Androgen Receptor and Breast Cancer

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Androgen receptor (AR) is a member of the family of steroid nuclear receptors which also include the estrogen and progesterone receptors. It has a number of ligands including the endogenous testosterone (T) and 5-dihydrotestosterone (DHT) as well as a variety of synthetic agonists and antagonists, and it is involved in a complex network of signaling pathways that collectively regulate cell proliferation. Androgen receptors (ARs) are frequently expressed in breast cancer (BC) cells, but molecular mechanisms underlying BC progression and their implication as a prognostic and/or predictive marker in BC patients are still controversial. Long-debated issue are: the androgen effect on BC cell lines, the prognostic significance of the presence of ARs in the different BC subtypes, and the resulting clinical implications of ARs' expression in breast cancer patients.

Androgens are the major circulating sex hormones in females. In *premenopausal women* testosterone is mainly synthesized and secreted by the ovaries and adrenal glands, with additional biosynthesis occurring within peripheral tissues via metabolic conversion of circulating adrenal proandrogens. In *postmenopausal women*, large amounts of active androgens and the totality of estrogens are synthesized in peripheral tissues from the adrenal precursor dehydroepiandrosterone (DHEA). A part of testosterone is metabolized to estradiol as a result of activity of aromatase. In *normal breast tissue,* androgen and AR signaling exerts an antiestrogenic, growth-inhibitory influence, and the relative levels of circulating sex hormones influence the proliferative capacity of breast epithelial cells. In the absence of estrogenic hormone stimulation, postmenopausal breast tissue undergoes a progressive

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involution characterized by increasing atrophy of glandular tissue and fibrosis of the stroma. These morphological changes may be due to unopposed androgen action.

The clinical-pathological implication of the androgen/AR pathway *on breast cancer growth* is not yet well known. Preclinical studies suggest that the action of androgens is *bidirectional:* mainly proliferative, because circulating androgens are the precursors of estrogens, but also antiproliferative, because AR activation restrains ER activity, inhibiting normal breast tissue growth.

The *proliferative action* is indirect: testosterone is metabolized by aromatase within breast tissue to 17-estradiol (E2), that is the most potent natural ER-ligand. Therefore the influence of circulating testosterone on the proliferative capacity of breast epithelial cells is in part dependent upon the relative expression and activity of aromatase. In studies of transgenic mice that overexpress the aromatase gene (AROM), males undergo abnormal breast development due to excess exposure to estradiol. Administration of an aromatase inhibitor (AI) to AROM transgenic male mice causes involution of the breast tissue, regression that is associated with increased exposure to testosterone, and induction of AR expression in the breast epithelium [1].

The antagonistic cross talk between AR and ER explains the *antiproliferative action* of androgens on ER-positive BC cells. In molecular study, AR did not bind to ERß, suggesting that this oppositional mechanism is specific for the ERα-isoform [2]. Peters et al. [3] demonstrated that *loss of AR expression* is significantly associated with poor 10-year survival outcome in grade III invasive breast ductal adenocarcinomas. They also evaluated potential regulatory mechanisms that may account for the loss of AR expression. Showing that DNA hypermethylation in the AR promoter is associated with loss of AR expression in breast cancer cells.

Recently, the androgen receptor is intensively discussed as a *prognostic and/or predictive* marker in BC patients. The AR is the most prevalent sex steroid receptor in in situ*, invasive, and metastatic* breast cancers, occurring in up to 90 % of primary tumors and 75 % of metastases [4]. AR-positive phenotype was found associated with favorable tumor characteristics, such as small tumor size, low histological grade, ER- and progesterone receptor (PR)-positive status, and with better outcomes than in patients with AR-negative tumors [5]. However, ARs play different roles at different stages of disease or in different subtypes of BC, and their significance is still under investigation.

ARs are expressed in up to 70 % of *ER-positive BC*. High levels of ARs confer a survival advantage, which suggests that ARs action may have a tumor-suppressive effect in malignant ER-positive BC cells. In this subtype of BC patients, AR expression is also associated with chemotherapy responsiveness [6].

Hickey et al. [2] observed that AR positivity was over 75 % in the large majority of prospectively collected cases of ER-positive breast cancers. This degree of AR positivity was higher than that observed in normal breast tissues. They hypothesized that AR levels increase with the progression of ER-positive tumor in a homeostatic attempt to restore the balance of sex hormone activity that normally regulates mammary epithelial cell proliferation. Failure to upregulate AR signaling may result in insufficient androgenic antagonism.

As mentioned above, multiple studies show that AR levels predict positive outcomes for women with luminal breast cancers; Castellano et al. [7] showed that AR is an independent prognostic factor in the luminal B subtype, which is a more aggressive form of luminal disease. They developed a new prognostic index (PI) specific for ER-positive breast cancers (ERPI), in contrast with other PIs that have been created for breast cancer in general. This new ERPI takes into account the expression of AR and demonstrates the prognostic relevance of its expression in breast cancers.

Up to 50 % of *ER-negative BC* are reported to be positive for ARs. Currently, epidemiological, clinical, and preclinical data on the role of androgens and ARs on this BC subtype are still controversial. The prognostic value of AR as an independent predictor of relapse-free or overall survival in ER-negative disease is less clear [2].

In *HER2-expressing cell lines*, preclinical studies suggest that ARs have a proliferative effect, probably due to the cross talk between ARs and HER2 pathways [8]. Micello et al. [9] studied a specific group of patients with breast cancer who were ER- and PR-negative and c-erbB-2-positive for their AR status and found that the group having positive AR had more frequent nodal involvement but similar survival rates. Arslan et al. [10] analyzed the same subtype of BC patients, but AR was not shown to be a prognostic factor. However, they concluded saying that they still do not exactly know the function of AR and its prognostic effect in this specific group of patients.

Finally, the biological significance of AR in *triple-negative breast cancer* (TNBC) has remained relatively unknown. The rate of AR positivity among TNBC cases varies depending on the study population (0–53 % of all TNBC patients) [11]. There are conflicting data on the issue; in the Tike et al. study [12], disease-free survival was significantly better in androgen receptor-positive, triple-negative breast cancer with a trend observed for improved overall survival. Androgen receptor positivity was associated with a favorable clinical outcome and a lower rate of recurrence within 5 years of diagnosis. The loss of AR expression was significantly associated with worse pathological parameters. However, there are data in the opposite direction that show AR as a negative prognostic factor for patients with TN breast cancer [13].

Many theoretical and experimental models indicate that androgen receptors can play an important role as prognostic factors in BC patients. But AR can be also considered as a *new therapeutic target*. Historically, systemic *androgen treatment* was used in the clinical management of breast cancer and was associated with a 15–30 % incidence of disease regression, particularly when the tumor expressed ER [14]. Additionally, treatment with the androgen resistant to metabolism fluoxymesterone was associated with a tumor-suppressive effect similar to the selective estrogen receptor modulator tamoxifen, with some evidence for beneficial combinatorial treatment effects [15]. Fluoxymesterone was also reported to improve the therapeutic efficacy of chemotherapy. Possibly, the efficacy of androgen treatment was in part due to its antiproliferative, antiestrogenic actions in the breast tumor cells, particularly those of a luminal phenotype. Recent literature has shown that dehydroepiandrosterone and its sulfate have growth-inhibitory effects on ER- and PR-negative breast cancer cell lines that show androgen receptor expression [16]. These may

potentially be applied as adjunctive therapy to ER-negative/androgen receptor-positive BC, considering the few treatment options for this BC subtype.

Another debated issue is the relationship between androgens and *aromatase inhibitors (AIs).* In contrast to tamoxifen, aromatase inhibition blocks conversion of androgens to estrogens increasing levels of available testosterone and/or DHT. Studies have implicated activation of AR as a partial mediator of aromatase inhibitor therapeutic efficacy in ER-positive BC [17]. Androgen treatment for hormone therapy may be considered in ER-positive disease that either do not respond to hormone therapy or become resistant [18].

In conclusion AR is an emerging target in breast cancer, with potential significance as a prognostic and/or predictive marker and for therapeutic management of both primary and advanced disease. Further prospective larger studies are needed for a more comprehensive investigation of the role of androgens and ARs in breast carcinogenesis. The simultaneous evaluation of ER status, AR expression, and circulating testosterone levels may identify different subsets of breast cancers whose management may be influenced by personalized treatment.

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