The Open Access Journal of Science and Technology
Vol. 3 (2015), Article ID 101131, 7 pages
doi:10.11131/2015/101131

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Review Article

Cellular Mechanisms of Oestrogen in Breast Cancer Development

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Received 11 September 2014; Accepted 12 December 2014

Academic Editors: Yusuf Tutar and Paola Venditti

Abstract. The association between oestrogen and breast cancer has been demonstrated for over a century however the exact cellular mechanisms by which oestrogen play a role in breast cancer development has not been fully established. Recent investigations have shown that oestrogen is involved in many aspects of cancer progression. This review evaluates how oestrogen at the cellular level induces or promotes the process of breast carcinogenesis through its action at multiple levels of cancer pathogenesis like cellular proliferation, inhibition apoptosis, angiogenesis and invasion-metastasis. Therapeutic approaches against these mechanisms by the use of anti-oestrogens and their effectiveness are also reviewed and areas requiring further investigation are highlighted.

Keywords: Oestrogen; breast cancer; mechanism; carcinogenesis

1. Introduction

Breast cancer is the most common cancer in the UK and the second most common cancer worldwide after Lung cancer. In the UK, over 49,000 women were diagnosed with breast cancer in 2010, with 1 in 8 developing the disease within their lifetime. It is the second most common cause of cancer death [1]. It was estimated that about 12% of female children born in the United States will be diagnosed with breast cancer sometime in their lifetime and close to 3% will die from it [2]. About 99 out of 100,000 women were estimated to have breast cancer in Canada in 2013 [3] while an incidence of 31 per 100,000 women was reported in West Africa [4].

Among other factors like race, family history, genetic mutations, lifestyle etc, oestrogen is a key factor in the pathogenesis of breast cancer. This association was first reported over a century ago by George Beatson after he noticed a reduction in tumour size and improvement in clinical status following removal of both ovaries (the major source of endogenous oestrogen) of women with breast cancer [5]. Factors that increase exposure to oestrogen like early menarche, late menopause, hormone replacement therapy, obesity have been shown to increase risk of breast cancer [6]. Also, studies have demonstrated reduced cancer risk in highly predisposed women with the use of anti-oestrogen [7, 8]. Level of plasma free oestrogen was also

shown to correlate directly with the risk of developing breast cancer in different studies [9, 10]. These evidence suggest a strong association between oestrogen and breast cancer. Over the years, understanding of the mechanisms of oestrogen's role as a carcinogen has been increasing as studies keep emerging.

Generally, the pathogenesis of cancer involve the acquisition of some characteristic biological capabilities by body tissues, these include; limitless proliferation, evasion of growth suppression signals, resisting cell death, immortalization, abnormal induction of angiogenesis, ability to invade and metastasize, genomic instability and mutation, induction of inflammation, anomalous cell energy metabolism and evasion of immunologic killing. These are cellular characteristics common to all neoplastic cells and they have been referred to as "Hallmarks of Cancer" by Hanahan and Weinberg [11, 12].

Oestrogen contributes to breast cancer pathogenesis through cellular mechanisms that employ some of these biological capabilities. This review therefore aims to evaluate the mechanisms by which oestrogen as a carcinogen initiate or promote these capabilities in the development of breast cancer. It will also be shown how understanding of these mechanisms has been used to develop therapeutic targets in breast cancer.

2. Oestrogen and Receptor

Oestrogen is a steroid hormone produced in the ovaries mostly as oestradiol (Oestradiol-17β, E2) and peripherally as Oestrone (E1) and Oestriol (E3) (Figure 1). It is transported in plasma bound to sex-hormone globulin. At the site of action, oestrogen diffuses directly through the cell membrane to the nucleus where it binds to the nuclear membrane based oestrogen receptors (ER). These ER exist in two isoforms; ERα and ERβ [13]. They are members of the nuclear receptor superfamily of transcription factors coded by separate genes on chromosome 6 (ERα) and chromosome 14 (ERβ) [14].

Oestrogen and ER complex further bind to the oestrogen response elements (ERE) which are specific nucleotides component of promoters of various genes. This interaction activates transcription and synthesis of proteins that mediate oestrogen's physiologic effect in several body tissues. In the breast, oestrogen promotes stromal development and ductal growth [13]. Both receptors are found in the breast (ERα predominates in breast cancer), uterus, ovary, heart, bone and brain. However, only the β isoform is found in the blood vessels, gastrointestinal tract and on inflammatory cells [15].

Oestrogen either indirectly through its proliferative effect on breast tissue or its metabolites' (estradiol-3,4-quinone) direct effect on DNA increase the risk of mutations of genes responsible for major cellular mechanisms like apoptosis, proliferation and DNA repair. At the same time, it also promotes the cells bearing these mutations leading to tumour development [17–19].

3. Continuous Cellular Proliferation

Proliferation is a well regulated process in normal cells however a characteristic trait in cancer cells is their ability to continuously proliferate without regulation. This process involves several intracellular pathways that regulate cell cycle in which Oestrogen has been found to play a key role. Frasor et al. [20] showed that ER positive breast cancer cells treated with oestrogen for up to 48 hours mostly demonstrated (70%) a down regulation in their gene expression patterns while few others (30%) were up regulated. Most of the genes up regulated were those involved in cell cycle promotion including; cyclin D1, cell division cycles (CDC) 2, 6 and 20. A significant proportion of the down regulated genes were cell cycle inhibiting in function including cyclin G2 (an inducer of cell cycle arrest), B cell translocation genes (BTG) 1 and 2 (inhibitor of cell cycle following p53 signalling). Similar studies have confirmed these findings and further noted c-Myc over expression (an important driver of cell cycle progression). Cyclin D1 and c-Myc were also noted to be down regulated with anti-oestrogen hence confirming the direct oestrogenic effect [21, 22].

Oestrogen was also shown to stimulate several growth factors including stromal cell-derived factor 1 (SDF-1), Amphiregulin and Vascular endothelial growth factor (VEGF) all of which act in autocrine fashion in activating breast cancer cell replication [20]. These multiple interactions under the influence of oestrogen cumulatively result in continuous cellular proliferation and hence cancer formation.

These cellular mechanisms were studied in breast cells that had already become cancerous and these cells may inherently respond to oestrogen interaction in a different way compared to normal breast tissue. How oestrogen causes or mediates these proliferative genetic and epigenetic changes in normal breast is yet to be established.

4. Evasion of Apoptosis

Apoptosis is a cellular protective mechanism which implement cell death in unfavourable conditions or when abnormalities in the DNA material are detected. This process is tightly regulated by interactions of pro and anti-apoptotic genes. Inhibition of apoptosis would promote continued cellular existence despite genetic defects and subsequent tumorigenesis [23].

By up-regulating the anti-apoptotic gene survivin and down regulating pro-apoptotic genes like caspase 9 and cyclin G2 oestrogen promotes continued breast cell survival by abolishing programmed cell death [20, 24]. Oestrogen also inhibits TNF-α induced apoptosis through the AKT pathway [25]. Recent investigation by Chaudhri et al. [26] further revealed that apart from the nuclear membrane based ER signalling, oestrogen also works via the newly discovered cell membrane based ERα36. Western blot analysis of membrane fragments of cultured ER- positive and ER-negative human

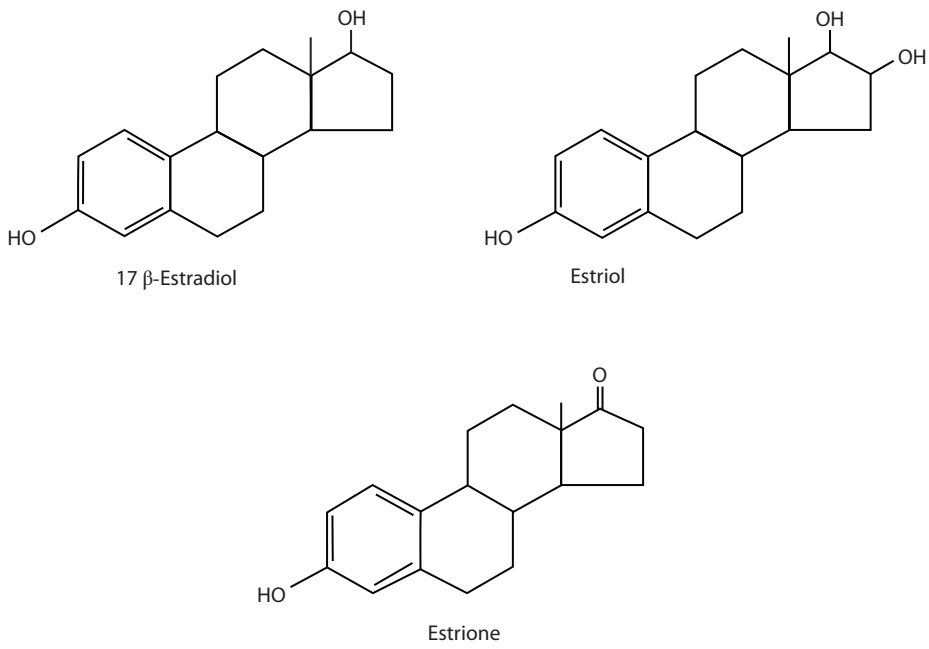

Figure 1: Chemical structures of endogenous oestrogens [16].

breast cancer cells treated with oestrogen bond to bovine serum albumin (E-BSA; a conjugate of oestrogen that cannot cross the cell membrane) was done which demonstrated the presence of ERα36 on both cell lines. Through this receptor signalling, pro-apoptotic activities of caspase 3 and TUNEL were inhibited and oestrogen creates insentivity to cell death signals and continued existence, hence fostering another biological capability of cancer cells.

How significant the ERα36 signalling is in breast cancer development requires further investigation as it is still unknown whether ERα36 is expressed in all breast cancer cells. In a similar manner wherein classical nuclear membrane ER expression is not positive in all breast cancers may also be variably expressed on the cell membranes. These findings also raise the question about the possibility of other ER subtypes existing on the cell membrane or in other parts of the cell that may have not been identified.

5. Sustaining Angiogenesis

Except during wound healing and female menstrual cycle, angiogenesis remains turned off in normal tissues and blood vessels remain quiescent. However, this angiogenic switch remains continuously activated in the process of carcinogenesis thus initiating sustained neovascularisation to provide nutrition and oxygen to the ever growing cancer cells [27].

Hypoxia is a key factor that initiates tumour angiogenesis. During hypoxia, hypoxia inducible factor 1 (HIF-1), a transcription factor existing in α and β subunits, becomes activated. It in turn activate genes that lead to transcription of angiogenic factors like Vascular endothelial growth factor (VEGF) and erythropoietin [28, 29]. Experimental models where murine breast cancer cells were treated with oestrogen has shown HIF-1 up regulation with associated induction of VEGF production which did not occur when anti-oestrogen was added to the model [30]. Oestrogen thus also enhances breast carcinogenesis by modulating mechanisms that turn on angiogenesis. The possibility of HIF induction by other factors like increase in cell number which could cause increased oxygen consumption with resulting hypoxia which oestrogen plays a more direct role in is worth considering as a possible explanation for this oestrogen/HIF relationship.

6. Invasion and Metastasis

Cancer cells undergo series of transformations that enable them to invade and metastasize. These transformations include loss of cell adhesion molecules, change from epithelial to fibroblastic morphology and increased motility. This transition process is called epithelial-mesenchymal transition (EMT) [9, 28, 32] and it is under the influence of transcriptional influence of transcriptional factors which include Snail, Slug and Twist [34, 35]. Acting via the ERα36, oestrogen directly up-regulate the expression of Snail 1 which plays a key role in EMT. It also inhibits E-Cadherin and Syndecan-4 involved in cell-cell interaction thus enhancing cell detachment and metastasis [26]. CXCR4, a chemotactic receptor was also shown by the same study to be expressed on breast cancer cells by oestrogen thereby stimulating migration to sites where ligands for this receptor can be found (e.g., bone). These processes under oestrogen control

facilitate the acquisition of metastatic potentials on breast cancer cell, another characteristic found in cancer.

Chimge et al [36] however suggested contrary in that oestrogen could be a protective factor against metastasis. It was shown that oestrogen inhibits Runx2 gene which usually function through SNAI2 stimulation (also known as Slug) to induce epithelial mesenchymal transition. They also noted that SNAI2 expression was found more commonly in ERα negative breast cancer and this promotes metastasis particularly to non-osseous sites. This contradiction may suggest that oestrogen may play different roles (probably opposing ones) with different ER expressions of breast cancer. There is therefore need to further investigate this aspect and characterize oestrogen's effect on ER positive and ER negative breast cancers.

7. Clinical Importance of Oestrogenic Mechanisms in Breast Cancer Management

With evidence of oestrogen as a key factor in the development of breast cancer and the increasing understanding of the mechanisms involved, therapeutic approaches targeted against these oestrogenic mechanisms have been explored and has improved the effectiveness of breast cancer management. Hormonal therapy aimed at reducing oestrogen production or its action has been applied in different ways to treat breast cancer over the last century. First was the surgical removal of both ovaries (the primary source of endogenous oestrogen) [5] then to ablation of the ovaries with radiation and more recently pharmacologic agents.

This understanding of cellular mechanisms of oestrogen in breast cancer has not only been used to treat the disease, but also to prognosticate and in prevention. Very key to these clinical applications is the understanding of oestrogen receptor expression in breast cancer.

8. Oestrogen Receptor Expression in Breast Cancer

Using ligand-binding assay and immunohistochemistry breast cancer expression of oestrogen receptor (and of lesser clinical significance progesterone receptor) can be detected and the level of receptor expression measured [15]. Of the two oestrogen receptor isoforms, ERα is more predominantly expressed in breast cancer and it is the one usually assayed for to diagnose ER positivity or negativity. The role of ERβ is less clearly understood. Receptor positivity is diagnosed when 1% or more of the tumour nuclei stain for ER [37].

9. Prognosis and ER Expression

Even in the absence of any treatment, ER positive breast cancers have a reduced risk of metastasis and better outcome. With treatment, ER positive tumours are of better prognosis as they respond well to hormonal therapy to which ER negative tumours are non-responsive [15]. Beyond just identifying the presence of ERα, measuring the quantity is also of clinical importance as it correlates to treatment responsiveness. A higher level of receptor expression is associated with lower mortality and better prognosis [38]. ER negative tumours tend not to be responsive to hormonal treatment and are associated with poorer prognosis. However, recent discovery of ERα36 on cell membrane of both ER positive and negative (other than the usual ER on nuclear membrane) may allow hormonal responsiveness in ER negative tumours though this has not been completely elucidated upon [26].

10. Anti-oestrogen Treatment of Breast Cancer

Over two-third of breast cancers are ER positive and anti-oestrogens have been introduced as part of adjuvant therapy for both pre and post-menopausal women with breast cancer having ER expression since the 1970s [39]. Several randomised clinical trials have proven reduced risk of recurrence, better clinical outcome and reduction in mortality with adjuvant anti-oestrogen use [40]. Mechanisms of anti-oestrogens commonly used involve competitive antagonists and agents that inhibit oestrogen production. Blockade by these means lead to the inhibition of oestrogen thereby preventing its cellular effects that lead to cancer development.

Selective oestrogen receptor modulators (SERMs) are agents that act as oestrogen antagonist at some tissues (breast, uterus) at the same time acting as agonist in other tissues (bone, cardiovascular system). Binding of ER by SERMs causes varying conformational changes in target sites that activate different cofactors causing antagonism in some tissues and agonist effect in others [15]. Examples of SERMs commonly used clinically are Tamoxifen and Raloxifen. They have shown benefit for both early and advanced cancer. Added non breast cancer related benefits of SERMs have also resulted in better acceptability as adjuvant treatment. Tamoxifen is associated with reduced risk of bone complications commonly experienced in postmenopausal women (osteoporosis, fractures) and also reducing the risk of coronary artery diseases [15]. These effects are as a result of ER agonist effect on tissues that normally suffer from reduced level of oestrogens in post-menopausal women. SERMs are however not without unfavourable effects as they are associated with early induction of menopause in pre-menopausal women, increased risk of thrombo-embolic disease and development of uterine cancer [40]. However, these risks have been estimated to be of little clinical significance and do not affect the overall survival benefit of SERM use.

Production from peripheral tissues (fatty tissue, muscles) is the major source of endogenous oestrogen in post-menopausal women in whom ovarian functions are diminished. This process is called aromatization. Aromatase

inhibitors (AIs) inhibit aromatase, the cytochrome P450 enzyme responsible for conversion of androgens to oestrogen [13]. It was introduced as a result of the unwanted effects of tamoxifen. AIs are now the standard treatment of choice in post-menopausal women with ER positive breast cancer [41]. Examples of AIs commonly used include anastrazole, letrozole and exemestane. Several trials have proven the benefit of AI similar to that of SERMs and with fewer side effects [42]. The few disadvantages associated with AIs are the presence of side effects that are prevented by non-breast cancer related benefits of tamoxifen i.e. bone and cardiovascular complications in post-menopausal women.

11. Anti-oestrogens and Breast Cancer Prevention

With the success of anti-oestrogens in breast cancer treatment, several trials investigated their use as an agent to prevent breast cancer in high risk women. The largest of such trials by the National Surgical Adjuvant Breast and Bowel Project (NSABP) tested use of tamoxifen for 5 years in 13,388 women at high risk of developing breast cancer. They found a 49% reduction in risk of developing invasive breast cancer and also reduced risk of contralateral breast cancer, recurrence and prolonged survival in those who had tamoxifen as adjuvant post operatively [43]. Anti-oestrogens are now recommended as chemoprevention for women with significant family history of breast cancer, genetic predisposition and atypical hyperplasia [44].

They are also used as part of routine post-operative adjuvant treatment of those with ER positive tumours for up to 5 years after surgery [15].

12. Conclusion

This review has evaluated the mechanisms by which oestrogen cause some intracellular changes in breast cells that drive cancer potentials like sustained proliferation, evasion of apoptosis, angiogenesis, invasion and metastasis. Most studies have shown evidences of genetic and cellular changes in breast cell interaction with oestrogen but how these changes eventually translate to become cancer is still not clear. For example, identifying up regulation

of a gene involved in proliferation as a result of oestrogen does not necessarily translate to increased overall cellular proliferation as a lot of counter-regulatory processes are at play. Also, the interaction between these mutations is still not understood and several questions remain yet to be answered. Could there be a master genetic alteration under the influence of oestrogen that plays out as these other multi-genetic and epigenetic changes that are increasingly being identified? Rather than just being isolated, could these mutations initiate or promote each other? At what point do these changes (which could be found in normal breast cell interaction with oestrogen to some extent) deviate from being physiologic into carcinogenic? Could these changes with oestrogen interaction differ in breast cancer cells of different histologic subtypes? Does oestrogen play any significant role in ER negative cancers? Does oestrogen drive these cellular events at all stages of breast cancer progression in a similar fashion or could it cause different effects in early and late cancer stages? These are questions that are yet to be answered and would be worth researching further into as we continue the quest to understand the biological basis of breast cancer.

Despite what is still unknown, what is already known about oestrogen and breast cancer has contributed significant value. Blocking oestrogen by different pharmacologic means has advanced the therapeutics and prevention of breast cancer. Evidence has shown improved clinical outcome, quality of life and survival with anti-oestrogen use. Routine assessment of ER expression of breast cancer (and classification into ER positive or negative) is now used to tailor management options. Selective blockade of ER on the breast with SERMs helps to ensure that other systems that are in need of oestrogen are still functioning optimally. With better characterisation of the cellular mechanism of oestrogen's role in breast cancer, more specificity in therapy targeting would hopefully emerge with resulting improvement in treatment effectiveness.

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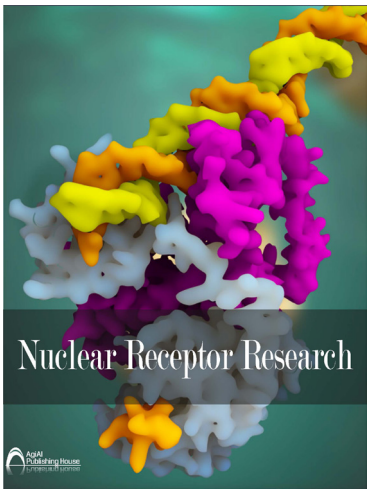

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