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Review

Estrogen receptors in breast carcinogenesis and endocrine therapy

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ABSTRACT

Excessive exposure to estrogen has long been associated with an increased risk for developing breast cancer and anti-estrogen therapy is the gold standard of care in the treatment of estrogen receptor (ER) α-positive breast cancers. However, there are several mysteries concerning both anti-estrogen, tamoxifen, and estrogen. The most important of these are: (1) some ERα-positive breast cancers do not respond to tamoxifen; (2) some ERα-negative breast cancers do respond to tamoxifen; (3) initial or acquired resistance to tamoxifen occurs with recurrent tumors; (4) estrogen can cause marked tumor regression in long-term tamoxifen-resistant ERα-positive breast cancer. These mysteries indicate that we do not know enough about estrogen signaling to understand the effects of targeting these receptors in cancer. The discovery of ERβ, the second estrogen receptor, has added another level of complexity to estrogen signaling. This review summarizes recent publications and makes an updated portrait of ERα and ERβ in breast carcinogenesis and endocrine cancer therapy.

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Contents

1. Introduction

Most of the effects of estrogen are mediated through its two receptors: estrogen receptor alpha (ERα) and beta (ERβ). ERα has been extensively studied in breast cancer. The protein is expressed in 50–80% of breast tumors and is a good indicator for the success of hormone therapy. After almost 20 years since its discovery, the role of ERβ in breast cancer is still being explored (Leygue and Murphy, 2013).

ERβ is more abundant than ERα in normal human and mouse mammary gland (Cheng et al., 2013; Huang et al., 2014). In ERα knockout mice, the breast is atrophic; while in ERβ knockout mice, epithelium is hyperproliferative. These mouse studies are consistent with research from in vitro cell culture and from immunohistochemical studies, which have suggested the anti-ERα and tumor-suppressor functions of ERβ. The present review will focus

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on the recent achievements from clinical and mouse studies. We will also discuss the current predicaments in applying endocrine therapy targeting estrogen receptors for treatment of breast cancer and provide prospective for future research.

1.1. Estrogen receptors in breast carcinogenesis

At both the clinical and molecular level, breast cancer is a complex, heterogeneous disorder. If we are going to design curative pharmaceuticals, we need to better understand the signaling pathways involved in normal development of mammary gland and how dysregulation of these pathways leads to development of cancer. Estrogen/ER signaling is clearly important in normal mammary gland development and breast carcinogenesis. We will discuss this signaling pathway in more detail in the following paragraphs.

1.1.1. ERs in normal mammary gland and breast cancer

Although much research has been done to decipher the role of ERs in mouse mammary gland development, we still do not understand how ERs work during human mammary gland development. In the last decade, some key developments have occurred which have filled in some of the gaps in our knowledge of estrogen signaling. In premenopausal women, ERα was localized mostly to the inner layer of epithelial cells lining acini and intralobular ducts, and to myoepithelial cells scattered in the external layer of interlobular ducts. ERβ was more widespread, in epithelial as well as stromal cells (Li et al., 2010). In postmenopausal women, ERα is expressed in less than 10% of normal mammary epithelial cells, while ERβ is expressed in more than 50% of normal mammary epithelial cells. Similar to the result from premenopausal women, stromal cells in postmenopausal women express nuclear ERβ, but not ERα (Cheng et al., 2013). From mouse work we know that ERα is responsible for the proliferative effect of estrogen but this is not a direct effect. It occurs through a paracrine mechanism involving non-proliferating ERα-positive cells (Brisken and O'Malley, 2010). ERβ represses proliferation and is pro-apoptotic (Thomas and Gustafsson, 2011). The breast is one of the few organs that undergoes the majority of its development after birth, so these results from normal mammary gland give us very fundamental insights about how ERs function normally and also provide some indications for understanding of what can go wrong during cancer initiation and progression.

Many studies have demonstrated a correlation between ERα and ERβ status with breast cancer survival outcomes (see recent reviews (Burns and Korach, 2012; Leygue and Murphy, 2013; Thomas and Gustafsson, 2011; Warner and Gustafsson, 2010)). ERα is considered to be a good indicator for endocrine therapy and breast cancer survival. Loss of ERα in breast cancer patients indicates invasiveness and poor prognosis (Herynk and Fuqua, 2007). Many labs have reported on ERβ expression in clinical samples (Bozkurt and Kapucuoglu, 2012; Esslimani-Sahla et al., 2004; Fuqua et al., 2003; Gruvberger-Saal et al., 2007; Jarvinen et al., 2000; Miller et al., 2006; Miyoshi et al., 2001; Omoto et al., 2002; O'Neill et al., 2004; Roger et al., 2001; Saunders et al., 2002; Shaaban et al., 2003; Shaw et al., 2002; Skliris et al., 2001, 2003, 2006; Speirs et al., 1999; Sugiura et al., 2007). Some, but not all, have linked high ERβ expression with better prognosis. Cell lines and pre-clinical breast cancer animal model studies also suggest a beneficial effect of ERβ (Murphy and Leygue, 2012; Warner and Gustafsson, 2010).

1.1.2. ERs in different stages of ductal breast carcinogenesis

Breast cancers are now classified according to gene expression profiles into luminal A (ERα and PR positive, low proliferation rate), luminal B (ERα- and PR-positive, high proliferation rate), HER2-overexpressing, and triple-negative carcinoma (TNC) which expresses neither ERα, PR or HER2. Clearly, this classification is based on the well-known receptors traditionally studied in breast cancer and will have to be modified as we learn more about other targetable receptors in breast cancer. In addition, this classification does not place lobular cancer and does not consider the tumor environment whose importance in invasiveness of breast cancer is becoming more recognized.

According to the "old" classification, approximately 80% of all breast cancer cases are ductal cancer while 10% are lobular cancers (Korhonen et al., 2004). Ductal cancers are well-studied and they are known to occur in stages progressing from normal terminal duct lobular unit (TDLU) to ductal carcinoma in situ (DCIS) and then finally to invasive ductal carcinoma (IDC) (Wellings and Jensen, 1973). DCIS is defined as non-invasive cancer, which has not spread beyond the duct into any normal surrounding breast tissue and is thought to be the direct precursor of IDC (Burstein et al., 2004; Sgroi, 2010). No genetic events have been identified to explain the transition of DCIS to IDC (Polyak, 2007). Investigation of the expression pattern of ERα and ERβ in normal tissue, DCIS and IDC is a first step in understanding the function of these two receptors in the progression of breast cancer. Our recent results (Huang et al., 2014) have shown that the number of ERα-positive cells increases, as normal breast tissue becomes DCIS while the number of ERβ-positive cells is markedly decreased during the transition. In IDC, less than 10% of tumor cells express ERβ.

The ERβ/ERα ratio declines significantly as disease progresses from normal epithelium to DCIS and IDC. In IDC, ERα expression is negatively correlated with histological grades while most of ERβ is only found in histological grade 1 (Huang et al., 2014). A recent study from a retrospective clinical trial has indicated that ERα level is inversely correlated to the grade of DCIS lesions and ERα in DCIS is a prognostic factor for tamoxifen adjuvant therapy (Allred et al., 2012). The roles of ERβ in the DCIS prognosis and endocrine therapy are under investigation.

1.1.3. ERs in lobular breast cancer

The incidence of invasive lobular cancer (ILC) is increasing (reviewed in Heldring et al., 2007), and the need to find better ways to treat this type of breast cancer has become more pressing. We have found that compared with ductal breast cancer; lobular breast cancer expresses high level of both estrogen receptors (Huang et al., 2014). Another marked difference between lobular and ductal cancer is the lack of proliferating cells in lobular cancer: Ki67-positive cells were very abundant in ductal cancer but very rare in lobular cancer. Thus our data support the previous conclusion (Derksen et al., 2006; Vlug et al., 2014) that lobular cancer is a disease resulting from resistance to anoikis and not one of proliferation.

Results from Breast Oncology Center at Dana-Farber Cancer Institute showed that the aromatase inhibitor letrozole works better than tamoxifen in the treatment of ILC in the Breast International Group (BIG) 1–98 clinical trial, while the difference of these two drugs in the treatment of IDC is very small (Metzger et al., 2012). Tamoxifen is an antagonist for ERα through EREs site, while tamoxifen in the presence of ERβ is an activator at AP-1 site and stimulates proliferation (Kushner et al., 2000), the different expression levels of ERβ in IDC vs. ILC (Huang et al., 2014) may account for the result from that clinical trial.

1.1.4. ERs in breast cancer microenvironment

Genetic mutations within cells are not the only driving force of neoplastic transformation. Recently several studies have indicated that tumor microenvironment has a strong influence on the tumor progression, particularly tumor invasion and metastasis. Tumor microenvironment includes surrounding blood vessels, immune

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