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Review

Aurora kinases: novel therapy targets in cancers

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ABSTRACT

Aurora kinases, a family of serine/threonine kinases, consisting of Aurora A (AURKA), Aurora B (AURKB) and Aurora C (AURKC), are essential kinases for cell division *via* regulating mitosis especially the process of chromosomal segregation. Besides regulating mitosis, Aurora kinases have been implicated in regulating meiosis. The deletion of Aurora kinases could lead to failure of cell division and impair the embryonic development. Overexpression or gene amplification of Aurora kinases has been clarified in a number of cancers. And a growing number of studies have demonstrated that inhibition of Aurora kinases could potentiate the effect of chemotherapies. For the past decades, a series of Aurora kinases inhibitors (AKIs) developed effectively repress the progression and growth of many cancers both *in vivo* and *in vitro*, suggesting that Aurora kinases could be a novel therapeutic target. In this review, we'll first briefly present the structure, localization and physiological functions of Aurora kinases in mitosis, then describe the oncogenic role of Aurora kinases in tumorigenesis, we shall finally discuss the outcomes of AKIs combination with conventional therapy.

INTRODUCTION

Mitosis controlling the mother cells to divide into two daughter cells with equal chromosomes and cytoplasm is accurately regulated by a series of serine/threonine kinases in cell cycle, and among which Aurora kinases are important and indispensable in multiple steps of mitotic progression. The three members of Aurora kinases family [1] hold high homogeneity in mammalian cells. In term of the role of mitotic regulators, deletion of AURKA caused mitotic spindle assembly and chromosome segregation failure, subsequently resulted in genetic instability and a significantly increased tumor incidence [2-4]. In addition, Aurora kinases deficiency also caused polyploid oocytes in mice [5], and early embryonic lethality has been observed in *AURKA*$^{-/-}$ mice [2, 6]. Loss of AURKB activity could override spindle assembly checkpoint (SAC) through premature removal of SAC proteins from the kinetochore [7], which leads to defect of chromosome segregation and conformation of polyploidy. Overexpression or amplification of Aurora kinases is generally detected in amount of human cancers, such as breast cancer [8-11], ovarian cancer [12-14], gastric/gastrointestinal cancer [15, 16] and other tumors [11, 17-33] (Table 1) and is associated with the poor prognosis [8, 34, 35]. Thus, Aurora kinases become promising therapeutic targets and numerous AKIs have been developed. In present review, we outline the recent progresses along with the emerging obstacles associated with Aurora kinases in cancers.

STRUCTURE, LOCALIZATION AND FUNCTIONS OF AURORA KINASES IN MITOSIS

Structure of Aurora kinases

Aurora kinases are highly conserved and hold homologous structure, constituting of a N-terminal domain, a protein kinase domain and C-terminal domain [36-39]. High consistency among Aurora kinases is found

Table 1: Summary of Aurora kinases and Aurora kinases inhibitors in clinical trails.

Kinases	Localization	Function	Tumors types	Inhibitors and clinical trials
AURKA	Centrosome, Spindle microtubule, Midbody	Centrosome maturation/ separation; Mitotic entry; Microtubule nucleation; Spindle assembly; Bipolar spindle microtubule formation; Cytokinesis; Mitosis exit	Breast cancer[8, 9]; Ovarian cancer[12-14]; Gastric/Gastrointestinal cancer[15, 16]; Colorectal cancer[17]; Esophageal squamous cell carcinoma[20, 21]; Lung cancer[22]; Cervical cancer[24]; Prostate cancer[11, 26]; Glioma[28]; Acute myeloid leukemia(AML)[30]; Oral cancer[32]	MLN8054; phase I[123] ENMD-2076; phase II[124] MLN8237; phase III[125, 126] AT9283; phase I/II[129, 130] VX-680/MK-0457; phase II[131] PHA-680632; preclinical[132] AMG-900; phase I[133] PHA-739358; phase II[134, 135] CYC-116; phase I[136]
AURKB	Chromosome Kinetochore Midbody	Chromosome condensation; Microtubule-kinetochore attachment; Chromosomal alignment; Chromosomal segregation; Regulating SAC Cytokinesis	Breast cancer[10]; Ovarian cancer[14]; Gastric/Gastrointestinal cancer[15]; Colorectal cancer[18]; Lung cancer[23]; Cervical cancer[24]; Prostate cancer[27]; Glioma[28, 29]; Acute myeloid leukemia(AML)[31]; Oral cancer[33]	AZD1152; phase II /III[127, 128] AT9283; phase I/II[129, 130] VX-680/MK-0457; phase II[131] PHA-680632; preclinical[132] AMG-900; phase[133] PHA-739358; phase II[134, 135] CYC-116; phase I[136]
AURKC	Chromosome Midbody	Meiotic chromosome segregation; Similar to AURKB, e.g. Cytokinesis	Breast cancer[11] ; Colorectal cancer[19]; Cervical cancer[25]; Prostate cancer[11]; Glioma[29];	VX-680/MK-0457; phase II[131] PHA-680632; preclinical[132] AMG-900; phase I[133] PHA-739358; phase II[134, 135] CYC-116; phase I[136]

in the catalytic domain of the C-terminal containing catalytic T-loop and degradation box (A-box/D-box/KEN-box). Under physical mitosis, Aurora kinases can be targeted and activated by several protein cofactors including target protein for *Xenopus* kinesin-like protein 2 (TPX2) and inner centromere protein (INCENP). Additionally, each kinase of Aurora family members is activated through auto-phosphorylation on catalytic T-loop residues which are Thr288 (AURKA), Thr232 (AURKB) and Thr195 (AURKC), respectively (Figure 1A). Upon dephosphorylation mediated by protein phosphatase 1(PP1), the activities of Aurora kinases become inactive [40]. In the late mitosis, Aurora kinases are recognized by anaphase-promoting complex/cyclosome (APC/C) and subsequently degraded.

Localization of Aurora kinases

AURKA localizes to the duplicate centrosomes from the beginning of S phase and shifts to the bipolar spindle microtubules during mitosis, finally, moves to perinuclear materials of the daughter cell at the end of mitosis [41]. By contrast, AURKB starts at early G2 and localizes to the chromosomes in prophase, the centromere in prometaphase and metaphase, the central spindle in anaphase and the mid-body in cytokinesis [42]. Recent study identified that AURKC localized to centrosome in the interphase and binded to chromosome during mitosis [43]. However, the exact distribution shift of AURKC during the mitosis is still non-established (Figure 1B). Based on their distinct subcellular localizations during mitosis (Table 1), the functions of Aurora kinases are distinguished and summarized in Table 1.

Functions of Aurora kinases

Once localizing to centrosome, AURKA is activated by LIM protein ajuba, and the expression and activity of AURKA arrives peak at G2/M transition, stimulating duplicated centrosomes to separate at G2/M transition and initiating the mitotic entry. Activated AURKA recruits several pericentriolar proteins including γ-tubulin and TACC/MAP215 [44, 45] to microtubule organizing center (MTOCs) which facilitates centrosome maturation and speedy microtubule nucleation in eukaryotic cell. After nuclear membrane breaks down in prometaphase, AURKA is activated, targeted to microtubule by TPX2 [46, 47], and required for spindle assembly and the conformation of bipolar spindle microtubule [48]. At the end of the mitosis, AURKA is degraded by cadherin-1(Cdh1)/APC/C complex [49], and mitotic exist.

AURKB is a component of chromosome passenger complex (CPC), composing of additional three activation regulators INCEP, survivin and borealin [50-53]. It mediates chromosome condensation by phosphorylating histone H3 on Ser10 and variant centrosome protein A (CENP-A) on Ser7 [54]. AURKB is also involved in regulating SAC, rectifying the faulty attachment between spindle and kinetochore, maintaining the correct chromosome alignment and the faithful chromosomal segregation. Most recent study demonstrated that activated AURKB mediated phosphorylation of Histone H2AX at Ser121, which in turn promoted the auto-phosphorylation of AURKB, forming a positive feedback and further accelerating AURKB activation [55]. During anaphase, AURKB phosphorylates a series of downstream substrates, including mitotic kinesin-like protein 1 (MKLP1) and RacGAP1 [56], facilitates their deposition

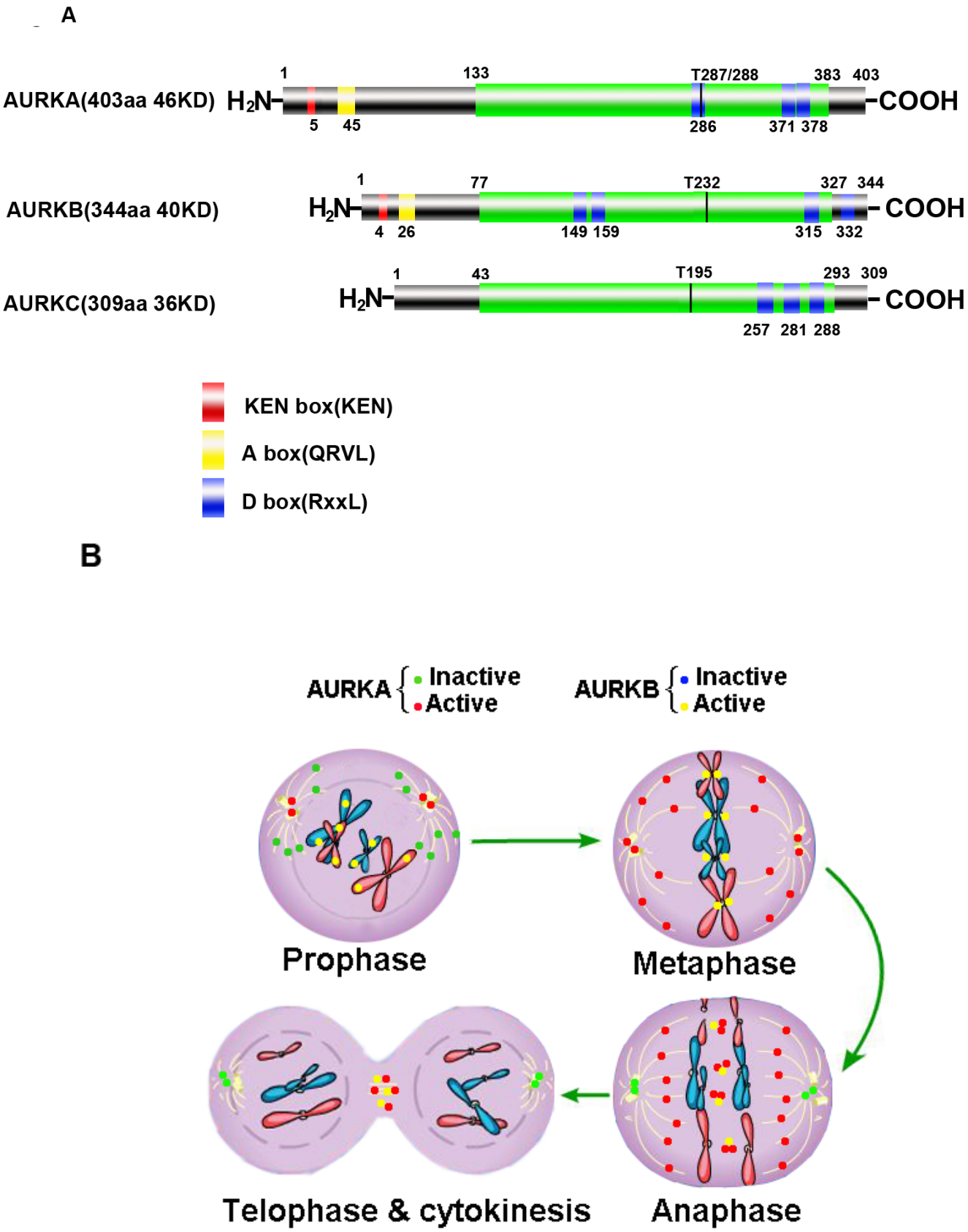

Figure 1: Structure and cellular distribution of Aurora kinases in mitosis. A. Schematic drawing of AURKA, AURKB and AURKC proteins with indicated domains. **B.** Cellular localization shift of Aurora kinases in mitosis (AURKC is not shown due to the elusive cellular localization and function).

at mid-body, and maintains the stabilization of central spindle. Moreover, AURKB could phosphorylate Kif2A, the microtubule de-polymerase, leading to shorten of central spindle, and promote cytokinesis [57].

Unlike AURKA and AURKB, AURKC is specifically expressed in mammalian testis compared to other somatic tissues [58]. Forced-expression of mutant AURKC in mouse oocytes causes oocytes cell cycle arrest at meiosis I and formulating eggs of aneuploidy, implicating that AURKC exerts pivotal role in meiotic chromosome segregation [59]. Since AURKC is required as part of the CPC [60, 61], AURKC has overlapping functions with AURKB in mitosis [62, 63]. Recent study demonstrated that AURKC interacted with transforming acidic coiled-coil 1 (TACC 1) and co-localized to the mid-body of Hela cells during cytokinesis [64].

THE ROLES OF AURORA KINASES IN CANCER

AURKA, B and C are mapped on intrinsic unstable with frequent defection, amplification and mutations regions of 20q13.2, 17p13.1 and 10q13, respectively [65-67], giving a good explanation of abnormal expression of Aurora kinases in human cancers. So far, no reports have shown that natural deficiency of Aurora kinases in human tumors. However, amount of studies have demonstrated that the overexpression or amplification of Aurora kinases has been observed in various human cancers as showed in Table 1, and several types of Aurora kinases mutations have been detected in different somatic cancer samples, including lung, colorectal and melanoma [62], which indicates that Aurora kinases play a determinant role in cell transformation and oncogenesis. For the past decades, increasing researches focus on these potential oncogenic proteins about how they function in tumor development.

AURKA controls proliferation, epithelial-mesenchymal transition (EMT) and metastasis, as well as self-renewal capacity of cancer stem cells (CSCs)

Recently, it's demonstrated that AURKA is overexpressed, distributed beyond the nucleus in cancer cells [68] and involved in the tumorigenesis through multiple mechanisms. AURKA could phosphorylate RAS-association domain family 1, isoform A (RASSF1A), a novel tumor suppressor, disrupt RASSF1A-mediated microtubules stabilization and M-phase cell cycle arrest, and lead to uncontrolled proliferation in cancers [69]. AURKA also phosphorylates IκBα, an inhibitor of NF-κB, hence activating NF-κB signaling pathway. Besides, AURKA could contribute to cancer cell survival *via* increasing anti-apoptotic modulators (Bcl-2 [70], MCL-1 [71]) and decreasing pro-apoptotic regulators (Bax [70], Bim [72], PUMA [73]) or suppressing autophagy through activating mammalian Target of Rapamycin (mTOR) signaling [74]. Moreover, overexpression of AURKA inhibits the release of cytochrome c (cyt c) from mitochondria, suppressing the formation of apoptotic body with Apaf-1 and apoptosis [75].

Patients with poor prognosis are normally due to metastasis mediated by EMT. AURKA upregulates the expression of SLUG [76], an EMT transcription factor, and fibrillin 1 (FBN1) that is an important fibrillin regulating microenvironment [77]. Meanwhile, AURKA induces a decrease in the expression of E-cadherin and β-catenin which play a pivotal role in regulating cell-cell adhesion, and consequently promotes EMT [78]. AURKA also activates Wnt and Akt signaling pathway simultaneously *via* reducing H3K4/H3K27 methylation on the promoter of Twist, a famous negative factor of MET, and then promotes EMT [79]. Also, other constitutive activation of oncogenic signalings, such as Raf-1 [80], Myc [81], OCT4 [82], promote the EMT progression *via* the stabilization and accumulation of AURKA. In addition, AURKA overexpression can significantly enhance the expression of matrix metalloproteinases (MMP)-2, MMP-7 and MMP-10, leading to degradation of extracellular matrix proteins, which stimulates tumor cell mobility and metastasis [20, 83].

Interestingly, overexpression of AURKA has been detected in CSCs [84] harboring the characteristics of self-renewal and differentiation into all cell types. Recent study confirmed that AURKA could activate Wnt signaling pathways in Glioma-initiating cells (GIC) *via* interacting with AXIN and stabilizing β-catenin, thereby promoting the ability of GICs to self-renewal [85]. On the other hand, the β-catenin/TCF4 complex could in turn transcriptionally activate AURKA and subsequently inhibit Glycogen synthase kinase 3β (GSK3β), which further stabilizes β-catenin. Therefore, AURKA/Wnt signal pathway forms a positive regulation loop and strengthens the expression of core CSCs.

AURKB promotes cell cycle and survival of cancer cells

Overexpression or amplification of AURKB has been clarified in various human tumors, which implies that it contributes to tumorigenesis in spite of its non-established role of oncogene.

Beside the aneuploidy resulting from AURKB overexpression, it's also implicated in promoting cell cycle *via* inhibiting or enhancing cell cycle-related targets. AURKB decreases the expression of the cell cycle inhibitor $p21^{WAF1/CIP1}$ *via* suppressing p53 activity [86], resulting in aberrant activation of Cyclin-dependent kinase 1 (Cdk1), leading to cell cycle progression and thereby promoting cell survival. Additionally, Cdk1

activates the acetyltransferase TIP60, causing acetylation and activation of AURKB, which further contributes to abnormal aneuploidy and uncontrolled cell cycle progression. In contrast to TIP60, histone deacetylases (HDACs) govern the opposite function that decrease the ability of histones to bind to DNA and thereby globally mediate transcriptional repression. However, Guise AJ et al identified that AURKB induced cell cycle progression through regulating its substrate Class IIa HDACs [87]. In consistence with Guise AJ group, it has been shown that AURKB and HDACs synergistically regulate cell survival and proliferation in lymphoma *via* activating AKT/mTOR signaling pathway [88].

Moreover, inhibition of AURKB by a selected inhibitor Barasertib (AZD1152-HQPA) induces apoptosis and necrosis in metastatic melanoma [89]. Inhibition of AURKB decreases the expression of Cyclin B1 and Cyclin D1, and elevates the Caspase 3 expression in lymphoma cells [88]. All of these data indicate that aberrant expression of AURKB might induce the cell survival-associated proteins expression and decrease the expression of pro-apoptosis proteins, although the precise molecular mechanism remains elusive.

AURKC may promote tumor progression

Given the highly expression in gametes, AURKC is required to regulate chromosome segregation during meiosis. Chromosome mis-segregation during meiosis due to aberrant AURKC expression or activity leads to aneuploidy in gametes, causing genetic infertility [90]. AURKC may promote tumor development in view of overlapping and complementary function with AURKB, as well as gene amplification and overexpression in cancers [11] though the mechanism is still in dispute.

AURORA KINASES FORM COMPLEX NETWORK WITH THEIR REGULATORS IN TUMORIGENESIS

Beside the well-established overexpression of Aurora kinases, Aurora kinases can collaborate with numerous protein including tumor suppressors and oncogenes and promote carcinogenesis.

Aurora kinases downregulate p53 and form feedback loop with p53

It's well-established that AURKA can regulate p53, the well-known tumor suppressor, through phosphorylation on both Ser215 and Ser315 residues [91, 92], which inhibits p53 transcriptional activity and enhances Mdm2-mediated p53 degradation, respectively. Interestingly, AURKA also inhibits p53 activity *via* phosphorylating heterogeneous nuclear ribonucleoprotein K (hnRNPK) on Ser379, a transcriptional coactivator of p53 required for p53 activation in the occurrence of gene damage [93]. Similarly, AURKB can suppress p53 transcriptional activity through forming complex with novel inhibitor of histone acetyltransferase repressor (NIR) and p53, in which NIR functions as a scaffold protein to mediate AURKB localization to the DNA binding domain (DBD) of p53 and then phosphorylates p53 on Ser269 and Thr284 in DBD. Recently, another study proved that AURKB also directly interacted with p53 *via* phosphorylating p53 on Ser183, Thr211 and Ser215, similar to AURKA [94]. So far, no interaction has been reported between p53 and AURKC.

In a feedback loop, p53 inhibits AURKA *via* both transcriptional and posttranscriptional regulation [95]. Silencing of p53 increases Cdk2 activity by reducing $p21^{wAF1/CIP1}$ expression, in turn Cdk2 phosphorylates Rb1 and dissociates E2F3, which then promotes AURKA expression *via* binding to its gene promoter [95]. In addition, Mutant p53 or loss of p53 functions causes elevated expression of miR-25 expression and leads to a decreased in level of F-box and WD repeat-containing 7 (FBXW7), a E3 ubiquitin ligase and well-known tumor suppressor, resulting in AURKA overexpression [96]. In agreement with AURKA, it's demonstrated that FBXW7 is also a negative regulator for AURKB, the mutant FBXW7 leads to upregulation of AURKB as well [97]. Taken together, any deviation in FBXW7/AURKB/p53 feedback loop could contribute to tumorigenesis and accelerate tumor progression. Intriguingly, AURKC overexpression gives rise to polyploidy and excessive centrosome, which can be aggravated in the absence of p53 [62], indicating p53 deficiency facilitates the role of AURKC in tumorigenesis. Since the Aurora kinases aberrant expression and p53 mutation are sometimes simultaneously detected in cancers, it is hard to clarify which one happens originally. It's possible that Aurora kinases coordinates with p53 to control tumorigenesis (Figure 2).

Aurora kinases suppress the functions of breast cancer susceptibility proteins (BRCA)

As known, checkpoint kinase 2 (CHK2)-BRCA1 tumor suppressor axis restrained AURKA oncogenic function [98] through recruiting serine/threonine protein phosphatase 6 catalytic subunit and regulatory subunit site 4-associated protein 3 (PP6C-SAPS3) phosphatase to AURKA catalytic T-loop, ensuring proper mitosis. However, unleashed AURKA activity resulting from the loss of CHK2 or PP6C-SAPS3 could in turn phosphorylate and inactivate BRCA1, which exacerbates chromosomal instability and contributes to tumorigenesis [99]. Tumor suppressor BRCA2 is also involved in maintaining

genomic stability and suppressing polyploidy [100] (Figure 3A). Previous study demonstrated that AURKA is commonly overexpressed in breast cancers with *BRCA2* mutation [101] and overexpressed AURKA could also suppress BRCA2 in ovarian cancer, indicating that there exists a negative correlation between AURKA and BRCA2 [13]. In circumstance of BRCA2 mutation, overexpressed AURKA might hyper-activate Cdk1 through phosphorylation of cell division cycle phosphatase 25B (CDC25B) on Ser353, leading to override of cell cycle arrest, contributing to cells transformation and tumorigenesis [101, 102] (Figure 3B). Therefore, AURKA has been regarded as a prognostic marker of breast cancer arising from BRCA2 mutation [101, 103]. However, the precise regulation mechanisms between AURKA and BRCA2 require further study. Intriguingly, both AURKA and BRCA2 are the downstream targets of RAS, overexpressed RAS abates BRCA2 expression but induces overexpression of AURKA, which in turn could increase the expression of farnesyl protein transferase β (FTβ), enhancing oncogene *RAS*-induced tumorigenesis *via* promoting RAS farnesylation [104] (Figure 3B).

Aurora kinases can be up-regulated by Myc and other signaling pathways

AURKA also mediates Myc (N-Myc, c-Myc, L-Myc) oncogenic effects in cancers. Overexpression or activation of Myc and AURKA are commonly simultaneously detected in human cancers. AURKA can function as a Myc regulator *via* binding to the CCCTCCCCA motif in the NHE III1 region and promote *c-Myc* transcription [105]. Conversely, c-Myc can transcriptionally up-regulate AURKA through binding to *AURKA* promoter [106], forming a positive regulation loop. Moreover, the *c-Myc* activation further leads to cell cycle-related genes transcription, which enhances cell proliferation and Myc-induced lymphomagenesis [107, 108]. In addition, AURKA interacts with N-Myc

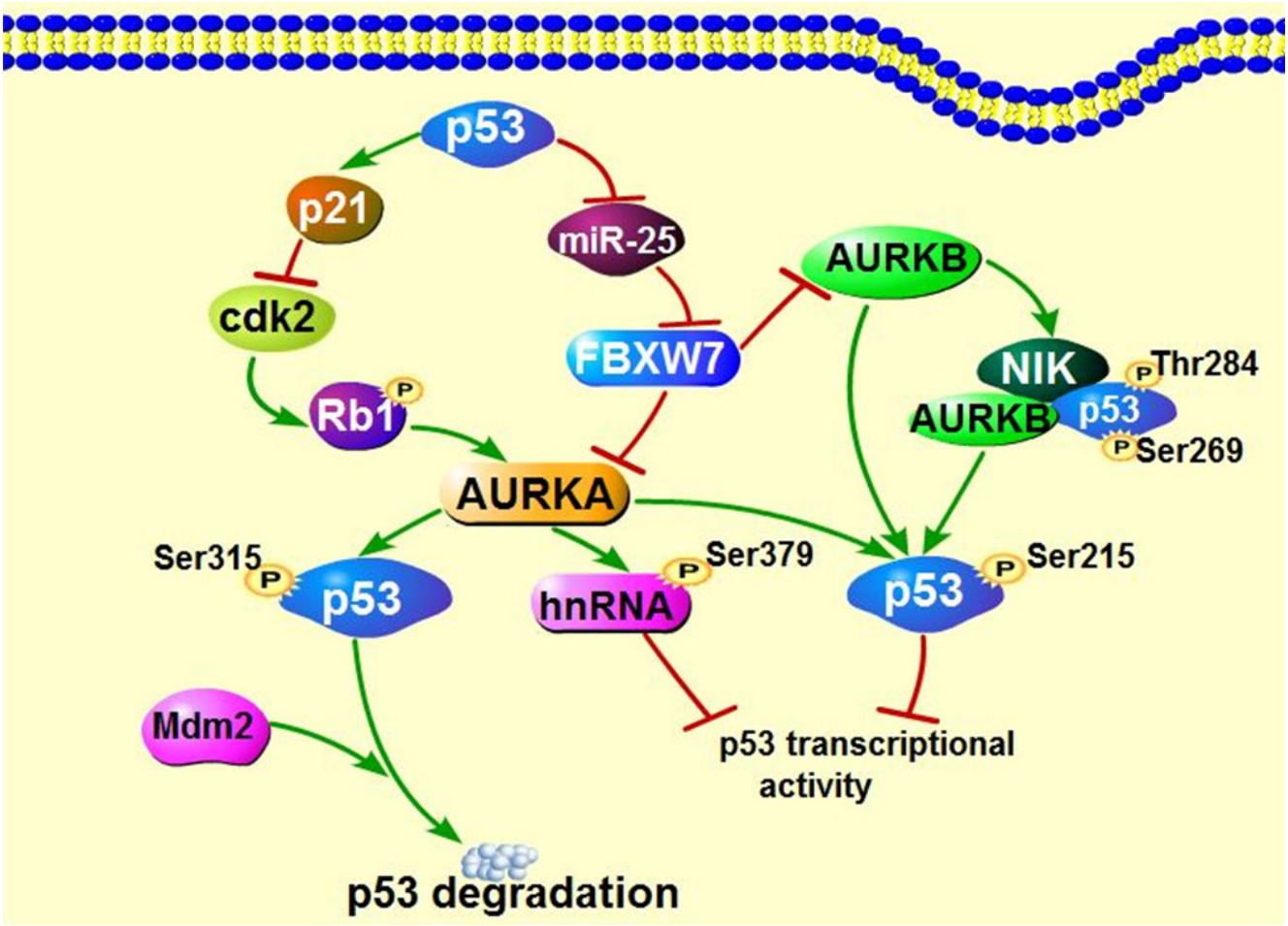

Figure 2: Interaction of Aurora kinases and tumor suppressor p53. Both AURKA and AURKB can regulate p53 through directly or indirectly mechanisms as indicated above. Moreover, the p53 deficiency which is often shown in numerous cancers further contributes to the expression of Aurora kinases, facilitating tumor development.

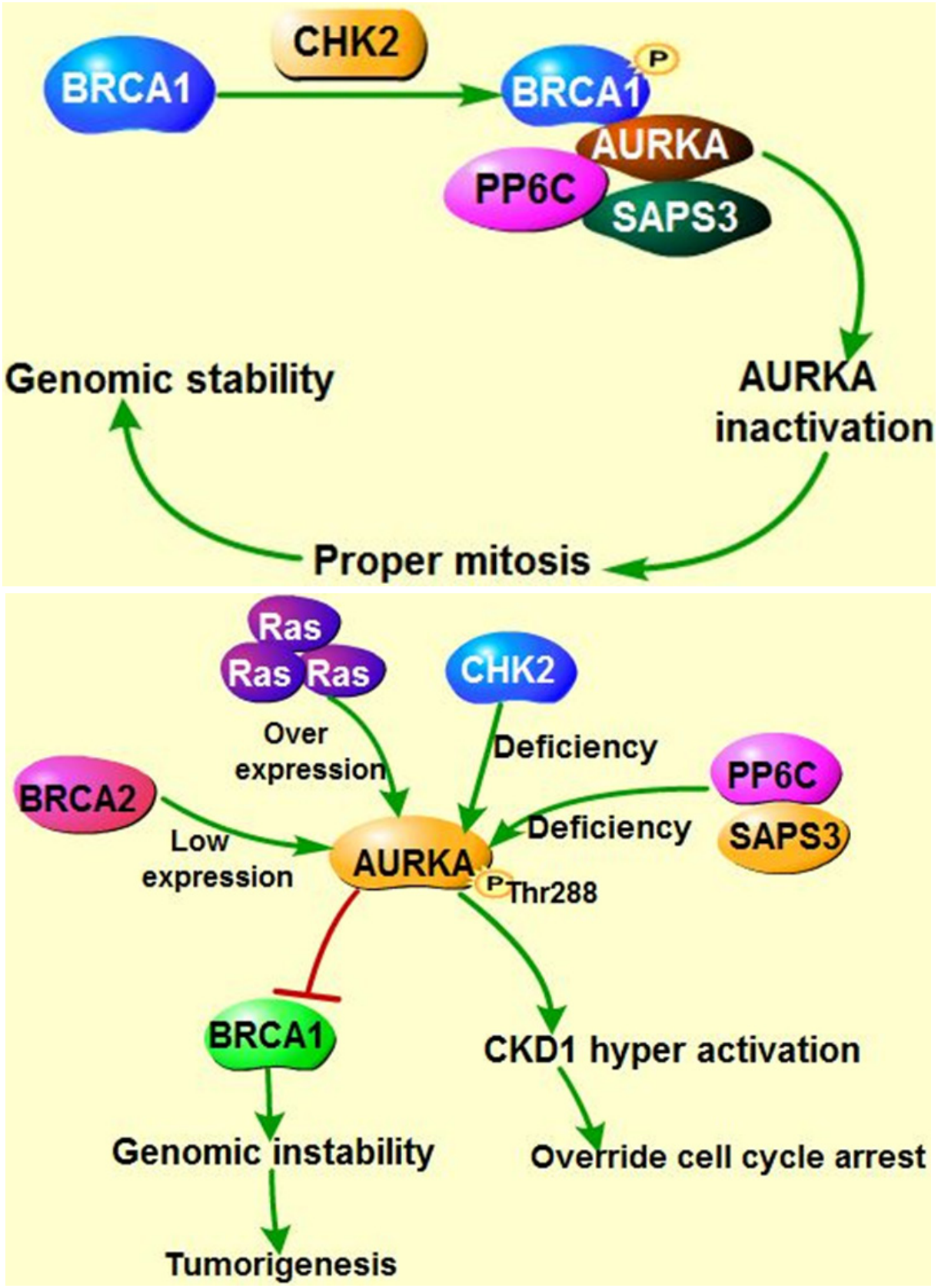

Figure 3: Co-regulation of AURKA, BRCA and Ras in tumorigenesis. A. CHK2-BRCA1 axis suppress AURKA oncogenic function. **B.** AURKA inactivates Tumor suppressor BRCA1, leading to genomic instability and contributing to cell transformation. In addition, AURKA overexpression along with BRCA2 mutation facilitates the cell cycle *via* hyper-phosphorylating cell cycle kinase CDK. Imbalance between AURKA and BRCA2 could enhance Ras-mediated tumorigenesis.

and protects N-Myc from FBXW7-mediated degradation [109, 110]. Opposite to AURKA, c-Myc could indirectly promote AURKB transcription though the unclear mechanisms [106] (Figure 4).

Besides the oncogenes or tumor suppressors, Aurora kinases are also regulated by other oncogenic proteins such as protein kinase C (PKC), thereby contributing to tumorigenesis. Aurora kinases are the cofactor in PKC-mediated oncogenesis in which the activation of PKC induces the mitogen-activated protein kinase (MAPK)-mediated phosphorylation of AURKA and AURKB, leading to activation of NF-κB/AP-1, consequently promoting the migration and invasion [111]. Moreover, our previous study confirmed that oncoprotein BCR-ABL can elevate expression of AURKA and AURKB through Akt signaling pathway in chronic myelogenous leukemia (CML) [112]. Studies demonstrated AURKA as a direct target of *β*-Catenin [113, 114]. Interestingly, AURKA can enhance *β*-Catenin activity *via* inactivating *β*-Catenin negative regulator GSK3*β* [115, 116], leading to increased level of *β*-Catenin nuclear translocation and transcriptionally activity [117, 118].

OUTCOME OF AKIS IN CLINICAL TRIALS

Given overexpression or gene amplification of Aurora kinases has been identified in diverse cancers, making them become potent targets of cancer therapy, a series of AKIs have been produced for the past decades and inhibition of expression or activity of Aurora kinases by AKIs indeed suppresses cell proliferation, migration and invasion in cancer cells [29, 119, 120], inhibits the progress and growth of many cancers [95, 121, 122] as Figure 5 shown, and more exciting is that some AKIs have already been used into clinical trials [123-136] (Table 1). Based on current researches and observations, MLN8237

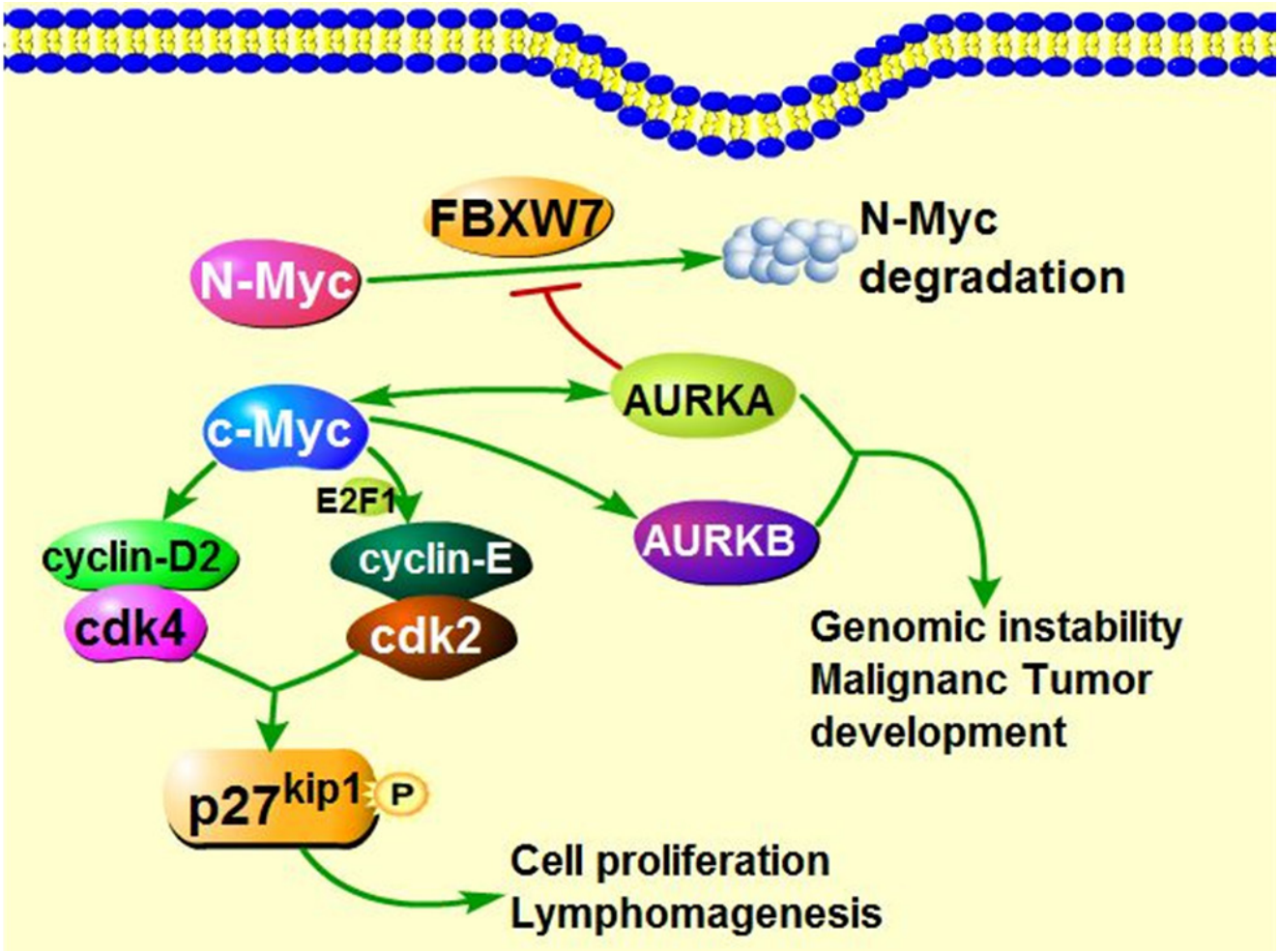

Figure 4: The interaction of Myc and Aurora Kinases in tumorigenesis. AURKA can transcriptionally upregulates the expression of c-Myc. On the other hand, c-Myc also binds to promoter of AURKA and transcriptionally increases the expression of AURKA. Additionally, activated c-Myc up-regulates the expression of cyclin D2, cdk4 as well as cyclin-E, contributing to the formation of cyclin-E/cdk2 complex, phosphorylating $p27^{Kip1}$ on Thr187, and consequently could provoke the cell proliferation and induce the Myc-mediated lymphomagenesis. c-Myc indirectly transcriptionally activate AURKB through unclear mechanisms. Besides, AURKA protects N-Myc from FBXW7-mediated degradation. High expression of AURKA and AURKB are implicated in tumorigenesis.

(Alisertib), one of AURKA selective inhibitor, and the AURKB selective inhibitor AZD1152 are successfully attracted researchers attention and are undergoing III clinical trials due to their potential dominant suppression for cancer treatment [125, 127].

In this part, we will take MLN8237 as an example to address the clinical outcome. A phase II study of MLN8237 [125] with multiple advanced solid tumors has been finished. The dosage of MLN8237 was orally at 50 mg, twice daily for 7 days followed by a break of 14 days in 21-day cycles. Partial responses were observed in nine patients (18%) of 49 women with breast cancer, ten patients (21%) of 48 participants with small-cell lung cancer (SCLC), one (4%) of 23 patients with non-small-cell lung cancer (NSCLC), four (9%) of 45 patients with squamous cell cancer of head and neck (SCCHN), and four (9%) of 47 people with gastro-esophageal adenocarcinoma. In another phase II trial, patients with platinum-resistant or refractory epithelial ovarian, fallopian tube carcinomas, or primary peritoneal carcinoma were treated with MLN8237. The median progression-free survival (PFS) was 1.9 months. Interestingly, sixteen out of 31 patients achieved stable disease with a mean duration of response of 2.86 months. These observations suggest that MLN8237 has modest single-agent antitumor activity and may produce responses and durable disease control [137].

COMBINATION WITH AKIS OVERCOMES CONVENTIONAL RESISTANCE IN CANCERS

A subset of AKIs have been developed, unfortunately, up to now, no AKIs have been proved for clinical use on patients and some obstacles we should take into consideration such as cell toxicity [138, 139]. Thus, AKIs that specifically and efficiently target cancer cells but not the normal cells should be developed in the future to reduce toxicity. A new study [140] demonstrated that AZD2811, an AURKB inhibitor, can be formulated in a nanoparticle named accurin to attenuate the side effect and increase the efficacy of AZD2811 in mouse tumor xenograft models, which may give a new direction for the development of AKIs.

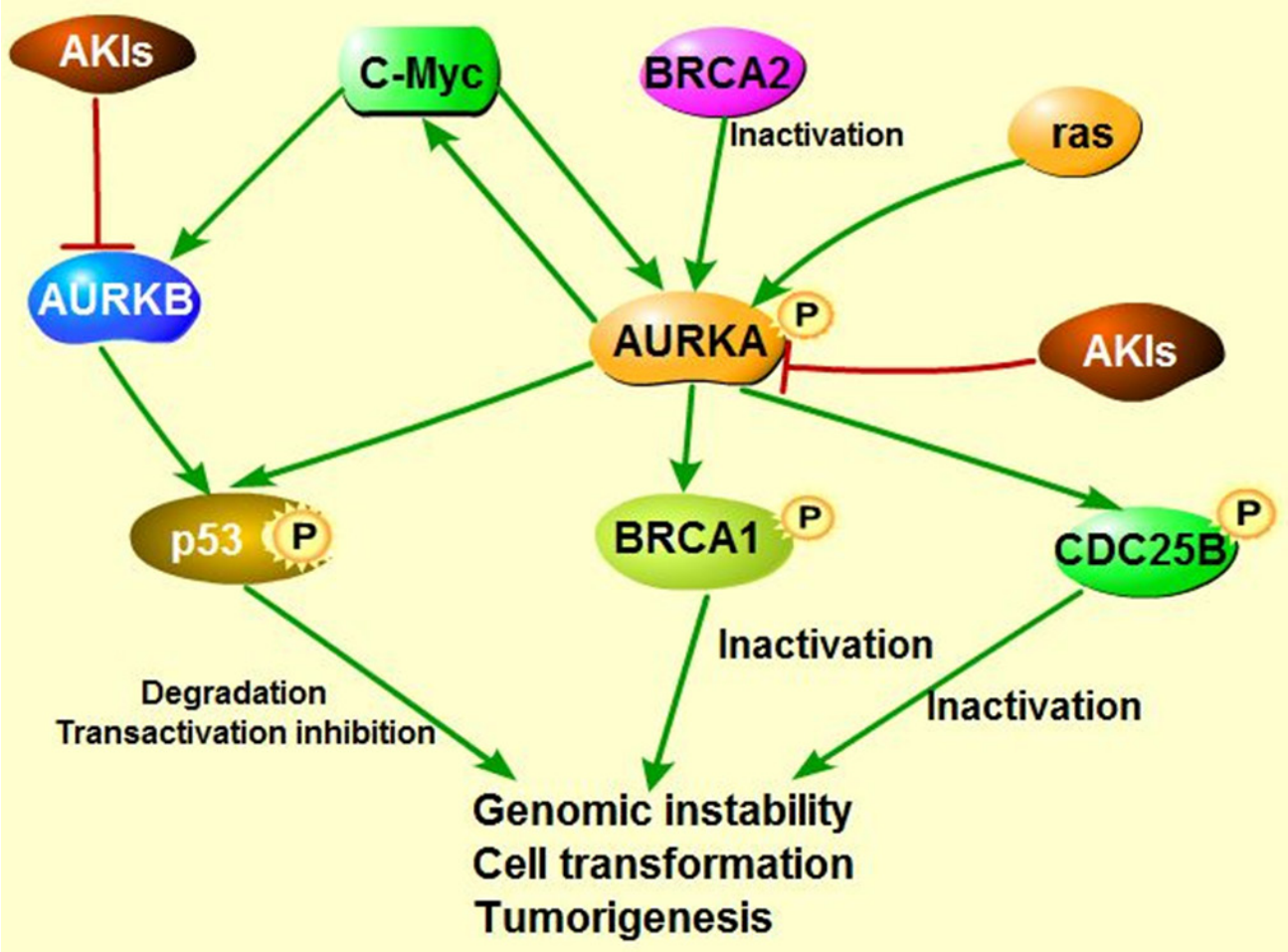

Figure 5: The model of AKIs targeting into several signaling pathways. Inhibition of Aurora kinases by AKIs could not only suppress the pro-oncogenic function, but also could block tumorigenesis *via* several signaling pathways.

Interestingly, increasing researches have uncovered that Aurora kinases are prone to confer cancer cell radio- and chemo-resistance. Recent research identified that AURKA was overexpressed in NSCLC and contributed to cisplatin-based chemotherapy resistance [141]. Consistently, AURKB overexpression also induces the tamoxifen resistance and poor prognosis in breast cancer [10, 142]. Additionally, it has been shown that AURKB conferred cancer cell resistance to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis *via* phosphorylating survivin [143].Taken together, Aurora kinases could become novel predictors in cancers prognosis, and simultaneously inhibition of Aurora kinases could overcome the drug resistance or/and enhance the anti-tumor effect of traditional compounds. Therefore, we herein mainly discuss the most recent progress of combination of AKIs and other cancer target therapy in cancers.

Tyrosine kinase inhibitors (TKIs) substantially ameliorated the outcome of CML, however, patients with BCR-ABL mutations have a poor response to TKIs, especially, *T315I BCR-ABL* mutation is even resistant to the second generation TKIs nilotinib and dasatinib, which actually can inhibit most BCR-ABL mutations [144, 145]. Notably, recent study addressed that inhibition of AURKA sensitized mutant BCR-ABL even T315I mutant CML cells to both generation TKIs, [146]. Additionally, another study showed that dual inhibition of BCR-ABL and AURKB could also suppressed proliferation and induced apoptosis of mutant BCR-ABL cells [147].

Opyrchal M et al firstly demonstrated that AURKA activated SMAD5 oncogenic signaling pathway and thereby down-regulated estrogen receptor α (ERα), leading to estrogen resistance in ERα$^+$ breast cancers and combination tamoxifen with MLN8237 abrogated the endocrine resistance [148]. Moreover, Inhibition of AURKB with AZD1152 inhibited the proliferation of estrogen-resistant breast cancer cells [149], which also sheds light on the overcome the estrogen-resistance breast cancer.

It has been shown that AURKA was involved in platinum-resistance and administration of either VX-680 or MLN8237 re-sensitized cancer cells to platinum and attenuated the migration ability of platinum-resistant NSCLC cells [141]. Besides, a group recently demonstrated that daurinol, a novel topoisomerase inhibitor, can inhibit the transcriptional activity of both AURKA and AURKB, which increased the radio-sensitivity of tumor cells *in vivo* and *in vitro* [150].

Sequential AURKB inhibition with AZD1152 synergistically enhanced the inhibitory effect of cisplatin in cisplatin-resistant ovarian cancer *via* downregulating c-Myc [151]. Furthermore, AURKA inhibitor PHA680632 [152] and MLN8237 [153], AURKB inhibitor AZD1152 [154] enhanced tumor response to radiotherapy in p53-deficient cancer cells, atypical teratoid/rhaboid tumors and androgen-resistant prostate cancer respectively. Overexpression of brain derived neurotrophic factor (BDNF) was associated with cisplatin-resistant neuroblastoma (NB) [155], combination chemotherapy with Aurora kinases inhibitor, PHA-680632, suppressed the transcription of BDNF 5'UTR exons 1, 2c, 4 and potentiated the cytotoxic effect of cisplatin in NB cell [156]. In addition, a combination of pan-AKIs R763 and EGFR antibody cetuximab activated cell cycle checkpoint and induced apoptosis in cetucimab-resistant SCCHN [157].

Given the involvement in conventional cancer therapy resistance, Aurora kinases are considered as predictors of chemotherapy response and prognosis [158, 159]. AKIs in combination with conventional modality, including chemotherapy and radiotherapy, could effectively inhibit tumor development and provide a promising new therapeutic strategy for individuals with cancer.

CONCLUSIONS AND PROSPECTIVE

Aurora kinases become promising therapeutic targets in cancers, however, the serious challenge is failure to distinguish the normal cells which acquire the physiological function of Aurora kinases and thereby gives rise to high toxicity, indicating that targeting Aurora kinases is likely a double-edged sword. Moreover, multiple researches have addressed that the participation of Aurora kinases in chemo-resistance in conventional therapy. However, inhibition of Aurora kinases somehow rescues chemo-resistance, which sheds light on cancer therapy through combination chemotherapy. We need to pay more concentration to further unearth Aurora kinases' complicated roles in tumorigenesis, and further studies discovering potential targets correlated to Aurora kinases and involved in tumorigenesis may broaden our eyes to invent new compounds and therapeutic strategy.

Abbreviations

AKIs: Aurora kinases inhibitors; SAC: spindle assembly checkpoint; APC/C: anaphase-promoting complex/cyclosome; TPX2: *Xenopus* kinesin-like protein 2; INCEP: inner centromere protein; PP1: protein phosphatase 1; MTOCs: microtubule organizing center; Cdh1: cadherin-1; CPC: chromosome passenger complex; CENP-A: centrosome protein A; MKLP1: mitotic kinesin-like protein 1; TACC 1: transforming acidic coiled-coil 1; EMT: epithelial-mesenchymal transition; CSCs: cancer stem cells; RASSF1A: RAS-association domain family 1, isoform A; mTOR: mammalian Target of Rapamycin; cyt c: cytochrome c; FBN1: fibrillin 1; MMP: matrix metalloproteinases; GIC: Glioma-initiating cells; GSK3β: Glycogen synthase kinase 3 beta; Cdk:

Cyclin-dependent kinase; HDACs: Histone Deacetylases; hnRNPK: heterogeneous nuclear ribonucleoprotein K; NIR: Novel inhibitor of histone acetyltransferase repressor; DBD: DNA binding domain; FBXW7: F-box and WD repeat-containing 7; BRCA: breast cancer susceptibility gene; CHK2: checkpoint kinase 2; PP6C-SAPS3: serine/threonine protein phosphatase 6 catalytic subunit and regulatory subunit site4-associated protein 3; CDC25B:cell division cycle phosphatase 25B; FTβ: farnesyl protein transferase β; PKC: protein kinase C; MAPK: mitogen-activated protein kinase; PKB: protein kinase B; CML: chronic myelogenous leukemia; SCLC: small-cell lung cancer; NSCLC: non-small-cell lung carcinoma; SCCHN: squamous cell cancer of head and neck; PFS: progression-free survival; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; AML: acute myeloid leukemia; TKIs: tyrosine kinase inhibitor; ERα: estrogen receptor alpha; BDNF: brain derived neurotrophic factor; NB: neuroblastoma.

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CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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