Review Article

Androgen receptor in breast cancer and its clinical implication

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Abstract: Breast cancer is a heterogeneous group of diseases characterized by diverse subtypes. Currently, the classification of breast cancer is based on the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). In addition to these receptors, the presence of the androgen receptor (AR) in breast cancer cells adds a layer of complexity to our understanding of the disease. The role of AR in breast cancer is intricate, as it can alter diverse signaling pathways in the presence of different hormone receptors (HRs). This complex interplay between signaling pathways affects patient outcomes and prognosis, and the presence of AR has a significant effect. While AR positivity is common in breast cancer, the efficacy of utilizing AR blockade as a monotherapy has been limited, demonstrating only modest results. To address this challenge, substantial efforts have been directed toward comprehending the intricacies of AR's role and pathways in breast cancer development in the hope of understanding its utility as a biomarker or drug target. Multiple ongoing clinical trials are currently investigating combination treatments involving AR inhibitors and other agents to disrupt oncogenic signaling pathways and their crosstalk. Particularly in the context of triple-negative breast cancer (TNBC), where targeted therapeutic options are lacking, extensive research efforts have been dedicated to exploring the potential of AR-related interventions. This review aims to provide an overview of the various breast cancer subtypes with AR signaling mechanisms, and ongoing clinical trials that hold the potential to reshape future clinical approaches.

Keywords: Androgen receptor (AR); breast cancer; triple-negative breast cancer (TNBC)

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Breast cancer and androgen receptor

Breast cancer is the most common cancer diagnosis among women worldwide and a leading cause of cancer-related deaths. Survival outcomes differ significantly, depending on the cancer subtype and the stage at diagnosis (1). Current classification based on the immunohistochemical expression of hormone receptors (HRs) divides breast cancer into three principal subtypes: HR-positive [comprised of estrogen receptor (ER) or progesterone receptor (PR) positivity], human epidermal growth factor receptor-2 (HER2)-positive, and triple-negative breast cancer (TNBC). Among these, TNBC is particularly challenging due to the lack of targeted treatment options available, especially when compared to HR-positive or HER2-positive disease. However, recent studies examining the role of androgen receptor (AR) in breast cancer, and TNBC in particular, offer potential new biomarkers and targets to improve outcomes in TNBC.

AR is a ligand-dependent transcription factor that governs the expression of genes and signaling networks critical for many physiological and pathological processes. AR receptor positivity has been described to influence

prognosis across breast cancer subtypes. A meta-analysis involving 19 studies and 7,693 patients conducted by Vera-Badillo *et al.* demonstrated that AR expression was present in 60.5% of cases, with a higher occurrence in ER-positive tumors (2). Tumors expressing AR were linked to improved overall survival (OS) and disease-free survival (DFS) at both 3 and 5 years, regardless of ER co-expression. In general, AR receptor positivity has been thought to have a protective effect, with AR-negative tumors demonstrating larger sizes, higher grades, and more lymph node involvement (3).

Classification of breast cancer into its molecular subtypes further reveals the significance of AR positivity on outcomes. Luminal A tumors, characterized by strong ER positivity and the absence of HER2, show a significant AR positivity rate of 91% and are associated with a better prognosis (3). Specifically, increased AR expression corresponds to a lower rate of recurrence, distant metastasis, or death (12.4%), as opposed to AR-negative cases (32.1%) (4). Luminal B tumors, although more aggressive and varied in HER2 expression than luminal A, still indicate a protective influence of AR, with a 75.6% positivity rate leading to better outcomes. However, the dynamics within HER2-overexpressing tumors are more intricate. While 55.8% display AR positivity, this does not unequivocally suggest a better prognosis. In fact, tumors that overexpress HER2 and are positive for AR have a higher rate of relapse distant metastasis or death than their AR-negative counterparts (37.5% *vs.* 26.3%). This paradoxical finding calls for more comprehensive research.

In the case of triple-negative or basal-like tumors, the presence or absence of AR becomes crucial. Despite being defined by the absence of HR expression, TNBC tumors have frequently been found to express AR. Lehman's classification of TNBC highlights the importance of AR expression in the prognosis of this classically aggressive form of breast cancer. These subtypes include two basal-like subtypes (BL1 and BL2), an immunomodulatory (IM) subtype, a mesenchymal (M) subtype, a mesenchymal stem-like (MSL) subtype, and a luminal androgen receptor (LAR) subtype (5). The LAR subtype is characterized by its expression of AR and shares some molecular features with luminal-type breast cancers. Although the prognostic impact of AR among TNBC patients is controversial, LAR TNBC has been mostly viewed as favorable. These tumors typically demonstrate lower Ki-67 and mitotic index, as well as lower tumor grade and clinical stage at diagnosis, suggesting a distinct AR-dependent biology in this subtype (6). Additionally, AR-positive TNBC tumors have shown a significantly lower risk of relapse compared to other TNBC subtypes (7). Given these promising findings, it is important to understand the specific characteristics of the LAR subtype to inform more targeted and effective treatment approaches for patients with TNBC.

Androgen receptor signaling in breast cancer

In the intricate realm of breast cancer biology, androgens stand out not merely as male hormones but as critical factors that shape a woman's physiological landscape throughout her life. Predominantly secreted by the ovaries and adrenal glands, androgens are consistently present in a woman's systemic circulation at concentrations often surpassing estrogen, even enduring post-menopause. Central to this interplay is the AR, the principle nuclear receptor in mammary epithelial cells, which frequently co-expresses with ER and PR. In fact, recent work using scRNA-seq and spatial profiling of breast tissues from transgender men following androgen therapy shows that androgen can reshape the breast stromal and immune microenvironment at the molecular and cellular levels (8). This persistent androgenic milieu, combined with AR's capacity to interact with a multitude of steroid signaling pathways, poses significant implications for tumor biology in breast cancer. Notably, the varied prognostic outcomes observed with AR-positivity across breast cancer subtypes suggest the existence of subtype-specific AR-related signaling mechanisms that offer possible targets for novel therapeutic that can impede tumor growth.

ER plays a critical role in many breast cancers by promoting tumor growth, a process that can be mitigated by ER-targeted therapies. In a healthy breast environment, AR-mediated androgen actions counterbalance the growth-promoting effects of estrogens (9-11). This may in part explain why ER^+ tumors with high AR expression tend to have a more favorable prognosis. Notably, one study demonstrated that AR activation can lead to the displacement of ERα from chromatin, leading to a loss of estrogen response (12). Additionally, ERα and AR compete for binding to a common co-activator, p300, which is essential for the activity of ERα. However, AR can bind directly to p300 while ERα requires a co-regulatory protein to facilitate the binding, giving AR an advantage and effectively downregulating the proliferative effect of ER in both begin and malignant breast tissue (12,13).

Tumors overexpressing HER2 have a less favorable outcome when AR is also co-expressed, suggesting a unique

mechanism of tumor survival than that observed in ER positive tumors. Research suggests that AR may play into a positive feedback loop of HER2 activation, promoting tumor survival (14). AR can interact with canonical WNT signaling by binding to β-catenin in the nucleus and translocating to the promoter region of HER3 to promote gene transcription (15). This enhances the activity of the HER3/HER2 complex, which can induce further activation of AR via MAPK signaling. This positive feedback loop promotes the survival of $HER2^+/AR^+$ tumors, possibly explaining the discrepancy between outcomes in ER^+ and $HER2^+$ breast cancer.

In breast cancer research, the role of androgens and their associated receptor, AR, is becoming increasingly prominent, notably within the realm of TNBC. While AR is detected in a significant 70% to 90% of primary breast tumors—a prevalence on par with, or even exceeding, that of ER or PR—its expression in TNBC varies considerably, with percentages spanning from 10% to 60% (3,16-18). This inconsistency, partially influenced by numerous study-specific variables, highlights a pressing need to clarify AR's function in TNBC. Within the breast milieu, androgens exhibit diverse impacts, either promoting or inhibiting cell growth, dependent on their interplay with other steroid receptors, signaling pathways, and the presence of breast adipose fibroblasts (BAFs). For instance, in ER-positive cell lines, testosterone is converted to estrogen by abundant aromatase in BAFs, leading to ER-driven cell proliferation (19). Conversely, dihydrotestosterone, not being an aromatase substrate, suppresses proliferation in TNBC-like cells. Adding to the complexity, recent research indicates that some ER-negative cell lines, typical of TNBC, proliferate in response to androgens—a mechanism potentially distinct from conventional estrogen signaling. These observations emphasize the urgent need for a deeper exploration of AR's intricate role and its prospective therapeutic potential in TNBC.

Clinical trials with androgen receptor inhibitors

With the diverse pathways proposed for AR's role in breast cancer pathogenesis, many studies are underway to determine if mitigating AR's effect in the breast milieu can improve patient outcomes, especially in the case of TNBC that historically lacks targeted treatment options.

Bicalutamide is the 1st generation of AR inhibitors that has been classically used in prostate cancer but has also recently been studied in breast cancer. A phase II trial in patients with metastatic ER-negative breast cancer in 2013 demonstrated a 19% clinical benefit rate (CBR) with minimal toxicity, suggesting its utility in AR-positive ER-negative tumors (20). Currently, there are several more studies underway to further examine the potential of bicalutamide as a treatment for AR^+ TNBC.

Abiraterone is another medication used in prostate cancer that suppresses the synthesis of androgens by inhibiting CYP17A1. It is commonly used in conjunction with prednisone in cancer treatments. One study in 2016 treated 34 women with AR^+ TNBC with 5 mg prednisone twice daily and abiraterone 1,000 mg daily until disease progression or intolerance. The CBR was 20.0%, including 1 compete response (CR) and 5 with stable disease (SD) (21). This data suggests abiraterone plus prednisone may be beneficial for some patients in this subtype of breast cancer.

Enzalutamide is a 2nd generation AR inhibitor also used to treat prostate cancer. Enzalutamide has shown enhanced efficacy and clinical benefit when compared to bicalutamide in prostate cancer treatment. It has also demonstrated promising clinical response in AR+ TNBC. For example, treatment with enzalutamide in AR^+ TNBC showed a 16-week CBR of 33%, progression-free survival of 3.3 months, and medial OS of 17.6 months in women whose tumors had at least 10% nuclear AR expression (22).

A selective androgen receptor modulator (SARM), enobosarm, has also recently showed promise in previously treated AR-positive breast cancer. In combination with immune checkpoint inhibitor pembrolizumab, treatment with enobosarm showed a modest CBR of 25% at 16 weeks in heavily pre-treated AR^+ TNBC (23). Additionally, a phase 2 study showed that AR expression levels could predict positive responses to enobosarm, with a CBR of 32% for 9 mg dosing (24). Enobosarm is also being investigated in the phase 3 ENABLAR-2 trial alongside CDK4/6 inhibitor abemaciclib for second-line treatment of AR-positive, ER-positive, HER2-negative breast cancer after progression on endocrine therapy combined with palbociclib (25).

Several preclinical studies have provided the rationale for exploring combination treatments, suggesting potential benefits. Lehmann *et al.* investigated the impact of targeting the PI3K pathway alone or in conjunction with an AR antagonist on AR^+ TNBC cells using cell lines and xenograft models. The study demonstrates that combining PI3K inhibitors with AR antagonists significantly reduces the growth and viability of AR^+ TNBC cells, suggesting a potential targeted treatment strategy for this subtype (26). One study investigated AR and programmed cell death

Table 1 Ongoing clinical trials with combined treatment with AR blockade

Breast cancer subtype	Trial agent	Phase	Goal accrual	NCT study number
AR$^+$ HER2$^-$ MBC	Abemaciclib with bicalutamide	Ib/II	60	NCT05095207
AR$^+$ and PTEN$^+$ MBC	Alpelisib (PI3K inhibitor) with enzalutamide	Ib	18	NCT03207529
AR$^+$ mTNBC	Docetaxel with seviteronel-D	Ib	65	NCT04947189
Early stage AR$^+$ TNBC	Paclitaxel with enzalutamide	II	37	NCT02689427
AR$^+$ mTNBC	Ribociclib (CDK 4/6i) with bicalutamide	Ib/II	37	NCT03090165

AR, androgen receptor; HER2, human epidermal growth factor receptor-2; MBC, metastatic breast cancer; PTEN, phosphatase and tensin homolog; mTNBC, metastatic triple-negative breast cancer; NCT, National Clinical Trial.

ligand 1 (PD-L1) expression in 197 TNBCs, including those from BRCA1 carriers and non-carriers (27). AR expression was less common in BRCA1 carriers (9.2%) compared to non-carriers (23.7%), while PD-L1 expression (26%) showed no significant difference. In addition, PD-L1 positivity in cancer cells significantly predicted AR expression on ≥1% of cancer cells. These findings could aid in treatment selection and clinical trial decisions for TNBC patients. There are currently several additional studies using AR inhibitors combined with other medications undergoing clinical trials shown in *Table 1* after modest responses were shown from single agent use of AR inhibitor in breast cancer.

Conclusions and future direction

The AR has emerged as a promising therapeutic target for breast cancer treatment. The complicated nature of its signaling pathway, intricately interconnected with other pivotal receptors like the ER and HER2, has posed challenges in the development of efficacious therapeutic interventions. However, recent scientific inquiries have made significant strides in unraveling the intricacies of AR signaling, thereby paving the way for the design of more potent therapeutic approaches. Presently, a multitude of clinical investigations are underway, focusing on synergistic treatment modalities that encompass combination therapies. These endeavors are predicated upon the newfound insights into AR signaling complexity, aiming to exploit this knowledge for enhanced treatment outcomes. The confluence of progressing research insights and strategically adapted clinical trials holds the potential to develop effective breast cancer treatments targeting the AR.

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Footnote

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