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The Aurora Kinases in Cell Cycle and Leukemia

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Abstract

The Aurora kinases, which include Aurora A (AURKA), Aurora B (AURKB) and Aurora C (AURKC), are serine/threonine kinases required for the control of mitosis (AURKA and AURKB) and meiosis (AURKC). Since their discovery nearly twenty years ago, Aurora kinases have been studied extensively in cell and cancer biology [1]. Several early studies found that Aurora kinases are amplified and overexpressed at the transcript and protein level in various malignancies, including several types of leukemia. These discoveries and others provided a rationale for the development of small molecule inhibitors of Aurora kinases as leukemia therapies. The first generation of Aurora kinase inhibitors did not fare well in clinical trials, owing to poor efficacy and high toxicity. However, the creation of second generation, highly selective Aurora kinase inhibitors has increased the enthusiasm for targeting these proteins in leukemia. This review will describe the functions of each Aurora kinase, summarize their involvement in leukemia and discuss inhibitor development and efficacy in leukemia clinical trials.

STRUCTURE AND REGULATION OF THE AURORA KINASES

The Aurora kinases are highly conserved serine/threonine kinases that regulate chromosomal alignment and segregation during mitosis and meiosis. Aurora A, B and C are comprised of 403, 344, and 309 amino acids, respectively. The proteins contain an N-terminal domain composed of 39 to 129 residues, a protein kinase domain and a C-terminal domain of 15 to 20 residues (Figure 1). Overall, the three Aurora kinases share high sequence identity. The kinases also share high homology between species and are evolutionarily ancient with Aurora A sharing 82% sequence identity between the human and rodent genes. They also share common ancestral genes in *Drosophila* and yeast. The functional similarity between Aurora A and B has been demonstrated by experiments showing that a single amino acid change in Aurora A, G198N, can convey an Aurora B kinase-like activity [2, 3]. However, the N-terminal domains of Aurora A, B and C share little sequence identity and confer unique protein–protein interaction abilities among the Aurora kinases [4].

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Conflicts of Interest

The authors declare no conflict of interest.

The activity of Aurora kinases is regulated at multiple levels. Aurora A, B and C all contain a key threonine, named the T-loop residue, within their kinase domains that must be phosphorylated to allow for kinase activity. This occurs via autophosphorylation of the T-loop residue T288 (Aurora A), T232 (Aurora B) or T195 (Aurora C), which is driven by clustering of kinase molecules [5–9]. Transcription of Aurora kinases, another mode of their control, is cell cycle-regulated. Aurora A mRNA typically peaks at G2/M with the protein expression peaking slightly later [5, 10]. The promoter of Aurora A contains specific sequences required for transcription in the G2 phase of the cell cycle [10–12]. The same is true for Aurora B: the level of this protein is cell cycle regulated and its activity peaks just after that of Aurora A [5]. The three kinases are differentially expressed at high levels in rapidly dividing tissues such as hematopoietic cells (A and B), germ cells (C only) [13]. Conversely, Aurora kinase expression is low or absent in most adult tissues due to their lower rates of proliferation [5].

Aurora kinase degradation is also highly regulated. All three family members contain destruction boxes (D-boxes) recognized by the multi-subunit E3-ubiquitin ligase anaphase promoting complex/cyclosome (APC/C), which mediates their proteasomal degradation (Figure 1). The APC/C, in conjunction with its specificity factor cdc20 homolog 1 (Cdh1), ubiquitylates Aurora A and targets it for degradation during mitotic exit [7, 14–20]. Of note, the D-boxes are not sufficient for APC/C mediated ubiquitylation: Aurora A degradation is also dependent on Cdh1 [20]. Moreover, in addition to its D-boxes, Aurora A contains a KEN degradation motif and an N-terminal D-Box-activating motif [14, 18, 21]. Other regulators of Aurora kinase degradation have been identified, such as Cdc4/Fbxw7, checkpoint with forkhead and ring finger domain (Chfr), and Aurora A interacting protein 1 [22–24]. Aurora B contains the same D-Box as Aurora A, but it is primarily degraded by proteasome alpha-subunit C8 in a proteasome-dependent manner [25].

FUNCTIONS OF THE AURORA KINASES

Although all three Aurora kinases are involved in cell division, the specific functions of each kinase vary. Aurora A, but not B or C, regulates centrosome maturation and separation and bipolar spindle assembly. Aurora B controls cytokinesis and chromosome bi-orientation as a member of the chromosome passenger complex. Aurora C coordinates meiotic spindles in spermatogenesis, while also cooperating with Aurora B to regulate mitotic chromosome dynamics [26, 27].

Aurora A Regulates Multiple Facets of Mitosis

The major function of Aurora A is to coordinate centrosome maturation, bipolar spindle assembly and chromosome separation (Figure 2). Aurora A is also important in the regulation of the spindle checkpoint and its activity contributes to the mitotic checkpoint response [28, 29]. The spindle checkpoint network inhibits the activity of the APC/C and subsequent sister chromatid separation and anaphase until all chromosomes have achieved proper bipolar attachment to the mitotic spindle [30].

The expression, localization and activity of Aurora A are consistent with its function as a centrosomal kinase. Aurora A levels are low during G1/S phase, but increase in G2, with

both function and expression peaking in early M phase [5, 10, 31]. With respect to localization, it is found at the centrosome in mitotic cells from late S and G2 until telophase, but also localizes to the spindle throughout mitosis [10, 31–33]. Functionally, Aurora A regulates the progression of mitosis by phosphorylation of multiple substrates, and it promotes mitotic entry by controlling activation of Cyclin-B/Cdk-1 [34–36,]. Aurora A also activates Polo-like kinase-1 (Plk-1) in G2 through direct phosphorylation of Plk-1 [37, 38]. Other cofactors and substrates include ajuba, enhancer of filamentation 1, BORA, TPX2, PLK-1, astrin, growth arrest and DNA damage-inducible 45α, transforming acidic coiled-coil containing protein 3 (TACC3) and centrosomin [39, 40]. Binding of Aurora A to TPX2 causes it to adopt an active conformation and also prevents dephosphorylation of Thr288 on Aurora A by protein phosphatase 1 [41]. PLK-1, which is also implicated in centrosome maturation, is involved in targeting Aurora A to centrosomes [42, 43]. Both PLK1 and CDK11 are required for Aurora A recruitment and centrosome maturation [40, 44, 45]. Other important functional interactions include the phosphorylation of LATS2, NDEl1 and TACC3 by Aurora A to enforce their recruitment to the centrosome and to promote centrosome maturation [46–48].

Aurora B Regulates Chromosome Condensation, the Spindle Checkpoint and Cytokinesis

Aurora B provides catalytic activity to the chromosome passenger complex (CPC). The CPC, which also consists of survivin, borealin and INCENP, localizes to the kinetochores and centromeres from prophase to metaphase and then relocates to the cleavage furrow and midbody during cytokinesis [26, 49]. One function of Aurora B is to phosphorylate chromatin proteins such as histone H3 to aid in mitotic chromosome condensation. Another is to contribute to the spindle checkpoint: Aurora B phosphorylates the microtubule depolymerase mitotic centromere-associated kinesin (MCAK) to target it to kinetochores where it functions to correct any incorrect kinetochore attachments to the spindle [50–52]. Finally, Aurora B is essential for proper cytokinesis; in its absence the two daughter cells remain attached to each other through bridges of cytoplasm, the chromosomes missegregate and binucleate daughter cells form [49, 53–55]. Aurora B phosphorylation of MgcRacGAP, a GTPase-activating protein, activates its activity towards RhoA and thus promotes cytokinesis [56, 57].

Aurora C is required for spermatogenesis

Less is known about Aurora C compared to the other Aurora kinases. Aurora C expression is restricted to the testis, but is aberrantly expressed in various cancer cell lines [58, 59]. It has been reported to be a chromosome passenger protein with similar localization as Aurora B [60]. Aurora C and Aurora B may have similar functions, as evidenced by the fact that Aurora C can rescue the phenotypes of Aurora B depleted cells [61, 62]. Aurora C is required for spermatogenesis and oocyte development: its deficiency causes cytokinesis failure in meiosis I resulting in the production of large polyploid oocytes in mice [63]. Mutations in Aurora C have been shown to cause infertility in humans, however, these individuals display no other obvious phenotype, supporting the idea that Aurora C is not required in somatic cells [63, 64].

Loss of Function Studies

Several cell based and murine knockout and conditional deletion studies have provided information on the requirements for the Aurora kinases. Knockdown of Aurora A using siRNA, disruption of its activity with blocking antibodies or inhibition with small molecules all cause defects in many mitotic processes, including centrosome maturation and chromosome separation, mitotic spindle pole organization, centriole function, microtubule stability and cell cycle progression [29, 34, 35, 37, 65–70.] Of note, germline deficiency of *Aurka* results in early embryonic lethality before the morula develops due to a defect in mitotic spindle assembly [71, 72]. A conditional knockout study expanded on these results and showed that loss of *Aurka* in the visceral endoderm and epiblast leads to apoptosis and lethality at embryonic day 9.5 [73]. Studies with Aurora A deficient cell lines showed that in the absence of the kinase the spindle checkpoint detects the failure to align chromosomes and arrests the cells in mitosis. However, the Aurora A deficient cells can escape the arrest and exit mitosis with segregation errors. The escaped cells then face a second checkpoint in G1: here cells with competent p53 arrest in G1 and die while cells without functional p53 enter S phase and progress through the cell cycle [74]. Knockdown of Aurora B by RNAi shows that Aurora B is required for histone H3 phosphorylation during chromosome condensation and for cytokinesis [75]. In contrast to Aurora A, *Aurkb* null embryos implant normally. However, defects appear later in embryonic development due to the decrease in Aurora C expression in somatic tissues post-implantation. Similarly, conditional deletion of Aurora B in somatic cells that do not express Aurora C results in chromosomal segregation and alignment errors [76]. *Aurkb* null cells exit mitosis with segregation errors due to a failure to align chromosomes and have defects in cytokinesis that result in binucleate cell formation. Cells lacking both Aurora A and Aurora B ($Aurka^{-/-}/Aurkb^{-/-}$) exit mitosis without completing anaphase [74]. In contrast to the phenotypes of *Aurka* and *Aurkb* mutants, *Aurkc* knockout mice appear normal other than defects in male fertility [63].

AURORA KINASES IN CANCER AND LEUKEMIA

The Aurora kinases are overexpressed in a wide range of human cancers including several forms of leukemia. For instance, multiple studies have examined Aurora kinase expression in AML and found that blasts overexpress Aurora A and Aurora B compared to control CD34+ cells. This overexpression of Aurora A and Aurora B is associated with unfavorable cytogenetic abnormalities and other adverse factors such as a high white blood cell count [77, 78].

Aurora A

The *AURKA* gene is located within a region of chromosome 20q13 that is amplified in many malignancies and the Aurora A F31L polymorphism is associated with an increased risk for esophageal, ovarian, non–small-cell lung, and breast cancers [79, 80]. Whether overexpression of Aurora A can promote tumorigenesis on its own is controversial. Some studies have found that Aurora A can drive transformation and tumors in nude mice [5, 6, 31]. In contrast, other studies suggest that overexpression alone is not sufficient to drive oncogenesis [81]. Instead, additional mutations may be required to cause malignant transformation. For

example, overexpression of Aurora A with activated Ras signaling was sufficient to promote transformation [31, 82].

The contributions of Aurora A to oncogenesis likely stem from its role in chromosome segregation. Defects in this process due to abnormal Aurora A function or expression cause aneuploidy and genetic instability, conditions that are associated with tumorigenesis. For instance, centrosome amplification caused by Aurora A overexpression induces multipolar spindles. Aurora A malfunction can also cause defects in the separation of centrosomes triggering the formation of a monopolar spindle, leading to abortive mitosis and ultimately the formation of tetraploid cells [83, 84]. Moreover, Aurora A overexpression disrupts the proper assembly of the mitotic checkpoint complex at the level of the Cdc20–BubR1 interaction [85]. Finally, overexpression of Aurora A disrupts spindle checkpoint activation by paclitaxel and nocodazole treatment, causing the cells to become resistant to these chemotherapy drugs [81].

One other possible mechanism by which Aurora A amplification could lead to tumor formation is via degradation of the tumor suppressor p53. Aurora A directly phosphorylates p53 to control its stability and transcriptional activity [86, 87]. Overexpression of Aurora A leads to increased p53 degradation, while its amplification shows a clear correlation with p53 mutational status [87, 88]. Inhibition of Aurora A in cells with wild type p53 results in apoptosis while its inhibition in cells lacking or with mutant p53 induces polyploidization [89].

Aurora B and Aurora C

Aurora B is also overexpressed in many primary tumors, resulting in multinucleation and polyploidy of human cells [90, 91]. Yet, unlike transformation mediated by Aurora A, overexpression of an inactive form of Aurora B results in multinucleation and polyploidy, indicating that kinase activity is not required for these malignant phenotypes [5]. Supporting the classification of Aurora B as a cancer promoting gene, its overexpression induced tetraploidy of murine epithelial cells and tumorigenesis in recipient mice [15, 91]. Another study found that overexpression of Aurora B induced metastasis after implantation of tumors in nude mice [92]. Finally, p53 deficiency caused cells overexpressing Aurora B to form more aggressive tumors than those with wild-type p53 [92]. How Aurora B kinase overexpression facilitates tumorigenesis is an interesting question. It is likely that tetraploidy and subsequent genomic instability, which result from high levels of Aurora B, rather than purely its overexpression, leads to tumorigenesis. Indeed, tetraploidy has been shown to increase the frequency of chromosomal alterations and promote tumorigenesis of p53 deficient cells [93].

Aurora C is aberrantly expressed in cancer cell lines [94]. One study showed that its overexpression induced abnormal cell division resulting in centrosome amplification, multinucleation and increased proliferation [95]. In another study, cells overexpressing Aurora C formed foci of colonies on soft agar, and transplantation of these cells induced tumor formation when injected into nude mice [96].

Aurora Kinases in Megakaryocytes and Acute Megakaryoblastic Leukemia

Megakaryocytes are one of the few cell types that undergo repeated rounds of the cell cycle without cytokinesis. Previous studies have demonstrated that the cells progress through mitosis with nuclear envelope breakdown and chromosome condensation, but fail to complete mitosis [97] (Figure 3). More recent studies have demonstrated that megakaryocytes progress to formation of a cleavage furrow, but the furrow regresses before cell division in polyploid megakaryocytes [98–100]. With respect to Aurora kinases, several studies have examined Aurora B localization and function in megakaryocytes. All studies agree that Aurora B is expressed and localized normally during prophase in megakaryocytes. However, one group found that Aurora B is downregulated in murine megakaryocytes and that transgenic mice overexpressing Aurora B exhibit increased megakaryocyte numbers and slightly decreased ploidy levels [101–103]. On the other hand, a different group found that Aurora B is present, appropriately localized and functional in endomitosis [104]. This was similar to a third study that showed that Aurora B is normally expressed and properly localized during the human megakaryocyte endomitotic process. However, the appropriately localized, functional Aurora B did not prevent furrow regression in megakaryocytes [105]. Aurora A was also found to be expressed and localized appropriately in megakaryocytes [104].

One rare subtype of leukemia that has a special involvement with the Aurora kinases is acute megakaryocytic leukemia (AMKL). In AMKL, immature megakaryocytes fail to exit the proliferative cell cycle, become polyploid or undergo terminal differentiation. The three major subgroups of AMKL are infants with Down syndrome (DS-AMKL), children without DS (non-DS AMKL) and adults (adult AMKL). In DS-AMKL, trisomy 21 and somatic mutations in the *GATA1* gene are found in nearly every patient [106]. In addition, mutations in the cohesin complex, epigenetic regulators and signaling cascades are seen in this malignancy [107, 108]. Various chromosomal abnormalities, such as t(1;22)(p13;q13), which leads to expression of the OTT-MAL fusion protein, inv(16) leading to the CBFA2T3-GLIS2 fusion, and t(5:11) leading to the NUP98/JARID1A fusion are associated with non-DS pediatric AMKL [109–113]. Pathways that are mutated in adults with AMKL include JAK/STAT, c-MPL, c-kit and FLT3 [114–120].

Recently, we demonstrated that Aurora A is an important and novel target in AMKL, and that Aurora kinase inhibitors are effective therapies in multiple pre-clinical models of this malignancy [121]. The initial hypothesis of the project was that small-molecule inducers of polyploidization would force malignant megakaryocytes to exit the proliferative cell cycle and undergo endomitosis and terminal differentiation. To test this idea, we leveraged an integrated screening approach that included chemical, proteomic and small interfering RNA (siRNA) screens to identify compounds and their cellular targets that induce polyploidy and differentiation of AMKL blasts. In the initial chemical screen, several small molecule inducers of polyploidy were identified, including the lead compound dimethylfasudil (diMF). Through our multi-pronged target ID approach, we discovered that Aurora A was among the top scoring protein targets of diMF. Additional experiments demonstrated that inhibition by diMF and the Aurora A inhibitor MLN8237 (Alisertib) increase the polyploidization and differentiation of AMKL blasts. We further showed that inhibition of Aurora A with diMF led to a significant increase in survival of a mouse model of AMKL:

forty percent of the mice in the group treated with 66 mg/kg diMF and 30% of the mice treated with 33 mg/kg diMF survived long-term compared to a rapid lethal disease in the vehicle treated mice. A subsequent study by Mercher and colleagues modeled human pediatric AMKL in immunodeficient mice and found that small molecule Aurora A inhibition by MLN8237 could effectively treat a xenograft model of AMKL [111].

It has been hypothesized that the efficacy of Aurora kinase inhibitors as cancer therapeutics depends on their general antimitotic effects and it is unlikely that most tumors are specifically addicted to Aurora kinase activity [122–125]. If this is true, Aurora kinase inhibitors mode of action may be different from other targeted therapies, like inhibitors of BCR–ABL or the HER2 oncoproteins that directly suppress proliferative signals. However, AMKL and malignancies with a prominent megakaryocyte role may be the exception. AMKL blasts appear to respond to Aurora A inhibition in a specific, targeted manner with terminal differentiation rather than a general antimitotic effect. This effect is analogous to targeted differentiation therapy in acute promyelocytic leukemia [126, 127]. The mechanism by which Aurora A inhibition selectively induces differentiation of megakaryocytic leukemia cells is unclear. One possibility is that the increase in differentiation is caused by decreased phosphorylation of a lineage specific transcription factor that controls terminal maturation and is active in the dephosphorylated state. Of note, consistent with an effect of Aurora A kinase inhibition on a megakaryocyte transcription factor, we have observed that megakaryocytes derived from murine bone marrow or human CD34+ cells also show increased differentiation with diMF or MLN8237 treatment [121]. Non-malignant megakaryocytes also increase their ploidy state in response to Aurora A kinase inhibition. This may be associated with decreased Aurora kinase activity in maturing megakaryocytes.

CLINICAL TRIALS OF AURORA KINASE INHIBITORS

The first clinical trials with Aurora kinase inhibitors were launched in 2005 and at least seventy trials have been initiated to date to evaluate the clinical activity of these compounds. Aurora kinase inhibitors that have progressed through preclinical testing and into phase I or phase II trials include the Aurora A inhibitors MLN8054, PF-03814735, AS703569, MK-0457, MK-5108, MSC1992371A, and the Aurora B inhibitors AT9283 and PHA-739358 (Table 2) [128]. Recently, a number of studies have examined the activities of the Aurora A inhibitor MLN8237 and the Aurora B inhibitor AZD1152 (Barasertib).

Aurora A and B dual inhibitors

Preclinical and clinical studies have been performed with the combined Aurora kinase inhibitor VX-680 (Tozasertib) in chronic myelogenous leukemia (CML). VX-680 is a pan inhibitor of Aurora kinases with inhibition constant (Ki) values of 0.6, 18 and 4.6 nM for Aurora A, Aurora B and Aurora C, respectively [129]. It was proven to be an efficacious inhibitor that decreased tumor growth in in vivo leukemia models [130]. In one study, VX-680 was shown to inhibit growth, promote apoptosis, and reduce the phosphorylation of BCR-ABL in a CML cell line [131]. Another preclinical study showed that in the KCL-22 CML cell line, inhibition of Aurora kinases with VX-680 sensitized CML cells to treatment with the BCR-ABL inhibitor imatinib and blocks acquisition of BCR-ABL mutations and relapse on imatinib [132]. Additionally VX-680 showed activity in patients with the T315I mutation who

are resistant to BCR-ABL inhibitors such as imatinib [133]. A CML clinical trial with VX-680 showed that it has activity in treating the disease with three patients achieving clinical responses [133]. Unfortunately, development of VX-680 was terminated due to its severe toxicities. Another combined Aurora A/B inhibitor, AT9283, was shown to significantly inhibit the growth and survival of ALL patient cell lines [134]. AT9283 was also shown to be effective at suppressing growth of CML and B-cell lymphoma cell lines [135, 136]. A phase I dose-escalation study of a third combined Aurora A and B inhibitor MSC1992371A, was performed in patients with hematologic malignancies. Complete responses occurred in 3 patients. However, there was hematologic and gastrointestinal toxicity at clinically effective doses [137]. Moreover, in two phase I trials of MSC1992371A in solid tumors the only responses seen were disease stabilization [138, 139].

Aurora A inhibitors

MLN8237 is an ATP-competitive, selective inhibitor of Aurora A (40-fold selective for Aurora A compared to Aurora B, IC50 4nM) [128, 140]. Treatment of cells with MLN8237 causes defects in bipolar spindle assembly resulting in chromosomal segregation abnormalities. In addition, cells treated with Aurora A inhibitors arrest in mitosis due to activation of the mitotic checkpoint [29, 47, 141]. The arrest is transient, and although inhibitors of Aurora A perturb the mitotic spindle, they do not cause a permanent mitotic arrest. After the initial mitotic arrest, treated cells exit mitosis, leading to aneuploidy and centrosome amplification [142]. Although anti-Aurora A antibody injection studies have shown defects in completing cytokinesis, inhibition of Aurora A with small molecules was shown to not affect cytokinesis [34, 142]. Aurora A inhibition phenotypes are similar to those observed upon its depletion by RNAi, underscoring that MLN8237 primarily targets Aurora A in vivo [31].

MLN8237 has proven to be effective in preclinical AML studies. Treatment of AML cell lines, primary AML cells and mouse models of AML with MLN8237 decreased their viability and colony forming ability on soft agar and increased their apoptosis. In addition, MLN8237 treatment was shown to potentiate the anti-leukemic activity of the standard chemotherapy cytarabine in both primary blasts and AML cell lines [143]. A phase I/II clinical trial reported a 13% response rate for MLN8237 in relapsed and refractory AML patients. Additionally, in this clinical trial 11% of patients had a partial response and 49% of patients achieved stable disease [144].

Aurora A inhibitors have also been tested in CML in both preclinical and clinical studies. One preclinical study of Aurora A inhibitors in CML found that MLN8237 was effective at killing cells with the T315I mutation, which confers the greatest degree of resistance to approved targeted therapies, through a BCR-ABL independent mechanism [145]. Inhibition of Aurora A with MLN8237 also significantly potentiated the in vitro and in vivo efficacy of the approved therapy nilotinib [145].

Aurora B inhibitors

Aurora B has been investigated as a potential target in leukemia for over 6 years after it was discovered that Aurora B is overexpressed in leukemia cells of ALL, AML and CLL patients [54, 78, 146, 147]. AZD1152, the most often tested Aurora B inhibitor, is a pro-drug that

undergoes phosphatase-mediated cleavage to release barasertib-hQPA, a selective Aurora B inhibitor [90]. In preclinical studies, treatment of AML cell lines and primary AML samples with AZD1152 reduced cell proliferation and increased cell death. In addition, AZD1152 decreased the growth of AML cell lines and primary AML in a xenotransplantation model [148]. These results were replicated in a two additional preclinical studies that showed that inhibition of Aurora B with AZD1152 inhibited proliferation and induced apoptosis of ALL and AML cells [147, 149]. AZD1152 also appears to function synergistically with clinically approved leukemia therapies. In one preclinical study, AZD1152 synergistically enhanced the anti-proliferative effects of vincristine and daunorubicin in vitro and in vivo [54]. In a second study, treatment with AZD1152 and cytarabine together caused a greater than additive cytotoxicity in leukemic cells in vitro [150].

AZD1152 has been tested in several phase I/II leukemia clinical trials with varying effectiveness. In one AML clinical trial, five patients with poor prognosis AML received AZD1152 and one entered complete remission [90]. In a different trial, 8 out of 32 AML patients had a hematologic response [151]. A similar overall hematologic response rate of 19% was reported in a third study of 16 AML patients [152]. In a phase I/II trial testing AZD1152 versus low-dose cytosine arabinoside in elderly patients with acute myeloid leukemia, a significant improvement (35.4% vs. 11.5%) in the response was observed in the AZD1152 group. The median OS was 8.2 months versus 4.5 months with cytosine arabinoside. However, AZD1152 did have a more toxic safety profile than cytosine arabinoside [153]. Due to its general anti-mitotic mechanism, myelosuppression and other side effects were a concern with the use of AZD1152. Preclinical studies treating human cord blood and mouse stem and progenitor cells with this agent showed that treatment results in inhibition of cell growth, apoptosis and delayed cell cycle progression both in vitro and in vivo [148]. In the clinical trials, the most common adverse events were neutropenia, febrile neutropenia and stomatitis/mucosal inflammation [151, 152]. Although myelosuppression is the most common side effect of treatment with AZD1152, it is not a dose-limiting toxicity.

Concluding remarks and perspectives

In this review, we have highlighted the regulation and functions of each Aurora kinase, their involvement in leukemia and Aurora kinase inhibitor efficacy in leukemia clinical trials. Since the discovery of the Aurora kinases, extensive research into their function has identified key roles for each kinase in mitosis and cancer. These insights have led to the emergence of Aurora kinases as therapeutic targets in the treatment of leukemia. The combination of these targeted inhibitors with conventional cytotoxic therapies also shows promise. Studies in the next several years will likely focus on the further integration of Aurora kinase inhibitors into combinations with conventional therapies and will establish whether inhibition of Aurora A, Aurora B, or their combined inhibition is most effective. Going forward, challenges for researchers in the field include understanding if Aurora kinases are true oncogenic drivers and determining if it is possible to kill malignant cells by inhibiting Aurora kinases without disrupting the function and survival of non-cancerous cells. To date, tolerated doses of Aurora kinase inhibitors have not proven overly effective at treating leukemia in clinical trials. One potential breakthrough that could aid in this goal is the identification of specific cancers with heightened sensitivity to Aurora inhibition such as

AMKL. Uncovering other cancers dependent on Aurora kinase signaling could lead to effective killing of the malignant cells at doses that spare non-tumor cells.

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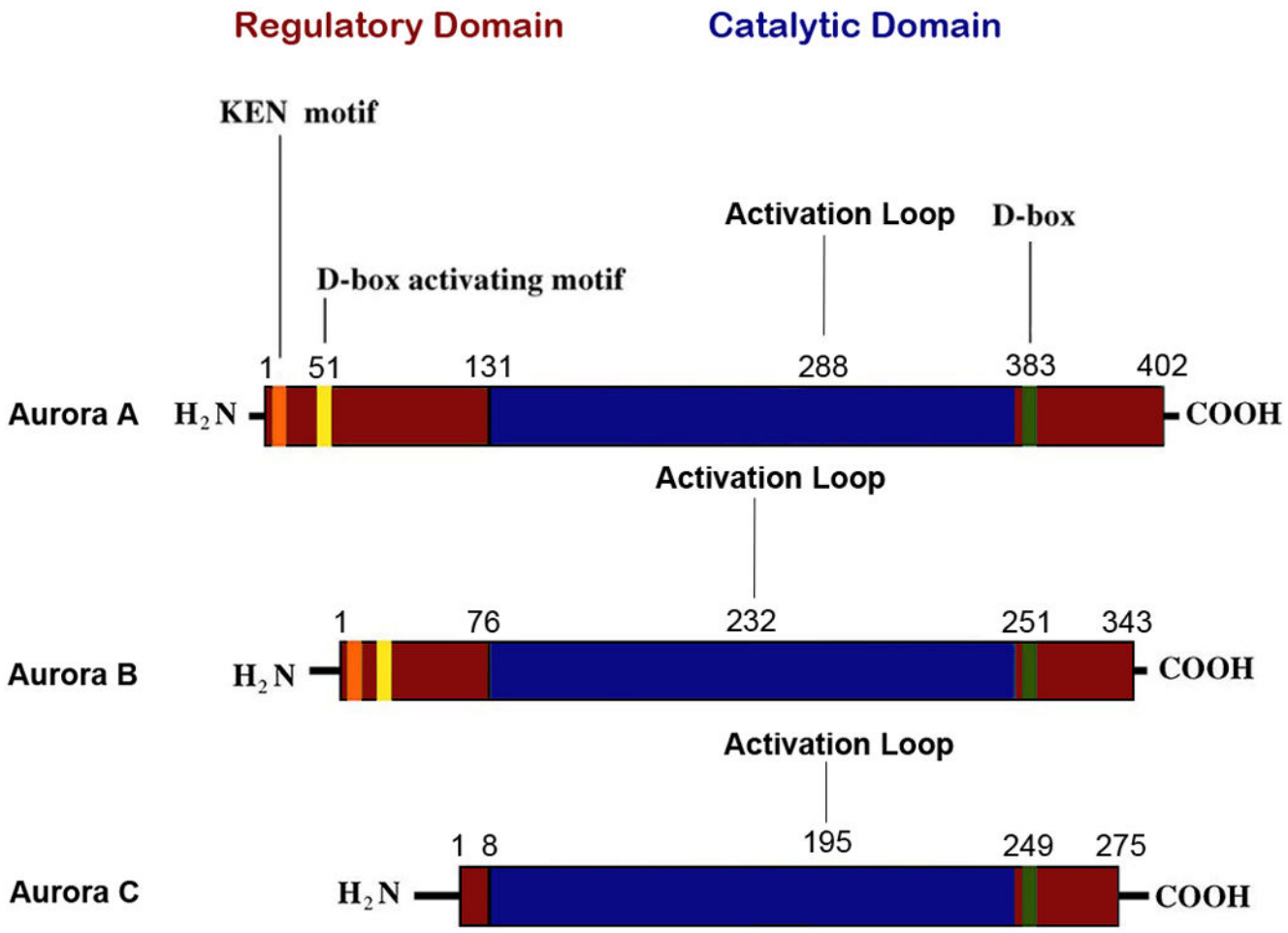

Figure 1. Structure and domains of the aurora kinases

The Aurora kinases N-terminal and C-terminal domains contain D-box and KEN regulatory motifs while the central kinase domain contributes the catalytic activity. The central domain also includes key regulatory motifs such as the activation (T-loop) residue.

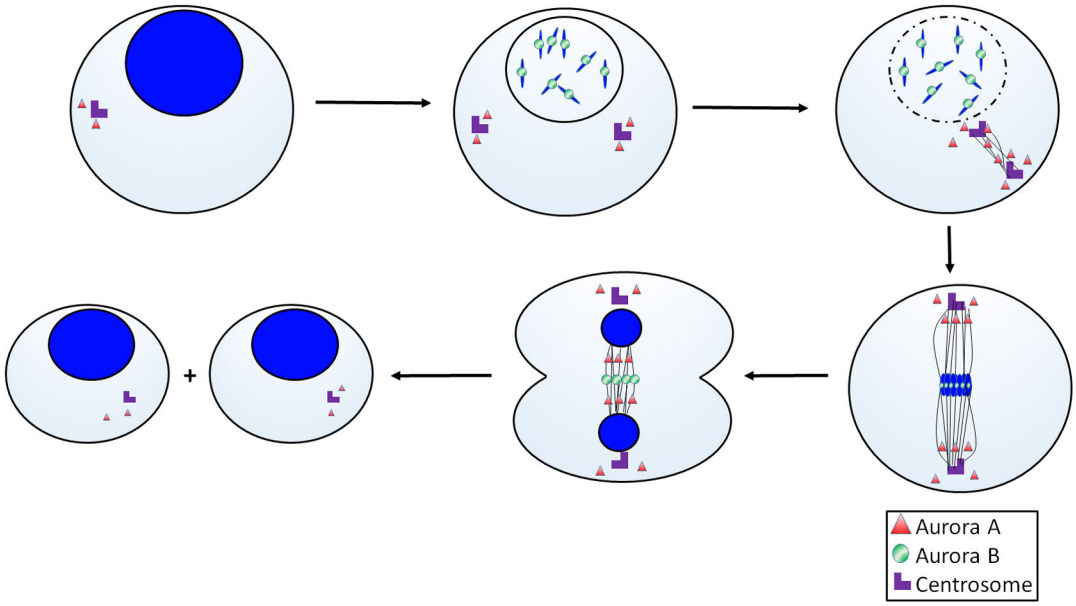

Figure 2. Aurora A and B are appropriately expressed and localized in mitosis

Aurora A localizes to the spindle poles, while Aurora B localizes to the midbody of the central spindle during mitosis. Triangles, Aurora A kinase; Circles, Aurora B kinase; L-shaped objects, centrosomes.

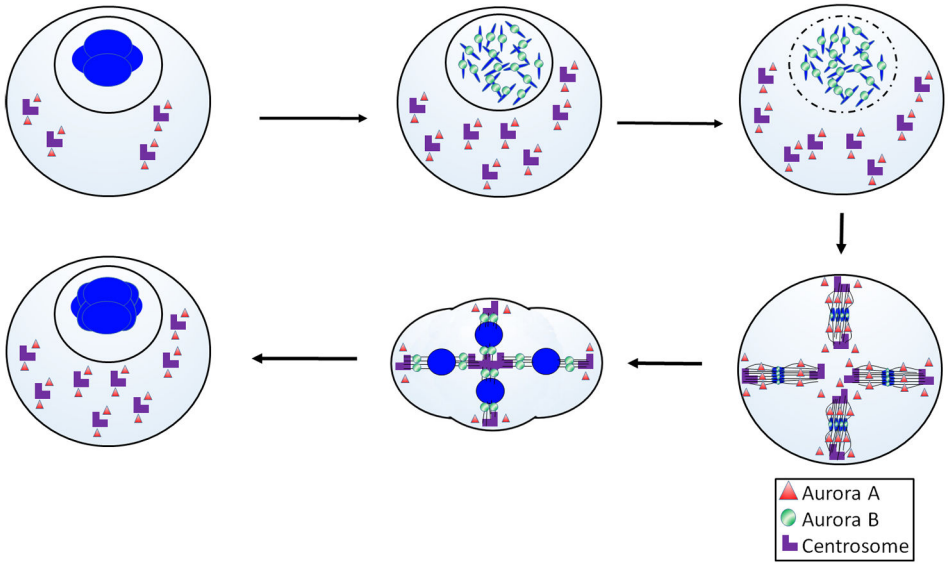

Figure 3. Aurora A and B are expressed and localized in endomitosis of megakaryocytes

Endomitotic cells are reported to show normal localization of both kinases [99, 104, 105]. The major difference from the proliferative cell cycle is the regression of the cleavage furrow, which leads to polyploidy [98–100]. Triangles, Aurora A kinase; Circles, Aurora B kinase; L-shaped objects, centrosomes.

Table 1

Aurora kinases exhibit different functions

KINASE	FUNCTIONS	REFERENCES
AURKA	Mitotic entry Chromosome alignment Centrosome maturation Centrosome separation Spindle assembly checkpoint	26, 34–36, 47, 67, 74
AURKB	Sister chromatid cohesion Bipolar spindle assembly Cytokinesis Spindle assembly checkpoint	26, 50–53, 55
AURKC	Spermatogenesis Chromosome segregation? Cytokinesis?	10, 59–64

Table 2

Aurora kinase inhibitors

TARGET	MOLECULE	PRECLINICAL ACTIVITY	CLINICAL DEVELOPMENT	REFERENCES
AURORA A	MLN8237/MLN-8054	Leukemia and solid tumors	Phase II	111, 121, 128, 140–145
	MK-5108	Solid tumors	Phase I	128
AURORA B				
	AZD1152	Leukemia and solid tumors	Phase II	54, 147–153
	PHA-739358	Leukemia and solid tumor	Phase II	128, 146
AURORA A AND B				
	VX-680/MK-0457	Leukemia and solid tumors	Terminated due to toxicity	129, 131–133
	AT9283	Leukemia and solid tumors	Phase II	130, 134–136
	MSC1992371A	Leukemia and solid tumors	Phase I	137–139
	PF-03814735	Solid tumors	Phase I	128
	AS703569	Leukemia and solid tumor	Phase I	128