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Endocrine resistance in breast cancer – An overview and update

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ABSTRACT

Tumors that express detectable levels of the product of the ESR1 gene (estrogen receptor-α; ERα) represent the single largest molecular subtype of breast cancer. More women eventually die from ERα+ breast cancer than from either HER2+ disease (almost half of which also express ERα) and/or from triple negative breast cancer (ERα-negative, progesterone receptor-negative, and HER2-negative). Antiestrogens and aromatase inhibitors are largely indistinguishable from each other in their abilities to improve overall survival and almost 50% of ERα+ breast cancers will eventually fail one or more of these endocrine interventions. The precise reasons why these therapies fail in ERα+ breast cancer remain largely unknown. Pharmacogenetic explanations for Tamoxifen resistance are controversial. The role of ERα mutations in endocrine resistance remains unclear. Targeting the growth factors and oncogenes most strongly correlated with endocrine resistance has proven mostly disappointing in their abilities to improve overall survival substantially, particularly in the metastatic setting. Nonetheless, there are new concepts in endocrine resistance that integrate molecular signaling, cellular metabolism, and stress responses including endoplasmic reticulum stress and the unfolded protein response (UPR) that provide novel insights and suggest innovative therapeutic targets. Encouraging evidence that drug combinations with CDK4/CDK6 inhibitors can extend recurrence free survival may yet translate to improvements in overall survival. Whether the improvements seen with immunotherapy in other cancers can be achieved in breast cancer remains to be determined, particularly for ERα+ breast cancers. This review explores the basic mechanisms of resistance to endocrine therapies, concluding with some new insights from systems biology approaches further implicating autophagy and the UPR in detail, and a brief discussion of exciting new avenues and future prospects.

1. Introduction

Breast cancer remains the most prevalent cancer diagnosed in women and the second most common cause of cancer mortality. It is estimated that almost 40,000 women die of breast cancer each year in the U.S. (Kohler et al., 2015), a number that averages to approximately one death every 13 min. The largest single breast cancer subtype is defined by the expression of the proteins for estrogen receptor-alpha (ERα; ESR1) and/or the progesterone receptor (PR; PGR). The first molecularly target therapy for cancer, Tamoxifen (TAM), is still widely used and remains standard-of-care for ERα+ breast cancers in premenopausal women. TAM reduces the 10-year risk of recurrence by almost one-half and the risk of death by approximately one-third (Early Breast Cancer Trialist's Collaborative Group, 1998). Aromatase inhibitors have broadly similar efficacy in postmenopausal women and they increase time to recurrence to a greater degree than TAM, although overall survival outcomes show very limited improvements over TAM (Cuzick et al., 2010; Aihara et al., 2014; Dowsett et al., 2010). Despite the favorable improvements in overall survival associated with endocrine therapies, more women die from ERα+ breast cancer than from any other breast cancer subtype. Moreover, the annual risks of recurrence and death, beyond the first five years after diagnosis, are generally higher for ERα+ breast cancer than for the other two subtypes (Demicheli et al., 2010). ERα+ breast cancers can recur decades after diagnosis and apparently successful adjuvant interventions, evidence of emergence from dormancy in micrometastases likely already present at the time of initial diagnosis.

This overview explores some of the basic principles that have

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emerged in understanding how and why some breast cancers respond to endocrine therapies and others do not. The intent is to provide general insight, rather than an exhaustive review. To assist readers explore several aspects of endocrine resistance in more detail, citations to other reviews have been included liberally, rather than citations to all of the supporting primary materials.

1.1. Molecular subtypes and endocrine responsiveness

While many studies have attempted to define new molecular subtypes for breast cancer, most are not sufficiently reproducible for clinical use. Some classification schemes are no better predictors than random gene sets (Venet et al., 2011). Even the widely cited luminal A,B,C, HER2 positive, basal, normal-like scheme (Perou et al., 2000) is not statistically robust (Mackay et al., 2011). In general, molecular classification schemes have two primary goals, (i) to estimate a patient's prognosis, and/or (ii) to determine what specific treatment a patient should receive. Some classifiers are built more to explore the molecular drivers of breast cancer and are not intended for clinical use. Despite some classification schemes being in widespread use, their limitations are often inadequately considered (Venet et al., 2011; Weigelt et al., 2010; Clarke et al., 2008; Pusztai et al., 2006; Gusterson, 2009).

Molecular prognostic tools predict a patient's likely recurrence risk over a period of time, such as during the first 10 years post diagnosis; although, many patients with ERα+ breast cancer recur after this time point. Mammaprint (Agendia; based on the Amsterdam 70-gene breast cancer gene signature) is used mostly to predict the risk of distant recurrence and so can aid in the determination of which breast cancer patients may receive little or no benefit from chemotherapy. Prosigna (NanoString Technologies; based on the PAM50 score) and OncotypeDX (Genomic Health, Inc.) are focused on ERα+ breast cancers and also used mostly to determine who does not need to receive chemotherapy; most patients will still receive an endocrine therapy. These tools do not determine which specific treatment should be used; for example they do not predict which chemotherapy to apply and generally do not influence whether or not a patient will receive endocrine therapy. Predictive markers determine which patients should receive which type of treatment. For clinical use in the selection of treatment type, the simple three gene classification scheme of ERα+ and/or PR+ (predicts for an ERα-targeted endocrine therapy of choice), HER2+ (predicts for a HER2-targeted therapy of choice), and triple negative breast cancer (TNBC; ERα−, PR−, HER2−; predicts for selection of a chemotherapy regimen of choice) remains widely used.

Tumors in the ERα+ and/or PR+ group, also called luminal breast tumors, appear to arise from within the luminal cells of the mammary duct and are candidates for an endocrine therapy such as surgical (ovariectomy) or chemical ablation (aromatase inhibitors, luteinizing hormone releasing hormone agonists), or chemical blockade of ERα function/expression (antiestrogens). Tumors in this molecular subtype account for approximately 70% of all breast cancers. A high proportion of these tumors respond to one or more endocrine therapies; approximately 50% of all patients with ERα+ breast cancer, and up to 75% if both ERα and PR are coexpressed, will benefit.

The HER2+ group represents approximately 15–20% of all breast cancers. These tumors are prime candidates for treatment with drugs that target HER2 or its signaling including Trastuzumab (Herceptin®; monoclonal antibody against HER2), Pertuzumab (Perjeta® a HER2 and HER3 dimerisation inhibitor) and Lapatinib (Tykerb®; tyrosine kinase inhibitor). A significant proportion of these tumors will respond to a HER2-targeted therapy. Almost one-half of the tumors in the HER2+ group will also express ERα and/or PR and may also receive endocrine therapy in addition to therapy that targets HER2. ERα+/HER2+ tumors generally respond to endocrine therapies, although the response rate may be lower, and the duration of response may be shorter, than ERα+/HER2− cancers (Webber and Dixon, 2014).

The TNBC group, which comprises ~15% of all breast cancers, has no molecularly targeted therapies yet available. While often referred to as “basal-like” because they are thought to arise mostly in the basal cells of the mammary ducts, the TNBC group is molecularly diverse, and comprises at least three separate subgroups (basal, metaplastic, apocrine) (Turner and Reis-Filho, 2013). Chemotherapy remains standard-of-care for these patients. Endocrine therapies are not usually administered because responses are rare in this group (Early Breast Cancer Trialist's Collaborative Group, 1998) and are generally thought to reflect false negative ERα and/or PR measurements. More recently, the role of anti-androgens as interventions for the TNBC subgroup that express androgen receptors has begun to attract attention and may offer clinical benefit to some patients (Barton et al., 2015a,b).

1.2. Antiestrogens: SERMs and SERDs

Antiestrogens are drugs that act primarily at the receptor to block or compete with endogenous estrogens for activation of ERα. TAM was the first antiestrogen in clinical use (Cole et al., 1971) and it acts as a pharmacological partial agonist. Thus, TAM binds to the receptor and can exhibit both agonist and antagonist properties; these outcomes are both tissue and species specific (Jordan and Robinson, 1987). The selectivity of responses to TAM led to it being described as a selective estrogen receptor modulator (SERM). Other examples of SERMs include raloxifene and toremifene. The agonist activity of TAM in the endometrium is thought to partly explain the increased incidence of endometrial cancers in women receiving TAM (Hu et al., 2015a). Other SERMS do not necessarily have this agonist effect in the endometrium; raloxifene is a good example (DeMichele et al., 2008).

Some antiestrogens affect ERα stability and cause down-regulation of the receptor protein. Fulvestrant (Faslodex®; ICI 182780) is currently the most widely studied of this growing class of antiestrogens. Often referred to as a “pure” antiestrogen (Thompson et al., 1989), essentially a pharmacological antagonist not partial agonist, Fulvestrant both inhibits ERα protein dimerization and targets the receptor for degradation (Yuhas and Tarleton, 1978; Dauvois et al., 1992; Long and Nephew, 2006). The ability to downregulate ERα protein led to it being described as a selective estrogen receptor downregulator (SERD); occasionally the “D” is described as “degrader.” New SERDS are already in clinical trials and include the orally active ARN-810/GDC-810; others are well advanced in preclinical testing.

Use of antiestrogens has begun to change in recent years. For example, while TAM was standard-of-care for decades, the improved disease free survival with the aromatase inhibitors has led to them often replacing TAM as a first line endocrine therapy for postmenopausal women. Fulvestrant (250 mg) is non-inferior to some aromatase inhibitors (Howell et al., 2002; Robertson et al., 2003; Vergote and Robertson, 2004), and appears to be more effective at the higher dose of 500 mg (Di et al., 2010). In their recent meta analysis, Al-Mubarak et al. (Al-Mubarak et al., 2013) implied superiority over aromatase inhibitors where Fulvestrant was used as first line therapy or where there was a smaller proportion of cases that had earlier adjuvant endocrine interventions. Confirmation of the superiority of Fulvestrant over aromatase inhibitors awaits the outcomes of ongoing randomized clinical trials (Al-Mubarak et al., 2013). Like aromatase inhibitors, its use is mostly restricted to postmenopausal women. Whether Fulvestrant