Androgen Receptor Expression Associates With Distinctive Clinicopathological and Molecular Features in ER-Positive and ER-Negative Breast Cancer

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Abstract

Background

Androgen receptor (AR) expression is frequently observed in breast cancer, but its association with estrogen receptor (ER) expression of breast cancer remains unclear.

Methods

In this study, we analyzed the clinicopathological and molecular features associated AR loss in ER-positive and ER-negative breast cancer respectively, trying to elucidate the molecular correlation between AR and ER.

Results

Our results showed that AR loss was associated with different clinicopathological characteristics in ER-positive and ER-negative breast cancer. Moreover, the expression of AR was correlated with different molecular features in ER-positive and ER-negative breast cancer.

Conclusions

These results suggest that the role of AR in ER-positive breast cancer is distinctive from that in ER-negative breast cancer.

Background

Breast cancer was the most common malignancy in women in which 70%-80% of them expressed steroid hormone receptor including estrogen receptor (ER) and progesterone receptor (PR) [1, 2]. ER-positive breast cancer was estrogen-dependent and was driven mostly by the activated ER pathway which was also effectively used as a therapeutic target. As another hormonal receptor, androgen receptor (AR) was expressed in 70-85% of all breast cancer and that ratio was about 10-63% in triple negative breast cancer (TNBC) which did not express ER, PR or HER2 [3, 4]. While in ER positive breast cancer, AR was expressed in 70%-95% of cases, varying in different studies [4, 5]. The expression of AR was reported to be related with good prognosis in early breast cancer in terms of both disease-free survival and overall survival [6, 7]. While in ER+ and ER- breast cancer, the expression of AR was reported to have opposite prognostic value as AR expression was correlated with increased DFS in luminal breast cancer and decreased DFS in triple negative breast cancer (TNBC) [8].

While AR expression was more prevalent in breast cancer than ER [9, 10], the detailed molecular role of AR in breast cancer still remains unresolved. AR has previous been shown to support estradiol mediated ER

activity in ER+/AR+ breast cancer and AR inhibition can be synergized with tamoxifen to reduce proliferation of ER+ breast cancer [11]. A recent study showed that in ER-positive breast cancer, AR act as a tumor suppressor gene by inhibiting the binding of ER to the estrogen response elements (EREs) and consequently suppressing the activated ER pathway [12]. Moreover, the activity of AR pathway calculated by expression of a gene panel was positively correlated with disease-free survival in ER+ breast cancer, suggesting that AR agonist instead of antagonist should be applied in ER+ breast cancer. In ER- breast cancer, the expression of AR activates subsequent transcriptional program and its activation can promote cell proliferation [13, 14]. Although prognostic value of AR expression was controversial, AR antagonist enzalutamide has been investigated for the treatment of TNBC patients with clinical benefit rate (CBR) reaching 33% at 16 weeks [15]. Selective androgen receptor modulators (SARMs) are clinically available and are being investigated as a medicine for AR-positive breast cancer [16, 17]. It is important to understand the role of AR in ER+ and ER- breast cancer for the precise application of SARMs in breast cancer.

In this study, we analyzed the clinicopathological and molecular features associated AR loss in both ER-positive and ER-negative breast cancer and excluded HER2-amplified cases, trying to elucidate the molecular correlation between AR and ER. Our results shown that AR-positive breast cancer has better clinicopathological features that AR-negative BC especially in ER-negative subtype.

Results

1. Correlation between expression of AR and clinicopathological features in ER+ and ER- breast cancer

A total of 323 invasive breast cancer cases were recruited in our study diagnosed from September 2019 to May 2021 from Peking University Cancer Hospital (Figure 1). All cases have immunostaining or fluorescent *in situ* hybridization (FISH) result of ER, PR, AR and HER2. Positivity of ER, PR and AR was defined as $\geq 1\%$ cancer cells showing positive nuclear staining. Two hundred and seventy-four cases (85%) were ER positive and 49 (15%) cases were ER negative. The clinicopathological characteristics between AR+ and AR- groups was analyzed and compared in ER+ and ER- breast cancer respectively (Table 1 and Table 2).

Table 1
Clinicopathological characteristics of the ER+/AR- and ER+/AR+ group

Group	ER+/AR- (n=21)	ER+/AR+ (n=253)	<i>P</i>
Age			
Mean (SD)	52.2 (11.7)	53.5 (11.4)	0.603
Grade			
I	1 (4.8)	26 (10.3)	0.062
II	16 (76.2)	212 (83.8)	
III	4 (19.0)	15 (5.9)	
Histology			
IDC-NST	21 (100.0)	243 (96.0)	0.835
Invasive lobular carcinoma	0 (0)	5 (2.0)	
Micropapillary carcinoma	0 (0)	3 (1.2)	
Mucinous carcinoma	0 (0)	2 (0.8)	
EGFR			
Negative	16 (76.2)	210 (83.0)	0.386
Positive	3 (14.3)	16 (6.3)	
Unknown	2 (9.5)	27 (10.7)	
CK5/6			
Negative	19 (90.5)	246 (97.2)	0.168
Positive	2 (9.5)	6 (2.4)	
Unknown	0 (0)	1 (0.4)	
PR			
Negative	5 (23.8)	15 (5.9)	0.010
Positive	16 (76.2)	238 (94.1)	

Table 2
Clinicopathological characteristics of the ER-/AR- and ER-/AR+ group

Group	ER-/AR- (n=26)	ER-/AR+ (n=23)	<i>P</i>
Age			
Mean (SD)	49.1 (12.9)	58.1 (12.9)	0.019
Grade			
I	0 (0)	0 (0)	0.016
II	5 (19.2)	13 (56.5)	
III	21 (80.8)	10 (43.5)	
Histology			
IDC-NST	26 (100.0)	22 (95.7)	0.951
Apocrine Carcinoma		1 (4.3)	
EGFR			
Negative	3 (11.5)	2 (8.7)	0.943
Positive	21 (80.8)	19 (82.6)	
Unknown	2 (7.7)	2 (8.7)	
CK5/6			
Negative	6 (23.1)	8 (34.8)	0.556
Positive	20 (76.9)	15 (65.2)	
PR			
Negative	26 (100.0)	19 (82.6)	0.090
Positive	0 (0)	4 (17.4)	

In ER+ breast cancer, PR expression was the only clinicopathological characteristics that showed difference between ER+/AR- and ER+/AR+ groups. The expression of PR was significantly lower in ER+/AR- group than in ER+/AR+ groups ($P = 0.01$), indicating a common mechanism behind the loss of expression for the two steroid hormone receptors (Table 1). In ER- breast cancer group, the expression of PR also showed the same trend though the P value was marginal ($P = 0.09$). Patients diagnosed with ER-/AR+ breast cancer were 9 years older than those with ER-/AR- breast cancer, consistent with previous findings [3]. The histologic grade of ER-/AR+ and ER-/AR- groups showed a significant difference with AR loss correlated with a more advanced histologic grade. Nevertheless, the positivity of CK5/6 and EGFR which can be served as an indicator for basal-like character was not different between the ER-/AR+ and

ER-/AR- group (Table 2). The above results indicated that AR-loss in ER- breast cancer has stronger impact than AR-loss in ER+ breast cancer. To further confirm this, Ki67 proliferation index was plotted and compared (Figure 2). No difference was detected in ER+ breast cancer while the Ki67 index was much higher in ER-/AR- group than in ER-/AR+ group.

2. Estrogen receptor expression correlates with androgen receptor expression

To further look at the correlation between ER and AR, the expression of them in IHC were plotted in Figure 3A. In IHC level, it can be noticed that though the expression of AR was mostly enriched in ER-high expression cases, there were many cases in which the expression of AR and ER were discordant. Also, we have selected 466 cases of breast cancer in TCGA by excluding the HER2-enriched cases. The expression of AR and ESR1 genes were displayed as heatmap in Figure 3B. The expression of AR and ESR1 were highly correlated. To further look at the correlation of AR and ER in different subtypes of breast cancer, the expression of AR and ESR1 in the five molecular subtype of breast cancer along with in normal breast tissue was plotted in Figure 4. Compared with normal breast tissue, expression of AR and ESR1 were higher in luminal A and B subtype and lower in basal-like subtype. Whereas, in HER2-enriched subtype, AR showed higher expression compared with normal breast tissue while ESR1 was expressed at a lower level than normal breast tissue. The correlation between the expression of AR and ESR1 was only significant in luminal A and basal-like subtype while not significant in luminal B and HER2-enriched subtype (Figure 5).

3. Androgen receptor expression regulation was different in ER+ and ER- breast cancer

To further look at the molecular features related with AR-expression in ER+ and ER- breast cancers, the above 466 breast cancer cases from TCGA were divided into AR-high and AR-low groups according to AR expression with the median expression value of AR as the threshold. Among all breast cancer cases, 406 of them were ER positive and 60 of them were ER negative. The baseline clinicopathological characteristics and comparison between AR-high and AR-low groups in ER+ and ER- breast cancers were listed in Supplementary Table 1 and Supplementary Table 2 respectively. Differentially expressed genes between AR-high and AR-low groups were identified in ER+ and ER- breast cancer respectively. In ER+ breast cancer, the upregulated and downregulated genes between AR-high and AR-low groups were plotted in Figure 6A while those upregulated and downregulated in ER- breast cancer were plotted in Figure 6B. To analyze the similarity of the differentially expressed genes (DEGs) between the ER+ and ER- breast cancer, the number of DEGs and the number of overlapped genes was plotted in Figure 6C. The overlapped genes among the four DEG groups were designated as group I-IV respectively. The genelist for group I-IV were provided in Supplementary Table 3. Most of the DEGs have no overlap, suggesting molecular mechanisms related with AR loss were different between ER+ and ER-breast cancer.

Methods

1. Patient selection

The pathology database in Peking university Cancer hospital (PUCH) was queried and all breast core need biopsy (CNB) cases diagnosed from September 2019 to May 2020 were retrieved. A total of 323 breast carcinoma cases were selected. The cases were reviewed by two experienced pathologists (Y Liu and M Long). Ki-67 score is defined as the percentage of positively nuclear stained cells divided by the total number of malignant cells scored. When the staining is homogenous across sample, global Ki-67 score was used and for heterogenous staining Ki-67 score counted in hot spots region. For breast cancer from TCGA, UCSC Xena an online exploration tool for public and private, multi-omic, and clinical/phenotype data, was used to download data of selected samples [18]. The 'TCGA Breast Cancer (BRCA)' cohort in the UCSC Xena was selected. All raw data used was downloaded from the 'Phenotypes TCGA Hub'.

2. Analysis of differentially expressed genes

The Fragments Per Kilobase of transcript per Million mapped reads upper quartile (FPKM-UQ) RNA-seq data were log2-transformed before further process. The FPKM-UQ is implemented at the GDC on gene-level read counts that are produced by HTSeq and based on a modified version of the FPKM normalization method [19]. The log2-transformed FPKM-UQ data were analyzed using limma20 (Version 3.44.3) functions `lmFit`, `eBayes` and `topTable` to identify DEGs [20]. Student t-test was utilized to calculate the P values of genes. Genes with $P < 0.05$ were considered as DEGs [21]. *P* values were calculated as two-sided, with statistical significance declared for *P* less than 0.05.

Discussion

In this study, AR was expressed in 76% and 47% of ER+ and ER- breast cancer respectively in PUCH cohort. Our results showed that AR loss was associated with distinctive clinicopathological characteristics in ER+ and ER- breast cancer. While AR-expression only associates with PR positivity in ER+ breast cancer, it correlates with greater age at diagnosis and less advanced histologic grade. Our findings differ with previous study in which AR expression was found associated with lower histologic grade, pathological T stage in ER+ breast cancer but not in ER- breast cancer [22].

Molecular subtyping of TNBC identified that about 15–20% of TNBC can be classified as luminal androgen receptor (LAR) subtype which has greater age at diagnosis and low proliferation index [23–25]. However, for AR-positive TNBC, the report on the age at diagnosis compared with other TNBC is controversial [3, 26–30]. Moreover, previous study has identified no difference between ER-/AR+ and ER-/AR- breast cancer in terms of age at diagnosis [22]. Our result showed that ER-/AR+ breast cancer shares similar characteristics with LAR in terms of low proliferation index and older age of diagnosis. Also, we found that the expression of AR was correlated with different molecular features in ER+ and ER- breast cancer, suggesting that the role of AR in ER+ breast cancer may be distinct from those in ER- breast cancer.

There are several limitations of our study. First, the PUCH cohort was a retrospective study without survival information, thus the prognostic value of AR-loss in ER+ and ER- breast cancer cannot be

investigated. Secondly, our analysis only focused on the HER2-negative breast cancer, previous studies demonstrated that the correlation between AR pathway activity and AR expression varied in HER2-positive and HER2-negative breast cancer [14, 31].

Conclusions

Our findings demonstrate that the expression of AR is associated with distinctive clinicopathological and molecular features in ER-positive and ER-negative breast cancer. Further characterization of the altered pathways and molecular features associated with AR expression in both ER+ and ER- breast cancer is required for the precise application of androgen receptor targeted therapy.

Declarations

All data used in this publication were generated by the TCGA project. The authors declare no competing interest.

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<https://www.cancer.gov/tcga>.

Authors' contributions

TH and ML contributed to the conception of the study; TH, SW, YL and ML performed the data analyses; YL and GZ contributed to the methodology; YL, GZ and SW helped the manuscript writing with constructive discussion; TH and ML wrote the final manuscript.

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Ethics declarations

Ethics approval

The study was approved by Peking University Cancer Hospital ethics committee (Reference number 2020KT113).

Consent for publication

Written consent was obtained from all patients participated in this study.

Competing interests

None.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the manuscript.

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Figures

Figure 1

Flow chart of patient selection from the Peking University Cancer Hospital (PUCH) cohort

Figure 2

Comparison of Ki67 expression between AR+ and AR- groups. Box plot of Ki67 proliferation index in ER+ breast cancer (A) and in ER- breast cancer (B) respectively in the PUCH cohort.

Figure 3

Summarize of number of patients with specific AR and ER expression (A) Cell percentage categories of AR and ER expression in IHC. Case number of each specific AR and ER expression status were summarized and presented. AR and ER expression were reported either as negative or as the percentage of cell showed positive expression which were sub-grouped into 10 categories with a 10 percent interval.

(B) The expression profile of AR and ESR1 in HER2- breast cancers from TCGA. The expression of AR and ESR1 gene were divided into ten equal parts according to the maximum and minimum value and presented in heatmap.

Figure 4

Expression of AR and ESR1 gene in normal breast tissue and four intrinsic subtypes of breast cancer in TCGA cohort.

Figure 5

Correlation between the expression of AR and ESR1 in four intrinsic subtypes of breast cancer in TCGA cohort. Correlation plot of the expression of AR and ESR1 in four intrinsic subtypes of breast cancer. Regression line, Pearson's correlation coefficient and p-value were also displayed.

Figure 6

Molecular features associated with AR expression in ER+ and ER- breast cancer are distinct. (A-B) Differentially expressed genes (Volcano plot) of AR low expression and AR high expression groups in ER+ and ER- breast cancer from TCGA (Red: upregulated; Blue: downregulated; Black: no significant change). (C) Groups of DEGs identified above. All the genes are classified according to whether it was differentially expressed between AR low and AR high groups in ER+ and ER- breast cancer. A total of 9 groups genes can be identified including four groups (group I-IV) composed of overlapped gene.

Supplementary Files

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