·Review·

Roles of Aurora-A in tumorigenesis and prognosis of breast cancer

Liang-Ping Xia,[1,2] Fei-Fei Zhou,[1,2] Ming-Tian Yang[1,3] and Qiang Liu[1,4]

1. State Key Laboratory of Oncology in South China, Guangzhou, Guangdong, 510060, P.R. China
2. VIP Region, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, 510060, P.R. China
3. Department of Breast Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, 510060, P.R. China
4. Cancer Research Institute, Sun Yat-sen University, Guangzhou, Guangdong, 510060, P.R. China

Correspondence to: Liang-Ping Xia
Tel.: 86.20.87343107
Fax: 86.20.87343922
Email: xialiangping@163.com

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[Abstract] Aurora kinases play key roles in the transition of G_2/M phase by regulating functions of centrosomes and microtubules. Overexpression of Aurora-A, a new oncogene, can induce centrosome amplification, aneuploidy and tumor formation. Aurora kinases are closely associated with breast cancer. In this article, we reviewed the mechanisms of Aurora kinases inducing tumorigenesis of breast cancer via interacting with p53 gene, BRCA1 gene, PTEN/PI3K/AKT pathway, gene polymorphism, estrogen, and so on, analyzed the expression of Aurora kinases in breast cancer and its relationship with prognosis.

Key words: Aurora kinase, breast neoplasm, tumorigenesis, prognosis

Aurora family belongs to the serine/threonine protein kinase and can be classified into three categories of Aurora-A, Aurora-B and Aurora-C. They ensure the precise and effective separation of chromosome and cytoplasma by taking part in the regulation of centrosomes and microtubules functions. Aurora kinase levels generally reach their peak at G_2/M phase, regulating the G_2/M transition in cell cycle and are the key factors mediating the progression of M phase.[1] Among them, the Aurora-A and Aurora-B are closely associated with tumors: first of all, the Aurora-A and Aurora-B are located in chromosomal regions of 20q13.2 and 17p13, respectively that are prone to translocation, deletion and amplification, indicating their inherent instability;[2] secondly, these two regions present ubiquitous amplification in tumor tissues of breast and colon cancer, as well as cell strains of breast cancer, ovarian cancer, colon cancer, prostate cancer, neuroblastoma and cervical caner;[2] finally, the transfection of highly expressed Aurora-A into Rat1 and NIH3T3 cells can transform these cells into tumor cells, and injection of these transfected cells into nude mice can lead to tumorigenesis.[3,4]

Tumorigenesis of breast cancer by Aurora-A

Aurora-A/BTAK/STK15/ AURKA/AIK1 was initially separated as breast tumor amplified kinase (BTAK) gene product from breast cancer. The amplifications of 20q11-q13 region in primary lesion and cell strain of breast cancer are 12% -18% and 40% , respectively, and the amplification is closely associated with the

prognosis of the breast cancer patient with negative lymph node metastasis. Therefore, Sen et al.[5] proposed that this region probably contained new genes associated with the tumorigenesis and progression of breast cancer. Furthermore, he compared the 20q13 regions in breast cancer cell strains of BT474, MCF7 and SKBR3 with control cell strains of WI38 and MCF10, and finally separated the BTAK gene from this region. Wang et al.[6] established the MMTV-Aurora-A transgenic mouse model and found that those with highly expressed Aurora-A had long latent phase and low rate of tumorigenesis. At two months, the genomes of transgenic mice were similar to the controls; until four months, the transgenic mice began to show centrosome amplification and aneuploidy; and 40% mice developed breast cancer at 20 months. Before tumorigenesis, highly expressed Aurora-A causes genetic instability such as centrosome amplification, tetraploid formation and separation of immature sister chromatid. The author comfirmed that, the malignant transformation by Aurora-A as an oncogene was resulted from the genetic instability and the activation of AKT as well as its downstream signal pathway. The investigation by Zhang et al. 7 showed that the high expression of Aurora-A could not lead to the breast cancer formation, which was probably due to the following reasons[6]: firstly, although the promoters in aforementioned two models both need estrogen stimulation, the preconditions of expression are different. Expression of former promoter is relatively easy, because the promoter per se is highly expressed during pregnancy and the experimental mice has experienced at least five pregnant cycles, having high estrogen levels. However, the prerequisite for the expression of later promoter is the elimination of stopper, which requires activation of WAP-Cre by high estrogen level, but the experimental mice has experienced only one pregnant cycle, the low estrogen level is not sufficient to eliminate stopper. Secondly, one pregnant cycle is not enough to activate the Aurora-A to the level of suppressing P53.

Mechanisms of breast carcinogenesis by Aurora–A

Its relationship with p53. Aurora-A and p53 interact with each other. P53 combines with Aurora-A by Aurora-box located at the N end of Aurora-A, thereby suppressing the activity of Aurora-A kinase, inhibiting centrosome amplification induced by Aurora-A and the ability of Aurora-A to transform NIH3T3 cell. Conversely, Aurora-A is able to phosphorylate the serine at 315 position of p53 which is subsequently degraded through ubiquitin pathway,[8] and the phosphorylation of serine at 215 position of p53 by Aurora-A is another more important mechanism inactivating p53.[9] In the MMTV-Aurora-A transgenic mouse model,[6] tumor is formed at six months in the p53 (+/-) mutation background, and the proportion of carcinoma reaches 70% at the 18 months, these two figures are significantly higher than those without p53 (+/-) mutation background. In addition, 15 p53 (+/-) mice matching for ages show no tumorigenesis, these findings all suggest that the p53 (+/-) mutation can promote the tumorigenesis ability of the highly expressed Aurora-A in breast. Although tumorigenesis was not induced by highly expressed Aurora-A in Zhang et al.[7] animal experiment, the p53 aggregation and p53 dependent apoptosis were increased. Does that indicate the carcinogenesis of Aurora-A is mediated by the p53 degradation? However, in MMTV-Aurora-A transgenic mouse model, neither the increased p53 protein nor apoptosis is identified, which is probably due to the balance of p53 activation caused by Aurora-A mediated genetic instability and p53 degradation caused by the highly expressed Aurora-A maintained by pregnant hormones.

Its relationship with BRCA1. Breast cancer associated gene 1 (BRCA1) is specific to the breast and ovarian cancer, it is located on centrosome and plays important role in the regulation of centrosomes number. Physiologically, Aurora-A is combined with BRCA1 and phosphorylate its S308, promoting the cell transiting from G2 to M phase. When BRCA1 is mutated to BRCA1-S308N, the Aurora-A can not phosphorylate it. Since BRCA1 function-associated RING region and E3 ubiquitin ligase are intact, most of the BRCA1

mutations are shifting or nonsense mutation. While BRCA1 ubiquitin ligase directly inhibits centrosome dependent microtubule nucleation in S phase, the centrosome microtubule nucleation increased by five times and the BRCA1 concentration reaches its peak in M phase, which is starkly different from the S phase conditions. Sankaran et al.[10] found that the inhibition of BRCA1 dependent centrosome microtubule nucleation was high at S phase and low at M phase, that is because the centrosome is not regulated by BRCA1 at M phase. The rising Aurora-A at M phase suppresses the inhibitory effect of BRCA1 against centrosome microtubule nucleation through reducing the activity of BRCA1 E3 ubiquitin ligase, the dephosphorylation of BRCA1 by protein phosphatase 1 alpha (PP1α) enhances the activity of BRCA1 E3 ubiquitin ligase, whereby further inhibiting the centrosome microtubule nucleation. A regulatory circle among BRCA1, Aurora-A and PP1α is formed during the process: at G2/M phase, the increased Aurora-A inhibits BRCA1 and PP1 simultaneously, leading to significantly increased centrosome microtubule nucleation; at the late phase of mitosis, with the degradation of Aurora-A, the functions of BRCA1 and PP1 restore, PP1 will subsequently inhibit Aurora-A, whereas the PP1 is regulated by cdc2, cdc25 and Aurora-A.

Its relationship with PTEN/PI3K/AKT signal pathway. How does the cell with aneuploidy caused by increased Aurora-A manage to escape death or apoptosis but form tumor? In the MMTV-Aurora-A transgenic mouse model,[6] the author pointed out that the activation of PTEN/PI3K/AKT signal pathway might play an important role. At four months, pAKT level at breast tissue of transgenic mouse was higher than the controls, which was significantly increased in the multiparous mice during pregnancy. Not only the phosphorylated AKT increased, the downstream genes of AKT such as mTOR and GSK-3β increased as well, and the pAKT and GSK-3β relevant cyclin D1 increased. These findings all suggest the activation of PTEN/PI3K/AKT signal pathway is likely to survive the tetraploid cells for further hyperplasia. Interestingly, the pAKT levels of MMTV-Aurora-A, MMTV-Aurora-A and p53 (+/-) mice are similar, indicating the phosphorylation of AKT is not caused by p53. Moreover, the PTEN/PI3K/AKT signal pathway is likely to be involved in the carcinogenesis induced by Aurora-A.[2]

Its relationship with polymorphisms of Aurora kinase. F31I and V57I are two common polymorphic variations of Aurora-A. In a study involving 941 western breast cancer patients and 830 controls from general population,[11] the risk of breast cancer in I31/V57 homozygote carriers (AA＋GG genotype) was 60% higher than the common genotype (TT＋GG) of the population, and the risk was more prominent in the menopause women (OR=1.96). The interaction between functional F31I and breast cancer risk factors associated with estrogen is not significant, and the combined high risk genotype I31/V57 doesnt show increased risk as compared with reference genotype F31/I57, which may be associated with the low proportion of high risk genotype in this population. However, Cox et al. [12] found that F31I polymorphism of Aurora-A gene was associated with breast cancer risk in American population. In eastern population,[13,14] Ile31 allele of Aurora-A gene is associated with high risk of breast cancer, especially for the overweight menopausal women, and this positive association changes with long term exposure to the estrogen of high concentration. Furthermore, Ile/Ile genotype takes more than 40% of Chinese population,[13] which is significantly higher than 6% in Caucasians, while there is no difference in the 57 codon. Those bearing the Ile31 and Ile57 alleles show 40% higher risk of breast cancer than the homozygote of Phe31 and Val57 alleles, which, however, is not statistically significant. Interestingly, the Aurora-A amplification in breast cancer is only 12% to 18%, while the protein overexpression reaches more than 90%, this is probably due to the up-regulated gene by estrogen in the breast tissue. Moreover, Ile/Ile in Chinese population is seven times that of Caucasians, however, the incidence of breast cancer in Chinese population is significantly lower than western population, suggesting there

are other factors such as environmental factors, genetic polymorphism buffering the carcinogenesis of Ile/Ile genotype.

Are there any relationship between Aurora-A F31I polymorphism and breast cancer risk? Ewart-Toland et al.[15] conducted F31I polymorphism analyses in case control studies involving 10 independent diseases including colon cancer, breast cancer, skin cancer, lung cancer, esophageal cancer and so on. The results were then combined with data from five other published papers for meta-analysis, totally, there were 9549 cases and 8326 controls. Generally, both heterozygote and homozygote of T+91A shows increased risk (OR＝1.10, P=0.006 and OR＝1.40, P<0.001, respectively). Meta analysis of four breast cancer cases indicate only homozygote of T+91A shows increased risk (OR=1.35). Nine of the ten independent studies individually indicate the effect of T+91A homozygote is approaching the statistical significance. Fletcher et al.[16] conducted meta analysis in breast cancer. Firstly, they collected 507 cases with bilateral breast cancer and 875 healthy controls in order to provide stronger evidences elucidating the role of genetic polymorphism in breast cancer than case control studies enrolling unselected cases, because the unselected cases are mostly those with unilateral cancer and without family history. Odds ratio (OR) of Ile/Ile homozygote getting breast cancer is 0.63, which is consistent with risk of unilateral breast cancer (OR=0.79). Secondly, pooled meta-analyses of his own data and the data from five papers investigating with association of F31I polymorphism of Aurora-A gene with breast cancer risk (published before 2005) [11,13-15,17]show that there are significant heterogeneities in the results of these studies, and there is only one report showing strong association, when this paper is excluded, the rest data shows negative result. And three papers of these two meta-analyses are the same.[11,13,17]

Aurora –A is probably the early event of breast carcinogenesis

Aurora-A is probably the early event of breast carcinogenesis regulating the transformation from ductal carcinoma in situ (DCIS) to infiltrative carcinoma. The overexpression of Aurora-A in ductal epithelium adjacent to the breast cancer lesion, DCIS and infiltrative ductal carcinoma are 78%, 70% and 32%, respectively. The former two types are significantly higher than the later.[18] The breast cancer risk of those with AA+GG in Aurora-A gene is not high (OR=1.45), while the risk of carcinoma in situ is nearly three times the normal (OR=2.93).[11] Aurora-A amplification[19] in mouse model of breast cancer, as well as Aurora-A overexpression[20] in human ovarian cancer are early events in the carcinogenesis. Moreover, the Aurora-A gene is found in MMTV-Aurora-A transgenic mouse model to cause centrosome abnormality in breast epithelium, genetic instability, and ultimately lead to breast carcinogenesis.[6] However, there are conflicting reports[21] showing that Aurora-A is lowly expressed in normal or DCIS tissues while highly expressed in infiltrative cancers. Li et al.[22] treated the August/Copenhagen/Irish (ACI) mouse with estrogen and found that, 100% of the subjects showed mammary gland tumor (MGT) at three to six months, 30% showed centrosome amplification in the atypical hyperplasia area at three months of E2 (17 beta-estradiol) treatment, and 38% showed centrosome amplification in DCIS at four months, more than 90% showed centrosome amplification in MGT, while less than 7% showed centrosome amplification in ductal tissues without atypical hyperplasia. These findings suggest that the centrosome amplification is the early event of MGT. The molecular changes before aneuploidy appearance in the process of obtaining MG (mammary gland) and MGT by E2 treatment are similar to those in early infiltration stage of human sporadic breast cancer. In addition, both mRNA and protein of Aurora-A in the MG treated with E2 for four months rise to the level of MGT, indicating that the Aurora-A overexpression in DCISs is likely to be the crucial event in the early stage of MGT.

The relationship of Aurora–A and estrogen

Estrogen is able to induce malignant

hyperplasia of breast epithelium and subsequent breast carcinogenesis by mitogen effect, since the Aurora-A is involved in the regulation of mitosis, they may be associated with each other.[14] Aurora-A gene is up-regulated notably in MCF7 after cultured with E2.[23] Li[22] found that 100% of the ACI mice showed MGT with three to six months estrogen treatment at the dose of 2 mg or 3 mg, and the tumors in the high dose E2 group are larger in size and more in number. As compared with control breast tissues, Aurora-A mRNAs in low dose and high dose groups are increased by 1.4 and 1.5 times respectively, while the Aurora-A protein is increased by 7.2 and 7.5 times respectively. The number of centrosomes in MGT induced by E2 is increased significantly, while the centrosomes are normal in the unaffected breast epithelium adjacent to the cancerous lesion and untreated breast epithelium. Interestingly, MGT induced by applied chemistry and environmental carcinogens usually presents diploid, while those induced by E2 are aneuploidy.[24] The dynamic balance of centrosomes in the atypical hyperplasia, DCIS and MGT induced by E2 is lost in early stage, which is associated with the c-myc overexpression mediated by estrogen.[25] In order to understand how the estrogen regulates Aurora-A, Lee et al.[26] treated MCF7 cell with 10nM E2 and discovered the estrogen receptor dependent Aurora-A upregulation, the upregulation however, is not restricted to Aurora-A. Eradicating the tamoxifen induced growth arrest, the performance of Aurora-A is similar to the other mitotic markers with the existence of estrogen. The downregulation of Aurora-A with RNA interference can lead to significant decline of the estrogen induced-anchorage dependent growth; and Aurora-A knockout can counterbalance the estrogen induced decrease of MCF7 sensitivity to docetaxel. The author proposed that the Aurora-A increase is the indirect consequence of estrogen induced cellular proliferation. BMI (body mass index) and WHR (waist-to-hip ratio) are two indices reflecting in vivo estrogen exposure levels. Phe/Ile and Ile/Ile are found to be significantly associated with the high breast cancer risk in population with high BMI or WHR,[13] particularly in the menopausal women. And the menopausal and overweight women with Ile/Ile genotype have four times risk of suffering from breast cancer than the population carrying Phe/Phe genotype (OR=4.1).

Aurora–A and the prognosis

In a 15-year cohort study involving 638 breast cancer cases, Nadler et al.[27] found that Aurora-A overexpression was strongly associated with low survival rate (P=0.0005), in both whole population and negative lymph nodes cases, and the Aurora-A overexpression was significantly associated with high nuclear grade, HER-2/neu overexpression and PR+. In multivariate analysis, Aurora-A overexpression, along with indices such as diameter of tumor more than 2 cm, ER status, positive lymph nodes was independent prognostic predictors. Meanwhile, the author found that the Aurora-B didnt have such prognostic value. Attentions should be paid to some special features of the study, firstly, the included cases were between 1962 and 1980, chemotherapy was not conducted for those with negative lymph nodes, 15% patients with positive lymph nodes received chemotherapy, and patients receiving treatment after 1978 accounted for 27% who had received Tamoxifen therapy. Therefore, cases included in the study were too old and the treatment principles at that time were quite different from nowadays. Secondly, the author adopted new pathological scoring system automated quantitative analysis (AQUA) which differed from the conventional one. In a breast cancer data involving 112 cases in whom there were 31% with negative lymph nodes, the relapse free survival rates in both Aurora-A positive and negative groups were not statistically different (P = 0.34), as well as total survival rates (P=0.42), and there was borderline association between Aurora-A and nuclear grade.[28] Royce ME[28] proposed that the disparity was likely to be associated with the sample size, proportion of patients with negative lymph node, the methods used to calculate the Aurora-A expression, the small number of death and relapse cases in the follow up period, and that the Aurora-A

Table 1 The expression of Aurora-A in breast cancer

Reference	Pathologic type	Cases	Test method	Expression rate
Tanaka et al.[21](1999)	Invasive ductal carcinoma	33	Immunohistochemistry	94%
	Fibrocystic disease	6	Immunohistochemistry	Weak expression
	Intraductal papilloma	3	Immunohistochemistry	Very weak and was only seen in certain parts
	Normal mammary tissue	6	Immunohistochemistry	No staining
Miyoshi et al.[29](2001)	Breast cancer	47	RT-PCR	mRNA increase in 64% cases, (mRNA level was 0.310 ± 0.413)
	Normal mammary tissue	9	RT-PCR	(mRNA level was 0.044±0.029)
Hoque et al.[18](2003)	Invasive ductal carcinoma	37	Immunohistochemistry	32%
	Ductal carcinoma in situ	25	Immunohistochemistry	70%
	Non-malignant mammary ducts	25	Immunohistochemistry	78%
Royce et al.[28](2004)	Invasive ductal carcinoma	112	Immunohistochemistry	26%
	BT474 cell line		Immunohistochemistry	Overexpression
	MCF10 cell line		Immunohistochemistry	Low expression

functions in early stage instead of in the progressive stage. Nadler et al.[27] proposed that the Aurora-A was a beneficial complement to the conventional pathological indices, facilitating the selection of patients with poor prognosis from those without lymph node metastasis, and breast cancer patients in the early stage with Aurora-A overexpression mandate active intervention.

Aurora –A expression in breast cancer

In the breast cancer cell lines MDA-MB-231, MDA-MB-435, MDA-MB-436, MCF-7, T47D, SKBR3, BT-474, BT-20 and ZR-7510, the result of Western blot show no development in Aurora-B of T47D and SKBR3, weak development in MDA-MB-435 and obvious development of Aurora-A and Aurora-B in other cell lines.[27] In the study by Royce et al.[28] the Aurora-A was highly expressed in breast cancer cell line BT474 and lowly expressed in the normal cell line MCF10. The Aurora-A expression in breast tissues are shown in table 1.

Conclusions and outlook

Aurora kinase is closely associated with breast cancer, which was first separated from breast cancer tissue.[5] It can induce breast cancer successfully,[6] and the Aurora-A and/or Aurora-B expression is common in breast cancer with the expression rates of 26% to 94%. The Aurora-A overexpression is an independent prognostic indicator of the breast cancer and is associated with prognosis. The Aurora-A kinase has been used as the target of anti-tumor treatment[30-32] and Aurora-A kinase inhibitors has entered the clinical trial.[33] Those entering the preclinical trials include CHR-3520, CTK-110, CYC-116, ENMD-981693, JNJ-7706621, PHA-680632, SNS-314, MP-529 and MP-235. Those entering phase I clinical trials include PHA-739358, AT-9283, MLN-8054, R-763, SU6668, Hesperadin and ZM447439, and those entering phase II clinical trials include VX-680. Similarly, we believe that the trial of Aurora kinase inhibitors in the treatment of breast cancer will be in the near future.

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