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REVIEW

Androgen Receptor (AR) and Breast Cancer: Reference to the AR Status in Normal/Benign Breast Luminal Cells

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The role of androgen and androgen receptor pathway in breast cancer development, prognosis and treatment has gained enormous attentions in recent years, largely because of the effort to identify new markers for targeted treatment of triple (ER/PR/Her2) negative breast carcinomas. This mini-review will discuss AR and breast cancer from the perspectives of normal/benign breast luminal epithelium.

Keywords: AR; breast cancer; luminal cells

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Breast carcinogenesis is regarded as a hormone driven malignant transformation process[1]. Estrogen and Estrogen Receptor (ER) pathway has been studied extensively and has been applied in breast cancer prognosis and treatment for decades. In comparison, the role of androgen and androgen receptor pathway in breast cancer is less clear. Androgen is a normal circulating hormone in females, with a relatively stable serum level during the menstrual cycle and menopause, compared with estrogen[2]. Epidemiologic studies on the association of serum androgen levels and breast cancer risk have produced inconsistent, sometimes contradictory results[3-10], although there seems to be a positive association in postmenopausal women. Failure to distinguish between different subtypes of breast carcinomas, such as AR positive versus AR negative carcinomas may have at least partially contributed to the inconsistent results in these studies.

Nevertheless, AR is strongly and diffusely expressed in the majority of breast carcinomas. Depending on the methodology and study population, AR positivity in breast carcinomas has been reported ranging from 50% to 90%, with the similar staining intensity as ER[11-13]. While most of the ER-positive breast carcinomas are also positive for AR[14], AR is also positive in some of the triple negative and high grade breast carcinomas, even though the reported percentage is considerably variable among different studies (ranging from 0-53%)[11, 12, 14-17]. Furthermore, studies have shown that the AR expression in breast carcinomas is clinically relevant. It has been reported that AR positivity is associated with favorable tumor differentiation (such as lower Bloom-Richardson grade, lower Ki67 labeling index, etc) and lower tumor burden[14, 15, 18]. In addition, AR expression has been shown to correlate with a better clinical outcome in ER-positive tumors[13, 18-20], although this correlation may not always be obvious in ER negative tumors[21-29], in part because of the insensitivity of AR-positive only tumors to routine chemotherapy compared to triple-negative and AR-negative tumors. Moreover, Yu *et al.* [30] and Gonzales *et al.* [31] compared the AR status in ductal carcinoma in-situ (DCIS) with adjacent invasive ductal carcinoma (IDC) and pure DCIS, and concluded that AR may play a role in the progression of DCIS to IDC.

These clinical-pathological findings, together with in-vitro studies on breast cancer cell lines, have led to diverse hypotheses regarding the role of androgen-AR pathway in breast carcinogenesis. One of the limitations of these studies is that they mostly focused on tumors and tumor cells, without reference to the AR status of the precursor/progenitor cells. A better knowledge of the biology of the normal/benign breast luminal cells needs to be emphasized when we are trying to understand the steps in breast cancer initiation and progression.

It is well recognized that terminal ductal lobular unit (TDLU) is the primary site where the breast carcinogenesis initiates. Normally, the epithelium of the TDLU is composed of two main cellular lineages: luminal cells surrounding the central lumen and myoepithelial cells located basally adjacent to the basement membrane. However, even inside the luminal epithelium, not all the cells are phenotypically the same. The prevailing concept is that there might be distinct subtypes of luminal cells in normal human breast which may serve as the cell of origin of different subtypes of breast cancers. Studies have shown that the expression of ER and PR in luminal epithelium is present in a scattered or clustered pattern in a minority of cell population [32, 33]. We demonstrated that there is a similar distribution pattern of AR expression in the luminal cells of TDLUs as well [34]. We then used regular and dual-labeling immunohistochemical staining for ER and AR on consecutive sections of normal/benign breast tissue and showed that most hormone receptor-positive luminal cells were simultaneously positive for ER and AR; about 10% of the cells were AR-positive only, while AR-negative/ER-positive cells were rare. This distribution pattern of hormone receptor expression is similar to that reported in invasive breast carcinomas[14].Similarly, Santagara *et al.*[35] systematically analyzed the expression of a large set of breast epithelial markers and hormone receptors in normal human breast epithelium and identified 11 differentiation states in the luminal cells. They further observed that 95% of human breast carcinomas were phenotypically identical to one of these normal luminal breast cell subtypes. Visvader *et al.* proposed a model of human breast epithelial hierarchy, based on the similarity of gene signatures by gene expression analysis, suggesting that the different subtypes of breast cancer may arise from their normal counterparts within the luminal sub-lineages[36]. In fact, ER/PR-positive luminal cells have been shown to hold progenitor/stem cell features [37, 38]. One would speculate that this would also hold for AR-positive luminal cells. Distinct oncogenic events may target different progenitor cells, including AR-positive only cells, in breast luminal epithelium to give rise to distinct breast cancer subtypes.

Indeed, studies have shown that the cell-autonomous factor of the cell of origin and the distinct oncogenic process initiated in these cells may have contributed to breast cancer heterogeneity. Ince *et al.* [39] transformed two cell populations with the same set of genetic elements and demonstrated that the normal cell phenotype strongly influenced the phenotype of tumors derived in terms of histopathology, tumorigenicity and metastasis behavior. On the other hand, Elenbaas *et al.* [40] showed that transformation of different cell types may involve different oncogenic pathways. Comprehensive molecular studies across breast cancer subtypes showed that certain genes, such as GATA3 and PIK3CA, were mutated mostly in hormone receptor-positive breast carcinomas, including AR-positive/triple-negative carcinomas, while p53 mutation was more common in hormone receptor-negative basal-like tumors[41].

However, the steroid hormone receptor-positive luminal cells in normal/benign breast tissue appear to be proliferatively inactive. The dissociation between ER/PR expression and Ki67 labeling in normal breast luminal cells has been reported in human and animal models by many different groups[33,42]. A similar staining pattern has been reported for AR expression and Ki67 labeling [35]. Another way to assess the activeness of the hormone receptor positive cells could be to exam the expression of their downstream proteins. Studies at different levels indicated that PSA and GCDFP are the AR downstream proteins and are co-expressed with AR in breast carcinomas [43-46]. However, using immunohistochemical staining on consecutive sections, we observed no immunohistochemically identifiable PSA expression in AR-positive luminal cells and no association between GCDFP and AR expression in luminal cells [34]. Our findings suggest that although the AR is strongly expressed in luminal cells in normal/benign breast tissue it may not be functionally active. Further carcinogenic events will be needed for the initiation and progression of carcinogenesis in these AR-positive luminal cells.

The molecular sub-classification based on gene expression profiling using immunohistochemical surrogates has subdivided breast carcinomas into luminal A (ER/PR+, Her2-); luminal B (ER/PR/Her2+); Her2 overexpression (ER/PR -, Her2+, any CK5/6 and EGFR); basal-like (ER/PR/Her2 -, CK5/6 and/or EGFR +); and triple-negative, non-basal (ER/PR/Her2 -, CK5/6 and EGFR -) types. Based on this classification, AR-positive only breast tumors would be classified as a triple-negative, non-basal subtype, with a notoriously poor prognosis. Santagara *et al.* [35] proposed a normal-cell type-based ontological classification system, which is phenotype-oriented to better reflect the pathophysiology of breast cancer. In this system, AR

positive-tumors are considered to be one of the luminal types of breast cancer and associated with a better prognosis compared to ER/PR/AR and VDR (vitamin D receptor)-negative tumors.

In summary, AR-positive breast carcinomas may arise from AR-positive progenitor cells in normal/benign breast luminal epithelium. The presence of diverse sub-lineage breast luminal cells, together with their distinct carcinogenic events, could explain breast cancer as a heterogeneous group of diseases. However, like ER-positive progenitor cells, AR-positive progenitor cells may be functionally inactive.

Conflicting interests

The authors have declared that no competing interests exist.

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