Endocrine-Resistant Breast Cancer: Underlying Mechanisms and Strategies for Overcoming Resistance

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Estrogen plays important roles in the development and progression of breast cancer. However, one-third of breast cancers fail to respond to endocrine therapy and most endocrine-responsive breast cancers subsequently become resistant to endocrine therapy. A tremendous effort has been made to elucidate the mechanisms responsible for the development of endocrine-resistance in breast cancer. Since the main target molecule of estrogen in breast cancer is estrogen receptor (ER)-\(\alpha\), most studies have focused on investigating quantitative and qualitative changes in ER-\(\alpha\) in endocrine-resistant breast cancer. Breast cancers expressing no ER-\(\alpha\) fail to respond to endocrine therapy. Some breast cancers expressing ER-\(\alpha\) also fail to respond to endocrine therapy and most breast cancers with acquired endocrine resistance retain ER-\(\alpha\) expression, which suggests that the disappearance of ER-\(\alpha\) in breast cancer cells is not a common cause of resistance to endocrine therapy. Recent molecular biological studies have shown evidence that qualitative and functional changes, such as gene mutations and phosphorylation of ER-\(\alpha\), cause endocrine resistance in breast cancer. In addition, it has been suggested that endocrine resistance could be induced by epigenetic changes, such as hypoxia, in breast cancer tissues. Understanding the precise mechanisms that underlie endocrine resistance may enable clinicians to develop new strategies for retarding or overcoming endocrine resistance in breast cancer.


Key words: Endocrine resistance, Breast cancer, Growth factor, Signaling pathway, Hypoxia

Accumulated knowledge provided from the results of clinical studies has suggested that endocrine therapy is useful for chemoprevention and treatment for patients with clinical breast cancer in either adjuvant or metastatic settings. However, the clinical benefit provided by endocrine therapy is not available to patients with estrogen receptor (ER)-negative and progesterone receptor (PgR)-negative breast cancer. In addition, one-third of ER-positive recurrent breast cancer cases fail to respond to endocrine therapy. Furthermore, even if recurrent breast tumors respond to first- and/or second-line endocrine therapies, they frequently develop resistance to these therapies after varying durations of response. Most endocrine-responsive breast tumors ultimately become endocrine-resistant.

Breast cancer with acquired resistance to first-line endocrine therapies, such as the antiestrogen tamoxifen frequently responds to second-line endocrine therapies, such as aromatase inhibitors or progestins. In addition, third-line endocrine therapy sometimes provides clinical benefit to patients that suffer from endocrine-refractory breast cancer. These findings support the clinical strategy of treating ER- and/or PgR-positive breast cancer with as many endocrine therapies as possible, and subsequently applying cytotoxic chemotherapy. These findings also suggest that there are several steps or complicated mechanisms causing endocrine resistance.

It should be noted that endocrine resistance is a term sometimes used to designate resistance to a certain endocrine therapeutic agent, such as tamoxifen. Tamoxifen resistance is a common problem in clinics and the underlying mecha-
nisms have been extensively investigated for the last two decades. Endocrine resistance in breast cancer was divided into four categories by possible mechanisms in the present review as follows: 1) specific resistance to antiestrogens, 2) ligand-independent ER activation, 3) modified ER-interacting proteins, and 4) loss of ER expression. In addition, possible clinical approaches to retard or overcome endocrine resistance are discussed.

**Possible Mechanisms of Action Underlying Endocrine Resistance (Table 1)**

1) **Specific Resistance to Antiestrogens**

Tamoxifen has been used as a chemoprevention agent (unfortunately, not in Japan) as well as a therapeutic agent for patients with breast cancer in the preoperative, postoperative and metastatic settings. Other antiestrogens, such as toremifene, have also been used as alternatives to tamoxifen. Therefore, antiestrogen resistance is very common in clinics. In addition, tamoxifen-withdrawal response and tamoxifen-stimulated tumor growth have been observed in clinics and experimental studies. Tamoxifen might be deleterious in some antiestrogen-resistant tumors. Several hypothetical mechanisms responsible for antiestrogen resistance have been advocated.

1) Modified tamoxifen metabolism is suspected to cause tamoxifen resistance. Approximately one decade ago, tamoxifen metabolites, a less potent antiestrogenic cis-isomer of 4-hydroxytamoxifen and an estrogenic metabolite, metabolite E, were detected in both animal models and tamoxifen-resistant breast tumors. However, the causal relation between the increased levels of these metabolites and tamoxifen resistance remains to be clarified.

2) Tamoxifen has been known to stimulate ovarian estrogen production and an elevated level of serum estrogen may interfere with the antiestrogenic activity of tamoxifen. Actually, combined tamoxifen and luteinizing hormone-releasing hormone (LH-RH) agonists has been suggested to be superior to either agent alone in clinics.

3) Enhancement of estrogenic activity of antiestrogens by a certain mutational change in the ER-α gene or the prominent activating protein (AP)-1-mediated transactivation might induce antiestrogen resistance as well as antiestrogen-stimulated growth. However, no common mutation in the ER-α gene has been detected in antiestrogen-resistant breast tumors. A series of experimental and clinical results suggests a positive correlation between up-regulation of AP-1 activity and acquired tamoxifen resistance. It has been suggested that cellular oxidative stress induced by tamoxifen might activate signaling pathways leading to the activation of AP-1.

2) **Ligand-Independent ER Activation**

It has been classically presumed that transactivation of target genes by ER requires a ligand, such as estrogen, binding to ER. Recently, experimental studies have revealed that several growth factors and their intracellular signaling pathways can stimulate ER activity in the absence of a ligand. In addition, it has been suggested that this ligand-independent ER activation is caused by the phosphorylation of different sites in the ER protein. These mechanisms may explain the development of endocrine-resistant breast cancer.

1) Overexpression of HER1 (also known as epidermal growth factor receptor, EGF-R) and/or HER2 (also known as ErbB-2) has been detected in 20-30% of primary breast cancers. Experimental and clinical studies have suggested that overexpression of HER1 and/or HER2 causes tamoxifen-resistance. Recent fundamental studies also revealed that the intracellular signaling pathway activated by HER1 or HER2, RAS/RAF/MEK/ERK1/2, phosphorylates the serine 118 residue located in ER and results in ligand-independent transactivation of target genes of ER. It was also reported that increased ERK1/2 activity correlates with endocrine resistance and shorter survival in patients with breast cancer. Moreover, experimental studies have suggested that the