ER ligand-binding domain (LBD). The most common ESR1 mutations in endocrine resistance were the missense mutations Y537 and D538. Other models demonstrated cell lines transfected with a Y537C, D538G, L536Q, Y537N, S463P, Y537S, or E380Q ESR1 mutation activity in the lack of estrogen [43]. In brief, ESR1 mutation exerts activity in the absence of estrogen, and ESR1 amplification is associated with a poor outcome [39, 44]. However, whether ESR1 gene mutation could be a biomarker is still uncertain since the detection methods are varied. Many centers apply circulating tumor DNA (ctDNA) to detect ESR1 LBD mutations in a non-invasive manner. Some studies indicated that ctDNA might better reflect the total ESR1 mutation burden across multiple metastatic sites since the ESR1 mutant content is usually higher in ctDNA than in match tumor tissue in the same patients with both samples [45]. So far, by utilizing the NGS with genome or exome sequencing, we can detect ESR1 mutations [46, 47]. Recently, ddPCR detection of ESR1 mutation is increasingly being adopted in solid tumors and liquid biopsies for cost-effective and more powerful sensitivity, compared with NGS technology [45]. A clinical, updated study

Table 2. The over-review of genomic alternation in Hormone-positive breast cancer (BC)

Gene	Alteration	Implication and comments	incidence
PIK3CA [95]	Hot spot mutation in exons 9 and 20	PTEN loss and *PIK3CA* mutation were frequently concordant, suggesting different contributions to pathophysiology	30-40%
ESR1 [130]	Mutation in ligand-binding domain	Hot-spot activating missense mutations (E380Q, Y537S/C/N, D538G). Treatment with AIs may exert a selective pressure favoring the expansion of *ESR1*-mutated clones	18-39%
FGFR1 [131]	amplification	1. 11q12-14 chromosome 2. resistance to hormone therapies can be motivated by *FGFR1* amplifications 3. related to a lower PFS correlation between *FGFR1* amplification and resistance to CDK4/6 inhibitors ribociclib or palbociclib	Around 15-23%
CCND1 [82, 132]	amplification	1. 11q13 chromosome BC 2. CCND1 amplification could serve as a biomarker for the prediction of response to cyclin-dependent kinase 4/6 inhibitors	9-30%
ERBB2 [133, 134]	amplification	1.Hot-spot activating missense mutations (e.g. S310F/Y, L755S, V777L); Inframe insertion exon 20 (Ex: Y772_A775dup) 2. HR and ERBB2 cross-talk as a mechanism for resistance to endocrine therapy	In 10% ER+ BC
PTEN [135]	loss or mutation	Homozygous deletions; Loss-of-function mutations: truncated mutations and known inactivating missense mutations (Ex: R130Q/G) acquired *PTEN* mutation is a resistance mechanism to PI3Kα inhibitors in ER+ *PIK3CA* mutant BC	Mutations: 5-10% Loss: 30%
MDM2 [136]	amplification	Most frequently co-occurred with *MDM2* amplification were *CDK4* amplification, *CDKN2A/B* loss, and *MYC* amplification	5.7%
AKT1 [137, 138]	E17K mutation	1. E17K mutation activates AKT1 by recruiting it to the membrane through a PI3K-independent mechanism 2. E17K-AKT1, PIK3CA, and PTEN mutations are usually mutually exclusive	In 3% of ER+ BC
BRCA1/BRCA2 [139]	mutation	Truncated mutations: insertions or deletions, splice-site, nonsense (except known truncating polymorphic variant)	3%
RB1 [140]	Loss of function mutations/ deletions	RB-pathway dysregulation is strongly correlated with poor response to tamoxifen therapy	20%
EGFR [141]	Amplifications	Aberrant EGFR expression was associated with poor prognosis in ER+ BCs, especially the Luminal B subtype	10% of ER+ BCs
ERBB2 [142]	Mutations or amplification	1. Hot-spot activating missense mutations (e.g. S310F/Y, L755S, V777L) 2. A potential signaling cross-talk between EGFR or IGF1R and ERBB2, which could influence response of *ERBB2*-positive BCs to inhibitors	20%

noted that BC with ESR1 mutations was more sensitive and better response to fulvestrant-containing regimen [48].

Cross talk between ER and other signaling networks

BC is as intelligent as developing new pathways to obtain resistance to new agents. Concerning Hormone-positive BC, we learned that a complicated biological network formed the ER signaling pathway. Different intracellular signaling pathway activation in preclinical models results in endocrine resistance, and targeting specific pathways will be a potential solution to prevent resistance [49]. In detail, the hormone resistance encompasses several regulators and "cross-talk" between ER and membrane receptor tyrosine kinases such as epidermal growth factor receptor (EGFR), epidermal growth factor receptor 2 (human HER2), and insulin-like growth factor 1 receptor (IGFR) or fibroblast growth factor receptor (FGFR), mitogen-activated protein kinase (MAPK) and famous mTOR (mechanistic target of rapamycin) pathway. Activation of these alternative signaling pathways that promote cell proliferation will induce tamoxifen resistance. Recent studies revealed that breast malignancies harboring FGFR1 amplification display resistance to endocrine treatment, and TORC1 inhibitors play a therapeutic role in treating ER+/FGFR1+ mBC [50].

According to a previous study, estrogen could activate the growth stimulatory properties of the IGF pathway via ER's genomic and non-genomic functions [51]. The role of the IGF system in endocrine-resistant BC has also been investigated. So far, the only study to report results that involved monoclonal antibodies against IGFR-1 is ganitumab, which regulates the PI3K/Akt and MAPK Pathways [52]. Cross-talk exists between IGF1R and the ERBB family, activating downstream signaling pathways such as PI3K/AKT [53]. Endocrine-resistant metastatic BC could acquire mutations in ER and MAPK pathways, including activating ERBB2 (which encodes HER2) [41, 54].

A recent study showed RBP2 (retinoblastoma-binding protein 2) could be a critical target molecule for tamoxifen-resistant ER+ BC since it enforces the cross-talk between IGF1R and ErbB receptors through promoting the stability of EGFR and HER2 protein, and activating the PI3K/AKT pathway and thereby leads to tamoxifen resistance [55].

Regarding HER pathways, the bidirectional cross-talk between the ER and HER pathways results in resistance to the endocrine therapy and anti-HER2 treatments [56]. It has been revealed that HER signaling members can reduce ER expression both at the mRNA and protein levels. The bidirectional ER/HER cross-talk can influence these pathways at their expression or activity [57].

The PI3K/AKT/mTOR/signaling pathway is a critical driver in many tumors. Aberrations in this intracellular pathway also related to hormone therapy resistance [58]. Based on the previous study, patients with HR+/HER2- BC and PIK3CA mutation have worse overall survival and were less sensitive to chemotherapy due to the HR+/HER2- BC with enrichment of *PIK3CA* mutations usually lost HR expression in the metastatic setting [59]. However, longer PFS was founded in patients with the PIK3CA/H1047R mutation than patients with wild-type or other mutant forms of PIK3CA. The PIK3CA/H1047R mutation might be a potential predictor of sensitivity to everolimus [60, 61]. ER levels increase by blocking the PI3K pathway *in vitro*, and PI3K inhibitor is promising in overcoming the hormone resistance.

It is well-known that treatment strategies targeting only sure of the pathways usually lead to the up-regulation of others and ultimately contribute to treatment resistance. Hence, combining different targeted agents with a broader blockade of multiple direction pathways may be more effective in reversing resistance development.

Aberrance of cell cycle regulators

The cell cycle's deregulation is a character of cancer that leads to limitless cell division. In Hormone-positive BC, by binding to the ER, estrogen drives cell cycle progression, generating its dimerization and translocation to the nucleus and induces the transcriptional activity at estrogen response elements (EREs) [62]. C-myc gene regulation explains more than half of estrogen-regulated genes and comprised more than 80% of the cell growth signature.

Overexpression of MYC has been revealed to contribute resistance to tamoxifen in vitro;

more deeply, the siRNA-mediated MYC down-regulation impairs estrogen-induced growth [63]. The expression of MYC is up-regulated through the cross-talk between ER and HER2 in AI-resistant BC cells. The mechanism is probably due to the glutamine transporter solute carrier (SLC) family 1A5 was significantly up-regulated in AI-resistant BC cells [64].

On the other hand, the aberrant expression of cell-cycle regulators (cyclin A, cyclin D1, cyclin E, RB1, p21, and p27) will lead to chromosomal instability; thus, overexpression of cyclin D1 was significantly correlated with increased chromosomal instability [65], and dysregulation of the cyclin D1/CDK4/6 pathway is confirmed as a crucial hallmark for breast tumorigenesis [66].

Many studies noted that CCNE1/RB1 ratio could be served as a potential biomarker of cdk4/6 inhibitor such as palbociclib resistance, which has been discussed in the above section [67]. The cell division cycle associated 8 genes (CDCA8) in humans are presented as a putative oncogene reported to be up-regulated in many cancers. Research also noted that overexpression of CDCA8 would promote the growth of tamoxifen-sensitive BC cells and induce tamoxifen resistance [68].

Resistance from Cancer stem cell and tumor microenvironment (TME)

Cancer stem cells (CSCs) play an essential role in cancer evolution and treatment resistance. In BC, hormone therapy contributes to maintain cells harboring elevations in ER signaling, growth factor receptor (GFR)-PI3K-AKT-mTOR, NOTCH, or other pathways GFR-PI3K-AKT-mTOR pathway inhibits the ER and NOTCH signaling. Further, these pathways render the tumors progression with endocrine therapy resistance [69].

The NOTCH signaling pathway is critical in hormone resistance by promoting breast cancer stem cells (BCSCs) [70]. Upregulation of NOTCH4 confers resistance to tamoxifen and contributes to the stemness of tamoxifen-resistant MCF7 cells [71]. Two models have been proposed by Dr. David et al., and one is endocrine therapy inducing the existed BCSCs to produce resistant BCs containing a proportion of BCSCs; the other is via the dedifferentiation of BCs will produce tumors resistant to endocrine therapy and leading to the acquisition of BCSCs [69].

In addition, many researchers have shown that the TME is critical in determining tumor sensitivity or resistance to target therapies [72]. Antiestrogens can induce immunosuppression through a TGFβ-dependent mechanism in the TME, contributing to the development of antiestrogen resistance in BC [73]. A study screened a group of micro-environmental proteins that revealed fibroblast growth factor 2 (FGF2) is a potent mediator of resistance to anti-estrogens [74]. Moreover, exogenous and endogenous FGF2 promotes FGFR-MEK-ERK signaling to drive cell cycle progression and survival in ER+ BC, rendering FGF2 a potential therapeutic target in ER+ BC- microenvironment [74]. In the BC microenvironment, infiltrating immune cells produce growth factors, cytokines, and chemokines that contribute to angiogenesis and remodel the extracellular matrix (ECM); cytokines such as TNF, IL1β, IL6 have been correlated to suppression of ERα in BCs; and increased IL6 serum levels also lead to hormone therapy resistance [75]. On the other hand, an ECM gene cluster has been connected to endocrine resistance [76, 77]. Fibronectin, lysyl oxidase, SPARC, and TIMP3 expression levels were related to the prognosis in BC, while levels of tenascin C are associated with tamoxifen resistance [78].

To sum up, the noncancerous components of the TME, both noncellular components such as ECM, cytokines, and oxygenation, and cellular components such as fibroblasts, endothelial cells, immune cells, and adipocytes play an essential role in modulating treatment response. Further research should focus on TME and CSC in improving drug resistance or new drug development.

Recent development in hormone inhibitors (cdk4/6) and relevant signaling pathways to overcome endocrine resistance

The cyclinD1/cyclin-dependent kinase 4/6 cell cycle pathways, and PI3K/AKT/mTOR cell signaling pathway, are two major pathways that have recently been extensively investigated for therapeutic intervention in endocrine-resistant breast tumors [79].

CDK4/6 cell cycle pathway

In metastatic BC, the mechanism behind the observed efficacy of CDK inhibition is related to a dependence of HR+ BC on CDK4/6 activity to override Rb mediated repression of cell cycle progression [80]. The D-type cyclins form complexes with cyclin-dependent kinases (CDK4/6), which then hypophosphorylated the retinoblastoma protein (Rb) in phase G1. Once hypophosphorylated, Rb is primed for hyperphosphorylation by cyclin E-CDK2 complexes, leading to the E2F transcription factors releasing which is vital for entering the S phase. Other CDK-cyclin pairs operate during late phases of the cell cycle [81]. From a molecular aspect, RB transcriptional control is a crucial node in controlling the therapeutic response to ER antagonists; therefore, compromised RB-mediated transcriptional control, presumably as a result of cyclin D1 deregulation, might be an essential feature of ER-positive BC biology [80].

Recent trials showed that cdk4/6 inhibitors, plus fulvestrant, significantly improved PFS compared with fulvestrant in the context of advanced HR+/HER2- BC [82-84]. Despite this combination's benefit, nearly 80% of patients develop resistance after using cdk4/6 inhibitor for 12 to 36 months [84]. Some research has explored the development of acquired resistance after exposure of HR+ BC cell lines to CDK4/6 inhibition in vitro. CCNE1 overexpression and loss of RB1 expression occurred in HR+ BC cells cultured to resistance in the prolonged presence of palbociclib as well as in ribociclib [85]. Another study indicated that the CCNE1/RB1 ratio could be a potential biomarker in HR+ BC and to be able to differentiate palbociclib-sensitive versus resistant populations [67]. Some revealed that PI3K inhibitors might prevent resistance to CDK4/6 inhibitors, yet they failed to resensitize cells once resistance had been acquired. Nevertheless, cells resistant to CDK4/6 inhibitors due to CCNE1 amplification can probably be resensitized by targeting CDK2 [85]. Furthermore, loss of RB1 and FAT1 tumor suppressor could serve as another resistance mechanism to CDK4/6i through Hippo signaling in ER+ BC [86].

PI3K/AKT/mTOR cell signaling pathway

Alterations in the PI3K signaling pathway are critical in tumor initiation and survival, angiogenesis, and the development of resistance to cancer therapies [87]. AKT is a crucial downstream target of the PI3K signaling pathway, regulating the cell survival, proliferation, growth, apoptosis, and glycogen metabolism, while mTOR is a downstream effector AKT [88]. Endocrine therapy has significantly worse efficacy in the AKT-positive than in the AKT-negative patients. AKT activation induces endocrine resistance irrespective of the endocrine agents that were given for metastatic BC [58]. The irregular activation of the PI3K/AKT/mTOR pathway, such as the amplification or mutations of PI3K subunits and PI3K modulators, was noted in more than half of HR-positive metastatic BC [89]. Prominent alterations in the PI3K pathway included mutations [e.g. PIK3CA (E542K), AKT1 (E17K)], amplifications (MDM2), frameshifts [TSC2 (R1753fs*58+)] and loss [PTEN]. The highest number of alterations was observed in the CCND1 gene, followed by alterations in the RB1 gene [90]. The mTOR1 inhibitors, including sirolimus and its analogs (temsirolimus, everolimus, and deforolimus), are irreversible allosteric inhibitors of mTOR1 kinase [91]. Everolimus, which targets mTOR1, is approved for the treatment of HR+/HER2-BC [92]; and even after or on previous AI treatment, the everolimus-exemestane combination remains effective and well-tolerated regardless of PIK3CA mutational status [93].

Furthermore, in patients who have resistance to mTOR inhibitors after treating with endocrine therapy and mTOR inhibitors, PI3K inhibitors such as Buparlisib plus endocrine therapy (Fulvestrant) might still be efficient in BELLE 3 trial [94]. Another PI3K inhibitor, alpelisib, combined with fulvestrant, also benefits in prolonging progression-free survival in PIK3CA-mutated, HR+ HER2-advanced BC who had received hormone therapy previously [95].

Moreover, regarding the aromatase inhibitors acquired resistance, the study also noted that inhibiting autophagy or PI3K pathway could probably revert exemestane resistance through disruption of the cell cycle, apoptosis promotion, and inhibiting cell survival pathways [96].

However, some cancer cells eventually evolve resistance to PI3K inhibitors, and preclinical studies demonstrated that PI3Ki insensitiveness is evident by persistent RB phosphorylation and can be effectively suppressed by com-

bining a CDK inhibitor with a PI3Ki due to the synergetic effect in depressing the growth and proliferation of BC cells in vitro [90, 97].

Find the predictive biomarker and response gene in hormone-positive BC

Recently, the most popular genomic test is the Oncotype DX. It can survey the expression of 21 genes by RT-PCR. The current consensus is that it is a marker of good prognosis in Hormone-positive tumors (ER and PR) and a worse prognosis marker in triple-negative BC. However, the study also revealed that the absence of PR expression in the lymph node metastases of ER-positive, HER2-negative BC is correlated with relapse on tamoxifen [98].

In the strategy of Hormone-positive cancer, the ER signaling pathway, from PI3K/AKT/MTOR pathway, CDK4/6-RB pathway to p53/MDM2 pathways are all complicated with much network crosstalk.

Each of these pathways may lead biomarkers to confer sensitivity or resistance to endocrine therapy [13].

For example, the PALOMA-3 clinical trial investigates the intrinsic resistance of the combining use of palbociclib and fulvestrant and noted that CCNE1 mRNA levels associated with the degree of benefit; patients with low levels of CCNE1 had marked improvement with the addition of palbociclib, referring that CCNE1 could be a potential biomarker [99]. Another study in 2018 noted that PIK3CA mutation, with high levels of ERα phospho-Ser167 and low levels of AKT phospho-Ser473, are positive prognostic indicators in ER+ BC [100].

As has been mentioned, the ESR1 mutations can be prognostic and predictive biomarkers for ESR1 amplification, which is associated with a poor outcome [101]. The development of targeted therapy directed to ESR1-mutated clones is an appealing idea.

On the other hand, MYC, a transcription factor, plays an important signaling hub in multiple cellular processes that sustains growth [102]. A previous study indicated that an activated MYC and high MYC protein levels predict a shorter time to recurrence following adjuvant tamoxifen, rendering MYC a therapeutic target in endocrine-resistant BCs. [63]. Further, HSPC111 as estrogen and c-Myc target gene, overexpressed in BC, refers to poor outcome [103]. So far, only cdk4/6 inhibitors and mTOR inhibitors have been found with corresponding drug development; most of the studies remain in a preclinical state. Furthermore, since some miRNAs can be detectable in blood and their dysregulations are associated with the development or progression of the disease; such as, the suppression of miR-221 and miR-222 could increase the sensitivity of estrogen receptor-positive MCF-7 BC cells to tamoxifen [104]; thus, miRNA can be utilized as a non-invasive biomarker [105].

Whether there are other biomarkers or response genes over the related pathway is worth investigating.

Immunotherapy in HR+ BC

Nowadays, we are in the era of personalized medicine where the crosstalk between genomics and immunology contributes to successful cancer treatment. Some solid tumors that harbor TILs and express PD-L1 are tended to respond to programmed cell death-1 (PD-1)/PD-L1 blockade [106], which could also cause BCs.

Consequently, the evaluation of tumor-infiltrating lymphocytes becomes increasingly relevant with the emerging role of immunotherapy in BC, and it has been noted that the TILs are correlated with higher PD-1 and PD-L1 expression in BC [107]. Nevertheless, it may be intrinsically less immunogenic in luminal ER-positive/HER2 negative BC as they arise from a less antigenic cell of origin.

Lower levels of stromal tumor-infiltrating lymphocytes (sTIL) and PD-L1 refer to inadequate responses to checkpoint inhibitor therapy [108], which contrast to the triple-negative and HER2+ BC with high immunogenicity and high proliferation index [109]. Moreover, determination and standardization of PD-L1 expression has not been reported, leading to no standardization of assays, percentage cutoff for establishing positivity, or scoring methodology. Therefore, a unified PD-L1 expression measurement might need to be established in future studies [110]. An early clinical trial indicated that in previously treated, PD-L1-positive, ER+/

HER2-advanced BC, pembrolizumab has been noted with well-tolerated and results in durable overall responses in certain patients [111].

Another checkpoint inhibitor targeting CTLA4 (cytotoxic T-lymphocyte antigen 4), which is noted on Treg cells, could promote suppressive Treg activity. CTLA-4 downstream signaling may inhibit T cell activation directly; some studies of CTLA-4 blockade have been conducted with ipilimumab or tremelimumab in diverse cancer types, including BC [110].

The new aspects of the progress on endocrine-resistant HR-positive BC

Regarding the progress on endocrine-resistant HR+ BC, on the one hand, in molecular respect, TME has been a hot spot for treatment target as the cellular crosstalk and cell-to-ECM communication are active in TME. These interactions induce soluble factors and contribute to immune evasion and ECM remodeling, which lead to therapy resistance [112]. The updated study indicates that the characteristics of the TME and its effects on treatment resistance, including the sum of interaction between carcinoma-associated fibroblasts (CAFs), adipocytes, immune cells, endothelial cells, pericytes, the ECM, and soluble factors, all contribute to tumor evolution [113]. Hypoxia or metabolic disarrangements such as lactate, lipid, or reactive oxygen species (ROS) metabolic aberrance are linked to drug or endocrine resistance [114]. The ECM might have a central role in establishing mechanical cues and directly regulate the impact of hormone action in BC cells. In ECM, fibronectin (FN) is associated with disease progression in BC. Culturing ERα human BC cells on FN leads to endocrine resistance through binding to b1 integrin [79, 115]. TME is indeed a promising area in evaluating how cancer evolves and how to overcome the treatment resistance.

On the other hand, in clinical respect, in hormone-resistant HR+ BC, apart from fulvestrant (selective ER down regulator) combined with CDK4/6 inhibitor or mTOR inhibitor, patients with PIK3CA mutation could consider alpelisib, which can prolong progression-free survival [93, 95]. Furthermore, in a population with germline wildtype BRCA genes and an actionable somatic BRCA mutation, olaparib can be considered as later-line therapy for ER+, HER2-mBC, for which PARPi could provide substantial clinical benefits [116]. At the same time, talazoparib is suggested for BRCA2 nutation in EMBRACA trial [117]. Lastly, nearly 30% of endocrine-resistant BC is still dependent on ERα signaling; the need for the next generation of ERα antagonists to overcome aberrant ERα activity is critical [118]. A recent study indicates that H3B-5942, a novel ERα antagonist, exhibits enhanced potency due to its ability to target a unique cysteine in ER [119] covalently. Besides, next-generation oral selective estrogen receptor modulators (SERMs) or selective estrogen receptor down regulators (SERDs) that target both wild-type and mutant ER are clinically developed [120]. For instance, elacestrant and SAR439859, oral SERD, have been proved with preliminary clinical activity in ESR1-mutant MBCs with tolerable toxicity profiles [121, 122], yet most of these new drugs are pending further data of phase II or III trials [123].

Discussion: the prospect and implication for overcome endocrine resistance in HR-positive BC

This article reviewed endocrine-resistant BC from a molecular to clinical perspective, examining the mechanism, recent new drug development, and crosstalk between relevant pathways. The prospect for overcome endocrine resistance should focus not only on advanced technology to identify some mutation and biomarker but also more attention in changes in the TME after multiple lines of treatment.

Firstly, a methodology such as next-generation sequencing (NGS) is also a critical issue. In past years, the methodologies have evolved from tissue to plasma, followed by digital droplet PCR (ddPCR), and eventually entered an NGS era [124]. Advanced NGS platforms and modified ddPCR will facilitate treatment decisions efficiently and benefit patients [125]. Other new methods include Nanopore technology and BEAMing. The Nanopore technology is independent of amplification steps involving with fluorescence labeling and DNA polymerase even with high sequencing error rate [126]; the BEAMing is a modified digital PCR using beads, emulsion, amplification, and magnetics which has been applied in a large-scale clinical trial such as PALOMA-3 [127, 128].

So far, what we concerned about is how to accurately translate NGS into the clinical setting since the interpretation of cell sequencing data is complicated by various amplification biases introduced in the cell's DNA or RNA sample; therefore, combined artificial intelligence to make NGS a more powerful tool could be a direction [129]. Second, the change in TME in therapy-resistant HR+ BC has sparked researcher's attention; as TME is also in a dynamic change which contributes to drug resistance, a further understanding of the interaction between various components of the TME may stimulate the development of new therapies. Therefore, future study needs to focus more on net-talk or cytokine change in TME.

Last but not least, though immunotherapy role applied in hormone-positive BC is not as critical as in triple-negative and HER2 positive cancer, there are heterogeneous genes and phenotypes in hormone-positive BC. Accordingly, further investigation to merge immunotherapy and conventional therapy (chemotherapy, radiotherapy, hormone therapy) according to more detailed gene expression or correspondent TME change is worthwhile.

In summary, BC is a molecularly complicated disease. The more we understand the diversity of molecule and epigenetic character about BC, the more precise decision we can make in treating the disease.

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Disclosure of conflict of interest

None.

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