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ORIGINAL ARTICLE / RESEARCH

The Significance Of Oestrogen And Progesterone Receptors In Breast Cancer

VARGHESE C

ABSTRACT

It was 40 years ago, that the importance of steroid hormone receptors in the biology of breast cancer was recognized. This important finding was the result of a study in which radiolabelled oestrogens concentrated preferentially in the oestrogen-influenced target organs of animals, and also in human breast cancers. Thus, the concept of an oestrogen receptor (ER) was established. Ever since, it has been observed that human breast cancers are dependent upon oestrogen and/or progesterone for growth, and that this effect is mediated through ERs and progesterone receptors (PRs). Thus ER and PR are both found to be overexpressed in malignant breast tissue. Oestrogen receptor (ER) and/or progesterone receptor (PR) expressing breast cancers are found to have different clinical, pathological, and molecular features. They have been found to play a significant role in the prognosis and treatment of breast cancers. Recent developments which provided new insights into hormone receptor biology and the increasing array of proteins that can modify their function, have helped modulate better therapies for breast cancer.(eg). ,Selective oestrogen receptor modulators (SERMS), which are drugs that interact with the oestrogen receptor, have been approved for the treatment and prevention of breast cancer. Also, less expensive, simpler, and possibly more accurate measurements of ER and PR have been made possible by methods for assaying receptor proteins.

Keywords: oestrogen receptor, progesterone receptor, prognosis, breast cancer, tamoxifen, aromatase inhibitors

Introduction

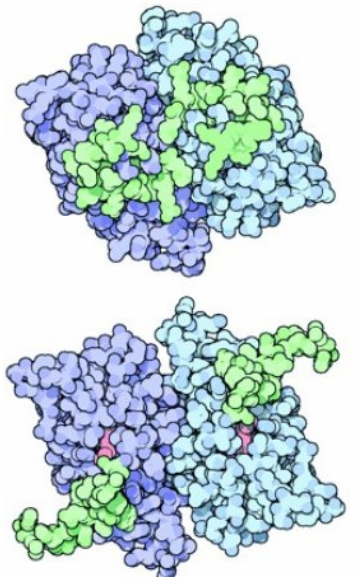
Female reproductive activity is mainly regulated by oestrogen and progesterone receptors. Oestrogen and progesterone regulate the normal development of the ovary, the uterus and the mammary gland through their cognate receptors, and play key roles in the tumorigenesis of these tissues. It has been observed that oestrogen controls the early ductal morphogenesis of the mammary gland, whereas progesterone controls ductal branching and alveolar development of the mammary gland during pregnancy, as has been demonstrated by studies on the oestrogen receptor (ER) and PR knockout mice [1].

In spite of considerable homology between these receptor forms, it is their structural and functional differences that may be important for tissue and promoter- specific regulation of gene expression.

Breast cancers classified by oestrogen receptor (ER) and/or progesterone receptor (PR) expression have different clinical, pathological, and molecular features. Exposure to oestrogen during reproduction carries a high risk of ER-positive tumour formation, than ER-negative tumour formation. Nulliparous women and those who had delayed childbearing, carry a high risk to develop ER positive tumours than ER-negative tumours. ER/PR positive tumours were found to be associated with early menarche than ER-negative/PR-negative tumours. The possibility of increased oestrogen synthesis in adipose stores and greater bioavailability, has been reflected in hormone receptor positive tumours. It is

probably due to this reason, that postmenopausal obesity has been found to be more consistently associated with increased risk of hormone receptor-positive, than hormone receptor-negative tumours [2]. Oestrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive) breast cancer patients are found to have lower risks of mortality after their diagnosis, compared to women with ER- and/or PR-negative disease [3]. A lower rate of cell proliferation and histological evidence of tumour differentiation has been found to be favourable prognostic features in patients with positive receptor status. ER and PR have their greatest significance in predicting response to hormonal therapy, both in the adjuvant setting, and for advanced disease [4].[Table/Fig 1]

Table/Fig 1



The Oestrogen receptor. The oestrogen receptor is a protein with several functional parts: a DNA-binding domain, two activation domains, and an oestrogen-binding domain. The oestrogen-binding domain (blue) and the associated activation domain AF-2 (green) are shown here. Estradiol binds deep within a pocket in the receptor and is covered by a loop of protein chain, as shown in the upper illustration (estradiol is covered by the loop in green—on the left-hand subunit, the loop is transparent to show estradiol underneath, in pink). This loop forms part of the activation signal that will stimulate growth in the cell. However, when tamoxifen (in pink in the lower illustration) binds, the extra tail of the drug is too bulky and the receptor loop is not able to adopt its active conformation (The Molecular Perspective: Tamoxifen and the Oestrogen Receptor. David S. Goodsell. The Oncologist, Vol. 7, No. 2, 163-164, April 2002)

About the receptors

Both ER and PR belong to the nuclear hormone receptor superfamily, that includes the androgen and retinoid receptors. Being located in the cytosol of target cells, they operate as ligand-dependent transcription factors. The DNA-binding sites on the receptor are unmasked by the attachment of a lipid-soluble hormone to the ligand-binding domain . This causes the receptors to migrate into the nucleus, and bind to specific hormone responsive elements near the genes that are responsible for the physiologic actions of the hormone. This is followed by transcription of messenger RNA and ribosomal RNA, and the eventual synthesis of new proteins [5].

Oestrogen receptor

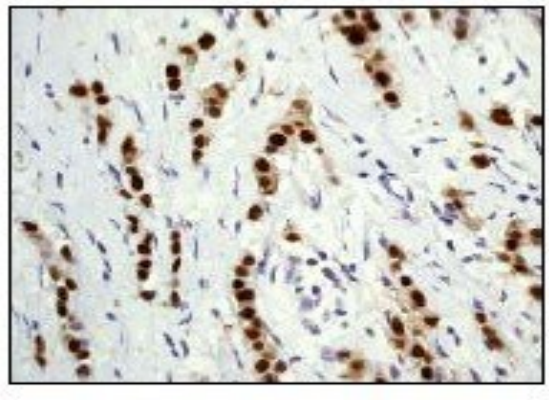
It has been observed that only about 50 to 70 percent of breast cancers require the female hormone oestrogen (oestradiol) to grow; other breast cancers are able to grow without oestrogen. Molecules called hormone receptors, which are essential for the cell to use oestrogen for growth, are produced by oestrogen-dependent breast cancer cells. These hormone receptors can be either oestrogen or progesterone receptors, or both. The development and growth of breast cancers are promoted by oestrogens and genetic changes together. ER is present in more than half of breast tumours, because oestrogenic hormones act via the oestrogen receptors (ERs), ER-alpha and ER-beta, and thus, this receptor has been the most widely targeted protein in breast cancer therapy. Women are significantly more likely to benefit from treatments that lower oestrogen levels or block the actions of oestrogen, thus depriving the cancer cells of the material that stimulates their growth, if hormone receptors are present within a breast cancer. Improved disease-free survival and response to selective ER modulators (SERMs), such as tamoxifen, or other forms of endocrine therapy, are predicted by the presence of the ER in breast tumours . The treatment of breast cancers, and also the prevention of breast cancer in women at high risk for the disease, can be achieved by suppression of ER activity by SERMs [6]. SERMs exhibit tissue-specific oestrogenic agonist/antagonist activity through their ability to bind to the oestrogen receptor (ER) protein, and interact with co-regulatory proteins, thereby modulating transcription of oestrogen target genes [7]. Though

different than oestrogen, SERMs appear chemically similar to it. Tamoxifen and other SERMs prevent oestrogen from binding to the ER (and thereby preventing it from stimulating growth of the cells). Tamoxifen also interacts directly with the ER, disrupting the normal function of breast cancer cells, and the cells of other organs as well [8].

Progesterone receptor

Progesterone, an ovarian steroid hormone, plays a key role in the development and function of the uterus and the ovary, and also of the mammary gland. The progesterone receptor (PR), which is the intracellular cognate receptor of progesterone, functions as a transcription factor that regulates gene expression. As with other nuclear receptors, the function of the PR is modulated by co-regulators (co-activators and co-repressors) which are recruited by the liganded or unliganded PR, either to enhance or to suppress transcription activity. The normal function of the PR is affected by the mutation or aberrant expression of the co-regulators, thus disrupting the normal development of the mammary gland, and leading to breast cancer [9].

Table/Fig 2



Immunohistochemical analysis of progesterone receptor expression in paraffin embedded human breast carcinoma, using 1/100 ab32085. (Mulac-Jericevic B & Conneely OM Reproductive tissue selective actions of progesterone receptors. Reproduction 128:139-46(2004 Giangrande PH et al. The opposing transcriptional activities of the two isoforms of the human progesterone receptor are due to differential cofactor binding. Mol Cell Biol 20:3102-15 (2000).

Detection of ER and PgR in breast cancer

Traditionally, radio ligand labelling/ enzyme immunoassay was the method used to detect the presence of the ER and PR proteins. This was achieved by isolating the protein fraction from the tumours, and treating this fraction with ER and PR specific antibodies in 96-well plates. The antigen-antibody reaction was detected either by an enzyme-substrate reaction, or by a radioisotope system. These plates were subsequently read on a plate reader. However, this has been replaced gradually by Immunohistochemistry (IHC), which has shown an equal reliability[10]. In IHC, currently available mouse monoclonal or rabbit polyclonal ER/PR antibodies are used on formalin-fixed, paraffin embedded tissue sections to get specific staining areas in positive tumours, as compared to no staining in negative tumours. (This test is done at Tata Memorial Hospital, Parel, Mumbai, and at the Cancer Welfare Home and Research Institute, Shakurpukur, Kolkata. The cost is not known, but the report will be available within 7 days of sample collection.)

Significance of ER and PgR receptor status on the prognosis of breast cancer

The measurement of oestrogen receptor (ER) concentrations in breast cancer tissue is an established method of predicting the response of a tumour to endocrine therapy, either using the traditional radioligand binding assay, or the more recent immunocytochemical techniques. Response to endocrine therapy clearly correlates with receptor positivity ie. the richer the tumour in oestrogen receptors, the better is the prognosis for the patient. Almost 70% of breast cancer patients have oestrogen receptor-positive (ER+ve) tumours, and of these, around 60% are found to respond to endocrine therapy. The prediction of the prognosis of breast cancer patients is expected to be achieved by a sub-grouping of ER-positive patients, based on the physiology of oestrogen signalling. Identification of a poor-prognosis population among ER-positive breast cancer patients can be achieved by the use of selected oestrogen-regulated genes (ERGs)[11].

Only low levels of response to treatment are achieved in those patients with oestrogen receptor-negative (ER-ve) tumours,.

Progesterone receptors (PR) which reflect the functional oestrogenic stimulus, have also been investigated, and are believed to be at least as significant a prognostic and predictive factor as the oestrogen receptor status. Patients whose tumours are ER+ve and/or PR+ve, have demonstrated good

levels of response to endocrine agents in recent clinical trials [12],[13].

Oestrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive breast cancer patients have lower risks of mortality after their diagnosis, compared to women with ER- and/or PR-negative disease.

Significance of ER and PgR receptor status on the treatment of breast cancer

Currently, ER, PR, and HER2/neu status are molecular markers used in the routine treatment of breast cancer. The potential benefits from hormonal therapy can be predicted by the presence or absence of ER and PR as valuable prognostic factors. Oestrogen is the prominent breast cell mitogen, and inhibition of ER activation is an important prevention and treatment strategy [14]. A selective ER modulator, Tamoxifen, can be used to target ER/PR positive metastatic breast tumours, and these patients tend to have a greater chance of effective tumour response and longer overall survival than patients with ER/PR-negative tumours. Risk of recurrence and death following adjuvant hormonal therapy are much reduced in patients with ER/PR-positive early breast cancer, whereas patients with ER/PR-negative disease are minimally benefited from these treatments. In patients with ER negative tumours, who appear to gain greater benefit from chemotherapy in both the metastatic and adjuvant settings, the value of ER status as a predictive marker extends to potential benefit from chemotherapy. However, treatment decisions on the basis of ER have not yet been evaluated prospectively [15],[16],[17].

Historically, Tamoxifen has been the standard treatment for hormone receptor-positive breast cancer, resulting in a significant improvement in disease-free survival (DFS), regardless of nodal status. For women with early breast cancer that is ER positive, standard adjuvant treatment is with the anti-oestrogen tamoxifen for 5 years, which reduces risk of recurrence by 47% and risk of death by 26% over the next 10 years (14). After the initiation of therapy, resistance to tamoxifen therapy in early breast cancer may occur as early as 12–18 months. Tamoxifen can stimulate breast cancer cell growth in some patients with resistant disease. Therefore, for early breast cancer, the role of more effective, less toxic agents, such as the third-generation Aromatase inhibitors (AIs), has been evaluated in adjuvant therapy[18].

Aromatase,a product of the CYP19 gene, converts adrenal androgen substrate, androstenedione to oestrogen in peripheral tissues, which is the predominant source of oestrogen in postmenopausal women. AIs can reduce oestrogen production by more than 90%. Unlike tamoxifen , however, AIs lack oestrogen-agonist activity. Aromatase inhibitors prevent ER-mediated breast cancer cell stimulation by suppression of oestrogen synthesis rather than by blocking the ER [14]. Only women without functioning ovaries can benefit from the use of AIs, as they do not affect the ovarian production of oestrogen. According to the specificity and potency with which they inhibit the aromatase enzyme, AIs are classified as first, second, or third generation inhibitors. Third-generation AIs (i.e., anastrozole, letrozole, and exemestane) are the most potent, most selective, and least toxic. These can reduce serum oestrogen by more than 95% [14],[19]). While all the three agents effectively reduce total body oestrogen synthesis after menopause (when ovarian production of oestrogen has virtually ceased), letrozole is the most potent agent, achieving the greatest degree of reduction of oestrogen production in experimental and clinical studies.

The efficacy of AIs as neo-adjuvant therapy for hormone receptor-positive breast cancers, have been investigated by several studies. In a phase II trial, 112 postmenopausal women with locally advanced ER-positive breast cancer, were treated with neoadjuvant anastrozole . Fifty-five percent of the patients had complete clinical responses, and 29% had partial clinical responses. However, an impressive 23% of the patients had complete pathological responses[20],[21].

Conclusion

Treatment of cancer patients can be revolutionized by the identification and exploitation of biomarkers that may predict response to anti-cancer treatments. In breast cancer, the oestrogen receptor (ER) and the progesterone receptor (PR) are known to have a significant predictive value in determining sensitivity to endocrine therapies. Clinical outcome is affected by tumour expression of ER or PR, and this information is often used to determine a patient's optimal treatment regimen. However, the measurement of ER and PR alone is more complex than originally thought, and due to the recently identified isoforms of ER (ERα and ERβ) and PR (PRA and PRB), as well as several variant and mutant forms, the choice of treatment remains difficult. The recent advances in genomic- or proteomic-based approaches has enabled to understand the molecular picture of breast cancers , which in turn, allows biomarkers of response and

prognosis to be identified and characterized more accurately than before. In the future, to maximize the therapeutic benefit of the patients, they could be treated according to the molecular portrait of their tumour biomarker expression[22].

Key messages

Oestrogen and progesterone receptors are known prognostic indicators in breast cancer. The response of breast cancer to a particular therapy can be determined by its oestrogen receptor positivity status. Breast cancer drugs like tamoxifen and aromatase inhibitors act by suppression of oestrogen receptor activity.

Conflict of Interest: None Declared

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