Am J Cancer Res 2020;10(9):2705-2729
www.ajcr.us /ISSN:2156-6976/ajcr0117754

Review Article

The role of Aurora-A in human cancers and future therapeutics

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Received July 8, 2020; Accepted August 5, 2020; Epub September 1, 2020; Published September 15, 2020

Abstract: Aurora-A is a mitotic serine/threonine-protein kinase and an oncogene. In normal cells, Aurora-A appears from G2 phase and localizes at the centrosome, where it participates in centrosome replication, isolation and maturation. Aurora-A also maintains Golgi apparatus structure and spindle assembly. Aurora-A undergoes ubiquitination-mediated degradation after the cell division phase. Aurora-A is abnormally expressed in tumor cells and promotes cell proliferation by regulating mitotic substrates, such as PP1, PLK1, TPX2, and LAST2, and affects other molecules through a non-mitotic pathway to promote cell invasion and metastasis. Some molecules in tumor cells also indirectly act on Aurora-A to regulate tumor cells. Aurora-A also mediates resistance to chemotherapy and radiotherapy and is involved in tumor immunotherapy. Clinical trials of Aurora-A molecular inhibitors are currently underway, and clinical transformation is just around the corner.

Keywords: Aurora-A, cancer, clinical

Introduction

The Aurora kinase family is a class of serine/threonine protein kinases that was first discovered by Chan et al. in 1993 and named Ipl1 [1]. In 1995, Glover discovered a gene homologous to Ipl1 and named it Aurora-A (also known as aurka, STK6/BTAK) [2]. The Aurora gene family in humans includes Aurora-A, Aurora-B, and Aurora-C [3]. Aurora-A has been the subject of intense investigation because of its powerful regulatory roles on a variety of signaling pathways. The human Aurora-A gene is located on chromosome 20q13 [4, 5], and the structure of Aurora-A is shown in **Figure 1**. The N-terminal contains a localization domain that localizes Aurora-A on the centrosome in a microtubule-dependent manner. The C-terminal, a catalytic domain, contains two conserved domains: an activation loop and a degradation box (D-Box) [6, 7]. The activation loop comprises a highly conserved RxT motif, and phosphorylation of the motif at the threonine induces activation of Aurora-A [8]. The D-Box mediates degradation of Aurora-A through the ubiquitin-mediated proteasome pathway [9, 10].

Aurora-A was first discovered as a mitotic kinase that phosphorylates specific substrates and participates in centrosome and spindle activity during mitosis [11]. As studies on tumor development increased, Aurora-A was later found to be an oncogene that shows gene amplification and overexpression in a variety of human tumors [12, 13]. Aurora-A is used not only as a target for cancer treatment but also has such uses as a molecular marker for cancer diagnosis and prognosis, and for influencing cell proliferation, migration and metastasis [14-20]. In this review, we discuss the role of Aurora-A in mitosis and the regulatory mechanisms of Aurora-A in tumor cells. We also summarize the current clinical trials and results from Aurora-A inhibitors.

Biological function

The expression of Aurora-A is dependent on the cell cycle. Aurora-A is expressed at low levels in

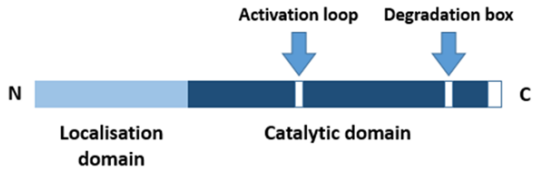

Figure 1. Aurora-A structure diagram.

the G1 and S phases and peaks at the G2 and M phases. Aurora-A is then ubiquitinated and degraded after the cell division phase [8, 21]. Aurora-A is activated during the G2 to M phase transition, when it is mainly responsible for the maturation and separation of centrosomes, assembly of bipolar spindles, and regulation of mitotic processes (**Figure 2**).

Aurora-A localizes on the centrosome in G2 and M phases, a process that is regulated by the Golgi apparatus [22-24]. The Golgi apparatus raises Aurora-A to target centrosomes in G2 phase, which is crucial to promoting the maturity of centrosomes [25]. Aurora-A simultaneously regulates Golgi structure stability after mitosis [26]. The centrosome replicates into two undivided centrosomes before the late S phase, but this process does not seem to involve Aurora-A, which only appears in the G2 phase. However, in vitro experiments have shown that Aurora-A overexpression causes centrosome amplification [27, 28]. Therefore, we speculate that Aurora-A may be indirectly involved in centrosome replication in some way. The copied centrosome must be separated to form a bipolar spindle, which requires the participation of Aurora-A. Inhibition of Aurora-A results in the formation of a unipolar spindle containing two unseparated centrosomes [2, 22, 29]. For mitosis to continue, the isolated centrosome needs to recruit various proteins, such as g-tubulin and centrosome proteins, which also requires Aurora-A [30]. During this process, Aurora-A also assists the spindle assembly checkpoint (SAC) to check the accuracy of the chromosomal centromere connection with microtubules [31]. The main role of Aurora-A after the spindle is formed is to stabilize the structure of the spindle [32]. Inhibiting Aurora-A not only renders the spindle structure unstable, but also reduces the star-shaped microtubules and spindle length [33-35].

Regulatory mechanisms in tumors

Tumorigenesis and development

Aurora-A exhibits a dual role in tumor cells. Aurora-A regulates molecules and substrates during mitosis, and it influences molecules and signals involved in tumor biological processes, such as proliferation, migration, invasion, metastasis, tumorigenesis, and apoptosis [36-40]. Aurora-A regulates multiple molecules and signaling pathways, such as p53/p73, p27, PP1, BRCA, Ras, the MEK/ERK signaling pathway, PLK1, TPX2, the NF-κB signaling pathway, the Hippo signaling pathway, the PI3K/Akt/mTOR signaling pathway, RIPK1/3, MLKL, the Wnt/β-catenin pathway, and the p38 MAPK signaling pathway, among other factors. Aurora-A is also regulated by several cellular microRNAs and long non-coding RNAs (lncRNAs) [41-43] (**Figure 3**).

p53/p73

P53, a pro-apoptotic factor, is phosphorylated by Aurora-A at Ser 315, which facilitates MDM2-mediated ubiquitination of p53 [44], and at Ser 215, which inhibits transcriptional activity of p53 [45]. In HCT116 cells, multiple myeloma SET domain proteins (MMSET), an epigenetically modified molecule, methylates Aurora-A to promote ubiquitination of p53 and reduction of p53 stability [46]. In response to decreased p53 levels, apoptosis is reduced, indicating a potential anti-cancer activity of p53. p73, a member of the p53 family, shows a similar structure and biological activity to p53 and also acts as a pro-apoptotic protein [47]. In p53-deficient hepatocellular carcinoma cells, inhibition of Aurora-A activates p73-mediated apoptosis, and p73 is regarded as a new target for p53-deficient cancer cells [48, 49].

p27

P27 (Cyclin-dependent kinase inhibitor 1B) serves as a regulator of cell proliferation as well as a tumor suppressor relying on varying post-translational modifications [50]. In gastric cancer, Aurora-A promotes p27 to reduce c-Bax-mediated apoptosis. Bcl-2 binds to Bax to inhibit Bax-mediated apoptosis. In gastric cancer, p27 inhibits the cleavage of Bax, a mitochondrial apoptosis activator, which leads to increased apoptosis and disruption of suppres-

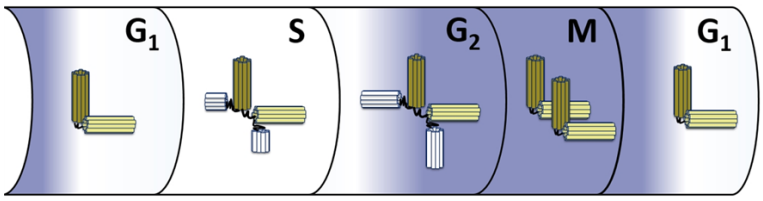

Figure 2. Schematic diagram of changes in centromere and Aurora-A during the cell cycle. The background color in the figure represents the expression level of Aurora-A.

sion by Bcl-2. Overexpressed Aurora-A downregulates calpain, which represses p27 and mediates Bax cleavage [51].

PP1

Aurora-A interacts with protein phosphatase 1 (PP1) in a balanced feedback regulation mechanism that is required for cell cycle progression of normal cells. PP1 binding to Aurora-A is essential for Aurora-A activation. Activated Aurora-A then phosphorylates PP1 to repress PP1, and in turn, PP1 inhibits Aurora-A by dephosphorylating certain sites in Aurora-A [52]. When this balance is disrupted, cells tend to undergo malignant changes. Phosphatase 1 nuclear targeting subunit (PNUTS), a protein that is crucial for mitotic stability and that is overexpressed in cancer cells, is involved in the process by which PP1 dephosphorylates Aurora-A in mammalian cells [53]. Thus, the ratio of Aurora-A to PP1 may be a prospective biomarker to predict tumorigenesis and allow for early diagnosis.

BRCA1/2

Oxidative stress induces single strand DNA single-strain break (SSB) in normal cells, which requires poly ADP-ribose polymerase (PARP) intervention for repair. If PARP is inhibited during this process, the SSBs leads to double-strain breaks (DSB), which requires BRCA for repair. In the absence of BRCA, these types of DNA damage lead to cell aberrations and subsequent tumorigenesis [54]. In normal cells, BRCA1 is phosphorylated and restrained by Aurora-A, while it is positively regulated by PP1 [55]. In ovarian carcinoma, overexpressed Aurora-A regulates DNA repair through its negative effects on BRCA1/2 [56, 57].

Ras

The oncogene Ras, which contains three mutations, K-Ras, H-Ras, and N-Ras, promotes genomic instability through a positive effect on Aurora-A [58]. In ovarian cancer, Ras promotes Aurora-A expression and downregulates BRCA2, resulting in an imbalance in the ratio of Aurora-A to BRCA2, leading to chromosomal instability and tumorigenesis [59]. KRAS exhibits similar biological activity as RAS and has a positive effect on Aurora-A in lung cancer [60]. In gastrointestinal cancer, KRAS promotes the expression of Aurora-A and subsequent Aurora-A-mediated phosphorylation of ribosomal protein S6 kinase B1 (RPS6KB1, mitosis-related protein) at T389, thereby promoting cell proliferation [61]. In breast cancer, Ras downstream signaling pathways such as the Ras-MAPK signaling pathway also participate in the regulation of Aurora-A [62].

MEK/ERK signaling pathway

The MEK/ERK signaling pathway is a Ras-MAPK signaling pathway that is activated by Aurora-A and Ras in triple-negative breast cancer, bladder cancer, and melanoma. In turn, ERK reacts to Aurora-A, promoting ERK and Aurora-A [63-65].

PLK1

Polo-like kinase 1 (PLK1) is a powerful cell cycle regulator that is activated in G2 phase under the combined action of Aurora-A and its cofactor Bora (protein aurora borealis) and functions in the M phase. PLK1 is phosphorylated by Aurora-A at Thr 210 and regulates centrosome maturation, spindle assembly, and chromosome segregation [66, 67]. Both Aurora-A and PLK1 have been identified as potential targets in chondrosarcoma [68]. In HeLa cells and nasopharyngeal carcinoma cells, the combined use of inhibitors against Aurora-A and PLK1 results in mitotic catastrophe [69]. In breast cancer, activated PLK1 motivates cell division cycle 25 (CDC25) to promote the cell cycle-related CCND1-CDK4/6 axis and proliferation. However, BRCA1 disturbs the interaction bet-

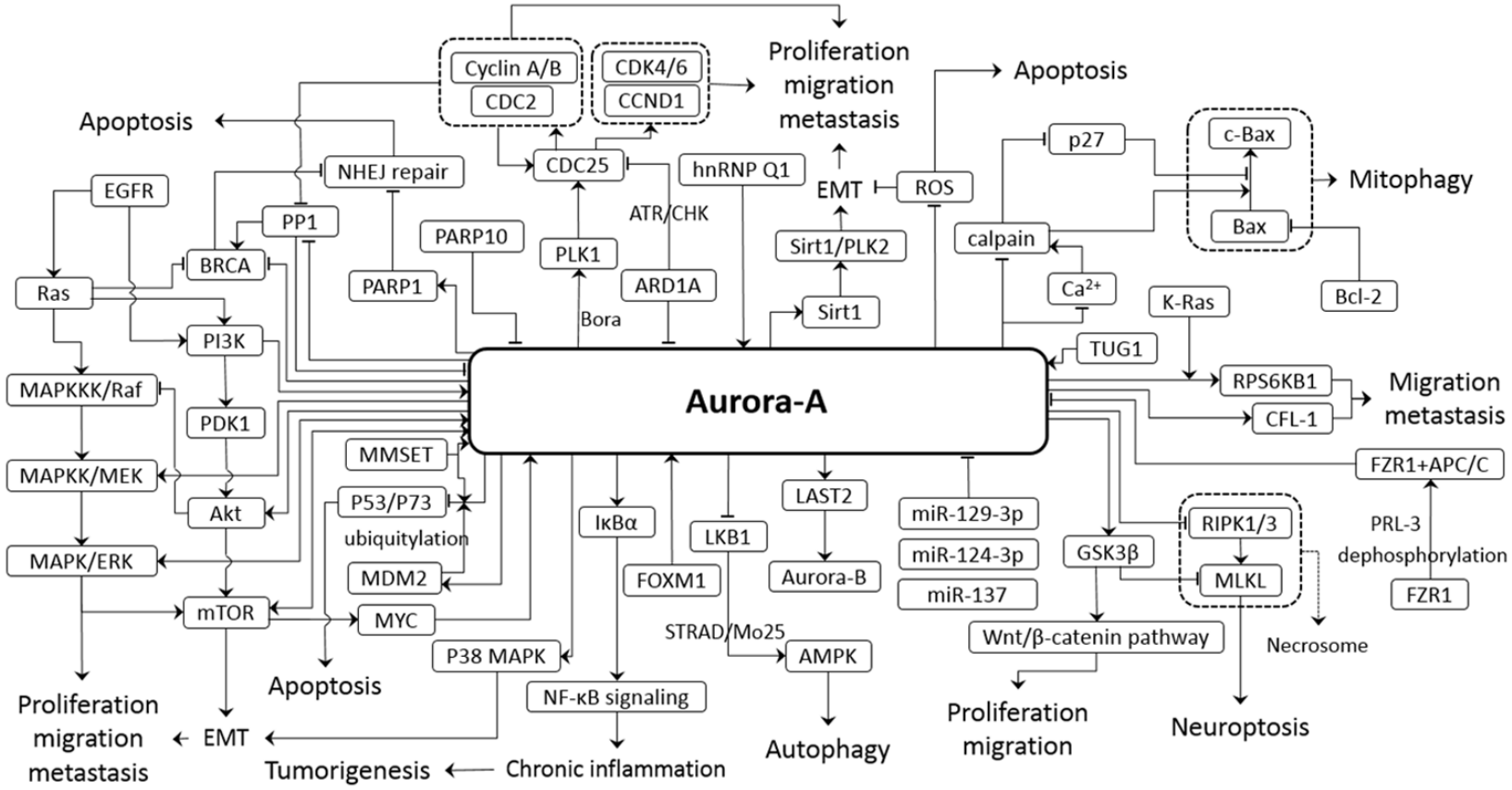

Figure 3. Regulation of tumorigenesis and development.

ween Aurora-A and Bora to repress PLK1 [70]. Therefore, molecules that activate BRCA1 may represent new opportunities for the treatment of breast cancer.

TPX2

Targeting protein for XKLP2 (TPX2) is a substrate of Aurora-A and is highly expressed in cancer cells. TPX2 helps Aurora-A localization to the spindle, while Aurora-A phosphorylates TPX2 to regulate the process of the spindle [71, 72]. TPX2 deficiency causes genomic instability and apoptosis [73].

NF-κB signaling pathway

In gastric cancer, Aurora-A phosphorylates IκBα, a key molecule in the NF-κB signaling pathway, to activate the NF-κB signaling pathway. Activation of NF-κB causes chronic inflammation of the stomach, resulting in tumorigenesis [74].

Hippo signaling pathway

Large tumor suppressor 1/2 (LAST1/2) are kinases in the Hippo signaling pathway that act as tumor suppressors [75, 76]. In normal cells, LAST2 is phosphorylated by Aurora-A at Ser 380 during mitosis to activate Aurora-B, promising well-balanced cell cycle, which makes no difference with LAST2 to serve in Hippo signaling pathway [77]. Both Aurora-A and LATS2 are overexpressed in chronic myeloid leukemia [78]. Therefore, we speculate that the Aurora-A-LAST2-Aurora-B axis may be important in chronic myeloid leukemia or other solid tumors.

PI3K/Akt/mTOR signaling pathway

The PI3K/Akt/mTOR signaling pathway and Aurora-A have a mutual feedback regulation effect in human epithelial ovarian cancer, glioblastoma, prostate cancer, and breast cancer [79-83]. In lung cancer, both the EGF/EGFR signaling pathway and Aurora-A overexpression activate the PI3K/Akt/mTOR signaling pathway [84]. In neuroblastoma, PI3K and mTOR act on Aurora-A to promote Aurora-A expression directly and regulate its transcription level by promoting MYC indirectly, which is activated to promote epithelial-mesenchymal transition (EMT), thereby promoting tumor proliferation, migration, metastasis, and invasion and inhibiting apoptosis [85]. In human glioblastoma multiform stem cells, phosphoinositide-dependent kinase-1 (PDK1) serves as a link between PI3K and Akt [86].

RIPK1/3 and MLKL

Necroptosis, a form of apoptosis, involves receptor-interacting serine/threonine kinase 1 (RIPK1), receptor-interacting serine/threonine kinase 1 (RIPK3), and mixed lineage kinase domain-like (MLKL), which are all necrosome components. During necroptosis, the RIPK1-RIPK3 complex activates MLKL to mediate the final lethal step [87, 88]. In pancreatic carcinoma, Aurora-A represses both the RIPK1-RIPK3 complex and MLKL, thus inhibiting necroptosis. Aurora-A binds the RIPK1-RIPK3 complex to inhibit it. Aurora-A suppresses the RIPK3-MLKL complex via phosphorylating glycogen synthase kinase 3β (GSK3β) at Ser 9 [89].

Wnt/β-catenin pathway

Wnt/β-catenin pathway is closely related to Aurora-A. In colorectal cancer, the Wnt/β-catenin pathway is downregulated by Aurora-A, although the mechanisms have not been identified and require further exploration [90]. Active GSK3β phosphorylates β-catenin, leading to β-catenin degradation [91]. As mentioned above, in pancreatic carcinoma, Aurora-A phosphorylates GSK3β at Ser 9 to restrain GSK3β [89]. We thus speculate that inactive GSK3β issue in β-catenin accumulation mediates Wnt/β-catenin pathway activation.

p38 MAPK signaling pathway

p38 MAPK is a member of the MAPK family of proteins. p38 MAPK is activated by Aurora-A and plays a role in promoting tumor EMT in melanoma and glioblastoma. Aurora-A inhibitors inhibit p38 MAPK activation, mediating apoptosis and autophagy. p38 MAPK is speculated to function in apoptosis and autophagy [83, 92].

MicroRNAs and lncRNA

Several microRNAs and long non-coding RNAs (lncRNA) that play vital regulatory roles in cells have also been shown to regulate Aurora-A. For example, some microRNAs, which are down-regulated in cancer cells, also limit Aurora-A

expression: methylation-mediated downregulated miR-129-3p which promotes EMT, invasion and metastasis in hepatocellular cancer; miR-124-3p, which affects proliferation, migration and apoptosis in bladder cancer [93]; and miR-137, which is involved in chromosomal instability in multiple myeloma [94]. In adult acute myeloid leukemia and epithelial ovarian cancer, the lncRNA taurine-upregulated gene 1 (TUG1) promotes proliferation via inducing Aurora-A expression [95, 96].

PARP

The PARP family is a group of ribozymes that contains 18 members. Both PARP1 and PARP10 have been shown to functionally interact with Aurora-A in cancer cells. In ovarian cancer, Aurora-A inhibition decreases PARP1, which mainly participates in DNA repair, leading to the more error-prone non-homologous end-joining (NHEJ) repair and eventually resulting in apoptosis [56]. In hepatocellular carcinoma, PARP10, which functions differently than PARP1, mono-ADP-ribosylates and inactivates Aurora-A, leading to reduced migration, invasion, and metastasis [97].

CDC25

The cell cycle regulator CDC25 is regulated by Aurora-A and AT-rich interactive domain 1A (ARID1A), a tumor suppressor that is mutated in many tumors. In colorectal cancer, ARID1A indirectly inhibits CDC25 and PLK1 by decreasing Aurora-A expression and directly inhibits CDC25 through the ARID1A/ATR/CHK pathway, thereby inhibiting the cell cycle and regulating cell proliferation [98]. In breast cancer, Aurora-A regulates CDC25 to promote cancer progression [70].

Sirtuin 1 (Sirt1)

Sirt1 is a key protein involved in centromeric replication. The interaction between Sirt1 and PLK2 facilitates the cell cycle and EMT [99]. In human epithelial ovarian cancer cells, the Aurora-A inhibitor induces cell apoptosis and autophagy, possibly through restraining Sirt1 expression. The specific regulatory mechanism needs further study [79].

LKB1

In non-small cell lung cancer (NSCLC), liver kinase B1 (LKB1, or STK11) interacts with STARD and Mo25 to catalyze the phosphorylation of AMPK to facilitate autophagy. Aurora-A phosphorylates and inactivates LKB1, preventing it from binding STARD and Mo25 to promote tumor cell development [100].

Other functions and pathways

In oral squamous cell carcinoma, inhibition of Aurora-A promotes reactive oxygen species (ROS) production and tumor apoptosis [101]. In colorectal cancer, hnRNP Q1 influences cell proliferation and tumorigenesis by controlling Aurora-A translation [102]. In papillary thyroid cancer, cofilin-1 (CFL-1), an actin-binding protein, is dephosphorylated by Aurora-A to catalyze its activation and tumor migration [103]. In colorectal cancer, fizzy and cell division cycle 20 related 1 (FZR1) is dephosphorylated by phosphatase of regenerating liver-3 (PRL-3) and interacts with the anaphase-promoting complex/cyclosome (APC/C) complex to promote Aurora-A ubiquitination [104].

Two spindle formation modes exist in mammalian cells: centrosome-dependent and non-centrosome-dependent mitosis. In NSCLC cells, Aurora-A plays a role in both processes. Inhibition of the centrosome-dependent protein SMARCA4 increases Aurora-A regulation of spindle formation and NSCLC cell sensitivity to Aurora-A inhibitors [105].

Aurora-A may localize in mitochondria in tumor cells to promote mitochondrial fusion, thereby generating more ATP and providing more energy support for tumor cells, which is beneficial to tumor cell proliferation [106].

Chemoresistance and radioresistance

In addition to directly regulating the occurrence and development of tumors, Aurora-A also exerts a negative influence on the efficacy of chemotherapy and radiotherapy, based in part on its increased expression in resistant tumor cells (**Figure 4**). Aurora-A overexpression induces radiotherapy resistance in many cancers such as lung cancer, hepatocellular carcinoma, cervical squamous cell carcinoma, glioblastoma, nasopharyngeal carcinoma, and prostate cancer [107-109]. In breast cancer, pancreatic cancer, and ovarian epithelial cancer, Aurora-A overexpression increases the chemoresistance and radioresistance of tumor cells by upregulating the ATM/Chk2-mediated DNA damage

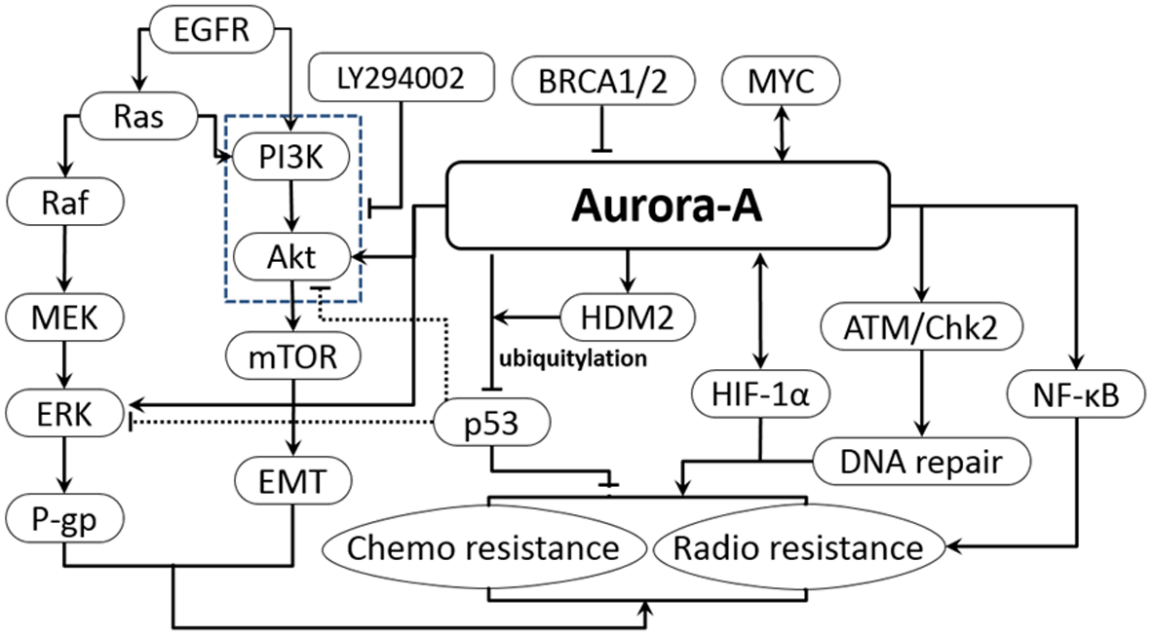

Figure 4. Mechanism of Aurora-A mediated chemotherapy and radiotherapy.

repair network, which can be inhibited by BRCA1/2 [110]. Clinical data suggest that elevated Aurora-A expression in NSCLC, ovarian cancer, and oral squamous cell carcinoma is related to cisplatin resistance [111-114]. In endometrial cancer, Aurora-A increases cisplatin and PTX resistance by sensitizing AKT/mTOR signaling pathway [115]. Aurora-A promotes ERK phosphorylation and regulates P-gp (a multidrug resistance transporter that takes Taxol as substrate), which ultimately leads to Taxol resistance in breast cancer [116]. In triple-negative breast cancer, FOXM1 is stabilized by Aurora-A to promote PTX resistance [117]. Aurora-A and MYC interact with each other in Myc-overexpressing lymphoma to mediate cancer cell resistance to cyclophosphamide. Inhibition of Aurora-A overexpression reduces the chemotherapy resistance of lymphoma while suppressing MYC overexpression [118]. Aurora-A causes laryngeal squamous cell carcinoma cells to hibernate in the manner of the activation ERK1/2 pathway [119]. High expression of Aurora-A enables cancer stem cells in colorectal cancer to develop resistance to 5-FU [120]. In lung cancer, EGFR-TKI resistance is related to the interaction between Aurora-A, Ras, and p53 [121, 122]. Imatinib resistance in chronic myelogenous leukemia cells is also closely related to Aurora-A overexpression in tumor cells, although the related signaling is unknown [123]. In nasopharyngeal carcinoma, Aurora-A works synergistically with HIF-1α to promote the radiotherapy and chemotherapy resistance of cancer cells [124]. In lung cancer cells, Aurora-A may affect radiotherapy sensitivity by upregulating NF-κB expression and downregulating p53 expression [125, 126]. NF-κB also functions in the radioresistance of hepatocellular carcinoma regulated by Aurora-A [127]. Intriguingly, radiation also promotes HCC metastasis by activating Aurora-A to promote tumor stem cell proliferation through the PI3K/Akt signaling pathway [128].

Immunotherapy

Tumor immunotherapy mobilizes the host immune system and enhances the ability of antitumor immunity in the tumor microenvironment to control and kill tumor cells [129]. Aurora-A is considered an antigen target for immunotherapeutic attacks [130-132]. In breast cancer, suppression of Aurora-A greatly changes the immunogenic microenvironment of tumor cells, which is conducive to the enrichment of cytotoxic T cells (CTLs). Also, the suppression of Aurora-A is harmful to immunosuppressive myeloid-derived suppressor cells (MDSCs) in which apoptosis is induced by reduced ROS production through the Stat3 pathway [133]. In peripheral T-cell lymphoma, the simultaneous application of PD-L1 and Aurora-A inhibitors

Table 1. Aurora kinase inhibitors

Inhibitor	Molecular Formula	Target	Current status	DLT	AE	Condition	Reference
PHA-79358 (Danusertib)	$C_{26}H_{30}N_6O_3$	Aurora-A (IC50: 13 nmol/L) Aurora-B (IC50: 79 nmol/L) Aurora-C (IC50: 61 nmol/L)	Phase 2	-Bullous dermatitis -Febrile neutropenia -Mucositis -Syncope	-Anorexia -Constipation -Diarrhea -Fatigue -Nausea -Progressive Pneumonia -Thrombocytopenia	-Advanced Solid Tumors -Breast, Ovarian, Colorectal, Pancreatic Cancer, SCLC, NSCLC -CML -Metastatic hormone refractory Prostate Cancer -Metastatic castration-resistant prostate cancer after docetaxel failure -Multiple Myeloma	[182-187]
MK-0457 (VX-680, Tozasertib)	$C_{23}H_{28}N_8OS$	Aurora-A (Ki: 0.6 nM) Aurora-B (Ki: 18 nM) Aurora-C (Ki: 4.6 nM)	Phase 2	-Herpes zoster -Neutropenia	-Alopecia -Diarrhea -Fatigue -Nausea -Transient mucositis -Vomiting	-Advanced Solid Tumors -BCR-ABL T315I mutant CML, Philadelphia chromosome-positive ALL -Colorectal Cancer	[188-190]
MSC1992371A	$C_{24}H_{30}FN_7O$	Aurora-A Aurora-B Aurora-C	Phase 1	-Diarrhea -(Febrile or not) Neutropenia -Mucositis/stomatitis -Sepsis	-Anemia -Fatigue. -Thrombocytopenia	-Advanced Hematologic Malignancies -Solid Tumors	[191, 192]
ABT-348 (Iloraser-tib)	$C_{25}H_{21}FN_6O_2S$	Aurora kinase VEGFR	Phase 2	-Hypertension -Pancreatitis	-Anemia -Hypokalemia -Hypophosphatemia	-Advanced Solid Tumors -ALL, AML, B-cell CLL, CML, Myelodysplasia -Hematologic Malignancies -Metastatic Malignant Neoplasm, Solid Neo-plasm, Unresectable Malignant Neoplasm	[193]
BI-847325	$C_{29}H_{28}N_4O_2$	Aurora kinase MEK	Phase 1	Reversible hematologic and gastrointestinal toxicities	-Anemia -Diarrhea -Decreased appetite -Fatigue -Nausea -Neutropenia -Vomiting	-Advanced Solid Tumors	[194]
ENMD-2076	$C_{21}H_{25}N_7$	Aurora kinase VEGFR	Phase 2	-Fatigue -Hypertension -Neutropenia -Syncope -Typhlitis -QTc prolongation	-Diarrhea -Fatigue -Nausea -Vomiting	-Advanced Solid Tumors -Advanced, Metastatic, Soft Tissue Sarcoma -Advanced Adult Hepatocellular Carcinoma, Advanced Fibrolamellar Carci-noma -Metastatic Triple-Negative Breast Cancer -Multiple Myeloma -Relapsed or Refractory Hematological Malignancies -Ovarian Clear Cell Carcinoma -Ovarian Cancer, Fallopian Cancer, Perito-neal Cancer	[195-198]

AT9283	$C_{19}H_{23}N_7O_2$	Aurora-A Aurora-B	Phase 2	-Cardiomyopathy -(Febrile or not) Neutropenia -Hypertension -Infection -Myocardial infarction -Multiorgan failure -Pneumonia -Tumor lysis syndrome	-Alopecia -Anemia -Fatigue -Gastrointestinal disturbance -Lymphocytopenia -Myelosuppression -Mucositis -Thrombocytopenia -Vomiting	-Advanced Solid Malignancies -Multiple Myeloma -Non-Hodgkins Lymphoma, Unspecified Adult Solid Tumor -AML, ALL, CML, Myelodysplastic Syndromes, Myelofibrosis -Unspecified Childhood Solid Tumor	[199-204]
AMG900	$C_{28}H_{21}N_7OS$	Aurora-A Aurora-B	Phase 1	-Abnormal pain -Increases in alanine aminotransferase and aspartate aminotransferase -Neutropenia -Pancytopenia -Thrombocytopenia	-Anemia -Diarrhea -Fatigue -Leukopenia -Nausea	-Advanced Adult Solid Tumors -AML -Hematologic Malignancies	[205, 206]
PF-03814735	$C_{23}H_{25}F_3N_6O_2$	Aurora-A Aurora-B	Phase 1	-Febrile neutropenia -Increase of aspartate aminotransferase -Left ventricular dysfunction	-Anemia -Diarrhea -Decreased appetite -Fatigue -Nausea -Vomiting	-Advanced Solid Tumors	[207]
MLN8237 (Alisertib)	$C_{27}H_{20}ClFN_4O_4$	Aurora-A	Phase 3	-Abdominal pain -Asthenia -Anorexia -Bullous dermatitis -Fatigue -(Febrile or not) Neutropenia -Headache -Leukopenia -Liver transaminases elevation -Mood alteration/depression -Nausea -Oropharyngeal mucositis -Oral pain -Somnolence -Stomatitis -Thrombocytopenia -Urinary tract infection	-Anemia -CNS toxicities -Cytopenia -Diarrhea -Dysgeusia -Hypocalcemia -Lymphopenia -Memory impairment -Neuropathy -Thrombocytopenia -Vomiting	-Advanced Solid Tumors -Ovarian Carcinoma, Fallopian Tube Cancer, Peritoneal Cancer, Breast Carcinoma -Unspecified Childhood Solid Tumor, Excluding CNS -Relapsed/Refractory Hematological Malignancies -Refractory Multiple Myeloma -etc.	[136-162, 208, 209]
MLN8054	$C_{25}H_{15}ClF_2N_4O_2$	Aurora-A	Phase 1	-Benzodiazepine-like effects -Somnolence -Transaminitis	-Asthenia -Anorexia -Fatigue -Insomnia -Confusion -Dizziness -Nausea	-Advanced Solid Tumors -Breast Neoplasm, Colon Neoplasm, Pancreatic Neoplasm, Bladder Neoplasm	[167-169]
MK-5108 (VX-689)	$C_{22}H_{21}ClFN_3O_3S$	Aurora-A (IC50: 0.064 nM)	Phase 1	-Febrile neutropenia -Infection	-Blood and lymphatic system disorders -General disorders and administration site conditions -Gastrointestinal disorders	-Advanced or Refractory Solid Tumors	[170]

AZD-1152 (Barasertib)	$C_{26}H_{31}FN_7O_6P$	Aurora-B	Phase 3	-Neutropenia -Stomatitis/mucositis	-Diarrhea -Fatigue -Infection -Nausea -Neutropenia -Pyrexia	-AML -Advanced Solid Tumors -Myeloid Leukemia -Relapsed/Refractory Diffuse Large B-cell Lymphoma	[210-217]
BI-831266	$C_{20}H_{14}O_2$	Aurora-B	Phase 1	-Febrile neutropenia	-Alopecia -Anemia -Dry skin -Fatigue -Nausea	-Advanced Solid Tumors	[218]
BI-811283	unknown	Aurora-B (IC50: 9 nM)	Phase 2	-Febrile neutropenia	-Fatigue -Leukopenia -Nausea	-AML -Advanced Solid Tumors	[219]

Part of the information comes from https://clinicaltrials.gov/and https://pubchem.ncbi.nlm.nih.gov/. Abbreviations: (i) DLT: dose-limiting toxicity, (ii) AE: adverse event, (iii) CML: chronic myeloid leukemia, (iv) SCLC: small-cell lung cancer, NSCLC: non-small-cell lung cancer (v) ALL: acute lymphoblastic leukemia (vi) AML: acute myeloid leukemia.

achieve better efficacy than PD-L1 monotherapy [134].

Clinical application

Dozens of inhibitors of the Aurora kinase family are currently under development, many of which have entered into clinical trials and achieved promising results. (**Table 1**) (**Figure 5**, these structure diagrams come from PubChem: https://pubchem.ncbi.nlm.nih.gov/) These inhibitors can be roughly divided into four categories: (i) Aurora-A, Aurora-B, and Aurora-C inhibitors, consisting of PHA-79358 (danusertib), MK-0457 (VX-680, tozasertib), MSC19923-71A, ABT-348 (ilorasertib), BI-847325, and ENMD-2076; (ii) Aurora-A and Aurora-B inhibitors, consisting of AT9283, AMG900, and PF-03814735; (iii) specific Aurora-A inhibitors, consisting of MLN8237, MLN8054, and MK-5108 (VX-689); and (iv) specific Aurora-B inhibitors, including AZD-1152 (barasertib), BI-83-1266, and BI-811283. Here we focus on the specific Aurora-A inhibitors.

MLN8237, which is a second generation Aurora-A inhibitor, is currently in a phase 3 clinical trial. The main mode of administration is oral and its metabolites are mainly excreted from feces [135]. In the phase 1 and 2 clinical trial results, most of dose-limiting toxicities (DLTs) and the most common drug-related adverse events (AEs) were 1/2 grade adverse events, while 3/4 grade adverse events rarely occurred. Regarding the effectiveness of drug treatment, the overall response rate in lymphoma, NSCLC, pancreatic cancer, and esophageal cancer has been relatively optimistic, and the median progression-free survival (PFS) and time to progression (TTP) improved. The current phase 3 clinical trial of MLN8237 is mainly focused on hematologic tumors [136-161]. Unfortunately, phase 3 clinical research shows no prospective improvement of therapeutic effect using MLN8237 in relapsed or refractory peripheral T-cell lymphoma patients [162]. The clinical dose of MLN8237 has no effects on the QTc interval of patients [163]. Some researchers studied the effect of food on the effect of MLN8237 and found no difference in the distribution of MLN8237 after high-fat meals and in fasting states [164]. In advanced breast cancer and recurrent ovarian cancer, the combination of MLN8237 with paclitaxel showed better therapeutic effect than paclitaxel monotherapy [165]. Some studies found that patients should avoid the simultaneous use of MLN8237 with gastric acid-reducing agents, potent CYP3A inhibitors, and strong metabolic enzyme inducers [166].

MLN8054 is a first generation Aurora-A inhibitor. It is currently in a phase 1 clinical trial and the main mode of administration is oral. The DLTs of MLN8054 are somnolence and transaminitis [167, 168]. In a phase 1 clinical study, it was found DLT with benzodiazepine-like effects [169].

MK-5108 (VX-689) is currently in a phase 1 clinical trial and its treatment was associated with DLTs such as febrile neutropenia and infection and AEs including blood and lymphatic system disorders and gastrointestinal disorders [170].

Clinical trial results of first-generation inhibitors to second-generation inhibitors show that DLTs and AEs are continuously decreasing, which shows promise for the clinical use of Aurora-A inhibitors. Some studies have found that the functional single nucleotide polymorphism (SNP) of Aurora-A is related to the prognosis of patients with solid tumors and sensitivity to inhibitors [171-181].

Conclusion

Since the discovery of the Aurora kinase family in 1993, research on the Aurora kinase family has continued to increase and its clinical transformation is entering the final stage. The second-generation Aurora-A inhibitor MLN8237 has entered phase III clinical trials, which are mainly focused on hematologic malignancies. However, the single-agent treatment of MLN-8237 showed limited benefit for patients, so the road to market of MLN8237 remains long. Aurora-A not only affects tumorigenesis and development, but also mediates tumor cell chemotherapy and radiotherapy resistance and participates in tumor immunotherapy. Thus, Aurora-A inhibitors have a wide range of clinical applications, not only as a therapeutic drug to kill tumor cells but also as an adjuvant drug in combination with other chemotherapy drugs or radiotherapy to improve the efficacy of existing treatments. Notably, the Aurora-A regulato-

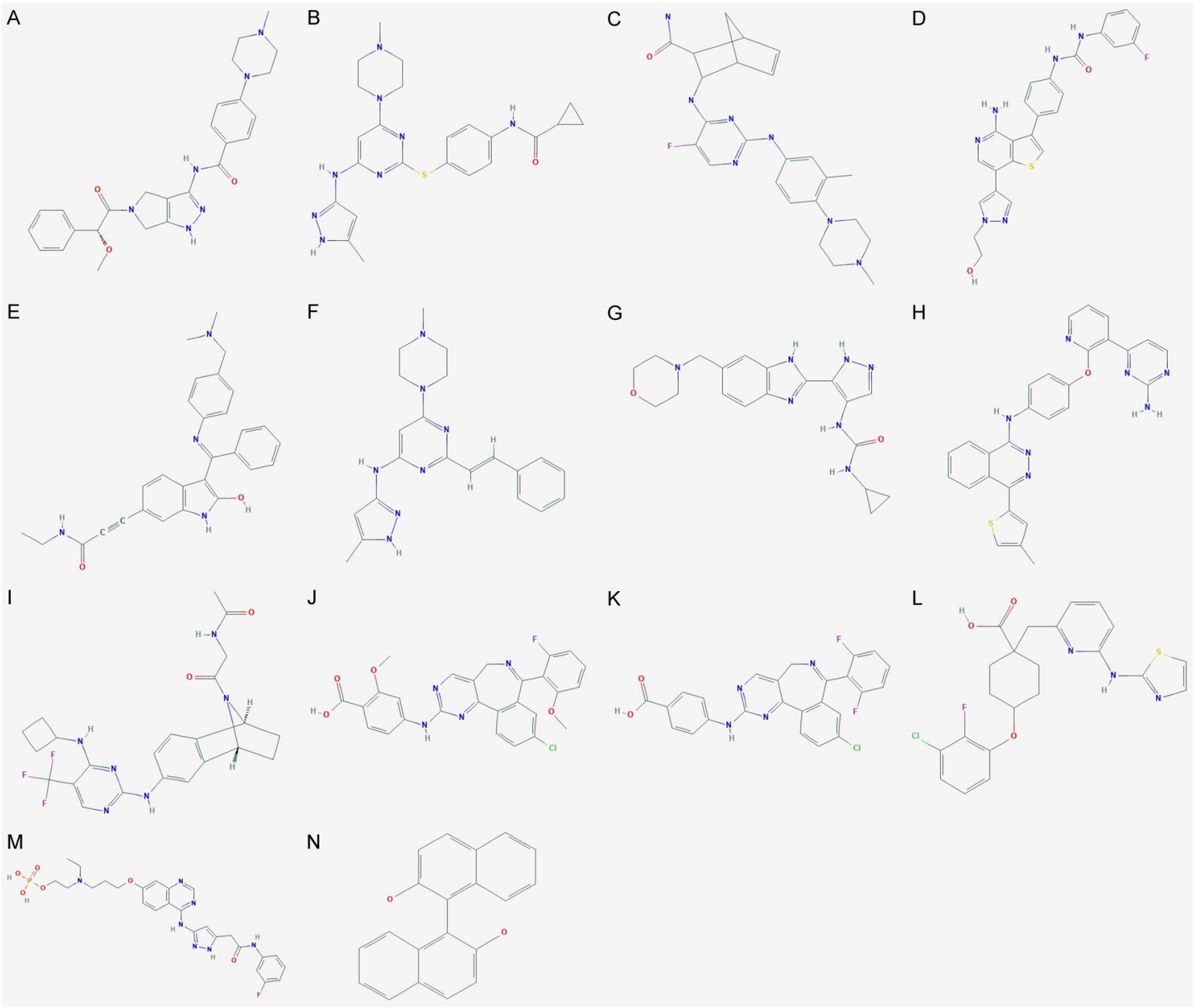
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Figure 5. The chemical structure of Aurora kinase inhibitors. (From PubChem: https://pubchem.ncbi.nlm.nih.gov/). A. Structure of PHA-79358. B. Structure of MK-0457. C. Structure of MSC1992371A. D. Structure of ABT-348. E. Structure of BI-847325. F. Structure of ENMD-2076. G. Structure of AT9283. H. Structure of AMG900. I. Structure of PF-03814735. J. Structure of MLN8237. K. Structure of MLN8054. L. Structure of MK-5108. M. Structure of AZD-1152. N. Structure of BI-831266.

ry pathways in cells are very complex. It is unlikely that blocking one of them will completely prevent tumor progression and induce large-scale tumor cell apoptosis in vivo. Given that the combination of Aurora-A inhibitors and other antineoplastic drugs has achieved surprising anti-tumor effects in in vitro and in vivo experiments, the possibility of combining medications may be an effective strategy.

Acknowledgements

This project was supported by grants from the National Natural Science Foundation of China (81472266 and 81772995) and the Excellent Youth Foundation of Jiangsu Province (BK20-140032). We thank Gabrielle White Wolf, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Disclosure of conflict of interest

None.

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References

[1] Chan CS and Botstein D. Isolation and characterization of chromosome-gain and increase-in-ploidy mutants in yeast. Genetics 1993; 135: 677-691.

[2] Glover DM, Leibowitz MH, McLean DA and Parry H. Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles. Cell 1995; 81: 95-105.

[3] Nigg EA. Mitotic kinases as regulators of cell division and its checkpoints. Nat Rev Mol Cell Biol 2001; 2: 21-32.

[4] Tanner MM, Tirkkonen M, Kallioniemi A, Holli K, Collins C, Kowbel D, Gray JW, Kallioniemi OP and Isola J. Amplification of chromosomal region 20q13 in invasive breast cancer: prognostic implications1. Clin Cancer Res 1995; 1: 1455-1461.

[5] Sen S, Zhou H and White RA. A putative serine/threonine kinase encoding gene BTAK on chromosome 20q13 is ampli®ed and overexpressed in human breast cancer cell lines. Oncogene 1997; 14: 2195-2200.

[6] Giet R and Prigent C. The non-catalytic domain of the Xenopus laevis auroraA kinase localises the protein to the centrosome. J Cell Sci 2001; 114: 2095-2104.

[7] Ruff EF, Muretta JM, Thompson AR, Lake EW, Cyphers S, Albanese SK, Hanson SM, Behr JM, Thomas DD, Chodera JD and Levinson NM. A dynamic mechanism for allosteric activation of Aurora kinase A by activation loop phosphorylation. Elife 2018; 7: e32766.

[8] Walter AO, Seghezzi W, Korver W, Sheung J and Lees E. The mitotic serine/threonine kinase Aurora2/AIK is regulated by phosphorylation and degradation. Oncogene 2000; 19: 4906-4916.

[9] Arlot-Bonnemains Y, Klotzbucher A, Giet R, Uzbekov R, Bihan R and Prigent C. Identification of a functional destruction box in the Xenopus laevis aurora-A kinase pEg2. FEBS Lett 2001; 508: 149-152.

[10] Castro A, Arlot-Bonnemains Y, Vigneron S, Labbé JC, Prigent C and Lorca T. APC/Fizzy-Related targets Aurora-A kinase for proteolysis. EMBO Rep 2002; 3: 457-462.

[11] McHedlishvili N, Jonak K and Saurin AT. Meeting report--getting into and out of mitosis. J Cell Sci 2015; 128: 4035-4038.

[12] Kanamori S, Kajihara I, Kanazawa-Yamada S, Otsuka-Maeda S and Ihn H. Expression of aurora kinase A expression in dermatofibrosarcoma protuberans. J Dermatol 2018; 45: 507-508.

[13] Lykkesfeldt AE, Iversen BR, Jensen MB, Ejlertsen B, Giobbie-Hurder A, Reiter BE, Kirkegaard T and Rasmussen BB. Aurora kinase A as a possible marker for endocrine resistance in early estrogen receptor positive breast cancer. Acta Oncol 2018; 57: 67-73.

[14] Guo M, Lu S, Huang H, Wang Y, Yang MQ, Yang Y, Fan Z, Jiang B and Deng Y. Increased AURKA promotes cell proliferation and predicts poor prognosis in bladder cancer. BMC Syst Biol 2018; 12: 118.

[15] Shaikh MH, Idris A, Johnson NW, Fallaha S, Clarke DTW, Martin D, Morgan IM, Gabrielli B and McMillan NAJ. Aurora kinases are a novel therapeutic target for HPV-positive head and neck cancers. Oral Oncol 2018; 86: 105-112.

[16] Xia JL, Fan WJ, Zheng FM, Zhang WW, Xie JJ, Yang MY, Kamran M, Wang P, Teng HM, Wang CL and Liu Q. Inhibition of AURKA kinase activity suppresses collective invasion in a microflu-

idic cell culture platform. Sci Rep 2017; 7: 2973.
[17] Goos JA, Coupe VM, Diosdado B, Delis-Van Diemen PM, Karga C, Beliën JA, Carvalho B, van den Tol MP, Verheul HM, Geldof AA, Meijer GA, Hoekstra OS and Fijneman RJ; DeCoDe PET group. Aurora kinase A (AURKA) expression in colorectal cancer liver metastasis is associated with poor prognosis. Br J Cancer 2013; 109: 2445-2452.
[18] Zhong N, Shi S, Wang H, Wu G, Wang Y, Ma Q, Wang H, Liu Y and Wang J. Silencing Aurora-A with siRNA inhibits cell proliferation in human lung adenocarcinoma cells. Int J Oncol 2016; 49: 1028-1038.
[19] Jiang Z, Jiang J, Yang H, Ge Z, Wang Q, Zhang L, Wu C and Wang J. Silencing of Aurora kinase A by RNA interference inhibits tumor growth in human osteosarcoma cells by inducing apoptosis and G2/M cell cycle arrest. Oncol Rep 2014; 31: 1249-1254.
[20] Mobley A, Zhang S, Bondaruk J, Wang Y, Majewski T, Caraway NP, Huang L, Shoshan E, Velazquez-Torres G, Nitti G, Lee S, Lee JG, Fuentes-Mattei E, Willis D, Zhang L, Guo CC, Yao H, Baggerly K, Lotan Y, Lerner SP, Dinney C, McConkey D, Bar-Eli M and Czerniak B. Aurora kinase a is a biomarker for bladder cancer detection and contributes to its aggressive behavior. Sci Rep 2017; 7: 40714.
[21] Honda K, Mihara H, Kato Y, Yamaguchi A, Tanaka H, Yasuda H, Furukawa K and Urano T. Degradation of human Aurora2 protein kinase by the anaphase-promoting complex-ubiquitin-proteasome pathway. Oncogene 2000; 19: 2812-2819.
[22] Roghi C, Giet R, Uzbekov R, Morin N, Chartrain I, Le Guellec R, Couturier A, Dorée M, Philippe M and Prigent C. The Xenopus protein kinase pEg2 associates with the centrosome in a cell cycle-dependent manner, binds to the spindle microtubules and is involved in bipolar mitotic spindle assembly. J Cell Sci 1998; 111: 557-572.
[23] Kimura M, Kotani S, Hattori T, Sumi N, Yoshioka T, Todokoro K and Okano Y. Cell cycle-dependent expression and spindle pole localization of a novel human protein kinase, Aik, related to Aurora of Drosophila and yeast Ipl1. J Biol Chem 1997; 272: 13766-13771.
[24] Stenoien DL, Sen S, Mancini MA and Brinkley BR. Dynamic association of a tumor amplified kinase, Aurora-A, with the centrosome and mitotic spindle. Cell Motil Cytoskeleton 2003; 55: 134-146.
[25] Barretta ML, Spano D, D'Ambrosio C, Cervigni RI, Scaloni A, Corda D and Colanzi A. Aurora-A recruitment and centrosomal maturation are regulated by a Golgi-activated pool of Src during G2. Nat Commun 2016; 7: 11727.
[26] Kimura M, Takagi S and Nakashima S. Aurora A regulates the architecture of the Golgi apparatus. Exp Cell Res 2018; 367: 73-80.
[27] Meraldi P, Honda R and Nigg EA. Aurora-A overexpression reveals tetraploidization as a major route to centrosome amplification in p53-/- cells. EMBO J 2002; 21: 483-492.
[28] Zhou H, Kuang J, Zhong L, Kuo WL, Gray JW, Sahin A, Brinkley BR and Sen S. Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat Genet 1998; 20: 189-193.
[29] Giet R, McLean D, Descamps S, Lee MJ, Raff JW, Prigent C and Glover DM. Drosophila Aurora A kinase is required to localize D-TACC to centrosomes and to regulate astral microtubules. J Cell Biol 2002; 156: 437-451.
[30] Berdnik D and Knoblich JA. Drosophila aurora-a is required for centrosome maturation and actin-dependent asymmetric protein localization during mitosis. Curr Biol 2002; 12: 640-647.
[31] Courtheoux T, Diallo A, Damodaran AP, Reboutier D, Watrin E and Prigent C. Aurora A kinase activity is required to maintain an active spindle assembly checkpoint during prometaphase. J Cell Sci 2018; 131: jcs191353.
[32] Cowley DO, Rivera-Perez JA, Schliekelman M, He YJ, Oliver TG, Lu L, O'Quinn R, Salmon ED, Magnuson T and Van Dyke T. Aurora-A kinase is essential for bipolar spindle formation and early development. Mol Cell Biol 2009; 29: 1059-1071.
[33] Hannak E, Kirkham M, Hyman AA and Oegema K. Aurora-A kinase is required for centrosome maturation in Caenorhabditis elegans. J Cell Biol 2001; 155: 1109-1116.
[34] Schumacher JM, Ashcroft N, Donovan PJ and Golden A. A highly conserved centrosomal kinase, AIR-1, is required for accurate cell cycle progression and segregation of developmental factors in Caenorhabditis elegans embryos. Development 1998; 125: 4391-4402.
[35] Kesisova IA, Nakos KC, Tsolou A, Angelis D, Lewis J, Chatzaki A, Agianian B, Giannis A and Koffa MD. Tripolin A, a novel small-molecule inhibitor of aurora A kinase, reveals new regulation of HURP's distribution on microtubules. PLoS One 2013; 8: e58485.
[36] Wang Z, Ma Z and Cao J. Effects of repeated aurora-A siRNA transfection on cilia generation and proliferation of SK-MES-1 or A549 cells. Cancer Biother Radiopharm 2018; 33: 110-117.
[37] Min YH, Kim W and Kim JE. The Aurora kinase A inhibitor TC-A2317 disrupts mitotic progres-

sion and inhibits cancer cell proliferation. Oncotarget 2016; 7: 84718-84735.
[38] Heo SK, Noh EK, Jeong YK, Ju LJ, Sung JY, Yu HM, Cheon J, Koh S, Min YJ, Choi Y and Jo JC. Radotinib inhibits mitosis entry in acute myeloid leukemia cells via suppression of Aurora kinase A expression. Tumour Biol 2019; 41: 1010428319848612.
[39] Do TV, Xiao F, Bickel LE, Klein-Szanto AJ, Pathak HB, Hua X, Howe C, O'Brien SW, Maglaty M, Ecsedy JA, Litwin S, Golemis EA, Schilder RJ, Godwin AK and Connolly DC. Aurora kinase A mediates epithelial ovarian cancer cell migration and adhesion. Oncogene 2014; 33: 539-549.
[40] Tatsuka M, Sato S, Kitajima S, Suto S, Kawai H, Miyauchi M, Ogawa I, Maeda M, Ota T and Takata T. Overexpression of Aurora-A potentiates HRAS-mediated oncogenic transformation and is implicated in oral carcinogenesis. Oncogene 2005; 24: 1122-1127.
[41] Yuan CX, Zhou ZW, Yang YX, He ZX, Zhang X, Wang D, Yang T, Wang NJ, Zhao RJ and Zhou SF. Inhibition of mitotic Aurora kinase A by alisertib induces apoptosis and autophagy of human gastric cancer AGS and NCI-N78 cells. Drug Des Devel Ther 2015; 9: 487-508.
[42] Xie CM, Lin XT, Wu D, Tan Y, Cheng CHK and Zhang J. Cardiac glycoside bufalin blocks cancer cell growth by inhibition of Aurora A and Aurora B activation via PI3K-Akt pathway. Oncotarget 2018; 9: 13783-13795.
[43] Fu Y, Zhang Y, Gao M, Quan L, Gui R and Liu J. Alisertib induces apoptosis and autophagy through targeting the AKT/mTOR/AMPK/p38 pathway in leukemic cells. Mol Med Rep 2016; 14: 394-398.
[44] Katayama H, Sasai K, Kawai H, Yuan ZM, Bondaruk J, Suzuki F, Fujii S, Arlinghaus RB, Czerniak BA and Sen S. Phosphorylation by aurora kinase A induces Mdm2-mediated destabilization and inhibition of p53. Nat Genet 2004; 36: 55-62.
[45] Liu Q, Kaneko S, Yang L, Feldman RI, Nicosia SV, Chen J and Cheng JQ. Aurora-A abrogation of p53 DNA binding and transactivation activity by phosphorylation of serine 215. J Biol Chem 2004; 279: 52175-52182.
[46] Park JW, Chae YC, Kim JY, Oh H and Seo SB. Methylation of Aurora kinase A by MMSET reduces p53 stability and regulates cell proliferation and apoptosis. Oncogene 2018; 37: 6212-6224.
[47] Ozaki T and Nakagawara A. p73, a sophisticated p53 family member in the cancer world. Cancer Sci 2005; 96: 729-737.
[48] Dar AA, Belkhiri A, Ecsedy J, Zaika A and El-Rifai W. Aurora kinase A inhibition leads to p73-dependent apoptosis in p53-deficient cancer cells. Cancer Res 2008; 68: 8998-9004.
[49] Zhao L, Fu L, Xu Z, Fan R, Xu R, Fu R, Zou S, Wang C, Zhang Y, Wang J, Bao J, Wang Z, Hou X, Zheng Y, Dai E and Wang F. The anticancer effects of cinobufagin on hepatocellular carcinoma Huh7 cells are associated with activation of the p73 signaling pathway. Mol Med Rep 2019; 19: 4119-4128.
[50] Chu IM, Hengst L and Slingerland JM. The Cdk inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy. Nat Rev Cancer 2008; 8: 253-267.
[51] Hou D, Che Z, Chen P, Zhang W, Chu Y, Yang D and Liu J. Suppression of AURKA alleviates p27 inhibition on Bax cleavage and induces more intensive apoptosis in gastric cancer. Cell Death Dis 2018; 9: 781.
[52] Katayama H, Zhou H, Li Q, Tatsuka M and Sen S. Interaction and feedback regulation between STK15/BTAK/Aurora-A kinase and protein phosphatase 1 through mitotic cell division cycle. J Biol Chem 2001; 276: 46219-46224.
[53] Wang F, Wang L, Fisher LA, Li C, Wang W and Peng A. Phosphatase 1 nuclear targeting subunit (PNUTS) regulates aurora kinases and mitotic progression. Mol Cancer Res 2019; 17: 10-19.
[54] Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC and Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434: 917-921.
[55] Sankaran S, Crone DE, Palazzo RE and Parvin JD. Aurora-A kinase regulates breast cancer associated gene 1 inhibition of centrosome-dependent microtubule nucleation. Cancer Res 2007; 67: 11186-11194.
[56] Do TV, Hirst J, Hyter S, Roby KF and Godwin AK. Godwin Aurora A kinase regulates non-homologous end-joining and poly (ADP-ribose) polymerase function in ovarian carcinoma cells. Oncotarget 2017; 8: 50376-50392.
[57] Yang G, Chang B, Yang F, Guo X, Cai KQ, Xiao XS, Wang H, Sen S, Hung MC, Mills GB, Chang S, Multani AS, Mercado-Uribe I and Liu J. Aurora kinase A promotes ovarian tumorigenesis through dysregulation of the cell cycle and suppression of BRCA2. Clin Cancer Res 2010; 16: 3171-3181.
[58] Biran A, Brownstein M, Haklai R and Kloog Y. Downregulation of survivin and aurora A by histone deacetylase and RAS inhibitors: a new drug combination for cancer therapy. Int J Cancer 2011; 128: 691-701.

[59] Yang G, Mercado-Uribe I, Multani AS, Sen S, Shih IeM, Wong KK, Gershenson DM and Liu J. RAS promotes tumorigenesis through genomic instability induced by imbalanced expression of Aurora-A and BRCA2 in midbody during cytokinesis. Int J Cancer 2013; 133: 275-285.
[60] Dos Santos EO, Carneiro-Lobo TC, Aoki MN, Levantini E and Basseres DS. Aurora kinase targeting in lung cancer reduces KRAS-induced transformation. Mol Cancer 2016; 15: 12.
[61] Wang-Bishop L, Chen Z, Gomaa A, Lockhart AC, Salaria S, Wang J, Lewis KB, Ecsedy J, Washington K, Beauchamp RD and El-Rifai W. Inhibition of AURKA reduces proliferation and survival of gastrointestinal cancer cells with activated KRAS by preventing activation of RPS6KB1. Gastroenterology 2019; 156: 662-675, e667.
[62] Umstead M, Xiong J, Qi Q, Du Y and Fu H. Aurora kinase A interacts with H-Ras and potentiates Ras-MAPK signaling. Oncotarget 2017; 8: 28359-28372.
[63] Tseng YS, Lee JC, Huang CY and Liu HS. Aurora-A overexpression enhances cell-aggregation of Ha-rastransformants through the MEK/ERK signaling pathway. BMC Cancer 2009; 9: 435.
[64] Zhang W, Xia D, Li Z, Zhou T, Chen T, Wu Z, Zhou W, Li Z, Li L and Xu J. Aurora-A/ERK1/2/mTOR axis promotes tumor progression in triple-negative breast cancer and dual-targeting Aurora-A/mTOR shows synthetic lethality. Cell Death Dis 2019; 10: 606.
[65] Puig-Butille JA, Vinyals A, Ferreres JR, Aguilera P, Cabre E, Tell-Marti G, Marcoval J, Mateo F, Palomero L, Badenas C, Piulats JM, Malvehy J, Pujana MA, Puig S and Fabra A. AURKA overexpression is driven by FOXM1 and MAPK/ERK activation in melanoma cells harboring BRAF or NRAS mutations: impact on melanoma prognosis and therapy. J Invest Dermatol 2017; 137: 1297-1310.
[66] Macurek L, Lindqvist A, Lim D, Lampson MA, Klompmaker R, Freire R, Clouin C, Taylor SS, Yaffe MB and Medema RH. Polo-like kinase-1 is activated by aurora A to promote checkpoint recovery. Nature 2008; 455: 119-123.
[67] Bruinsma W, Macurek L, Freire R, Lindqvist A and Medema RH. Bora and Aurora-A continue to activate Plk1 in mitosis. J Cell Sci 2014; 127: 801-811.
[68] de Jong Y, Bennani F, van Oosterwijk JG, Alberti G, Baranski Z, Wijers-Koster P, Venneker S, Briaire-de Bruij IH, van de Akker BE, Baelde H, Cleton-Jansen AM, van de Water B, Danen EHJ and Bovée JVMG. A screening-based approach identifies cell cycle regulators AURKA, CHK1 and PLK1 as targetable regulators of chondrosarcoma cell survival. J Bone Oncol 2019; 19: 100268.
[69] Li J, Hong MJ, Chow JP, Man WY, Mak JP, Ma HT and Poon RY. Co-inhibition of polo-like kinase 1 and Aurora kinases promotes mitotic catastrophe. Oncotarget 2015; 6: 9327-9340.
[70] Medina-Aguilar R, Marchat LA, Arechaga Ocampo E, Gariglio P, Garcia Mena J, Villegas Sepulveda N, Martinez Castillo M and Lopez-Camarillo C. Resveratrol inhibits cell cycle progression by targeting Aurora kinase A and Polo-like kinase 1 in breast cancer cells. Oncol Rep 2016; 35: 3696-3704.
[71] Kufer TA, Sillje HH, Korner R, Gruss OJ, Meraldi P and Nigg EA. Human TPX2 is required for targeting Aurora-A kinase to the spindle. J Cell Biol 2002; 158: 617-623.
[72] Garrido G and Vernos I. Non-centrosomal TPX2-dependent regulation of the aurora A kinase: functional implications for healthy and pathological cell division. Front Oncol 2016; 6: 88.
[73] van Gijn SE, Wierenga E, van den Tempel N, Kok YP, Heijink AM, Spierings DCJ, Foijer F, van Vugt MATM and Fehrmann RSN. TPX2/Aurora kinase A signaling as a potential therapeutic target in genomically unstable cancer cells. Oncogene 2019; 38: 852-867.
[74] Katsha A, Soutto M, Sehdev V, Peng D, Washington MK, Piazuelo MB, Tantawy MN, Manning HC, Lu P, Shyr Y, Ecsedy J, Belkhiri A and El-Rifai W. Aurora kinase A promotes inflammation and tumorigenesis in mice and human gastric neoplasia. Gastroenterology 2013; 145: 1312-1322, e1311-1318.
[75] Hansen CG, Moroishi T and Guan KL. YAP and TAZ: a nexus for Hippo signaling and beyond. Trends Cell Biol 2015; 25: 499-513.
[76] Park JH, Shin JE and Park HW. The role of hippo pathway in cancer stem cell biology. Mol Cells 2018; 41: 83-92.
[77] Yabuta N, Mukai S, Okada N, Aylon Y and Nojima H. The tumor suppressor Lats2 is pivotal in Aurora A and Aurora B signaling during mitosis. Cell Cycle 2011; 10: 2724-2736.
[78] Marsola A, Simoes BP, Palma LC, Berzoti-Coelho MG, Burin SM and de Castro FA. Expression of Hippo signaling pathway and Aurora kinase genes in chronic myeloid leukemia. Med Oncol 2018; 35: 26.
[79] Ding YH, Zhou ZW, Ha CF, Zhang XY, Pan ST, He ZX, Edelman JL, Wang D, Yang YX, Zhang X, Duan W, Yang T, Qiu JX and Zhou SF. Alisertib, an Aurora kinase A inhibitor, induces apoptosis and autophagy but inhibits epithelial to mesenchymal transition in human epithelial ovarian cancer cells. Drug Des Devel Ther 2015; 9: 425-464.
[80] Cui S, Zhang K, Li C, Chen J, Pan Y, Feng B, Lu L, Zhu Z, Wang R and Chen L. Methylation-associated silencing of microRNA-129-3p pro-

motes epithelial-mesenchymal transition, invasion and metastasis of hepatocelluar cancer by targeting Aurora-A. Oncotarget 2016; 7: 78009-78028.
[81] Donnella HJ, Webber JT, Levin RS, Camarda R, Momcilovic O, Bayani N, Shah KN, Korkola JE, Shokat KM, Goga A, Gordan JD and Bandyopadhyay S. Kinome rewiring reveals AURKA limits PI3K-pathway inhibitor efficacy in breast cancer. Nat Chem Biol 2018; 14: 768-777.
[82] Zhang S, Li J, Zhou G, Mu D, Yan J, Xing J, Yao Z, Sheng H, Li D, Lv C, Sun B, Hong Q and Guo H. Aurora-A regulates autophagy through the Akt pathway in human prostate cancer. Cancer Biomark 2017; 19: 27-34.
[83] Liu Z, Wang F, Zhou ZW, Xia HC, Wang XY, Yang YX, He ZX, Sun T and Zhou SF. Alisertib induces G2/M arrest, apoptosis, and autophagy via PI3K/Akt/mTOR- and p38 MAPK-mediated pathways in human glioblastoma cells. Am J Transl Res 2017; 9: 845-873.
[84] Lai CH, Tseng JT, Lee YC, Chen YJ, Lee JC, Lin BW, Huang TC, Liu YW, Leu TH, Liu YW, Chen YP, Chang WC and Hung LY. Translational upregulation of Aurora-A in EGFR-overexpressed cancer. J Cell Mol Med 2010; 14: 1520-1531.
[85] Romain C, Paul P, Kim KW, Lee S, Qiao J and Chung DH. Targeting Aurora kinase-A downregulates cell proliferation and angiogenesis in neuroblastoma. J Pediatr Surg 2014; 49: 159-165.
[86] Daniele S, Sestito S, Pietrobono D, Giacomelli C, Chiellini G, Di Maio D, Marinelli L, Novellino E, Martini C and Rapposelli S. Dual inhibition of PDK1 and aurora kinase a: an effective strategy to induce differentiation and apoptosis of human glioblastoma multiforme stem cells. ACS Chem Neurosci 2017; 8: 100-114.
[87] Galluzzi L, Kepp O, Chan FK and Kroemer G. Necroptosis: mechanisms and relevance to disease. Annu Rev Pathol 2017; 12: 103-130.
[88] Weinlich R, Oberst A, Beere HM and Green DR. Necroptosis in development, inflammation and disease. Nat Rev Mol Cell Biol 2017; 18: 127-136.
[89] Xie Y, Zhu S, Zhong M, Yang M, Sun X, Liu J, Kroemer G, Lotze M, Zeh HJ 3rd, Kang R and Tang D. Inhibition of aurora kinase a induces necroptosis in pancreatic carcinoma. Gastroenterology 2017; 153: 1429-1443, e1425.
[90] Jacobsen A, Bosch LJW, Martens-de Kemp SR, Carvalho B, Sillars-Hardebol AH, Dobson RJ, de Rinaldis E, Meijer GA, Abeln S, Heringa J, Fijneman RJA and Feenstra KA. Aurora kinase A (AURKA) interaction with Wnt and Ras-MAPK signalling pathways in colorectal cancer. Sci Rep 2018; 8: 7522.
[91] Jacobs KM, Bhave SR, Ferraro DJ, Jaboin JJ, Hallahan DE and Thotala D. GSK-3beta: a bifunctional role in cell death pathways. Int J Cell Biol 2012; 2012: 930710.
[92] Shang YY, Yao M, Zhou ZW, Cui J, Xia L, Hu RY, Yu YY, Gao Q, Yang B, Liu YX, Dang J, Zhou SF and Yu N. Alisertib promotes apoptosis and autophagy in melanoma through p38 MAPK-mediated aurora a signaling. Oncotarget 2017; 8: 107076-107088.
[93] Yuan Q, Sun T, Ye F, Kong W and Jin H. MicroRNA-124-3p affects proliferation, migration and apoptosis of bladder cancer cells through targeting AURKA. Cancer Biomark 2017; 19: 93-101.
[94] Qin Y, Zhang S, Deng S, An G, Qin X, Li F, Xu Y, Hao M, Yang Y, Zhou W, Chang H and Qiu L. Epigenetic silencing of miR-137 induces drug resistance and chromosomal instability by targeting AURKA in multiple myeloma. Leukemia 2017; 31: 1123-1135.
[95] Wang X, Zhang L, Zhao F, Xu R, Jiang J, Zhang C, Liu H and Huang H. Long non-coding RNA taurine-upregulated gene 1 correlates with poor prognosis, induces cell proliferation, and represses cell apoptosis via targeting aurora kinase A in adult acute myeloid leukemia. Ann Hematol 2018; 97: 1375-1389.
[96] Li T, Chen Y, Zhang J and Liu S. LncRNA TUG1 promotes cells proliferation and inhibits cells apoptosis through regulating AURKA in epithelial ovarian cancer cells. Medicine (Baltimore) 2018; 97: e12131.
[97] Zhao Y, Hu X, Wei L, Song D, Wang J, You L, Saiyin H, Li Z, Yu W, Yu L, Ding J and Wu J. PARP10 suppresses tumor metastasis through regulation of Aurora A activity. Oncogene 2018; 37: 2921-2935.
[98] Wu C, Lyu J, Yang EJ, Liu Y, Zhang B and Shim JS. Targeting AURKA-CDC25C axis to induce synthetic lethality in ARID1A-deficient colorectal cancer cells. Nat Commun 2018; 9: 3212.
[99] Ling H, Peng L, Wang J, Rahhal R and Seto E. Histone deacetylase SIRT1 targets Plk2 to regulate centriole duplication. Cell Rep 2018; 25: 2851-2865, e2853.
[100] Zheng X, Chi J, Zhi J, Zhang H, Yue D, Zhao J, Li D, Li Y, Gao M and Guo J. Aurora-A-mediated phosphorylation of LKB1 compromises LKB1/AMPK signaling axis to facilitate NSCLC growth and migration. Oncogene 2018; 37: 502-511.
[101] Dawei H, Honggang D and Qian W. AURKA contributes to the progression of oral squamous cell carcinoma (OSCC) through modulating epithelial-to-mesenchymal transition (EMT) and apoptosis via the regulation of ROS. Biochem Biophys Res Commun 2018; 507: 83-90.
[102] Lai CH, Huang YC, Lee JC, Tseng JT, Chang KC, Chen YJ, Ding NJ, Huang PH, Chang WC, Lin BW, Chen RY, Wang YC, Lai YC and Hung LY. Translational upregulation of Aurora-A by

hnRNP Q1 contributes to cell proliferation and tumorigenesis in colorectal cancer. Cell Death Dis 2017; 8: e2555.
[103] Maimaiti Y, Jie T, Jing Z, Changwen W, Pan Y, Chen C and Tao H. Aurora kinase A induces papillary thyroid cancer lymph node metastasis by promoting cofilin-1 activity. Biochem Biophys Res Commun 2016; 473: 212-218.
[104] Zhang C, Qu L, Lian S, Meng L, Min L, Liu J, Song Q, Shen L and Shou C. PRL-3 promotes ubiquitination and degradation of AURKA and colorectal cancer progression via dephosphorylation of FZR1. Cancer Res 2019; 79: 928-940.
[105] Tagal V, Wei S, Zhang W, Brekken RA, Posner BA, Peyton M, Girard L, Hwang T, Wheeler DA, Minna JD, White MA, Gazdar AF and Roth MG. SMARCA4-inactivating mutations increase sensitivity to Aurora kinase A inhibitor VX-680 in non-small cell lung cancers. Nat Commun 2017; 8: 14098.
[106] Bertolin G, Bulteau AL, Alves-Guerra MC, Burel A, Lavault MT, Gavard O, Le Bras S, Gagné JP, Poirier GG, Le Borgne R, Prigent C and Tramier M. Marc Tramier Aurora kinase A localises to mitochondria to control organelle dynamics and energy production. Elife 2018; 7: e38111.
[107] Ma Y, Yang J, Wang R, Zhang Z, Qi X, Liu C and Ma M. Aurora-A affects radiosenstivity in cervical squamous cell carcinoma and predicts poor prognosis. Oncotarget 2017; 8: 31509-31520.
[108] Willems E, Dedobbeleer M, Digregorio M, Lombard A, Goffart N, Lumapat PN, Lambert J, Van den Ackerveken P, Szpakowska M, Chevigne A, Scholtes F and Rogister B. Aurora A plays a dual role in migration and survival of human glioblastoma cells according to the CXCL12 concentration. Oncogene 2019; 38: 73-87.
[109] Moretti L, Niermann K, Schleicher S, Giacalone NJ, Varki V, Kim KW, Kopsombut P, Jung DK and Lu B. MLN8054, a small molecule inhibitor of aurora kinase a, sensitizes androgen-resistant prostate cancer to radiation. Int J Radiat Oncol Biol Phys 2011; 80: 1189-1197.
[110] Sun H, Wang Y, Wang Z, Meng J, Qi Z and Yang G. Aurora-A controls cancer cell radio- and chemoresistance via ATM/Chk2-mediated DNA repair networks. Biochim Biophys Acta 2014; 1843: 934-944.
[111] Mignogna C, Staropoli N, Botta C, De Marco C, Rizzuto A, Morelli M, Di Cello A, Franco R, Camastra C, Presta I, Malara N, Salvino A, Tassone P, Tagliaferri P, Barni T, Donato G and Di Vito A. Aurora Kinase A expression predicts platinum-resistance and adverse outcome in high-grade serous ovarian carcinoma patients. J Ovarian Res 2016; 9: 31.
[112] Li Y and Zhang J. AURKA is a predictor of chemotherapy response and prognosis for patients with advanced oral squamous cell carcinoma. Tumour Biol 2015; 36: 3557-3564.
[113] Xu J, Yue CF, Zhou WH, Qian YM, Zhang Y, Wang SW, Liu AW and Liu Q. Aurora-A contributes to cisplatin resistance and lymphatic metastasis in non-small cell lung cancer and predicts poor prognosis. J Transl Med 2014; 12: 200.
[114] Kuang P, Chen Z, Wang J, Liu Z, Wang J, Gao J and Shen L. Characterization of aurora A and Its impact on the effect of cisplatin-based chemotherapy in patients with non-small cell lung cancer. Transl Oncol 2017; 10: 367-377.
[115] Wu J, Cheng Z, Xu X, Fu J, Wang K, Liu T, Wu C, Kong X, Yang Q, Yan G and Zhou H. Aurora-A induces chemoresistance through activation of the AKT/mTOR pathway in endometrial cancer. Front Oncol 2019; 9: 422.
[116] Li Y, Tang K, Zhang H, Zhang Y, Zhou W and Chen X. Function of Aurora kinase A in Taxol-resistant breast cancer and its correlation with P-gp. Mol Med Rep 2011; 4: 739-746.
[117] Yang N, Wang C, Wang J, Wang Z, Huang D, Yan M, Kamran M, Liu Q and Xu B. Aurora kinase A stabilizes FOXM1 to enhance paclitaxel resistance in triple-negative breast cancer. J Cell Mol Med 2019; 23: 6442-6453.
[118] Park SI, Lin CP, Ren N, Angus SP, Dittmer DP, Foote M, Parton T, Bhatt AP, Fedoriw YD, Roth DP, Cann ML, Johnson GL and Damania B. Inhibition of aurora A kinase in combination with chemotherapy induces synthetic lethality and overcomes chemoresistance in myc-overexpressing lymphoma. Target Oncol 2019; 14: 563-575.
[119] Yang LY, Shan YM, Zhang Y, Zhou EH, Chen XP and Zhang H. Aurora kinase A induces chemotherapy resistance through revival of dormant cells in laryngeal squamous cell carcinoma. Head Neck 2019; 41: 2239-2248.
[120] Cammareri P, Scopelliti A, Todaro M, Eterno V, Francescangeli F, Moyer MP, Agrusa A, Dieli F, Zeuner A and Stassi G. Aurora-a is essential for the tumorigenic capacity and chemoresistance of colorectal cancer stem cells. Cancer Res 2010; 70: 4655-4665.
[121] Chen J, Lu H, Zhou W, Yin H, Zhu L, Liu C, Zhang P, Hu H, Yang Y and Han H. AURKA upregulation plays a role in fibroblast-reduced gefitinib sensitivity in the NSCLC cell line HCC827. Oncol Rep 2015; 33: 1860-1866.
[122] Shah KN, Bhatt R, Rotow J, Rohrberg J, Olivas V, Wang VE, Hemmati G, Martins MM, Maynard A, Kuhn J, Galeas J, Donnella HJ, Kaushik S, Ku A, Dumont S, Krings G, Haringsma HJ, Robillard L, Simmons AD, Harding TC, McCormick F, Goga A, Blakely CM, Bivona TG and Bandyopadhyay S. Aurora kinase A drives the evolu-

tion of resistance to third-generation EGFR inhibitors in lung cancer. Nat Med 2019; 25: 111-118.
[123] Long ZJ, Wang LX, Zheng FM, Chen JJ, Luo Y, Tu XX, Lin DJ, Lu G and Liu Q. A novel compound against oncogenic Aurora kinase A overcomes imatinib resistance in chronic myeloid leukemia cells. Int J Oncol 2015; 46: 2488-2496.
[124] Wan XB, Fan XJ, Huang PY, Dong D, Zhang Y, Chen MY, Xiang J, Xu J, Liu L, Zhou WH, Lv YC, Wu XY, Hong MH and Liu Q. Aurora-A activation, correlated with hypoxia-inducible factor-1alpha, promotes radiochemoresistance and predicts poor outcome for nasopharyngeal carcinoma. Cancer Sci 2012; 103: 1586-1594.
[125] Liu N, Wang YA, Sun Y, Ecsedy J, Sun J, Li X and Wang P. Inhibition of Aurora A enhances radiosensitivity in selected lung cancer cell lines. Respir Res 2019; 20: 230.
[126] Liu JB, Hu L, Yang Z, Sun YU, Hoffman RM and Yi Z. Aurora-A/NF-κB signaling is associated with radio-resistance in human lung adenocarcinoma. Anticancer Res 2019; 39: 5991-5998.
[127] Shen ZT, Chen Y, Huang GC, Zhu XX, Wang R and Chen LB. Aurora-a confers radioresistance in human hepatocellular carcinoma by activating NF-κB signaling pathway. BMC Cancer 2019; 19: 1075.
[128] Chen C, Song G, Xiang J, Zhang H, Zhao S and Zhan Y. AURKA promotes cancer metastasis by regulating epithelial-mesenchymal transition and cancer stem cell properties in hepatocellular carcinoma. Biochem Biophys Res Commun 2017; 486: 514-520.
[129] Helmy KY, Patel SA, Nahas GR and Rameshwar P. Cancer immunotherapy: accomplishments to date and future promise. Ther Deliv 2013; 4: 1307-1320.
[130] Kaštánková I, Poláková I, Dušková M and Šmahel M. Combined cancer immunotherapy against aurora kinase A. J Immunother 2016; 39: 160-170.
[131] Casey NP, Fujiwara H, Ochi T and Yasukawa M. Novel immunotherapy for adult T-cell leukemia/lymphoma: targeting aurora kinase A. Oncoimmunology 2016; 5: e1239006.
[132] Schneider V, Egenrieder S, Gotz M, Herbst C, Greiner J and Hofmann S. Specific immune responses against epitopes derived from Aurora kinase A and B in acute myeloid leukemia. Leuk Lymphoma 2013; 54: 1500-1504.
[133] Yin T, Zhao ZB, Guo J, Wang T, Yang JB, Wang C, Long J, Ma S, Huang Q, Zhang K, Ma X, Liu C, Liu S, Lian ZX and Yang Z. Aurora A inhibition eliminates myeloid cell-mediated immunosuppression and enhances the efficacy of Anti-PD-L1 therapy in breast cancer. Cancer Res 2019; 79: 3431-3444.
[134] Islam S, Vick E, Huber B, Morales C, Spier C, Cooke L, Weterings E and Mahadevan D. Co-targeting aurora kinase with PD-L1 and PI3K abrogates immune checkpoint mediated proliferation in peripheral T-cell lymphoma: a novel therapeutic strategy. Oncotarget 2017; 8: 100326-100338.
[135] Pusalkar S, Zhou X, Li Y, Cohen L, Yang JJ, Balani SK, Xia C, Shyu WC, Lu C, Venkatakrishnan K and Chowdhury SK. Biotransformation pathways and metabolite profiles of oral [14C]-alisertib (MLN8237), an investigational aurora A kinase inhibitor, in patients with advanced solid tumors. Drug Metab Dispos 2020; 48: 217-229.
[136] Cervantes A, Elez E, Roda D, Ecsedy J, Macarulla T, Venkatakrishnan K, Rosello S, Andreu J, Jung J, Sanchis-Garcia JM, Piera A, Blasco I, Manos L, Perez-Fidalgo JA, Fingert H, Baselga J and Tabernero J. Phase I pharmacokinetic/pharmacodynamic study of MLN8237, an investigational, oral, selective aurora a kinase inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2012; 18: 4764-4774.
[137] Dees EC, Cohen RB, von Mehren M, Stinchcombe TE, Liu H, Venkatakrishnan K, Manfredi M, Fingert H, Burris HA 3rd and Infante JR. Phase I study of aurora A kinase inhibitor MLN8237 in advanced solid tumors: safety, pharmacokinetics, pharmacodynamics, and bioavailability of two oral formulations. Clin Cancer Res 2012; 18: 4775-4784.
[138] Mosse YP, Lipsitz E, Fox E, Teachey DT, Maris JM, Weigel B, Adamson PC, Ingle MA, Ahern CH and Blaney SM. Pediatric phase I trial and pharmacokinetic study of MLN8237, an investigational oral selective small-molecule inhibitor of Aurora kinase A: a Children's Oncology Group Phase I Consortium study. Clin Cancer Res 2012; 18: 6058-6064.
[139] Falchook G, Kurzrock R, Gouw L, Hong D, McGregor KA, Zhou X, Shi H, Fingert H and Sharma S. Investigational Aurora A kinase inhibitor alisertib (MLN8237) as an enteric-coated tablet formulation in non-hematologic malignancies: phase 1 dose-escalation study. Invest New Drugs 2014; 32: 1181-1187.
[140] Kelly KR, Shea TC, Goy A, Berdeja JG, Reeder CB, McDonagh KT, Zhou X, Danaee H, Liu H, Ecsedy JA, Niu H, Benaim E and Iyer SP. Phase I study of MLN8237--investigational Aurora A kinase inhibitor--in relapsed/refractory multiple myeloma, non-Hodgkin lymphoma and chronic lymphocytic leukemia. Invest New Drugs 2014; 32: 489-499.
[141] Venkatakrishnan K, Kim TM, Lin CC, Thye LS, Chng WJ, Ma B, Chen MH, Zhou X, Liu H, Kelly V and Kim WS. Phase 1 study of the investigational Aurora A kinase inhibitor alisertib

(MLN8237) in East Asian cancer patients: pharmacokinetics and recommended phase 2 dose. Invest New Drugs 2015; 33: 942-953.
[142] DuBois SG, Marachelian A, Fox E, Kudgus RA, Reid JM, Groshen S, Malvar J, Bagatell R, Wagner L, Maris JM, Hawkins R, Courtier J, Lai H, Goodarzian F, Shimada H, Czarnecki S, Tsao-Wei D, Matthay KK and Mosse YP. Phase I study of the aurora a kinase inhibitor alisertib in combination with irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma: a NANT (new approaches to neuroblastoma therapy) trial. J Clin Oncol 2016; 34: 1368-1375.
[143] Graff JN, Higano CS, Hahn NM, Taylor MH, Zhang B, Zhou X, Venkatakrishnan K, Leonard EJ and Sarantopoulos J. Open-label, multicenter, phase 1 study of alisertib (MLN8237), an aurora A kinase inhibitor, with docetaxel in patients with solid tumors. Cancer 2016; 122: 2524-2533.
[144] Rosenthal A, Kumar S, Hofmeister C, Laubach J, Vij R, Dueck A, Gano K and Stewart AK. A Phase Ib study of the combination of the Aurora Kinase Inhibitor Alisertib (MLN8237) and bortezomib in relapsed multiple myeloma. Br J Haematol 2016; 174: 323-325.
[145] Fathi AT, Wander SA, Blonquist TM, Brunner AM, Amrein PC, Supko J, Hermance NM, Manning AL, Sadrzadeh H, Ballen KK, Attar EC, Graubert TA, Hobbs G, Joseph C, Perry AM, Burke M, Silver R, Foster J, Bergeron M, Ramos AY, Som TT, Fishman KM, McGregor KL, Connolly C, Neuberg DS and Chen YB. Phase I study of the aurora A kinase inhibitor alisertib with induction chemotherapy in patients with acute myeloid leukemia. Haematologica 2017; 102: 719-727.
[146] Haddad TC, D'Assoro A, Suman V, Opyrchal M, Peethambaram P, Liu MC, Goetz MP and Ingle JN. Phase I trial to evaluate the addition of alisertib to fulvestrant in women with endocrine-resistant, ER+ metastatic breast cancer. Breast Cancer Res Treat 2018; 168: 639-647.
[147] Kelly KR, Friedberg JW, Park SI, McDonagh K, Hayslip J, Persky D, Ruan J, Puvvada S, Rosen P, Iyer SP, Stefanovic A, Bernstein SH, Weitman S, Karnad A, Monohan G, VanderWalde A, Mena R, Schmelz M, Spier C, Groshen S, Venkatakrishnan K, Zhou X, Sheldon-Waniga E, Leonard EJ and Mahadevan D. Phase I study of the investigational aurora A kinase inhibitor alisertib plus rituximab or rituximab/vincristine in relapsed/refractory aggressive B-cell lymphoma. Clin Cancer Res 2018; 24: 6150-6159.
[148] Lin J, Patel SA, Sama AR, Hoffman-Censits JH, Kennedy B, Kilpatrick D, Ye Z, Yang H, Mu Z, Leiby B, Lewis N, Cristofanilli M and Kelly WK. A phase I/II study of the investigational drug alisertib in combination with abiraterone and prednisone for patients with metastatic castration-resistant prostate cancer progressing on abiraterone. Oncologist 2016; 21: 1296-1297e.
[149] Goff LW, Azad NS, Stein S, Whisenant JG, Koyama T, Vaishampayan U, Hochster H, Connolly R, Weise A, LoRusso PM, Salaria SN, El-Rifai W and Berlin JD. Phase I study combining the aurora kinase a inhibitor alisertib with mFOLFOX in gastrointestinal cancer. Invest New Drugs 2019; 37: 315-322.
[150] Shah HA, Fischer JH, Venepalli NK, Danciu OC, Christian S, Russell MJ, Liu LC, Zacny JP and Dudek AZ. Phase I study of aurora a kinase inhibitor alisertib (MLN8237) in combination with selective VEGFR inhibitor pazopanib for therapy of advanced solid tumors. Am J Clin Oncol 2019; 42: 413-420.
[151] Song A, Andrews DW, Werner-Wasik M, Kim L, Glass J, Bar-Ad V, Evans JJ, Farrell CJ, Judy KD, Daskalakis C, Zhan T and Shi W. Phase I trial of alisertib with concurrent fractionated stereotactic re-irradiation for recurrent high grade gliomas. Radiother Oncol 2019; 132: 135-141.
[152] Zhou X, Pusalkar S, Chowdhury SK, Searle S, Li Y, Ullmann CD and Venkatakrishnan K. Mass balance, routes of excretion, and pharmacokinetics of investigational oral [(14)C]-alisertib (MLN8237), an Aurora A kinase inhibitor in patients with advanced solid tumors. Invest New Drugs 2019; 37: 666-673.
[153] Matulonis UA, Sharma S, Ghamande S, Gordon MS, Del Prete SA, Ray-Coquard I, Kutarska E, Liu H, Fingert H, Zhou X, Danaee H and Schilder RJ. Phase II study of MLN8237 (alisertib), an investigational Aurora A kinase inhibitor, in patients with platinum-resistant or -refractory epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Gynecol Oncol 2012; 127: 63-69.
[154] Friedberg JW, Mahadevan D, Cebula E, Persky D, Lossos I, Agarwal AB, Jung J, Burack R, Zhou X, Leonard EJ, Fingert H, Danaee H and Bernstein SH. Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas. J Clin Oncol 2014; 32: 44-50.
[155] Barr PM, Li H, Spier C, Mahadevan D, LeBlanc M, Ul Haq M, Huber BD, Flowers CR, Wagner-Johnston ND, Horwitz SM, Fisher RI, Cheson BD, Smith SM, Kahl BS, Bartlett NL and Friedberg JW. Phase II intergroup trial of alisertib in relapsed and refractory peripheral T-cell lymphoma and transformed mycosis fungoides: SWOG 1108. J Clin Oncol 2015; 33: 2399-2404.
[156] Melichar B, Adenis A, Lockhart AC, Bennouna J, Dees EC, Kayaleh O, Obermannova R, DeMi-

chele A, Zatloukal P, Zhang B, Ullmann CD and Schusterbauer C. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm phase 2 study. Lancet Oncol 2015; 16: 395-405.

[157] Dickson MA, Mahoney MR, Tap WD, D'Angelo SP, Keohan ML, Van Tine BA, Agulnik M, Horvath LE, Nair JS and Schwartz GK. Phase II study of MLN8237 (Alisertib) in advanced/metastatic sarcoma. Ann Oncol 2016; 27: 1855-1860.

[158] Necchi A, Lo Vullo S, Mariani L, Raggi D, Giannatempo P, Calareso G, Togliardi E, Crippa F, Di Genova N, Perrone F, Colecchia M, Paolini B, Pelosi G, Nicolai N, Procopio G, Salvioni R and De Braud FG. An open-label, single-arm, phase 2 study of the Aurora kinase A inhibitor alisertib in patients with advanced urothelial cancer. Invest New Drugs 2016; 34: 236-242.

[159] Cohen JB, Maddocks KJ, Huang Y, Christian BA, Jaglowski SM, Flowers CR and Blum KA. A phase 2 trial of alisertib in patients with relapsed or refractory B-cellnon-Hodgkin lymphoma. Leuk Lymphoma 2017; 58: 1-2.

[160] Hyman DM, Sill MW, Lankes HA, Piekarz R, Shahin MS, Ridgway MR, Backes F, Tenney ME, Mathews CA, Hoffman JS, Aghajanian C and Hensley ML. A phase 2 study of alisertib (MLN8237) in recurrent or persistent uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study 0231D. Gynecol Oncol 2017; 144: 96-100.

[161] DuBois SG, Mosse YP, Fox E, Kudgus RA, Reid JM, McGovern R, Groshen S, Bagatell R, Maris JM, Twist CJ, Goldsmith K, Granger MM, Weiss B, Park JR, Macy ME, Cohn SL, Yanik G, Wagner LM, Hawkins R, Courtier J, Lai H, Goodarzian F, Shimada H, Boucher N, Czarnecki S, Luo C, Tsao-Wei D, Matthay KK and Marachelian A. Phase II trial of alisertib in combination with irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma. Clin Cancer Res 2018; 24: 6142-6149.

[162] O'Connor OA, Ozcan M, Jacobsen ED, Roncero JM, Trotman J, Demeter J, Masszi T, Pereira J, Ramchandren R, Beaven A, Caballero D, Horwitz SM, Lennard A, Turgut M, Hamerschlak N, d'Amore FA, Foss F, Kim WS, Leonard JP, Zinzani PL, Chiattone CS, Hsi ED, Trumper L, Liu H, Sheldon-Waniga E, Ullmann CD, Venkatakrishnan K, Leonard EJ, Shustov AR and Lumiere Study I. Randomized phase III study of alisertib or investigator's choice (Selected Single Agent) in patients with relapsed or refractory peripheral T-cell lymphoma. J Clin Oncol 2019; 37: 613-623.

[163] Zhou X, Nemunaitis J, Pant S, Bauer TM, Patel M, Sarantopoulos J, Craig Lockhart A, Goodman D, Huebner D, Mould DR and Venkatakrishnan K. Effect of alisertib, an investigational aurora a kinase inhibitor on the QTc interval in patients with advanced malignancies. Invest New Drugs 2018; 36: 240-247.

[164] Falchook GS, Zhou X, Venkatakrishnan K, Kurzrock R, Mahalingam D, Goldman JW, Jung J, Ullmann CD, Milch C, Rosen LS and Sarantopoulos J. Effect of food on the pharmacokinetics of the investigational aurora a kinase inhibitor alisertib (MLN8237) in patients with advanced solid tumors. Drugs R D 2016; 16: 45-52.

[165] Falchook G, Coleman RL, Roszak A, Behbakht K, Matulonis U, Ray-Coquard I, Sawrycki P, Duska LR, Tew W, Ghamande S, Lesoin A, Schwartz PE, Buscema J, Fabbro M, Lortholary A, Goff B, Kurzrock R, Martin LP, Gray HJ, Fu S, Sheldon-Waniga E, Lin HM, Venkatakrishnan K, Zhou X, Leonard EJ and Schilder RJ. Alisertib in combination with weekly paclitaxel in patients with advanced breast cancer or recurrent ovarian cancer: a randomized clinical trial. JAMA Oncol 2019; 5: e183773.

[166] Zhou X, Pant S, Nemunaitis J, Craig Lockhart A, Falchook G, Bauer TM, Patel M, Sarantopoulos J, Bargfrede M, Muehler A, Rangachari L, Zhang B and Venkatakrishnan K. Effects of rifampin, itraconazole and esomeprazole on the pharmacokinetics of alisertib, an investigational aurora a kinase inhibitor in patients with advanced malignancies. Invest New Drugs 2018; 36: 248-258.

[167] Macarulla T, Cervantes A, Elez E, Rodriguez-Braun E, Baselga J, Rosello S, Sala G, Blasco I, Danaee H, Lee Y, Ecsedy J, Shinde V, Chakravarty A, Bowman D, Liu H, Eton O, Fingert H and Tabernero J. Phase I study of the selective Aurora A kinase inhibitor MLN8054 in patients with advanced solid tumors: safety, pharmacokinetics, and pharmacodynamics. Mol Cancer Ther 2010; 9: 2844-2852.

[168] Chakravarty A, Shinde V, Tabernero J, Cervantes A, Cohen RB, Dees EC, Burris H, Infante JR, Macarulla T, Elez E, Andreu J, Rodriguez-Braun E, Rosello S, von Mehren M, Meropol NJ, Langer CJ, B ON, Bowman D, Zhang M, Danaee H, Faron-Yowe L, Gray G, Liu H, Pappas J, Silverman L, Simpson C, Stringer B, Tirrell S, Veiby OP, Venkatakrishnan K, Galvin K, Manfredi M and Ecsedy JA. Phase I assessment of new mechanism-based pharmacodynamic biomarkers for MLN8054, a small-molecule inhibitor of Aurora A kinase. Cancer Res 2011; 71: 675-685.

[169] Dees EC, Infante JR, Cohen RB, O'Neil BH, Jones S, von Mehren M, Danaee H, Lee Y, Ecsedy J, Manfredi M, Galvin K, Stringer B, Liu H, Eton O, Fingert H and Burris H. Phase 1 study of MLN8054, a selective inhibitor of Aurora A kinase in patients with advanced solid tumors. Cancer Chemother Pharmacol 2011; 67: 945-954.

[170] Amin M, Minton SE, LoRusso PM, Krishnamurthi SS, Pickett CA, Lunceford J, Hille D, Mauro D, Stein MN, Wang-Gillam A, Trull L and Lockhart AC. A phase I study of MK-5108, an oral aurora a kinase inhibitor, administered both as monotherapy and in combination with docetaxel, in patients with advanced or refractory solid tumors. Invest New Drugs 2016; 34: 84-95.

[171] Chou CH, Chou YE, Chuang CY, Yang SF and Lin CW. Combined effect of genetic polymorphisms of AURKA and environmental factors on oral cancer development in Taiwan. PLoS One 2017; 12: e0171583.

[172] Golmohammadi R, Namazi MJ, Going JJ and Derakhshan MH. A single nucleotide polymorphism in codon F31I and V57I of the AURKA gene in invasive ductal breast carcinoma in Middle East. Medicine (Baltimore) 2017; 96: e7933.

[173] Niu H, Shin H, Gao F, Zhang J, Bahamon B, Danaee H, Melichar B, Schilder RJ, Coleman RL, Falchook G, Adenis A, Behbakht K, DeMichele A, Dees EC, Perez K, Matulonis U, Sawrycki P, Huebner D and Ecsedy J. Aurora A functional single nucleotide polymorphism (SNP) correlates with clinical outcome in patients with advanced solid tumors treated with alisertib, an investigational Aurora A kinase inhibitor. EBioMedicine 2017; 25: 50-57.

[174] Baumann A, Buchberger AMS, Piontek G, Schüttler D, Rudelius M, Reiter R, Gebel L, Piendl G, Brockhoff G and Pickhard A. The Aurora-Kinase A Phe31-Ile polymorphism as possible predictor of response to treatment in head and neck squamous cell carcinoma. Oncotarget 2018; 9: 12769-12780.

[175] López-Cortés A, Cabrera-Andrade A, Oña-Cisneros F, Echeverría C, Rosales F, Ortiz M, Tejera E and Paz-Y-Miño C. Breast cancer risk associated with genotype polymorphisms of the aurora kinase a gene (AURKA): a case-control study in a high altitude ecuadorian mestizo population. Pathol Oncol Res 2018; 24: 457-465.

[176] Tang J, Qian Y, Zhu J, Zhang J, Wang FH, Zeng JH, Liang JH, Wang H, Xia H, He J and Liu W. Lack of associations between AURKA gene polymorphisms and neuroblastoma susceptibility in Chinese children. Biosci Rep 2018; 38: BSR20180292.

[177] Wang B, Hsu CJ, Chou CH, Lee HL, Chiang WL, Su CM, Tsai HC, Yang SF and Tang CH. Variations in the AURKA gene: biomarkers for the development and progression of hepatocellular carcinoma. Int J Med Sci 2018; 15: 170-175.

[178] Huang C, Wang L, Song H and Wu C. Interactive effects of AURKA polymorphisms with smoking on the susceptibility of oral cancer. Artif Cells Nanomed Biotechnol 2019; 47: 2333-2337.

[179] Lee CP, Chiang SL, Lee CH, Tsai YS, Wang ZH, Hua CH, Chen YC, Tsai EM and Ko YC. AURKA Phe31Ile polymorphism interacted with use of alcohol, betel quid, and cigarettes at multiplicative risk of oral cancer occurrence. Clin Oral Investig 2015; 19: 1825-1832.

[180] Necchi A, Pintarelli G, Raggi D, Giannatempo P and Colombo F. Association of an aurora kinase a (AURKA) gene polymorphism with progression-free survival in patients with advanced urothelial carcinoma treated with the selective aurora kinase a inhibitor alisertib. Invest New Drugs 2017; 35: 524-528.

[181] Provencio M, Camps C, Cobo M, De las Penas R, Massuti B, Blanco R, Alberola V, Jimenez U, Delgado JR, Cardenal F, Taron M, Ramirez JL, Sanchez A and Rosell R. Prospective assessment of XRCC3, XPD and Aurora kinase A single-nucleotide polymorphisms in advanced lung cancer. Cancer Chemother Pharmacol 2012; 70: 883-890.

[182] Borthakur G, Dombret H, Schafhausen P, Brummendorf TH, Boissel N, Jabbour E, Mariani M, Capolongo L, Carpinelli P, Davite C, Kantarjian H and Cortes JE. A phase I study of danusertib (PHA-739358) in adult patients with accelerated or blastic phase chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to imatinib and/or other second generation c-ABL therapy. Haematologica 2015; 100: 898-904.

[183] Cohen RB, Jones SF, Aggarwal C, von Mehren M, Cheng J, Spigel DR, Greco FA, Mariani M, Rocchetti M, Ceruti R, Comis S, Laffranchi B, Moll J and Burris HA. A phase I dose-escalation study of danusertib (PHA-739358) administered as a 24-hour infusion with and without granulocyte colony-stimulating factor in a 14-day cycle in patients with advanced solid tumors. Clin Cancer Res 2009; 15: 6694-6701.

[184] Meulenbeld HJ, Bleuse JP, Vinci EM, Raymond E, Vitali G, Santoro A, Dogliotti L, Berardi R, Cappuzzo F, Tagawa ST, Sternberg CN, Jannuzzo MG, Mariani M, Petroccione A and de Wit R. Randomized phase II study of danusertib in patients with metastatic castration-resistant prostate cancer after docetaxel failure. BJU Int 2013; 111: 44-52.

[185] Schoffski P, Besse B, Gauler T, de Jonge MJ, Scambia G, Santoro A, Davite C, Jannuzzo MG, Petroccione A and Delord JP. Efficacy and safety of biweekly i.v. administrations of the Aurora kinase inhibitor danusertib hydrochloride in independent cohorts of patients with advanced or metastatic breast, ovarian, colorectal, pancreatic, small-cell and non-small-cell lung cancer: a multi-tumour, multi-institutional phase II study. Ann Oncol 2015; 26: 598-607.

[186] Steeghs N, Eskens FA, Gelderblom H, Verweij J, Nortier JW, Ouwerkerk J, van Noort C, Mariani M, Spinelli R, Carpinelli P, Laffranchi B and de Jonge MJ. Phase I pharmacokinetic and pharmacodynamic study of the aurora kinase inhibitor danusertib in patients with advanced or metastatic solid tumors. J Clin Oncol 2009; 27: 5094-5101.

[187] Steeghs N, Mathijssen RH, Wessels JA, de Graan AJ, van der Straaten T, Mariani M, Laffranchi B, Comis S, de Jonge MJ, Gelderblom H and Guchelaar HJ. Influence of pharmacogenetic variability on the pharmacokinetics and toxicity of the aurora kinase inhibitor danusertib. Invest New Drugs 2011; 29: 953-962.

[188] Giles FJ, Swords RT, Nagler A, Hochhaus A, Ottmann OG, Rizzieri DA, Talpaz M, Clark J, Watson P, Xiao A, Zhao B, Bergstrom D, Le Coutre PD, Freedman SJ and Cortes JE. MK-0457, an Aurora kinase and BCR-ABL inhibitor, is active in patients with BCR-ABL T315I leukemia. Leukemia 2013; 27: 113-117.

[189] Seymour JF, Kim DW, Rubin E, Haregewoin A, Clark J, Watson P, Hughes T, Dufva I, Jimenez JL, Mahon FX, Rousselot P, Cortes J, Martinelli G, Papayannidis C, Nagler A and Giles FJ. A phase 2 study of MK-0457 in patients with BCR-ABL T315I mutant chronic myelogenous leukemia and philadelphia chromosome-positive acute lymphoblastic leukemia. Blood Cancer J 2014; 4: e238.

[190] Traynor AM, Hewitt M, Liu G, Flaherty KT, Clark J, Freedman SJ, Scott BB, Leighton AM, Watson PA, Zhao B, O'Dwyer PJ and Wilding G. Phase I dose escalation study of MK-0457, a novel Aurora kinase inhibitor, in adult patients with advanced solid tumors. Cancer Chemother Pharmacol 2011; 67: 305-314.

[191] Graux C, Sonet A, Maertens J, Duyster J, Greiner J, Chalandon Y, Martinelli G, Hess D, Heim D, Giles FJ, Kelly KR, Gianella-Borradori A, Longerey B, Asatiani E, Rejeb N and Ottmann OG. A phase I dose-escalation study of MSC1992371A, an oral inhibitor of aurora and other kinases, in advanced hematologic malignancies. Leuk Res 2013; 37: 1100-1106.

[192] Mita M, Gordon M, Rejeb N, Gianella-Borradori A, Jego V, Mita A, Sarantopoulos J, Sankhala K and Mendelson D. A phase I study of three different dosing schedules of the oral aurora kinase inhibitor MSC1992371A in patients with solid tumors. Target Oncol 2014; 9: 215-224.

[193] Garcia-Manero G, Tibes R, Kadia T, Kantarjian H, Arellano M, Knight EA, Xiong H, Qin Q, Munasinghe W, Roberts-Rapp L, Ansell P, Albert DH, Oliver B, McKee MD, Ricker JL and Khoury HJ. Phase 1 dose escalation trial of ilorasertib, a dual Aurora/VEGF receptor kinase inhibitor, in patients with hematologic malignancies. Invest New Drugs 2015; 33: 870-880.

[194] Schoffski P, Aftimos P, Dumez H, Deleporte A, De Block K, Costermans J, Billiet M, Meeus MA, Lee C, Schnell D, Goeldner RG and Awada A. A phase I study of two dosing schedules of oral BI 847325 in patients with advanced solid tumors. Cancer Chemother Pharmacol 2016; 77: 99-108.

[195] Diamond JR, Bastos BR, Hansen RJ, Gustafson DL, Eckhardt SG, Kwak EL, Pandya SS, Fletcher GC, Pitts TM, Kulikowski GN, Morrow M, Arnott J, Bray MR, Sidor C, Messersmith W and Shapiro GI. Phase I safety, pharmacokinetic, and pharmacodynamic study of ENMD-2076, a novel angiogenic and Aurora kinase inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2011; 17: 849-860.

[196] Diamond JR, Eckhardt SG, Pitts TM, van Bokhoven A, Aisner D, Gustafson DL, Capasso A, Sams S, Kabos P, Zolman K, Colvin T, Elias AD, Storniolo AM, Schneider BP, Gao D, Tentler JJ, Borges VF and Miller KD. A phase II clinical trial of the Aurora and angiogenic kinase inhibitor ENMD-2076 for previously treated, advanced, or metastatic triple-negative breast cancer. Breast Cancer Res 2018; 20: 82.

[197] Lheureux S, Tinker A, Clarke B, Ghatage P, Welch S, Weberpals JI, Dhani NC, Butler MO, Tonkin K, Tan Q, Tan DSP, Brooks K, Ramsahai J, Wang L, Pham NA, Shaw PA, Tsao MS, Garg S, Stockley T and Oza AM. A clinical and molecular Phase II Trial of Oral ENMD-2076 in Ovarian Clear Cell Carcinoma (OCCC): a study of the princess margaret Phase II consortium. Clin Cancer Res 2018; 24: 6168-6174.

[198] Yee KW, Chen HW, Hedley DW, Chow S, Brandwein J, Schuh AC, Schimmer AD, Gupta V, Sanfelice D, Johnson T, Le LW, Arnott J, Bray MR, Sidor C and Minden MD. A phase I trial of the aurora kinase inhibitor, ENMD-2076, in patients with relapsed or refractory acute myeloid leukemia or chronic myelomonocytic leukemia. Invest New Drugs 2016; 34: 614-624.

[199] Arkenau HT, Plummer R, Molife LR, Olmos D, Yap TA, Squires M, Lewis S, Lock V, Yule M, Lyons J, Calvert H and Judson I. A phase I dose escalation study of AT9283, a small molecule inhibitor of aurora kinases, in patients with advanced solid malignancies. Ann Oncol 2012; 23: 1307-1313.

[200] Dent SF, Gelmon KA, Chi KN, Jonker DJ, Wainman N, Capier CA, Chen EX, Lyons JF and Seymour L. NCIC CTG IND.181: phase I study of AT9283 given as a weekly 24 hour infusion in advanced malignancies. Invest New Drugs 2013; 31: 1522-1529.

[201] Foran J, Ravandi F, Wierda W, Garcia-Manero G, Verstovsek S, Kadia T, Burger J, Yule M, Langford G, Lyons J, Ayrton J, Lock V, Borthakur G, Cortes J and Kantarjian H. A phase I and pharmacodynamic study of AT9283, a small-molecule inhibitor of aurora kinases in patients with relapsed/refractory leukemia or myelofibrosis. Clin Lymphoma Myeloma Leuk 2014; 14: 223-230.

[202] Hay AE, Murugesan A, DiPasquale AM, Kouroukis T, Sandhu I, Kukreti V, Bahlis NJ, Lategan J, Reece DE, Lyons JF, Sederias J, Xu H, Powers J, Seymour LK and Reiman T. A phase II study of AT9283, an aurora kinase inhibitor, in patients with relapsed or refractory multiple myeloma: NCIC clinical trials group IND.191. Leuk Lymphoma 2016; 57: 1463-1466.

[203] Moreno L, Marshall LV, Pearson AD, Morland B, Elliott M, Campbell-Hewson Q, Makin G, Halford SE, Acton G, Ross P, Kazmi-Stokes S, Lock V, Rodriguez A, Lyons JF, Boddy AV, Griffin MJ, Yule M and Hargrave D. A phase I trial of AT9283 (a selective inhibitor of aurora kinases) in children and adolescents with solid tumors: a cancer research UK study. Clin Cancer Res 2015; 21: 267-273.

[204] Vormoor B, Veal GJ, Griffin MJ, Boddy AV, Irving J, Minto L, Case M, Banerji U, Swales KE, Tall JR, Moore AS, Toguchi M, Acton G, Dyer K, Schwab C, Harrison CJ, Grainger JD, Lancaster D, Kearns P, Hargrave D and Vormoor J. A phase I/II trial of AT9283, a selective inhibitor of aurora kinase in children with relapsed or refractory acute leukemia: challenges to run early phase clinical trials for children with leukemia. Pediatr Blood Cancer 2017; 64.

[205] Carducci M, Shaheen M, Markman B, Hurvitz S, Mahadevan D, Kotasek D, Goodman OB Jr, Rasmussen E, Chow V, Juan G, Friberg GR, Gamelin E, Vogl FD and Desai J. A phase 1, first-in-human study of AMG 900, an orally administered pan-Aurora kinase inhibitor, in adult patients with advanced solid tumors. Invest New Drugs 2018; 36: 1060-1071.

[206] Kantarjian HM, Schuster MW, Jain N, Advani A, Jabbour E, Gamelin E, Rasmussen E, Juan G, Anderson A, Chow VF, Friberg G, Vogl FD and Sekeres MA. A phase 1 study of AMG 900, an orally administered pan-aurora kinase inhibitor, in adult patients with acute myeloid leukemia. Am J Hematol 2017; 92: 660-667.

[207] Schoffski P, Jones SF, Dumez H, Infante JR, Van Mieghem E, Fowst C, Gerletti P, Xu H, Jakubczak JL, English PA, Pierce KJ and Burris HA. Phase I, open-label, multicentre, dose-escalation, pharmacokinetic and pharmacodynamic trial of the oral aurora kinase inhibitor PF-03814735 in advanced solid tumours. Eur J Cancer 2011; 47: 2256-2264.

[208] Korobeynikov V, Borakove M, Feng Y, Wuest WM, Koval AB, Nikonova AS, Serebriiskii I, Chernoff J, Borges VF, Golemis EA and Shagisultanova E. Combined inhibition of Aurora A and p21-activated kinase 1 as a new treatment strategy in breast cancer. Breast Cancer Res Treat 2019; 177: 369-382.

[209] Zumbar CT, Usubalieva A, King PD, Li X, Mifsud CS, Dalton HM, Sak M, Urio S, Bryant WM, McElroy JP, Farmer G and Lehman NL. The CNS penetrating taxane TPI 287 and the AURKA inhibitor alisertib induce synergistic apoptosis in glioblastoma cells. J Neurooncol 2018; 137: 481-492.

[210] Archer NM, Samnaliev M, Grace R and Brugnara C. The utility of the DDAVP challenge test in children with low von Willebrand factor. Br J Haematol 2015; 170: 884-886.

[211] Boss DS, Witteveen PO, van der Sar J, Lolkema MP, Voest EE, Stockman PK, Ataman O, Wilson D, Das S and Schellens JH. Clinical evaluation of AZD1152, an i.v. inhibitor of Aurora B kinase, in patients with solid malignant tumors. Ann Oncol 2011; 22: 431-437.

[212] Dennis M, Davies M, Oliver S, D'Souza R, Pike L and Stockman P. Phase I study of the Aurora B kinase inhibitor barasertib (AZD1152) to assess the pharmacokinetics, metabolism and excretion in patients with acute myeloid leukemia. Cancer Chemother Pharmacol 2012; 70: 461-469.

[213] Kantarjian HM, Martinelli G, Jabbour EJ, Quintas-Cardama A, Ando K, Bay JO, Wei A, Gropper S, Papayannidis C, Owen K, Pike L, Schmitt N, Stockman PK and Giagounidis A; SPARK-AML1 Investigators. Stage I of a phase 2 study assessing the efficacy, safety, and tolerability of barasertib (AZD1152) versus low-dose cytosine arabinoside in elderly patients with acute myeloid leukemia. Cancer 2013; 119: 2611-2619.

[214] Kantarjian HM, Sekeres MA, Ribrag V, Rousselot P, Garcia-Manero G, Jabbour EJ, Owen K, Stockman PK and Oliver SD. Phase I study assessing the safety and tolerability of barasertib (AZD1152) with low-dose cytosine arabinoside in elderly patients with AML. Clin Lymphoma Myeloma Leuk 2013; 13: 559-567.

[215] Lowenberg B, Muus P, Ossenkoppele G, Rousselot P, Cahn JY, Ifrah N, Martinelli G, Amadori S, Berman E, Sonneveld P, Jongen-Lavrencic M, Rigaudeau S, Stockman P, Goudie A, Faderl S, Jabbour E and Kantarjian H. Phase 1/2 study to assess the safety, efficacy, and pharmacokinetics of barasertib (AZD1152) in pa-

tients with advanced acute myeloid leukemia. Blood 2011; 118: 6030-6036.
[216] Schwartz GK, Carvajal RD, Midgley R, Rodig SJ, Stockman PK, Ataman O, Wilson D, Das S and Shapiro GI. Phase I study of barasertib (AZD1152), a selective inhibitor of Aurora B kinase, in patients with advanced solid tumors. Invest New Drugs 2013; 31: 370-380.
[217] Tsuboi K, Yokozawa T, Sakura T, Watanabe T, Fujisawa S, Yamauchi T, Uike N, Ando K, Kihara R, Tobinai K, Asou H, Hotta T and Miyawaki S. A Phase I study to assess the safety, pharmacokinetics and efficacy of barasertib (AZD1152), an Aurora B kinase inhibitor, in Japanese patients with advanced acute myeloid leukemia. Leuk Res 2011; 35: 1384-1389.
[218] Dittrich C, Fridrik MA, Koenigsberg R, Lee C, Goeldner RG, Hilbert J and Greil R. A phase 1 dose escalation study of BI 831266, an inhibitor of Aurora kinase B, in patients with advanced solid tumors. Investigational New Drugs 2014; 33: 409-422.
[219] Mross K, Richly H, Frost A, Scharr D, Nokay B, Graeser R, Lee C, Hilbert J, Goeldner RG, Fietz O and Scheulen ME. A phase I study of BI 811283, an Aurora B kinase inhibitor, in patients with advanced solid tumors. Cancer Chemother Pharmacol 2016; 78: 405-417.