

How far have we come in terms of estrogens in breast cancer?

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Abstract. Major advances in breast cancer treatment have almost always been linked to the actions of estrogen. Therefore, this review focused on estrogen actions in the breast, particularly the developments of the past 20 years, the present understanding of disease biology and possible future developments. Within these areas have focused on what is known about the underlying molecular biology and in particular integration of the bioinformatics revolution of the last 15 years with other facets of research. In addition, there will be an emphasis on the understanding brought about by a greater appreciation for the intracrinology of the breast.

Key words: Breast cancer, Sex steroid, Hormones, Hormone receptors

BREAST cancer is one of the most prevalent malignancies among women. Because of its high rates of both incidence and prevalence worldwide, numerous clinical, translational and basic studies have been directed at finding better treatments. In this endeavour, the scientific community has for the majority succeeded, as evidenced by the reduction in mortality rates reported in most developed countries. A large portion of this reduction in mortality has come from early detection through mass screening as well more effective targeted therapies, many of which revolve around targeting estrogens. It is this latter point that ties into the overall theme of this review, in particular regarding estrogens – how far we have come and, importantly how far have we to go?

Estrogen Receptor System

In order to yield the majority of their biological actions, estrogens are dependent on proteins within cells. These proteins either act as an interface to integrate the signal from the steroid to the biological process of the cell (nuclear receptors) or act to change the

signal type or strength (enzymes). The basic and well characterised signalling system of estrogens in breast cancers is usually classified into two different groups depending on menopausal status. In both cases the biological actions are through the alpha form of the estrogen receptor (ER α), however the source of estrogens is thought to be different. In premenopausal patients estrogens are principally derived from endocrine secretions by the ovary; while in postmenopausal patients, estrogens are locally produced through aromatisation of androgenic precursor steroids. The basic components of local estrogen action in the breast include the ER α , which exhibits a high affinity for estradiol and slightly lower affinity for estrone; and the cytochrome P450 aromatase enzyme (Arom), which acts on the first carbon ring of C19 steroid backbones and converts it into a benzoic/aromatised ring structure with an 18 carbon steroid backbone. While this brief description covers the basic components (Fig. 1) the picture that has been built from the last 20 years of research covers a much more complex system (Fig. 2) which we will progressively describe during this review. It is the latter components that are currently targets in developing breast cancer therapies.

Historical Perspective

Original breast cancer therapies

Breast cancer is by no means a recent disorder.

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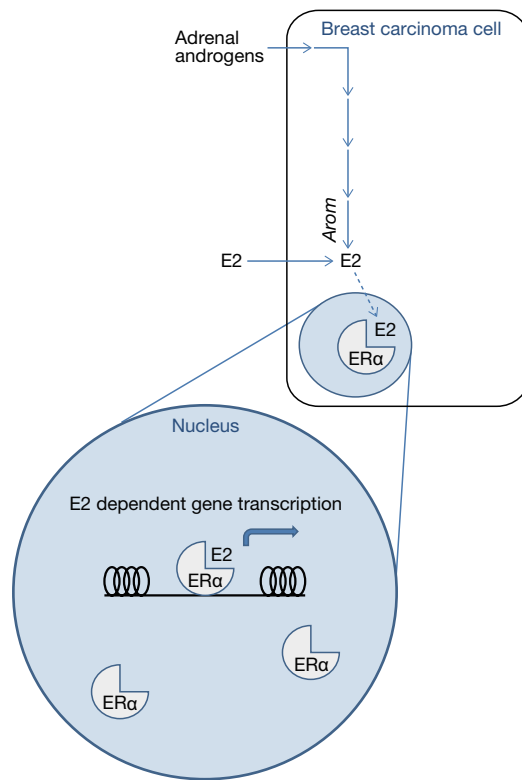


Fig. 1 An overview of estrogenic action in breast tissues
This figure shows the classical overview of estrogenic actions in breast tissues.

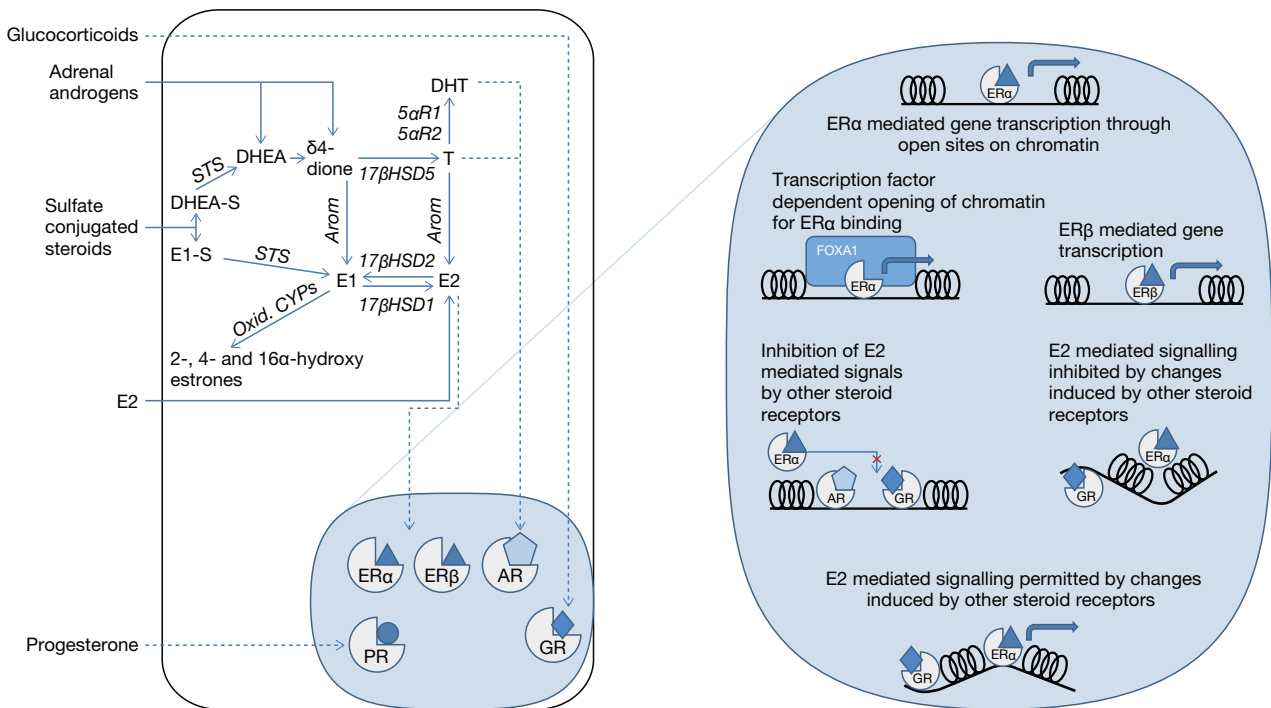


Fig. 2 An overview of estrogenic action in breast tissues
This figure shows the updated overview of estrogenic actions in breast tissues.

Because of the anatomical location of the breast close to the skin and the fact that advanced breast cancers can present as external ulcerated lesions, breast cancer has been discussed and reported in the medical literature since ancient Egyptian, Greek and Chinese times. Some of the earliest documented cases of breast cancer surgery comes from Wakayama prefecture in Japan in the 1800s by a surgeon named Hanaoka Seishu [1], and during the majority of human history up to and including the present day, breast cancer has and is managed primarily by surgery. Around the same time as the pioneering surgery of Seishu epidemiological evidence such as the higher incidence of breast cancer occurrence in nuns was giving the initial cues that factors involved in the reproduction and menstrual history of women could be related to the development of breast cancer [2]. Some of the earliest evidence of direct response of breast cancer patients to the cessation of endocrine stimulation was reported in the 1880s; it was documented that the cancerous mass in a number of breast cancer patients regressed following menopause [3]. From these observations and the epidemiological data, the removal of the ovaries and/or even adrenals was proposed as a means of mimicking a postmenopausal state with subsequent beneficial effects. This approach remained the standard of care for the next 50 years until the development of systematic chemotherapy for breast cancer in 1946 in the United States [3]. More specific endocrine surgeries were soon to follow with surgical hypophysectomy and adrenalectomy being developed in the 1950s, until chemical compounds able to directly target estrogen signalling in the breast were developed.

Aromatase inhibitors: an accidental targeted therapy

The first form of aromatase inhibition in breast cancer was actually an inadvertent targeting of the aromatase enzyme by two agents utilised for other rationales than their actions on aromatase, namely: testololactone, originally considered as a weak androgen, and aminogluethimide, originally intended as a form of medical adrenalectomy [4]. Introduced in 1960 and the 1970s respectively, both of them were used clinically until the 1980s. In both cases while their actions as aromatase inhibitors were entirely unintentional, this fortuitous circumstance contributed to the rationale behind the development of later and more effective forms of aromatase directed therapies. These included the second generation aromatase inhibitors

(e.g. 4-Hydroxyandrostenedione) in the 1980s and the third generation inhibitors in the 1990s [5].

The emergence of estrogen inhibition as a therapeutic mode

Surgical removal of estrogens, via the removal of ovaries, has a history dating back to the turn of the twentieth century. Although alternate endocrine manipulations were tried with varying degrees of success, they and thus non-surgical inhibition of estrogens through chemical suppression of estrogen receptor action did not really take off until early 1970 with the introduction of tamoxifen [6]. With hindsight, an indirect antagonism of the estrogens receptor potentially began with the administration of androgen agonist in the 1950s [7]. However, this was not the proposed mechanism at the time and the use of androgens ceased with the documented effectiveness and minimal side effects of tamoxifen treatment. Tamoxifen was being developed and introduced in a timeline parallel to that of the first generation aromatase inhibitors. Due to equal efficiency in terms of treatment, combined with a less complex treatment regimen and side effects, tamoxifen quickly became and remained the dominant breast cancer treatment approach for the next 20 years [8].

Current understanding of estrogen effects in breast tissues

With modern methods we now have a detailed understanding of the effect of estrogens, both in terms of circulating and tissue estrogen concentrations, with regards to breast cancer risk. Estrogen production occurs at various sites in the body (Fig. 3) and an ongoing debate regarding estrogens in breast cancer has been the relative risk of localised versus systematic concentrations of estrogens [9]. The precise measurement of tissue concentrations of estrogens has historically been technically difficult and therefore the majority of studies have focused on the potential association between serum estrogens and breast cancer risk. Studies of postmenopausal breast cancer patients, in the majority, have revealed a correlation between higher serum estrogens and increased breast cancer risk but the results of premenopausal breast cancer patients have not been as consistent [10].

Despite the associations suggested in postmenopausal women, studies evaluating the serum estrogens and breast cancer risk in postmenopausal women are hampered by characteristic low levels of circulating

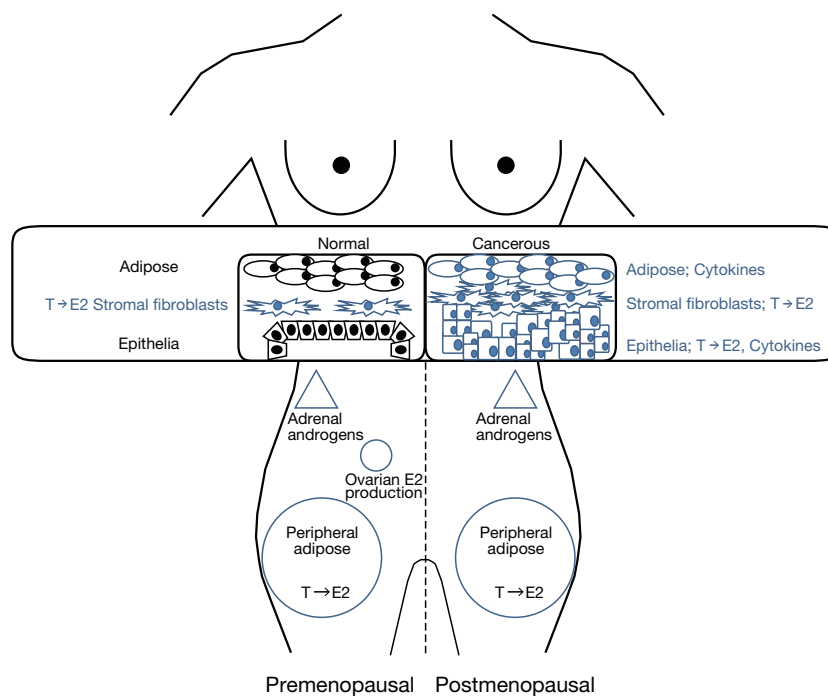


Fig. 3 Sites of estrogen production in pre and postmenopausal women and localised estrogen production in the breast. In this diagram blue colour indicates components that can contribute to estrogen production. The lower half shows the sites of estrogen production peripheral to the breast in both pre and post-menopausal women. The upper section shows the components of the breast that are suggested to contribute to localised estrogen production in normal and cancerous states of the breast, either through localised production of estrogens or paracrine effect on the surrounding tissues. T, testosterone; E2, Estradiol.

estrogens in these patients combined with limited sensitivity of detection methods [11]. The recent improvements in assay design and preparation, in particular next generation technology and gold standard steroid analysis methods such as LS-MSMS, should greatly aid the mapping of this interaction in precise detail. Ongoing efforts in this respect should help to clarify associations between estrogen levels and breast cancer risk once and for all.

The biochemistry and molecular biology of estrogen actions

Alongside the development of therapies and therapeutic regimes designed to exploit breast cancer's estrogen dependence, results of recent fruits of basic science have revealed the fine molecular mechanisms by which estrogens act. This interplay between basic and clinical research is an ongoing synergistic circle. Hence, due to the importance of these interactions the section below is an overview of what we currently know regarding estrogens and their interaction with various intracellular pathways.

A modern understanding of the mechanisms underlying the effects of nuclear receptors relies heavily on our better understanding of the various cofactors and pathways that regulate the interactions of the estrogen receptor with the DNA. In addition to this, those factors that regulate the levels and availability of estrogenic ligands are also increasingly recognised as pivotal to the overall actions of estrogens in the breast cancer tissues. While our understanding of the above is far from complete, great advances have been made in understanding both pre-receptor binding modulation of estrogen levels and factors that govern interactions of the bound estrogen receptor. Therefore, understanding the fine molecular dance that permits the complexity of signalling observed is something that is increasingly within our grasp.

Molecular biology of the estrogen receptor (alpha)

In the breast, the majority of estrogen receptors remain in the nucleus of the cell even when un-liganded [12], playing a role in the maintenance of luminal differentiation [13]. The diffusion of estrogen into the

nucleus allows estrogen receptor binding. As with all nuclear receptors, differences in signalling are caused by changes in the three dimensional conformations caused by the interactions between the ER protein with regulatory factors. This in turn affects the interactions of ER α and its cofactors leading to regulation of subsequent transcription [14].

Studies, reported primarily in the last decade, have increasingly been focusing on elucidating not only the roles of the estrogen receptor in breast cancer but its modulation by other transcription factors and elements of the DNA transcriptional machinery. While a comprehensive description of these interactions would form a review in itself, a task which has been done in a comprehensive fashion by other researchers (e.g. [15]), we will only briefly provide an overview in the following sections, especially with regards to the potential roles of bioinformatic approaches in deepening our understanding of breast cancer biology.

Large scale sequencing methodologies made it possible to look at global transcription patterns. These technologies heralded a change in our approach to the understanding of the underlying molecular biology of human malignancies. The milestone in the application of these methods to breast cancer patients was that of Perou *et al.*, who subdivided breast cancer into subgroups on the basis of similarities of gene expression [16-18]. Reassuringly, in line with the general approach previously used, this approach confirmed the importance of the estrogen receptor in governing breast cancer biology. These initial group of studies defined two separate ER α expressing groupings, one defined by harbouring a higher rate of cell proliferation and hence aggressive phenotype and the other the inverse, each termed luminal A and luminal B cancers respectively [16-18] a definition which has since lead to the gradual worldwide integration of cell proliferation, measured by MIB-1/Ki-67, in the standard panel of routine immunohistochemical approach to characterise breast cancers and define treatment options [19].

Additionally large scale sequencing approaches have also helped to validate the utility of breast carcinoma cell lines. Initially, the same studies as detailed above for breast cancer cases also studied the clustering of breast cancer cell lines within this classification and thus confirming the transcriptional similarity with breast cancer cases [20]. On the basis of this similarity, researchers have compared gene expression between non-stimulated and estradiol (E2) stimulated MCF-7 cells, revealing

that the larger part of the estrogen effects on the genome was to down regulate overall patterns of transcription but to specifically upregulate pathways related to the enhancement of cell proliferation [21].

The concept that a transcriptional complex, rather than ER α alone, existed and may be responsible for breast cancer biology arose late last century. It came from the contradictory findings in studies looking at the effects of ER α activation in various cell lines. While endogenous ER α agonist induced growth in breast carcinoma cells, transfection of ER α into ER negative cells was not sufficient to reproduce the effect of estrogen driven growth stimulation [22]. This contradiction led to the hypothesis that additional factors may be involved. Studies in MCF-7 cells led to the identification of ER α binding sites, and bioinformatics approaches allowed the identification of transcription factor binding sites located in close proximity to the ER α binding sites [23, 24]. This approach revealed two main transcription factors, GATA3 and FOXA1, as being commonly associated with binding in the regions of ER α transcription [23, 24]. As these factors had already been suggested by other experimental approaches to play roles in the regulation of mammary biology [25, 26] and in human tissues to co-localise at the mRNA [27] and protein level [28] they seemed good prospective candidates as regulators of ER α transcription.

Intricate studies utilising DNA ChiP methodology to examine the binding patterns of all three transcription factors revealed that E2 treatment facilitated the assembly of the transcription factors at estrogen responsive elements within the DNA. This suggested that their combination, along with other more generic transcription factors, was a characteristic transcription response that facilitates E2 mediated gene transcription [29]. The importance of this complex in estrogen positive breast cancers was confirmed as a subset of data drawn from breast cancer in the wider analysis performed by the cancer genome atlas project [30].

In fact, the wider purpose of this project was to map alterations in cancer across various platforms and their associated biological approaches (genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing and reverse-phase protein arrays), allowing an integrated overview of the driving process underlying breast cancers development. Alongside alteration in more central proliferation pathways, known to be associated with cancers such as signalling cascades and p53, both

GATA3 and FOXA1 were shown to be altered in breast cancer suggesting their importance in disease etiology [30]. Beyond these confirmations, these large scale genomic studies described above still have a great deal to offer us regarding our understanding of estrogen actions in breast cancer. Recent studies utilising further advances in bioinformatics have also revealed roles of new factors involved in the estrogen receptor transcriptome through the analysis of ER transcription events using the more powerful GRO-seq approaches [31] and further technological developments in the future should bring further understanding of estrogen receptor actions in breast cancer.

Estrogen metabolism pathways

Beyond an increased understanding of the estrogen receptor transcriptome, basic and translational research is gradually understanding the effects of various metabolism pathways of estrogens on biological behaviour of breast cancer patients. We previously mentioned the importance of aromatase in the generation of estrogens from androgens in breast cancers, but it should be emphasized that a much more complex intracrine system is involved. Therefore, estrogen signalling is controlled by the balance between the rate at which estrogens are activated compared to the rate at which they are inactivated. This is not an all or none equation, as many of the steps create more potent or weaker estrogens rather than ablating estrogen receptor actions completely. Various approaches have sought to determine the relevant importance of these pathways.

Involvement of 17 β HSD1 in estrogen metabolism

Immunohistochemical studies have examined the expression of the main estrogen modulating enzymes, 17 beta hydroxysteroid dehydrogenase type 1 and 2 (17 β HSD 1 and 2), in postmenopausal cancer patients. These studies indicated that an upregulation of 17 β HSD1 and/or loss of 17 β HSD2 could possibly contribute to the maintenance of high estrogens than subsequently fuel carcinoma growth [32, 33]. Changes in the expression of 17 β HSD1 have also been assessed in paired specimens of neoadjuvant chemotherapy in order to test for their potential roles in the development of therapeutic resistance. These studies revealed that patients with the most markedly decreased Ki-67 labelling index of carcinoma cells in paired sampling before and after neoadjuvant aromatase inhibitor-based therapy were also associated with significant increase of 17 β HSD1 expression. This suggests that the upreg-

ulation of this enzyme in response to growth signal deprivation via estrogen depletion could possibly be a mechanism underlying the development of therapeutic resistance [34]. Because of the potential significance of targeting this pathway, there are various attempts being made at designing specific 17 β HSD1 inhibitors to prevent compensatory estrogen production. This could provide an alternative route to targeting estrogen driven cancers, potentially prolonging the period would be clinically feasible to effectively suppress estrogen production in postmenopausal women [35].

STS as a promising target

Another source of estrogens being investigated is that of their local synthesis from sulfate bound estrogens and or androgens [36]. The main enzyme responsible for the hydrolysis of the bound sulfate group is the steroid sulfotransferase (STS) enzyme, principally because of its potential role in the generation of estrogen signal in breast cancers. The expression of the STS enzyme has been documented in the cases associated with worse clinical outcome, including those with therapeutic resistance and with higher grade carcinoma [37]. Because of these associations mentioned above, various studies have examined the possibility of targeting this enzyme as a treatment in breast cancer. At least one agent against STS has made it through a phase one clinical trial with promising results [38]. As such it remains a candidate for future therapeutic modes of estrogen suppression.

Interplay between the estrogenic and androgenic pathways

It should be also noted that estrogenic pathways do not exist in the absence of other avenues of steroid metabolism. The estrogen pathways are closely linked with that of the androgens, as estrogenic steroids are metabolised by the aromatase enzymes from androgenic steroids (Fig. 1b). Because of this close interrelationship researchers have examined the impact of the manipulation of estrogen pathways on androgens. Due to the 'hot topic' nature of androgens in breast cancer a number of recent review have dealt comprehensively with the topic including potential interactions with the estrogen receptor [7]. Of these, three studies warrant briefly touching on here due to their direct relevance with regards to interactions between estrogen manipulation and androgen actions.

One study, carried out in the neoadjuvant setting, examined the changes in the principle androgen amplifying enzymes. This study demonstrated that

the response to neoadjuvant aromatase inhibition, as defined by Ki-67 labelling index, was associated with increased 5 α -reductase 2 expression. This suggests that such therapies not only block estrogen formation, but could have an additional impact through an increased androgen signal and subsequent estrogen antagonism from that source [39]. The remaining two studies, somewhat at odds with the study above, reported that a higher androgen receptor (AR) compared to ER α level [40], or in general, the presence of AR in breast cancers [41] could predict a worse therapeutic resistance to Tamoxifen. A possible explanation for this discrepancy could be that over time, increased androgen signalling could cause the tumour to switch from recognising androgens as an inhibitory signal to utilising them for continued growth. Unravelling the biology underlying these studies forms part of the overall ongoing attempts to understand the importance of AR and ER interplay in breast cancers.

Beyond the canonical estrogens estrone (E1) and estradiol (E2), there are a number of hydroxylated forms. These estrogen variants are known as the catechol estrogens due to the presence of a catechol group in their structure and are formed from the parental estrogens E1 and E2 through the oxidative actions of cyp enzymes [42]. Despite an appreciation of the presence of these enzymes in the breast since the 1970s the measurements of these metabolites and their contribution to breast cancer risk have been relatively unexamined due to the challenges associated with assaying these specific compounds and distinguishing them from each other due to the high degree of structural similarity [43]. Modern mass spectrometric analysis provides a tool to overcome that challenge and has revealed that enhanced 2-hydroxylation of parental estrogens is indeed associated with reduced risk of postmenopausal breast cancers with similar trends noted in premenopausal breast cancers [43]. This is an area of research that is ongoing and may yet yield further developments in our understanding of variable impacts of steroid metabolism pathways on breast cancers in the future.

Interactions of estrogens and DNA damage pathways

With the discovery of the BRCA1 gene and its relationship with the DNA damage repair pathways, the possibility that these pathways could be central causative factors in breast cancer has come to the fore. Given the established importance of estrogens in breast cancer, it is then logical to look at any possible interactions between ER α and BRCA1 as well as other DNA

damage response pathways. This analysis has suggested that one of the main pathways through which estrogens may initiate cancer development is through its interactions with DNA damage pathways. Studies have demonstrated that E2 treatment is associated with DNA double-strand breaks and overall genomic instability (e.g. [44]). Such an unstable genetic environment is one in which cancer development may be favoured. Recently an excellent comprehensive review on this topic has been published and for more details we direct the reader towards this [45]. In short, one of the main biological implications of altered estrogen signalling in breast cancers may be an induction of genomic instability through alteration in DNA double-strand break repair pathways, resulting in a permissive environment for cancer development.

Interaction of estrogens with microRNA pathways

An important, modern development in the understanding of the importance of estrogens in breast cancer has been of their relationship with non-translational signalling. The roles of non-translated RNA species in regulating gene expression are becoming increasingly appreciated as important mediators of cellular biology. In the breast, an extensive network of microRNAs that regulate various aspect of breast cancer physiology has been reported in the literature including the tumour suppressive Let 7, miR200 and miR7 forms [46]. In particular, a number of these microRNAs appear to exert actions on estrogen related processes in breast carcinoma cell lines, including both the regulation of ER expression and the expression of ER co-regulators [47]. In addition, there appears to be dynamic changes associated with microRNA expression in breast cancer treatment. We have previously studied changes in the well characterised Let-7 tumour suppressor miRNA in regards to aromatase inhibition. These studies demonstrated that treatment was associated with increased levels of Let-7, suggesting that this may be an additional mechanism through which this treatment may work [48]. Additionally we showed a correlation between estrogen status and that of let-7 miRNA maturation through the correlation between ER status and expression of microRNA processing proteins [49] and a correlation between these microRNA and samples with better prognosis [50]. Further studies (reviewed in [47]) have also demonstrated interactions between miRNAs and estrogen resistance in breast cancer. As our understanding of these microRNA networks increases, it is likely to see more correlations

with various aspects of breast cancer biology and this area should be an exciting area for further and future research.

Interactions between estrogens, obesity and inflammation in postmenopausal breast cancer

Another important axis tying together estrogen actions and breast cancer prognosis has been that of the nexus among obesity, inflammation and breast cancer development. The link between obesity and increased risk of breast cancer has been well documented in the case of postmenopausal breast cancer in multiple ethnic populations (e.g. [51-55]) although such associations are more controversial in premenopausal breast cancers. Likewise, the correlation between breast cancer development and inflammatory states has also been documented [56]. Of interest, obesity itself has been recently proposed to share many hallmarks of low grade inflammatory states including increased circulating inflammatory cytokines (e.g. [57, 58]). The interesting part of this relationship comes from the fact that in the absence of ovarian estrogens, as in postmenopausal women, estrogens produced by the adipose tissue via the aromatisation of androgenic precursors could become the main source of estrogens [59]. This is particularly relevant to the breast given the presences of large deposits of adipose tissue adjacent to ductal breast tissues and potentially carcinomas. The production of estrogens by aromatase in adipose tissues occurs not in the adipocytes themselves but in their associated fibroblasts. In intricate molecular studies, primarily performed by Kristy Brown and Evan Simpson, [59] it has been demonstrated that inflammatory cytokines produced by the tumour, or potentially already present in the circulation in obese patients can act at the 1, 3, 4 and II aromatase promoters in order to upregulate aromatase expression in tumour adjacent fibroblasts, resulting in the production of estrogens that allow further tumour growth. This finding neatly ties together a number of epidemiological observations and the interactions of these axis, and molecular controls is another area of ongoing investigations regarding estrogen actions in breast cancer.

The 'other' estrogen receptor – the role of the ER β in estrogen actions in the breast

Finally any analysis of our understanding of estrogens actions in the breast would be incomplete without mention of the second estrogen receptor – the estro-

gen receptor beta (ER β). Discovered 40 years after what we now term the ER α it is located in a different chromosome and, while sharing a degree of homology, it has very different biological actions across a wide range of tissues [60]. This includes hormonally dependent glands such as the prostate and the breast (reviewed in [61-63]). The late discovery of this receptor contributes to some confusion in terminology when talking about estrogen receptor negative breast cancers, this term will typically refer to ER α -, but not necessarily ER β -negative breast cancers.

Given a shared affinity to the same ligand, unsurprisingly there have been studies examining the effects of ER β in breast cancer tissues and its interaction with ER α in ER α -positive breast cancers (e.g. [64]). In the normal breast, ER β is expressed in a higher proportion of tumour cells than ER α and its actions have been suggested to be anti-proliferative and pro-apoptotic [65]. The possibility that the presence of ER β raises, may be explained by the fact that estrogens could still be relevant in the traditionally termed ER negative subtypes such as triple negative and HER2 overexpressing cancers. There have been a number of studies looking at the effect of ER β on prognosis in both ER α positive and negative subtypes with some but not all demonstrating beneficial effects (e.g. [66-72]) A possible explanation for some of the variance observed that as multiple forms of the ER β exist and some studies suggest that different forms could exert different effects (e.g. [67]). Recent studies have shown that in breast cancer progression of ER β expression is reduced between ductal carcinoma in situ and invasive carcinoma, an inverse trend to that reported in ER α expression [73].

ER β has also been implied to be present, and thus have the potential for action in cell types other than the carcinoma cells [74] and this will be an exciting area for future research. A final yet important further extension of the presence of ER β in 'ER negative cancers', and one that has not been reported in the literature, is that estrogens metabolising enzymes such as aromatase could be biologically relevant. Given the relative novelty of this field there is much still to do in order to understand the effects of estrogens through ER β signalling in both ER α positive and negative breast cancer subtypes.

Interactions of estrogens with other nuclear receptors

Assessed in classical breast cancer diagnostic panels, progesterone receptor (PR) expression has always

been assumed as only a surrogate for functional estrogen receptor alpha. However research in 2015 showed that the progesterone receptor can actually modulate ER α binding [75] and through these actions may be of greater significance in breast cancers than has previously been acknowledged.

Likewise recent studies have also been uncovering roles for the glucocorticoid receptor in modulating estrogens actions both through direct actions in transcriptional events (e.g. [76, 77]) and through indirect actions on various components of the estrogenic intracrine system (e.g. [78]). These studies are particularly important due to the associations between inflammation, obesity and inflammatory processes as well as the common use of glucocorticoids as anti-emetics during cancer chemotherapy.

Conclusions

In conclusion we have come a long way in terms of our understanding of the impact of estrogens on breast cancer. This has led to both an improvement in the available therapeutics and, through a complementary process between basic and clinical research, a greater understanding of the underlying molecular biology of estrogen action in breast cancer. This is especially true in regards to our understanding the multifaceted nature of estrogen impact on breast cancer biology and estrogen metabolism and regulation within breast cancer

cells (Fig. 1b). Despite this, there are still many exciting new horizons in this area. The ability to extend the duration of suppression of estrogens actions without the development of resistance offers a promising perspective where the management of any residual disease in breast cancer patient may be a lifelong possibility, rather than the more limited window presented by current therapies. Betterments in our understanding of the molecular actions of breast cancer will underpin the development of these more effective estrogens directed therapies. Finally, exploration of the roles of the additional nuclear receptors broadens the horizons of the biological processes by which estrogens may act. While we have come a very long way from its inception, the story of estrogens in breast cancer is by no means at its end.

Disclosures

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