

Targeting Aromatase and Estrogen Signaling for Breast Cancer

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Although there are significant advancements in human health prevention and treatment, breast cancer is still the most frequently diagnosed form of cancer and is the second leading cause of death for women [1], particularly in western countries. About 75% of breast cancers are positive for the estrogen receptor (ER) and/or progesterone receptor (PR) [2,3]. Estrogen, which acts through the estrogen receptor alpha (ER α), is the major stimulus in both pre- and postmenopausal patients who exhibit hormone-dependent breast cancer [3,4].

Generally speaking, estrogen is synthesized from cholesterol in a multiple-step biosynthetic process [5,6]. This process is regulated by aromatase, a key enzyme involved in aromatization of C19 androgen precursors such as androstenedione and testosterone into estrogens [7,8]. As shown in Figure 1, aromatase first converts the androgenic substrates androstenedione and testosterone to estrogens: estrone and estradiol (E $_2$), respectively. and then these produced fat-soluble estrogens diffuse through the plasma membrane and bind to the ER α ; hence, leading to the dissociation of heat shock proteins and dimerization of the receptor [3]. This conformation change allows ER α to be phosphorylated at several serine residues within its N-terminal domain. The receptor dimer then translocates to the nucleus and binds to the estrogen response element (ERE) located upstream of the proximal TATA box. ER α then recruits coactivators such as steroid receptor coactivator-1 (SRC-1), amplified in breast cancer-1 (AIB-1), and cAMP response element bind (CREB) protein (CBP). This allows activation of estrogen-responsive genes such as progesterone receptor (PgR), pS2, cyclin D1 and *c-myc*. These events lead to cell cycle entry and progression [3,9]. Therefore, deprivation of estrogenic signaling pathways has been the main and key therapeutic form of hormonal therapy for patients with ER-positive and/or PR-positive disease [10].

There are three main approaches to the deprivation of estrogenic

signaling pathway. One approach is to affect the supply of estrogen to the breast tumor by surgical procedures such as oophorectomy, adrenalectomy, and even hypophysectomy. Oophorectomy was first suggested by George Beatson for the treatment of metastatic breast cancer more than 100 years ago [11]. These surgical procedures have demonstrated efficacy and survival benefit for women with advanced breast cancer by reducing systemic estrogens. However, because these procedures are irreversible and are associated with potential morbidity and mortality, pharmacological means of estrogen inhibition remains as the primary method of treatment [8].

The second approach is to counteract the effects of estrogen by blocking the estrogen activity at the receptor level. This is typically performed by targeting ER using the selective estrogen receptor modulators (SERMs) [12]. The first pioneer of the SERM drugs is tamoxifen, which has been used to block the binding of estrogen to its receptor by the competitive inhibition of the ER [13]. For the past three decades, tamoxifen has been the standard for prevention and for adjuvant and first line metastatic therapy in women with hormone-responsive breast cancer [8].

The third approach is to inhibit the production of estrogen. Due to key role of aromatase in the biosynthesis of estrogens from the androgen precursors (Figure 1), aromatase inhibitors and inactivators may represent interesting options in this setting in spite of the fact that SERMs are currently being approved for breast cancer prevention in several countries [7,14]. There is an increasing interest on inhibiting aromatase enzyme expression or activity to reduce the estrogen production to achieve an endocrine response in ER-positive breast cancer.

Both experimental and clinical data show that aromatase inhibitors, in ER-positive breast cancer, achieve greater response compared with the non-steroidal ER antagonist tamoxifen. This difference might be related to the partial agonist effects of tamoxifen, which limits its clinical effectiveness. Clinical trials have confirmed that aromatase inhibitors are more effective and better tolerated than tamoxifen in postmenopausal women with early or advanced ER-positive breast cancer [15-17]. Hence, aromatase inhibitors are set to replace tamoxifen as the standard of care for these patients [7].

Throughout the years, a large numbers of aromatase inhibitors have been developed and have been available for clinical and preclinical therapy, specifically for ER-positive breast cancer patients. Currently,

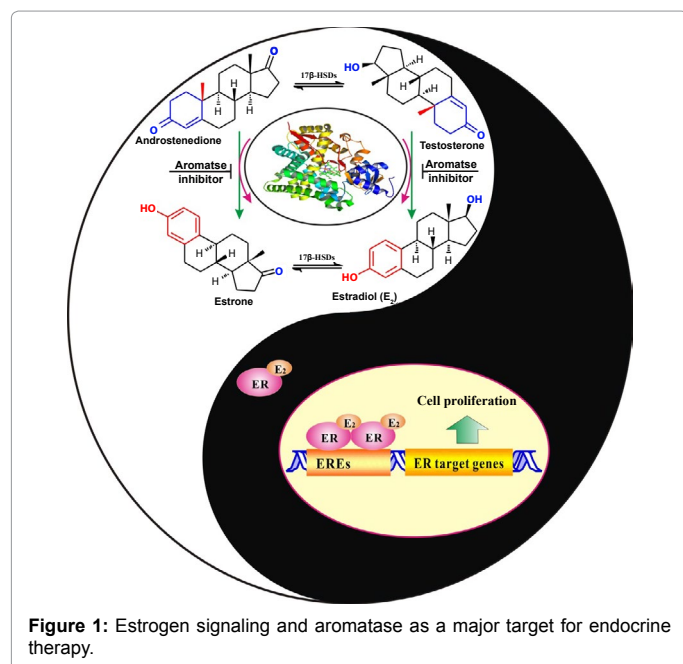


Figure 1: Estrogen signaling and aromatase as a major target for endocrine therapy.

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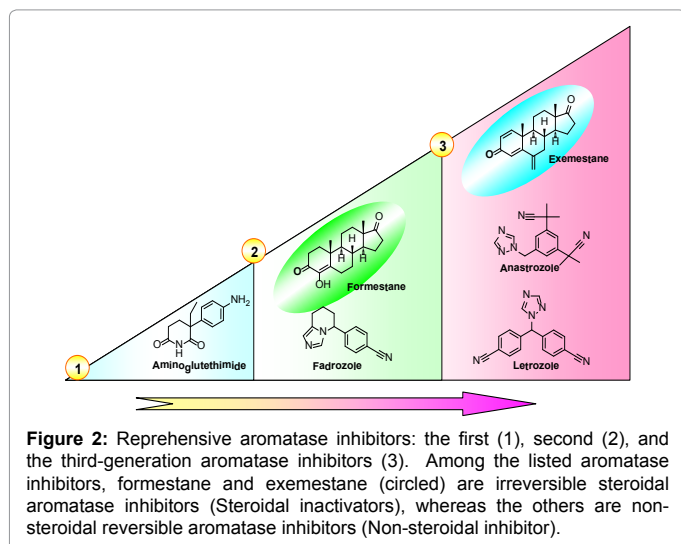
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in the United States, there are three-generation aromatase inhibitors including type I steroidal aromatase inactivators and type II non-steroidal inhibitors, which have been approved by the FDA for the treatment of ER-positive breast cancer [7,8,18,19] (Figure 2). Aminoglutethimide, a first-generation aromatase inhibitor, was first introduced in the 1970s for the second-line treatment of advanced breast cancer; however, its use was limited due to its toxicity and its lack of selectivity towards the aromatase enzyme. The second- (formestane and fadrozole) and third-generation (exemestane, anastrozole, letrozole) aromatase inhibitors have a lower overall toxicity and higher degree of selectivity towards the aromatase enzyme. Unlike the first- and second-generation aromatase inhibitors, the third-generation inhibitors have a greater oral bioavailability and are available as one dose per day [8,18].

Recently, a phase III trial showed that exemestane reduced the risk of developing breast cancer in high-risk, postmenopausal women [20]. This is the first evidence that an aromatase inhibitor reduces the risk of a breast cancer, and it leads to exemestane becoming an option for high-risk, postmenopausal women [21]. In addition, exemestane exhibits weak agonistic activity towards ER α ; thus, this eliminates some side effects associated with aromatase inhibition such as the loss in bone mineral density (BMD) and increase in bone fracture rates [22].

Besides the developed synthetic aromatase inhibitors [18,19], natural aromatase inhibitors is an attracting option for many people and also researchers alike [23,24]. Currently, many natural products have been found to possess aromatase inhibitory activity. Typically, flavonoid compounds such as flavones, flavanols, flavanones, flavonols and isoflavones exhibit a steroidal structure and they are the most common natural aromatase inhibitors [23,24]. Other natural aromatase inhibitors include: coumarins, lignans, stilbenoid, anthraquinones, diterpenoids, steroids, triterpenoids, alkaloids and peptides [23,24].

Despite these synthetic and natural aromatase inhibitors improved preclinical and clinical outcome, in both the adjuvant and metastatic setting for postmenopausal women with breast cancer [8], their inefficient systemic delivery, poor solubility and bioavailability have severely limited their use. In addition, these drug candidates undergo fast oxidation under basic conditions and first pass metabolism before reaching to systemic circulation. Thus, novel strategies are needed to enhance the bioavailability and reduced perceive toxicity associated with the long-term use [25].



In the last few decades, nanotechnology had an enormous impact on medical technology, significantly improving the performance of drugs in terms of efficacy, safety and patient compliance. Nanotechnology manifests wide range of materials which can be smartly designed with chemically modifiable surfaces to tag variety of chemical, molecular and biological entities. Modulation of surface properties offers advantageous properties like increased solubility and biocompatibility. Nanoscale materials and devices with unique therapeutic properties can be engineered to deeply infiltrate tumors with a high level of specificity [26]. Drug-loaded polymer nanoparticles or micelles are promising drug delivery systems for the treatment of severe diseases including cancer. Attaching polymers such as polyethyleneglycol (PEG), polyvinylpyrrolidone and polyvinylalcohol increase the solubility and provide protection to the degradation of proteins during in vivo applications. Encapsulation in nanoparticles allows the drug to be protected from destabilization and/or rapid clearance from the body, while protecting healthy tissues from the drug's inherent cytotoxicity. Another strategies, derived from the prodrug concept, also wide use to alleviate some of drawbacks witnessed with polymeric nanoparticulate systems. Drugs have been covalently linked to preformed amphiphilic copolymers, leading to a sustained anticancer drug release from the nanoparticles by hydrolysis [27].

For instance, PLGA nanoparticles in enhancing the tumor uptake of letrozole [28], hyaluronic acid-bound letrozole nanoparticles restore sensitivity to letrozole-resistant xenograft tumors in mice [29]. Targeted delivery [30] and combination therapy [31] can drastically improve the intracellular retention and transcytosis of drugs across the epithelial and endothelial barriers.

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