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REVIEW ARTICLE

Aurora kinases: novel anti-breast cancer targets

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Abstract

Aurora kinases regulate multiple steps of mitotic cell division in eukaryotic cells. Overexpression of aurora kinases has been observed in some tumor cells, which suggests that abnormalities in aurora kinases are closely related to tumorigenesis. In additon, aurora kinases are often amplified or overexpressed in breast cancer cells, leading to chromosomal segregation abnormalities and genomic disorder, and thereby activating oncogenic pathways. Novel Aurora A kinase inhibitors are currently being studied in multiple phase I and II studies. In this review, we describe the biological functions and mechanisms of aurora kinases in breast cancer cells and summarize the preclinical findings related to aurora kinases in breast cancer.

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Breast cancer is one of the most common malignant tumors in women in both developed and developing countries. It accounts for approximately one in three cancer diagnoses in women in the United States, and it is the second leading cause of cancer death in women. According to the latest statistics, there are an estimated 234, 580 new cases of breast cancer and 40,030 deaths from breast cancer in the US each year [1]. The incidence of breast cancer in developed countries is increasing due to various factors, including urbanization and changes in women's lifestyles [2]. Although there are many factors that determine the occurrence of breast cancer, including malformative, infective, endocrine, autoimmune, and psychological factors [3], the differentiation and proliferation of breast epithelial cells, which is mediated by hormonal factors, is the main factor driving tumorigenesis [4–5]. Biological targeted therapies are a major treatment modality for breast cancer and have further improved prognosis [6]. However, drug resistance is still a big clinical challenge. Thus, new treatment strategies for breast cancer are greatly needed.

Human epidermal growth factor receptor 2 (HER2) overexpression drives 20% of breast cancers, and this receptor is now a standard therapeutic target [7]. HER2-targeted therapies significantly improve outcomes for HER2-positive patients with both early and metastatic breast cancer. However, there are likely other potential targets in breast cancer.

Aurora kinases, which are a family of mitotically regulated serine/threonine kinases, are increasingly being recognized as key regulators of chromosome segregation and cytokinesis [8]. The first aurora kinase was discovered in 1995 [9]. Yeast has a single aurora kinase, while mammals have multiple genes encoding three, Aurora A, B, and C [10]. These three mammalian aurora paralogues are very similar in sequence, particularly in the carboxy terminal domain, and human Aurora A and B share 71% identity [11].

Aurora kinases are important for cell cycle progression. Aurora kinases A and B are expressed in most normal cells, but expression of these kinases has also been observed in several tumor types, including breast, lung, colon, prostate, pancreas, liver, skin, stomach, rectum, esophagus, endometrium, cervix, bladder, ovary, and thyroid cancers, and these tumors show high expression compared to the corresponding normal tissues[12–13]. Aurora A and B are expressed in most cell types, whereas Aurora C is specifically expressed in the testicles. Both Aurora A and B play key roles in regulating the cell cycle, from G2 phase to cell division. Aurora C plays a unique physiological role in spermatogenesis and functions as a passenger protein on chromosomes, like Aurora B during mitosis [14]. A previous study by Ye [15] examined aurora kinase expression in acute myelocytic leukemia (AML) and showed that blasts overexpress Aurora A and B compared to the levels in control CD34+ cells. Compared

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to other tissues, Aurora B and C are highly expressed in testis. Aurora B seems to play an essential role in the regulation of chromosome segregation and cytokinesis, while aurora C appears to have unique functions in late spermiogenesis [16].

Overexpression of aurora kinases in cancer cells leads to aberrant chromosome segregation, genomic instability, and activation of oncogenic pathways [17–18]. Recent research results identified Aurora A and B as part of the gene expression profile predicting poor prognosis. Novel targeted agents that inhibit the activities of Aurora A and/or B have been developed and are being tested for their anti-tumor efficacy [19]. This review is focused on the deregulation of aurora kinases in human cancers, with an emphasis on breast cancer, the progress in targeting these important regulators in the treatment of cancers, and the aurora kinase inhibitors being tested in preclinical trials [20].

Aurora kinase A in breast cancer

Human Aurora A is encoded by a gene (*AURKA*) that is located on chromosome 20q13.2. It is composed of 403 amino acids and has a molecular weight of 46 kDa. Aurora A has crucial roles in every step of mitosis [21–22], and it is involved in mitotic entry, separation of centriole pairs, accurate bipolar spindle assembly, alignment of metaphase chromosomes, and completion of cytokinesis [23]. It functions as a key regulator of multiple mitotic events, including centrosome maturation and separation [24], which are commonly amplified in a broad range of tumor tissues [25]. Aurora A expression levels are high, and then rapidly decrease via degradation by the ubiquitin-proteasome pathway [26].

Transcription of *AUKA* is cell-cycle regulated. Aurora A is expressed in all phases of the cell cycle. Thus, the promoters of *AUKA* contain specific elements that are responsible for inducing its transcription at G2 phase of the cell cycle [26]. In additionthe levels of Aurora A are usually regulated during the cell cycle by two different processes, including ubiquitin-independent proteolysis [27]. Aurora A and its activator interact with Polo-like kinase 1 (Plk1) to initiate mitosis. However, in cells transformed with Aurora A, the mTOR pathway is activated [28]. Aurora A expression levels are high, and then rapidly decrease via degradation by the ubiquitin proteasome pathway [26].

Aurora A regulates the G2 to M phase transition. The commitment of cells to mitosis in late G2 phase involves the activation of both Aurora A and CDK1-cyclin B. This activation involves a feedback mechanism in which Aurora A activation requires CDK1-cyclin B activation. Aurora A has been shown to phosphorylate BRCA1 , and other studies have shown that BRCA1 is also localized to the centrosome and binds to γ-tubulin [30–31].

Several trials have revealed that in breast cancer cells, knockdown of Aurora A expression with a specific siRNA significantly attenuates tumor cell growth and increases apoptotic cell death. In addition, recent studies have added new insights into how Aurora A induces cell transformation. Under physiological conditions, Aurora A and its activator collaborate with Plk1 to initiate mitosis. In cells transformed with Aurora A, the mTOR pathway is activated [28]. The Aurora A protein has a variable amino terminal regulatory domain, with three putative aurora boxes (A boxes I, II, and III), and a conserved carboxyl terminal catalytic domain, with an activation motif and a destruction box [32].

Imen Ferchichi *et al* reported that 84.6% of non-tumoral tissues overexpress Aurora A. This observation supports the reasoning underlying malignant processing; although this tissue is morphologically healthy, it may have already begun to become cancerous. In addition, an association has been reported between high Aurora A expression in malignant tissue and positive nodal status [33]. Another retrospective analysis showed that high Aurora A expression is strongly associated with decreased survival (P = 0.0005), and in the multivariable analysis, Aurora A remained an independent prognostic marker [34–36].

Gene expression profiling has provided a large number of different signatures that are related to breast cancer prognosis. The results of a meta-analysis of publicly available breast cancer gene expression and clinical data by Wiripati P *et al* [37] underscored the important role of proliferation in breast cancer prognosis.

Aurora kinase B in breast cancer

Aurora B kinase belongs to the family of chromosome passenger proteins, which includes inner centrosome protein (INCENP), survivin, and borealin [38]. The *AURKB* gene is located at 17p13 [39]. The substrates of Aurora B include two mitotic checkpoint proteins BubR1 and Mad2. It is also widely expressed in normal proliferating cells, with maximum expression at G2/M phase of the cell cycle [40], and it is mostly activated by autophosphorylation after association with the passenger complex [41–42].

Aurora B is a chromosomal passenger protein that localizes to centromeres during prometaphase and subsequently relocates to midzone microtubules and midbodies during anaphase and telophase [43]. Aurora B has also been implicated in microtubule-kinetochore attachment by interacting with the kinetochore-specific histone H3 variant CENP-A [44]. Inhibition of Aurora B by RNA interference compromised the mitotic checkpoint, resulting in increased numbers of aneuploid cells [45]. In addition, inhibition of Aurora B by RNA interference showed that it is required for cytokinesis [46].

Some studies have shown that forced expression of Aurora B can enhance cellular transformation. For example, Aurora B expression in CHO cells was reported to promote aneuploidy and increase invasiveness in xenograft experiments [47]. Furthermore, Aurora B has been mapped to a chromosomal region that is known to contain tumor-associated amplicons [48].

Aurora B inhibitors, unlike classic antimitotics (e.g., kinesin inhibitors), do not induce mitotic arrest but instead result in a failure of cytokinesis, leading to cell death. Therefore, inhibitors of Aurora B would be expected to show clinical effects that are distinct from those of antitubulin compounds and other antimitotic drugs known to cause mitotic arrest. A pan-aurora kinase inhibitor, ZM447439, has been studied in breast cell lines, and the results showed cellular changes that most resemble a loss of Aurora B function [49]. Therefore, it is not difficult to infer that Aurora B is an effective drug target and predictor of survival.

Aurora kinase C in breast cancer

Aurora C, which is also known as Aurora 3, is the less well studied member of the family. It was initially thought to be restricted to testicular tissue, where it plays a role in meiosis and spermatogenesis [50]. However, it was also recently found that Aurora C also functions as a chromosomal passenger protein and might compensate for a loss of Aurora B function [51]. Although several studies have detected aberrant expression of Aurora C in colorectal, breast, and prostate cancers, knowledge regarding the relationship between Aurora C and cancer is limited [52].

Aurora kinases in different molecular subtypes of breast cancer

Breast cancer is not a homogeneous disease, thus it is necessary to differentiate among the different molecular subtypes. Estrogen receptor (ER), progesterone receptor (PR), and HER2 tyrosine kinase are major determinants of the molecular phenotype and dictate the course of treatment [53–54]. There are at least four subtypes of breast cancer: luminal A, luminal B, HER2-enriched, and basal-like, as well as a normal-like type, which show significant differences in terms of risk factors, incidence, baseline prognoses, and responses to systemic therapies [55]. To date, no consistent molecular predictor of response to aurora kinase inhibitors has been defined [56]. Thus, the subset of breast cancer patients that would most likely benefit from aurora kinase inhibitor treatment has yet to be identified. Therefore, new molecular biomarkers are greatly needed.

Xu J *et al* concluded that Aurora A is a potential therapeutic target for triple-negative breast cancer (TNBC), and inhibition of Aurora A kinase is a promising regimen for TNBC cancer therapy [57]. The results of a study by Diamond JR *et al* [58] also showed that Aurora kinase inhibitors exhibited robust anticancer activity in models of TNBC, and that aurora kinases are candidate predictive biomarkers. *In vitro*, the aurora kinase inhibitor AMG900 induced polyploidy and apoptosis and inhibited the growth of P-gp-expressing TNBC cells at nanomolar concentrations [59–60].

Aurora kinase A overexpression in ER+ cell lines showed that there is a strong relationship between aurora kinase and luminal a cell lines. Some researchers have suggested aurora kinases as standard clinical biomarker with molecular covariates that outperform other markers [61].

Table 1 Clinical trials of Aurora kinase inhibitors

Drug	Manufacturer	Targeted Aurora	Clinical trial	Main toxicities	Dose	Route	IC_{50}	Reference
AZD1152	Astra Zeneca	B	Phase II	Fibric neutrogena, stomatitis	50–1600 mg/d, 7 d	IV	1369 nma and 0.36 nmb	65
MLN-8237	Millennium	A, B	Phase II	Fibric neutrogena, fatigue, stomatitis, anemia	50 mg bid, 7 d	PO	61 nm	66
AT9283	Astex Therapeutics	A, B	Phase II	–	–	PO	3 nm	67
ENMD-2076	EntreMed	A, B	Phase II	Fatigue, lyphlitis, syncope	225–236 mg/d, 7 d	PO	25–700 μm	68
AMG900	Amgen	A, B, C	Phase I	–	3.75–15 mg/d	PO	0.6 nma and 18 nmb	69
VX-680	Pfizer	A, B	Phase I	–	–	PO		70
CYC116	Cyclacel	A, B	Phase I	–	–	PO	34–1370 nm	71
AS703569	Merck Sereno	A, B	Phase I	–	3–37 mg bid, 7 d	PO		72
MK5108	Merck	A	Phase I	–	–	PO	0.16–6.4 μm	73
MLN8237	Millennium Pharmaceuticals	A	Phase II	Neutrogena, asthenia, thrombocytopenia	50 mg bid, 7d	PO		74
SNS-314	——	A, B	Phase I		–		9 nma and 31 nmb	75

No reported in breast cancer inhibiters: XL228, kw-2249

Another study demonstrated the antineoplastic activity of the AZD1152-HQPA inhibitor in HER2-overexpressing cell lines. AZD1152-HQPA specifically inhibited Aurora B kinase activity in breast cancer cells, thereby causing mitotic catastrophe and polyploidy, which led to apoptosis [62]. Siggelkow *et al* showed an association between the ER+/HER2- molecular subtype and Aurora A. In contrast, Aurora A was not significantly associated with metastasis-free survival in ER-/HER2- and HER2+ carcinomas [63].

A study by Schmidt also revealed a strong correlation between Aurora A and proliferation metagenes. AURKA RNA levels were correlated with histological grade ($P < 0.001$) and tumor size ($P < 0.001$), and AURKA mRNA levels were higher in ER-/HER2- and HER2+ tumors, whereas expression was lower in ER+/HER2- carcinomas. AURKA, also the proliferation metagene was associated with MFI in ER+/HER2- but not in ER-/HER2- or HER2+ carcinomas [64].

Transcriptome-based analysis of primary breast cancers showed that increased expression of AURKA and AURKB is correlated with elevated proliferation, ER negativity, and primarily (but not exclusively) poorly differentiated non-luminal tumors.

Conclusion

Aurora kinases are emerging as potential therapeutic targets in breast cancer, and the combination of aurora kinase inhibitors with other drugs could enhance treatment effects. In addition, aurora kinase expression levels can predict tumor stage and prognosis.

Inhibition of aurora kinases greatly inhibits tumor cell growth in culture and xenograft studies. Therefore, inhibition of aurora kinases is an attractive novel therapeutic strategy for breast cancer. Aurora kinase inhibitors might delay the development of drug resistance and reverse resistance, and should allow for more effective treatment of patients with aurora kinase-overexpressing tumors who are at high risk for disease recurrence.

We discovered that aurora kinases are highly active in breast cancer cell lines and identified biomarkers that predict response to aurora kinase inhibitors *in vitro*. Specifically, TP53 loss of function cell lines. However, this observation requires clinical validation, by TP53 somatic mutation analysis and/or p21 expression, to identify the patients who are most likely to benefit from aurora kinase inhibitor treatment.

The roles of aurora kinases in the various molecular subtypes of breast cancer are still unclear, if we can determine the relationship between aurora kinases and different subtypes, we could predict the risk of recurrence and improve treatment.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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