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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

Targeting the Androgen Receptor in Breast Cancer

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Abstract The androgen receptor (AR) is expressed in the majority of breast cancer and across the three main breast cancer subtypes. Historically, the oncogenic role of AR has best been described in molecular apocrine breast cancers, an estrogen receptor (ER)−/AR+ subtype which has a steroid response signature similar to that in the ER-positive breast cancer. The signalling effect of AR is likely to be different across breast cancer subtypes, and particularly important is its interaction with ER signalling. Despite the high frequency of AR expression in breast cancer, it is still not a standard clinical practice to use AR antagonists as therapy. Older trials of AR-directed therapies in breast cancer have had generally been disappointing. More recently, more potent, next-generation, AR-directed therapies have been developed in the context of prostate cancer. Here, we will review the emerging literature dissecting the role of AR signalling in a context-dependent manner in breast cancer and the renewed interest and wave of clinical trials targeting the AR in breast cancer.

Keywords Androgen receptor · Breast cancer · Breast cancer subtype · Androgen receptor-directed therapy

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Introduction

Breast cancer is a highly heterogeneous disease. The current clinical classification of breast cancers are based on the expression of ER, progesterone receptor (PR), and HER2 and are broadly divided into four groups, ER+/PR+/HER2−, ER+/PR+/HER2+, ER−/PR−/HER2+, and ER−/PR−/HER2−, also otherwise known as triple negative breast cancer (TNBC). ER and HER2 serve as prognostic markers and direct therapeutic strategies.

AR is expressed in approximately 80 and 60 % of primary and metastatic breast tumors, respectively [1]. Its expression varies across the clinical subtypes, approximately 84–95 % in ER+ tumors [2, 3], 50–63 % in ER−/HER2+ tumors [2, 4•], and 10–53 % in TNBC [3, 5•, 6, 7]. The signalling effect of AR is likely to be different across breast cancer subtypes, and particularly important is its interaction with ER signalling.

Modulation of AR signalling, either inhibitory or stimulatory, has previously been explored in breast cancer with somewhat contrasting results. Testosterone has historically been used as a therapy for non-selected breast cancer patients with a response rate of ≈20–25 % [8–10]. However, this treatment has largely been abandoned and replaced with multiple lines of ER-directed therapies. A recent small retrospective study demonstrated an impressive disease control rate (tumor regression and stable disease, $n=53$) of 58.5 % with testosterone treatment in patients with metastatic ER+ breast cancer who had progressed on ER-directed therapies [11].

Androgens have also been shown to improve response rates in combination with tamoxifen in the treatment of advanced ER+ breast cancer [12, 13]. This approach has not been validated in larger randomized control studies and is not standard clinical practice. An agonist approach is still currently being evaluated in clinical trials with DHEA (dehydroepiandrosterone) and CR1447 (4-OH-testosterone) in post-menopausal women who have progressed on ER-

directed therapies. Recently, selective androgen receptor modulators (SARMs) have been developed and demonstrated clinical utility in the context of cancer-associated cachexia [14]. These therapies are currently being evaluated in metastatic ER+ breast cancer (Table 1).

Early clinical trials with first-generation AR antagonists such as flutamide in unselected patients with breast cancer have generally been disappointing [15, 16]. Clinical reports of AR antagonism in AR+ TNBC in the past year have been promising and a recently concluded clinical trial of bicalutamide, a non-steroidal AR antagonist with partial agonist activity, in patients with metastatic AR+ TNBC reported a modest clinical benefit rate of 20 % [17•].

Second-generation AR antagonists have been recently developed that are more potent and clinically efficacious than bicalutamide. These include enzalutamide which has an affinity for AR sixfold higher than that of bicalutamide. It targets multiple steps in the AR signalling pathway, including inhibition of AR nuclear translocation, ligand–receptor complex [18]. Like enzalutamide, ARN509 is a complete AR antagonist a little further back in clinical development and has shown greater in vivo efficacy at lower doses compared to enzalutamide [19]. Another class of AR-directed therapies are CYP17 inhibitors, which inhibit a microsomal enzyme essential for the biosynthesis of androgens and adrenal hormones. This class of drugs include abiraterone acetate and orteronel, are now in clinical use in prostate cancer [20], and are being evaluated in breast cancer (Clinicaltrials.gov numbers NCT00755885 and NCT01990209). A novel AR-directed therapy is AZD5312, an antisense oligonucleotide targeting the AR mRNA and the subsequent translation of the AR protein. This therapy is in phase I clinical trial development (Clinicaltrials.gov number NCT02144051).

These developments in AR-directed therapy, in combination with an improved preclinical understanding of AR signalling in different subtypes of breast cancer, have led to renewed interest in breast cancer clinical trials targeting AR. In this mini-review, we will highlight the key preclinical studies and current clinical trials in progress (Table 1).

AR in ER+ Breast Cancer

AR is expressed in 84–95 % of ER+ breast cancer, which represents the predominant AR expressing breast cancer subtype [2, 3]. In this breast cancer subtype, ER signalling is a major oncogenic driver, a signalling pathway that shares a number of similarities with AR, including cofactors and nuclear binding sites, and it remains to be clarified the degree in which each pathway signals independently of the other [21, 22]. Historically, AR expression has been found to be associated with improved outcomes in ER+ breast cancer, but there

Table 1 Current clinical trials of AR-directed therapies in breast cancer

Therapy	Phase	Condition/breast cancer subtype	Sponsor	NCT number	Enrolment
AR antagonists					
Enzalutamide	2	Advanced AR+ TNBC	Astellas Pharmaceuticals	NCT01889238	May 2013–May 2016
Enzalutamide+Trastuzamab	2	Advanced HER2+/AR+ breast cancer	Astellas Pharmaceuticals	NCT02091960	Apr 2014–Nov 2017
Selective androgen receptor modulators					
GTx024 (Enobosarm)	2	Advanced ER+breast cancer, previously responsive to endocrine therapy	GTx	NCT01616758	Apr 2013–Dec 2014
CYP17 inhibitors					
Orteronel	2	Advanced AR+ ER+ and TNBC	SCRI Development Innovations, LLC	NCT01990209	Feb 2014–Jun 2018
Abiraterone	1,2	Advanced ER+ and/or AR+ breast cancer in post-menopausal women	Cancer Research UK	NCT00755885	Oct 2008–Mar 2014
Androgens					
DHEA (dehydroepiandrosterone)	2	Advanced HER2-/AR+ breast cancer in post-menopausal women. For ER+/AR+ disease, patients need to have progressed on ER-directed therapy	Istituto Scientifico Romagnolo per lo Studio e la cura dei Tumori	NCT02000375	Mar 2013–Mar 2016
CR1447 (4-OH-testosterone)	1,2	Advanced HER2-/AR+ breast cancer in post-menopausal women	Swiss Group for Clinical Cancer Research	NCT02067741	Apr 2014–Jun 2017
Antisense oligonucleotides targeting AR					
AZD5312 (ISIS-ARR$_x$)	1	Advanced solid tumors where AR signalling is involved	AstraZeneca	NCT02144051	May 2014–May 2016

is also evidence which suggests that AR may potentially be oncogenic in a tamoxifen-resistant setting [23–26]. Taken together, these studies indicate that AR may have opposing functions in a treatment-dependent manner.

ER-Directed Treatment Naïve ER+ Breast Cancer

A number of preclinical studies have demonstrated that AR signalling antagonizes the growth stimulatory effect of ER signalling in ER+ breast cancer cell lines [21, 27, 28]. These findings corroborate with clinical observations linking AR expression to improved clinical outcomes [21, 29]. ER+ breast cancers with high AR expression have also been associated with having a better response towards ER-directed therapies [30].

An indirect mechanism of ER signalling inhibition through AR-mediated upregulation of ERβ has also been demonstrated [28]. ERβ is an ER isoform with reported inhibitory effects in in vitro models of ER+ breast cancer, and its expression has been correlated with a favorable outcome in breast cancers that express both α and β ER isoforms [31–33]. ERβ signalling inhibits ER+breast cancer cell proliferation through its ability to bind co-factors and estrogen response elements (EREs) common to both ER isoforms, thereby repressing transcription of growth-promoting genes [34].

Finally, AR signalling has been proposed to contribute to the antitumor effects of aromatase inhibitors in ER+ breast cancer, which acts primarily by reducing the peripheral conversion of androgen precursors to estradiol. The resulting increase in peripheral androgen levels and resulting increased AR signalling could potentially contribute to an antiproliferative effect [35]. These findings support the clinical observations that high circulating androgen and tumoral AR levels in post-menopausal women are associated with an improved response to aromatase inhibitors [36].

It remains to be clarified how autonomous ER and AR signalling are in this breast cancer subtype and to what extent each signalling pathway affects the other. A recent study has reported that a nuclear AR/ER ratio of ≥2 increases the risk of tamoxifen failure [37•]. These authors also demonstrated that enzalutamide but not bicalutamide, abolished estrodiol-induced proliferation of an ER+/AR+ cell line model, raising the distinct possibility that nuclear AR may be in fact be required for ER-induced proliferation effects [37•].

ER-Directed Treatment-Resistant ER+ Breast Cancer

There is increasing evidence that the role of AR signalling in ER+ breast cancer that have become resistant to ER-directed therapies is different compared to a treatment-naive tumors. This is perhaps not surprising as there is increasing evidence of upregulation of alternate growth stimulatory pathways in the setting of tamoxifen resistance, including EGFR/HER2, STAT1, and Wnt signalling pathways [38–41]. Interestingly, AR has also been shown to be upregulated in ER+ breast cancers that have become resistant to tamoxifen and, conversely, tamoxifen resistance could be induced by AR overexpression [26]. The finding that a high nuclear AR/ER ratio was associated with tamoxifen failure further adds weight to the hypothesis that AR signalling contributes to acquired tamoxifen resistance [37•]. Collectively, the current literature suggests that AR may play a part in tamoxifen resistance and studies clarifying the role of AR on established mechanisms of tamoxifen resistance are warranted.

The roles of HER and PI3K in mediating resistance to aromatase inhibitor-treated breast cancers are increasingly evident [42, 43]. While AR signalling has been hypothesized to contribute to the efficacy of aromatase inhibitors in postmenopausal women, its signalling consequences in an aromatase inhibitor resistance setting remains undefined and elucidation of AR signalling in a treatment-naïve and –resistant setting is imperative in clarifying the role of AR in these settings [36].

Collectively, the current literature suggests that AR may contribute to acquired-resistance against ER+-directed treatment for ER+ breast cancer. The role of AR in aromatase inhibitor-resistant breast cancers is less clear, and a better understanding is required to determine if AR directed therapies is applicable for this treatment subset of breast cancers.

AR in ER− Breast Cancer

Historically, the oncogenic role of AR has best been described in molecular apocrine breast cancers, an ER−/AR+ subtype which have a steroid response signature similar to that in the ER+ breast cancer [44]. This is thought to comprise of ER−/HER2+ and TNBC tumors, where the AR+ subgroup represents approximately 50–63 and 10–53 % of their respective breast cancer subtype [2, 3, 4•, 5•, 6, 7]. In the absence of ER, the role of AR signalling in driving cell proliferation has been a little clearer. We will discuss AR signalling in these two broad groups based on HER2 expression separately below.

AR Signalling in ER−/HER2+ Breast Cancer

The global AR chromatin-binding profile of MDA-MB-453, a representative ER−/AR+/HER2+ cell line, has a high degree of overlap with that of ER in ER+ disease. This suggests that AR may have assumed a similar oncogenic role to ER in driving cell proliferation [4•, 5•, 45].

AR expression is strongly associated with the overexpression of HER2 in ER− breast cancers [1, 4•]. Recent studies have provided evidence of a proliferative role for AR

signalling and an insight into the functional interplay between AR and HER2 critical for survival in this subtype of breast cancers. Mechanism underlying this functional crosstalk includes a positive feedback loop leading to direct transcriptional upregulation of HER2 by AR, which in turn activates AR transcription through its downstream mediators involving ERK-CREB1 [46]. AR signalling has also been shown to interact with HER2 signalling via its heterodimer HER3. Wnt7B, a ligand of the Wnt signalling pathway, is induced by AR signalling and activates β-catenin leading to its nuclear translocation and subsequent activation of HER3 transcriptional activation [4•]. The activated HER2/HER3 signalling leads to activation of C-Myc-mediated amplification of AR signalling resulting in an intricate network of positive regulatory loops [47].

Various preclinical strategies targeting AR have been investigated in this breast cancer subtype. AR antagonists have been shown to be efficacious in reducing the cell proliferation [4•, 48]. As HER2 signalling is the dominant oncogenic driver and effective HER2-directed therapies are standard of care for HER2+ breast cancers, clinical trials are underway to explore if there is improved efficacy with combination AR- and HER-directed therapies (Table 1). Other therapeutic combinations that have demonstrated promise in this subgroup in the preclinical setting include co-targeting AR and MEK, the latter a downstream mediator of HER2 [48].

AR Signalling in TNBC

The frequency of AR expression in the TNBC ranges from 10 to 53 % [3, 5•, 6, 7]. Accounting for the large range are the small study cohorts and differences in definition of AR positivity.

TNBC with an AR molecular signature has been termed luminal androgen receptor (LAR) subtype due the resemblance of their gene expression profiles to that of the ER+ breast cancer [5•]. LAR breast cancer cell lines are sensitive to AR antagonists and Hsp90 inhibitors, supporting a functional role for AR. Further to this, the same authors recently identified a significant association between activating PI3KCA mutations and AR expression in this subtype, and an additive anti-proliferative effect was achieved with combined AR and PI3K inhibition [49•].

Interestingly, another study reported that cell line models of AR+ TNBC which did not possess the LAR expression profiles were similarly sensitive to AR inhibition [50]. These AR+ TNBC cell line models had increased activation of membrane receptor kinases such as EGFR and PDGFRβ, resulting in sensitivity to inhibition of these receptors as well as ERK and PI3K. As with the ER−/HER2+/AR+ models, there is preclinical rationale for co-targeting the AR and ERK pathways in AR+ TNBCs [48]. Taken together, these studies suggest that AR in this subtype of breast cancers, regardless of the LAR expression profile, has a functional role in maintaining cell proliferation and can also act as a biomarker for sensitivity to both PI3K and ERK inhibition. With the clinical availability of more potent AR-directed therapies and promising combined therapeutic strategies, there is reason for optimism for an improvement in the clinical outcomes with these therapeutic strategies.

Concluding Statements

Elucidating the role of AR signalling in the different subtypes of breast cancers and in a treatment-dependent context manner has shed new light on the signalling consequences of AR. Importantly, understanding the differential AR signalling effects in a contextual manner would allow us to harness the clinical availability of new potent AR-antagonists to potentially improve current endocrine therapies for ER+ breast cancers. The conclusion of the current generation of AR-directed monotherapies in clinical trials will likely initiate a new wave of combinational approaches of AR-directed therapies in accompaniment with other pathway-directed therapies such as HER2, PI3K, and ERK in ER−/AR+ breast cancers. While the oncogenic role of AR signalling in ER− breast cancer is well established now, its role in ER-directed treatment-resistant breast cancers will require clarification before AR-directed therapies can be considered for this group of breast cancers.

Compliance with Ethics Guidelines

Conflict of Interest KeeMing Chia and Megan O'Brien declare that they have no conflict of interest.

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