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Original Article

Aurora kinase B is an exceptional prognostic biomarker for invasive ductal carcinoma and may be a new target for endocrine therapy-resistant breast cancer

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Abstract: *Background:* New treatments and molecular biomarkers should be researched and developed to improve the therapeutic outcomes of breast cancer patients. Objective: To investigate the correlations of Aurora kinase B expression with the clinicopathological characteristics of invasive ductal carcinoma (IDC). Methods: Tissue microarrays containing primary IDC specimens from 310 patients with 93.37±38.41 months follow-up were employed to assess the expression of Aurora kinase B using immunohistochemistry. Association of pathological characteristics with cumulative survival was analyzed by Kaplan-Meier analysis. Results: Aurora kinase B was expressed in 25.5% of the IDC samples. Aurora kinase B-positive patients had significantly poorer survival than Aurora kinase B-negative patients (P = 0.016). For subgroup analysis, in ER and/or PR positive subgroup, which is also endocrine therapy-receiving group, Aurora kinase B expression was associated with a poorer prognosis (P<0.05) both in premenopause patients and postmenopause patients. While in ER- and PR-negative subgroup, aurora kinase B expression was not correlated with patient's survival. Conclusion: Our results indicate that aurora kinase B is an exceptional prognostic biomarker for invasive ductal carcinoma. Aurora kinase B may be related to endocrine therapy resistance. Inhibition of Aurora kinase B might be a candidate breast cancer treatment for patients with acquired resistance to anti-estrogen.

Keywords: Aurora kinase B, endocrine therapy resistance, invasive ductal carcinoma, tissue microarray

Introduction

Breast cancer is the most common carcinoma in women, and also the second most common cause of cancer death among women worldwide. The incidence of breast cancer has increased over the past decades [1-3]. As the considerable progress in treatment (surgery, chemotherapy as well as radiation, hormonal and targeted therapies), breast cancer mortality decreased for few years [4]. However, not all cases have benefited from those measures, there are still a part of patients eventually failed to obtain the effective treatment. Suitable biomarker for breast cancer which predicts the prognosis would be very useful for the treatment of breast cancer.

Tumor expansion depends on continued growth of tumor cells through mitotic cell division. A key mitotic regulator is the chromosomal passenger complex (CPC), which is important for chromosome condensation, correction of erroneous kinetochore-microtubule attachments, activation of the spindle-assembly checkpoint and cytokinesis 22. Aurora kinase B is part of the CPC, whose function is linked to chromatin modification in relation to the phosphorylation of histone H3 at Ser10 23. Aurora kinase B is overexpressed in a range of primary cancers (including head, neck, prostate, colon, and thyroid cancers), and significantly associated with clinical aggressiveness [5-8]. Furthermore, the expression of Aurora kinase B is tightly associated with breast cancer progression and particularly with metastasis [7, 9, 10]. Thus, studies are urgently needed to determine whether Aurora kinase B is a prognostic biomarker for IDC. Therefore, the present study

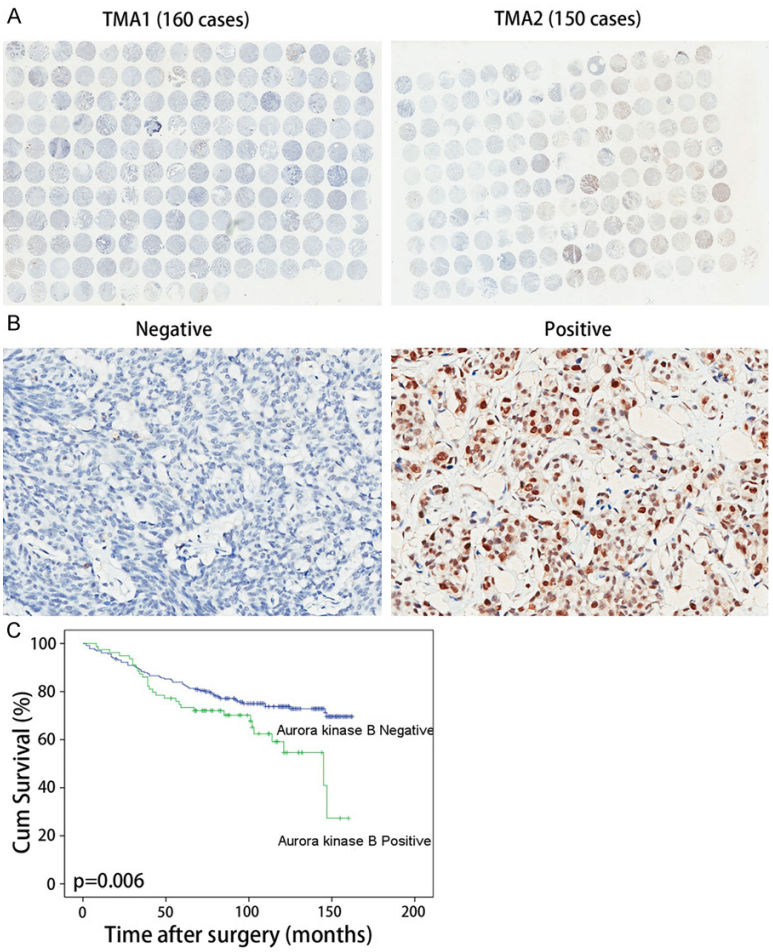

Figure 1. Tissue microarray (TMA) and IHC staining of Aurora kinase B in IDC tumor samples (310 cases) and association of Aurora B status with cumulative survival in IDC patients. Two TMA were used in our study, the 10 adjacent noncancerous tissue were excluded. Association of Aurora B status with cumulative survival of IDC patients is shown in Kaplan-Meier survival graphs. The *p* value shown in the figure was calculated from Log-rank test.

aimed to investigate the correlations between Aurora kinase B expression and the clinicopathological characteristics of IDC.

Methods

Ethical approval for this study was granted by the Human Research Ethics Committee of the Wuhan Union Hospital. Two tissue microarrays with a total of 310 paraffin-embedded IDC tissue specimens were purchased from the National Engineering Center for BioChips (Shanghai, China). Normal breast tissues removed for cosmetic purposes were prepared as the controls. All 310 patients had undergone mastectomy and/or axillary dissection (based on their clinical examinations: ultrasonography, magnetic resonance imaging, and mammography) between 2001 and 2008. Patients who had received preoperative hormone therapy or chemotherapy were excluded. All 310 patients had undergone standard chemotherapy, endocrine therapy, and radiotherapy after their surgical treatment according to NCCN. For endocrine therapy, premenopause patients take tamoxifen for 5 years while most postmenopause patients take AI for 5 years.

The expressions of Aurora kinase B, ER, PR, Ki-67, and human epidermal growth factor receptor 2 (HER2) were evaluated using immunohistochemistry (IHC) by three pathologists. Aurora kinase B expression was evaluated using an Aurora kinase B-specific antibody (ab2254; Abcam, USA) at a 1:100 dilution. This antibody recognizes both ectopically and endogenously expressed Aurora kinase B, and is highly specific for Aurora kinase B in both denaturing and non-denaturing conditions. Negative expressions of ER and PR were defined according to the current Swedish clinical guidelines (<1% positive nuclei), and Ki-67 expression was defined as positive (>14% positive nuclei) or negative (≤14% positive nuclei). HER2 status was assessed semi-quantitatively using a standard protocol (HercepTest; DakoCytomation) [11], with strong membranous staining (3+) defined as positive expression and membranous staining of 0 or 1+ defined as negative expression. Cases with membranous staining of 2+ were evaluated for HER2 amplification using fluorescent in situ hybridization.

The patients' clinical data were obtained from their medical records, and included age, distant metastasis, and TNM stage. We classified the breast cancer molecular subtypes according to the expression of various markers [12]:

Table 1. Pathological information of IDC

Pathological category		Case number (%)	Aurora B status positive	*p*
Age	<50	110 (35.5)	23	0.177
	≥50	200 (64.5)	56	
T category	T1	78 (25.2)	17	0.370
	T2	197 (63.5)	50	
	T3/T4	35 (11.3)	12	
N category	N0	145 (46.8)	39	0.545
	N1	86 (27.7)	22	
	N2	58 (18.8)	11	
	N3	21 (6.7)	7	
TNM-stage	0/I	41 (13.2)	12	0.812
	II	180 (58.1)	44	
	III	89 (28.7)	23	
ER status	Negative	109 (35.2)	27	0.832
	Positive	201 (64.8)	52	
PR status	Negative	156 (50.3)	41	0.745
	Positive	154 (48.7)	38	
HER-2 status	Negative	220 (71.0)	50	0.001*
	Positive	90 (29.0)	29	
Ki67 status	Negative	215 (69.4)	51	0.284
	Positive	95 (30.6)	28	
Molecular subtypes	Luminal A	136 (43.8)	29	0.008*
	Luminal B	75 (24.2)	25	
	HER-2	36 (11.6)	15	
	TNBC	63 (20.4)	10	

IDC: invasive ductal breast cancer. TNBC: triple negative breast cancer.
*P<0.05.

luminal A: ER+ and/or PR+, with HER2- and Ki67-; luminal B (HER2-): ER+ and/or PR+, with Ki67+ and/or HER2-; luminal B (HER2+): ER+ and HER2+, with any PR, Ki67, or HER2 overexpression; HER2-type: ER-, PR-, and HER2+; basal-like/triple negative: ER-, PR-, and HER2-.

Scoring and statistical analysis

Three experienced pathologists who were blinded to the patients' clinical information evaluated the IHC data. The expression of Aurora kinase B was graded according to the proportion of positive cells (0 = 0-5%, 1 = 6-25%, 2 = 26-50%, 3 = 51-75%, and 4 = 76-100%), and the intensity of the Aurora kinase B staining was graded as 0-3. The final score for Aurora kinase B expression (positive or negative) was calculated as the sum of both grades (negative: total grade 0-3, positive: total grade 4-7) (**Figure 1**).

All slides were scanned using an Aperio ScanScope slide scanner, and images of representative areas were obtained using Image Scope software (Aperio) and Adobe Illustrator. The primary clinical and histopathological data were compiled using EpiData software (version 3.1; EpiData Association, Odense, Denmark). SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA) was used to analyze the data. Clinical data were analyzed by Pearson Correlation test. Kaplan-Meier survival curves and the log-rank test were used to evaluate OS. Univariate and multivariate regression analyses were performed using a Cox proportional hazards model. All tests were two-sided, and *P*-values of <0.05 were considered statistically significant.

Results

Pathological information for the IDC tissue microarrays

The pathological information for the tissue microarrays is listed in **Table 1**. Among the 310 patients with IDC, the incidence of IDC varied in age (110 cases for patients who were <50 years old, and 220 cases for patients who were ≥60 years old). Approximately half of the patients had been diagnosed at a tumor size of T2, with no metastasis to the lymph nodes (N0), or at a TNM stage of II. Approximately two-thirds of the tumors were ER+, PR-, HER2-, or Ki67-. Based on the expression of ER, PR, HER2, and Ki67, the tumors could classified as luminal A (43.8%), luminal B (24.2%), HER2+ (11.6%), or triple negative (20.4%).

Aurora kinase B is tightly associated with a poor IDC prognosis

After reviewing the post-surgery survival rates, we discovered that the mean OS was 93.37± 38.41 months (95% confidential interval (CI): 88.94-97.61 months). As shown in **Table 1**, 79 of the 310 IDC tumors (25.5%) were strongly

Table 2. Univariate and multivariate analysis of prognostic factors in IDC for overall survival

Pathological category	Univariate analysis			Multivariate analysis		
	HR	*p*	95% CI	HR	*p*	95% CI
Aurora B status						
Negative versus positive	1.708	0.017*	1.099-2.656	1.604	0.038*	1.027-2.504
Age						
<50 versus ≥50	0.988	0.957	0.644-1.517			
T category						
T1 versus T2 versus T3/T4	1.819	0.001*	1.263-2.620	1.402	0.149	0.886-2.217
N category						
N0 versus N1 versus N2 versus N3	1.432	0.001*	1.167-1.758	1.164	0.426	0.801-1.691
TNM-stage						
0/I versus II versus III	1.977	0.000*	1.397-2.797	1.399	0.355	0.686-2.854
ER status						
Negative versus positive	0.607	0.019*	0.400-0.920	1.937	0.145	0.796-4.711
PR status						
Negative versus positive	0.513	0.022*	0.335-0.785	0.579	0.060	0.327-1.024
HER-2 status						
Negative versus positive	1.164	0.536	0.720-1.881			
Ki67 status						
Negative versus positive	1.303	0.233	0.843-2.014			
Molecular subtypes						
Luminal A versus Luminal B versus HER-2 versus TNBC	1.317	0.001*	1.114-1.558	1.402	0.065	0.979-2.007

IDC: invasive ductal breast cancer. *P<0.05.

stained for Aurora kinase B, which indicated that Aurora kinase B was expressed in IDC at a relatively low frequency. We also constructed a Kaplan-Meier survival curve and used the log-rank test to evaluate the association of Aurora kinase B expression with OS (**Figure 1**). This test revealed that Aurora kinase B expression was significantly and inversely associated with OS, and that patients with Aurora kinase B expression experienced a significantly poorer prognosis, compared to patients without Aurora kinase B expression (P = 0.016).

We also used a multivariate Cox regression model to analyze the association of OS with the standard pathological categories and Aurora kinase B expression (**Table 2**). The survival rate for Aurora kinase B-positive patients was much lower than that for the other pathological categories (T category: hazard ratio [HR] = 1.402, 95% confidence interval [CI]: 0.886-2.217; N category: HR = 1.164. 95% CI: 0.801-1.691; TNM stages: HR = 1.399, 95% CI: 0.686-2.854; ER status: HR = 1.937, 95% CI: 0.796-4.711; PR status: HR = 0.579, 95% CI: 0.327-1.024; molecular subtypes: HR = 1.402 95% CI: 0.979-2.007). These data clearly indicated that Aurora kinase B expression was an exceptional predictor of poor prognosis for IDC.

In ER and/or PR positive subgroup, Aurora kinase B is significantly associated with OS

To further assess the role of Aurora kinase B in IDC prognosis, we evaluated the associations of Aurora kinase B expression with OS in different ER and PR status using a Kaplan-Meier survival curve and the log-rank test (**Figure 2A**, **2B**). We found that in ER and/or PR positive subgroup, patients with Aurora kinase B high expression has a poor OS (**Figure 2A**, P<0.05), while in ER and PR negative subgroup there were no connection between Aurora kinase B status and OS (**Figure 2B**, P>0.05). To deeply explore the reason we compare pathological information of patients in different Aurora B status in ER and/or PR positive subgroup (**Table 3**). We found that only menstruation status has statistics significance, others have none statistics significance. Then to avoid the error cause by menstruation status, we evaluated the associations of Aurora kinase B expression with menstruation status using a Kaplan-Meier survival curve and the log-rank test. We found that in both premenopause patients and postmenopause patients, patients with Aurora kinase B high expression has a poor OS (**Figure 2B** and **2C**, P<0.05). Thus, in

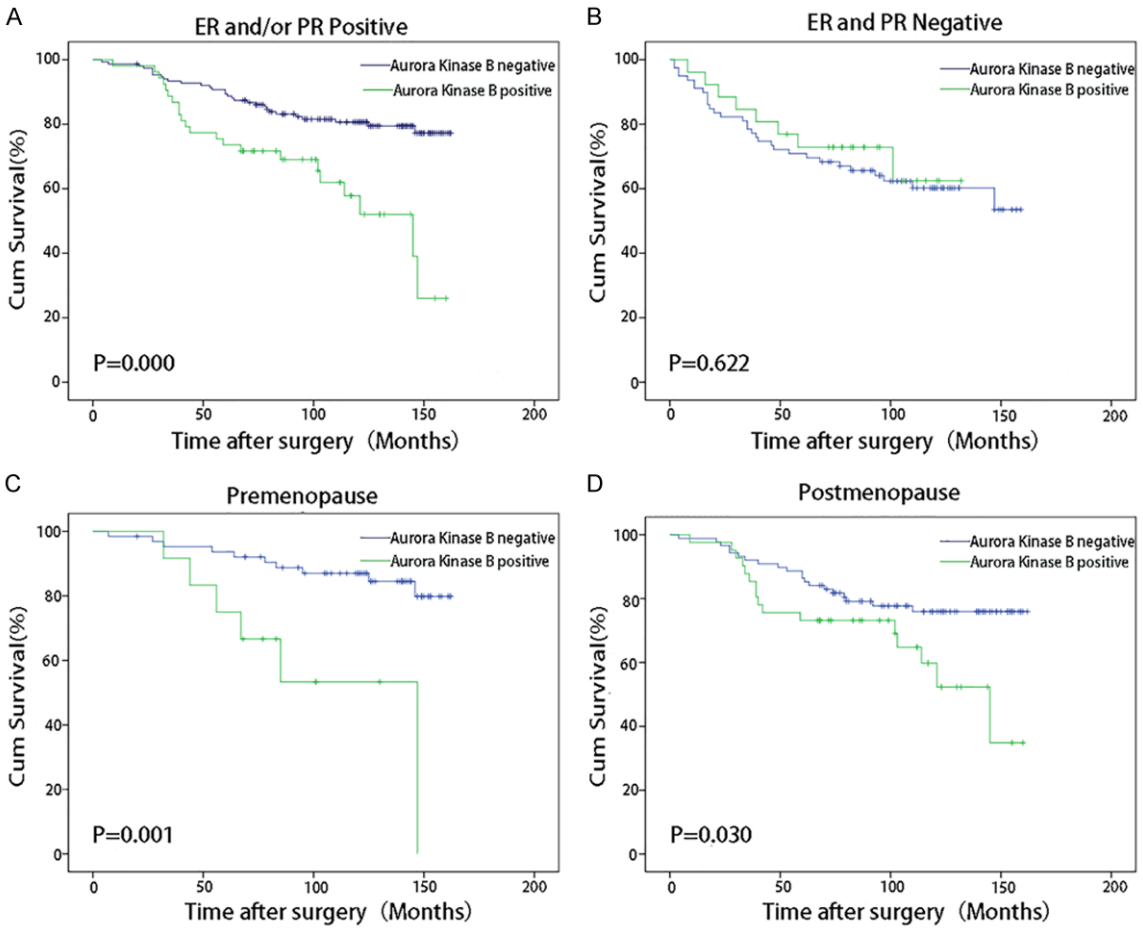

Figure 2. Aurora B is expressed in IDC and the expression is crucial negatively correlated with cumulative survival of IDC patients. Association of Aurora B expression with cumulative survival of the IDC patients in ER, PR status and menopausal state are shown in Kaplan-Meier survival graphs. The *p* value shown in the figure was calculated from Log-rank test.

ER and/or PR positive subgroup, Aurora kinase B is significantly associated with OS.

Discussion

The gene for Aurora kinase B, located at 17p13 [13], is expressed during late G2 and M phase, and remains active throughout the process of mitosis [7]. As a regulator of chromosome segregation, Aurora kinase B play a key role in the maintenance of normal ploidy during cell division [6]. It is also part of the chromosomal passenger complex, which includes INCENP, borealin, and survivin as substrates. Expression of Aurora kinase B has been detected in multiple tumor types (including IDC) using IHC [9, 14, 15]. In the present study, we assessed Aurora kinase B expression in breast cancer tissues, and studied the associations with clinicopathological characteristics (especially ER and PR status).

In the present study, patients with positive Aurora kinase B expression experienced significantly poorer OS, compared to patients with negative expression (**Figure 1**, P = 0.016), and this finding is similar to that of a previous study which evaluated the role of Aurora kinase B in breast cancer prognosis among a cohort of 312 patients [16]. Furthermore, to identify whether Aurora kinase B was an independent prognostic biomarker, we analyzed its expression using univariate and multivariate regression models. Our results indicate that Aurora kinase B had the highest HR and lowest *p*-value among all pathological categories, which indicate that Aurora kinase B may be an independent biomarker for IDC prognosis. This may be

Table 3. Pathological informations of patients in different Aurora B status in ER and/or PR positive subgroup

Pathological category		Aurora B Negative	Aurora B Positive	*p*
Age		62.13±1.89	54.44±1.05	0.307
T category	T1	39	14	0.816
	T2	96	35	
	T3/T4	17	4	
N category	N0	72	25	0.771
	N1	45	15	
	N2	31	10	
	N3	4	3	
TNM-stage	0/I	20	8	0.710
	II	93	29	
	III	39	16	
HER-2 status	Negative	130	39	0.420
	Positive	22	14	
Ki67 status	Negative	117	37	0.356
	Positive	35	16	
Menstruation status	Premenopause	64	12	0.013*
	Postmenopause	88	41	

*P<0.05.

explained by Aurora kinase B overexpression compromising the tumor suppressor function of p53, which could result in an aggressive tumor phenotype [9, 17, 18]. However, the precise mechanism for this role is not yet known, although our current findings may be useful in guiding therapy for patients with IDC.

Moreover, our findings highlight the prognostic value of Aurora kinase B expression in the different ER/PR status. In the subgroup analysis, we found that in the ER and/or PR positive subgroup, also called endocrine therapy-receiving group, Aurora kinase B expression was associated with a poorer prognosis (P<0.05). While in ER and PR negative subgroup, Aurora kinase B expression was not correlated with patient survival. And these results were not affected by menstruation status.

Tamoxifen and aromatase inhibitors (AI) are the main endocrine therapies for IDC, but not all patients benefit from these therapies. Some studies have demonstrated that AI-resistant cells are more dependent on Aurora kinase B to achieve correct cell division, and therapy targeting both ER and Aurora kinases may be a potent treatment strategy for overcoming AI resistance in breast cancer [19]. And some other study has suggested that Aurora kinase B drives growth in antiestrogen-resistant T47D breast cancer cell lines, and may be a biomarker for reduced response to tamoxifen treatment [20]. Given that all of the patients in our study, both premenopause and postmenopause, had undergone standard endocrine therapy after their surgical treatment, the association of poor OS with Aurora kinase B expression in patients who were ER- and/or PR-positive appears to provide evidence that Aurora kinase B is a biomarker for reduced response to endocrine treatment, not only to tamoxifen but also to AI. Therefore, it is possible that inhibition of Aurora kinase B, with the highly selective kinase inhibitor (e.g., PHA-680632, GSK1070916, AZD1152, and barasertib, which have the potential for antitumor activity in a wide range of human cancers, including acute myeloid leukemia, multiple myeloma and colorectal cancer [5, 13, 21-25]), could be a candidate new treatment for breast cancer patients with acquired resistance to antiestrogens. But further preclinical studies are needed to examine the mechanism for these drugs' potential antitumor activity in breast cancer.

The present study included three important limitations. First, the present study used a retrospective design to evaluate tissue samples from patients who were treated at a single center. Second, we only analyzed OS and we were unable to access data regarding disease-free survival. Third, the present study did not include any molecular experiments. Therefore, a prospective multicenter study with a long-term follow-up is needed to demonstrate that Aurora kinase B is an independent prognostic biomarker for IDC.

Our results indicate that Aurora kinase B is an exceptional prognostic biomarker for IDC. Furthermore, Aurora kinase B may be related to endocrine therapy resistance. Inhibition of

Aurora kinase B may be a candidate treatment for patients with breast cancer who have acquired resistance to antiestrogens.

Disclosure of conflict of interest

None.

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