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Aurora-A kinase (AURKA) in normal and pathological cell growth

Anna S. Nikonova, **Igor Astsaturov**, **Ilya G. Serebriiskii**, **Roland L. Dunbrack Jr.**, and **Erica A. Golemis***
Program in Developmental Therapeutics, Fox Chase Cancer Center, Philadelphia, PA 19111

Abstract

Temporally and spatially controlled activation of the Aurora-A kinase (AURKA) is regulates centrosome maturation, entry into mitosis, formation and function of the bipolar spindle, and cytokinesis. Genetic amplification, and mRNA and protein overexpression of Aurora-A are common in many types of solid tumor, and associated with aneuploidy, supernumerary centrosomes, defective mitotic spindles, and resistance to apoptosis. These properties have led Aurora-A to be considered a high value target for development of cancer therapeutics, with multiple agents currently in early phase clinical trials. More recently, identification of additional, non-mitotic functions and means of activation of Aurora-A during interphase neurite elongation and ciliary resorption have significantly expanded understanding of its function, and may offer insights into clinical performance of Aurora-A inhibitors. We here review mitotic and non-mitotic functions of Aurora-A, discuss Aurora-A regulation in the context of protein structural information, and evaluate progress in understanding and inhibiting Aurora-A in cancer.

Keywords

Aurora-A; AURKA; cancer; mitosis; cell cycle; kinase; centrosome; cilia

I. Introduction

Aurora-A kinase (official gene symbol AURKA) has many aliases, including more commonly Aurora, Aurora-2, serine/threonine kinase 15 (STK15), serine/threonine kinase 6 (STK6), breast tumor amplified kinase (BTAK), aurora-related kinase 1 (ARK1), Homo sapiens Aurora/IPL1-related kinase (HsAirk1), Eg2, and Ipl- and Aurora-related kinase 1 (IAK1). As these names indicate, this protein is a member of Aurora/IPL1-related kinase family of serine/threonine kinases. The founding member of the family, Ipl (increase-in-ploidy) 1, was first identified in 1993, in a screen for mitotic mutants that failed to undergo normal chromosome segregation in *Saccharomyces cerevisiae* [1]. Ipl1-like kinases were independently identified in cell cycle studies in *Xenopus laevis* and *Drosophila melanogaster* [1–5]. The *Xenopus laevis* Eg2 transcript emerged in a screen for *Xenopus* egg mRNAs that became deadenylated after fertilization, and the encoded kinase was subsequently defined as a regulator of the G2/meiosis I transition in *Xenopus* oocytes and of mitotic spindle function in *Xenopus laevis* eggs [3, 4]. Severe mutations at the *Drosophila aurora* locus result in pupal lethality and mitotic arrest that is characterized by the presence of monopolar spindles; less severe mutations include defects in centrosome separation, formation of astral microtubules, chromosome segregation, and spindle positioning [5–9]. All of the early studies in model organisms indicated a requirement for this protein in mitotic progression.

*corresponding author: Erica A. Golemis Fox Chase Cancer Center, W406 333 Cottman Ave. Philadelphia, PA 19111 USA (215) 728-2860 ph, -3616 fax EA_Golemis@fccc.edu.

Subsequent studies determined that Ipl1 is the unique *S. cerevisiae* representative of a family that diverges into two Ipl1-like kinases (Aurora-A and Aurora-B) in *Drosophila*, *C. elegans* and *X. laevis*, and three Ipl1-like kinases (Aurora-A, Aurora-B and Aurora-C) in mammals. All of these kinases have been found to have essential functions in mitosis and/or meiosis. However, among the three mammalian kinases, Aurora-A has attracted very significant attention in the past decade, based on the recognition that it is overexpressed in many tumors arising from breast, colon, ovary, skin and other tissues, and because it has been shown to function as an oncogene when exogenously expressed in numerous cell line models [10–14]. Aurora-A overexpression, whether in naturally occurring tumors or following deliberate overexpression, is associated with increased number of centrosomes and multipolar spindles, which arise as consequence of failed cytokinesis. For these reasons, Aurora-A has been a popular target for development of targeted therapeutic agents for cancer, with multiple Aurora-A-specific or pan-Aurora kinase inhibitors undergoing clinical assessment. At the same time, continuing investigation of Aurora-A has unexpectedly suggested that the activity of this protein is not confined to regulation of mitosis, with new functions observed in interphase and post-mitotic cells. Given the recent nature of these discoveries, they are not yet broadly appreciated, although they may impact the use of Aurora-A-targeted drugs in the clinic, and also expand the general understanding of the biological role of this protein in cell physiology.

In this review, we describe and discuss the signaling and structure of human Aurora-A in normal cell division, and the deregulation of Aurora-A signaling in cancer. We also review the current status of drugs targeting Aurora-A for cancer, and summarize recent insights into Aurora-A function emerging from systems biology resources. Because of space constraints, we do not discuss functions of the other Aurora kinases in depth. For useful recent reviews of the function of Aurora-B, see [15, 16]; at present, Aurora-C function is much less well understood.

II. Aurora-A actions relevant to mitosis

Aurora-A expression, localization, and activities as cells enter and exit mitosis are summarized in Figure 1. Initial genetic studies of Aurora-A mutants all identified defects in formation and control of the bipolar spindle in mitosis. More detailed analysis of Aurora-A expression, activation, and direct phosphorylation substrates parses Aurora-A contribution to a series of steps that extend earlier in cell cycle, establishing conditions for appropriate progress into and through mitosis. Aurora-A regulated processes include centrosome maturation and separation, followed by assembly of a bipolar spindle, trigger of mitotic entry, alignment of chromosomes in metaphase, cytokinesis/abscission, and the return to G1. Aurora-A interacting proteins relevant to this activity are listed in Table 1, and described below.

Centrosome maturation

During S-phase, following centrosomal duplication, Aurora-A starts to accumulate at the centrosomes. As cells progress toward the point of mitotic initiation, centrosomes undergo a maturation process that renders them capable of nucleating the many microtubules that form the mitotic spindle, and also allows them to act as a signaling platform for mitotic regulators [17, 18]. During this maturation process, which is most noticeable in late G2, centrosomes expand in diameter due to the accretion of a pericentriolar mass (PCM) composed ot γ-tubulin, the γ-tubulin ring complex (γ-TURC), and a number of additional regulatory proteins [18]. PCM protein recruitment during centrosome maturation is controlled by centrosome protein of 192 kDa (Cep192/spindle defective 2 (Spd-2)), which helps target Aurora-A to the centrosome as well as activate the protein in mitosis [19]. Defective

expression of Aurora-A activators, such Bora and NEDD9, similarly lead to defects in centrosome maturation [20, 21].

At the centrosome, Aurora-A helps in recruiting γ-tubulin, centrosomin, LATS2, TACC, and NDEL1 to the PCM [22–26]. Comparison of studies performed in *Drosophila*, *C. elegans*, and mammals indicates some variance in Aurora-A-dependent PCM growth dependent on organismal and cellular context, with Aurora-A required for γ-tubulin recruitment in *C. elegans* and in *Drosophila* sensory organ precursor cells [22, 27], but not in *Drosophila* neuroblasts or S2 cells [7]. Aurora-A phosphorylation of LATS2 promotes recruitment of the kinase LATS2 to the centrosome [23]. At least in some cell systems, LATS2 is required for recruitment of γ-tubulin, working in concert with the Aurora-A partner Ajuba [24]. Another target of Aurora-A in centrosome maturation is nuclear distribution element-like 1 (NDEL1), an evolutionarily conserved coiled-coil containing protein. NDEL1 S251 phosphorylation by Aurora-A in late G2 is required for NDEL1 localization to the centrosome, and also triggers ubiquitin-mediated degradation of NDEL1; expression of phosphomimetic mutant of NDEL1 fully compensates for the centrosome maturation defect seen with depletion of Aurora-A [26]. Downstream, one important role of NDEL1 in G2 is targeting of TACC3 (also known as maskin, and discussed extensively below in control of spindle function) to the centrosome [26].

Timing mitotic entry

Concurrent with centrosomal maturation, Aurora-A also supports the activation of the CDK1/cyclin B complex to allow nuclear entry. CDK1/cyclin B activation occurs initially at the centrosome, before propagating throughout the cell [28, 29], with this initial activation dependent on positive-reinforcement cycles involving Aurora-A. Aurora-A in association with its partner Bora phosphorylates T210 in the T-loop of the PLK1 phosphatase during G2; Bora is later degraded in a PLK1-dependent manner after entry to mitosis [30–32]. PLK1 promotes the recruitment of Aurora-A to centrosome in late G2, where Aurora-A phosphorylates the CDK-activating phosphatase CDC25B (cell division cycle 25B) on S353, promoting mitotic entry [33]. Activated PLK1 also promotes the activation of CDK1/cyclin B by inducing the degradation of the CDK-inhibitory kinase WEE1, and by activating phosphatase CDC25C [34, 35].

Studies in *Xenopus* oocytes have identified an additional role for Aurora-A in regulating the accumulation of cyclin B1 by enhancing its mRNA translation [36–40]. In cycling extracts from non-mitotic oocytes, a complex with TACC3/maskin, the translational control factor CPEB, eIF4E, and PUM2, binds the maternal cyclin-B1 mRNA, precluding the formation of an active translation initiation complex. Upon cell entry to M phase, Eg2 (Aurora-A) phosphorylates CPEB on S174, causing the complex to dissociate and inducing cyclin-B1 mRNA polydenylation and translation [36–40]. However, this particular activity of Aurora-A has not been demonstrated in mammalian somatic cells, and may be species-specific.

Aurora-A also controls the G2/M transition via interactions with the C-terminal domain of centrosomally localized BRCA1 (breast cancer associated gene 1) [41]. These interactions help localize BRCA1 to the centrosome [42]; further, Aurora-A phosphorylation of S308 of BRCA1 is required for M phase entry; exposure of cells to DNA damage induced by ionizing radiation triggers a cell cycle checkpoint in part through elimination of this phosphorylation. At present, downstream targets of BRCA1 in this pathway are not defined.

Some critical Aurora-A activities permissive for mitosis extend beyond functions exerted at the centrosome, and are also coordinated with CDK1/Cyclin B effector function. For example, mitochondria must undergo fission, to be segregated equally between daughter cells post-mitosis. Aurora-A phosphorylation of the Ras family GTPase RALA or S194

drives it to the mitochondria, where phosphorylated RALA associates with its effector RALBP1 and with DRP1. DRP1 was separately directed to the mitochondria by phosphorylation by activated CDK1/cyclin B: together, the RALA-RALBP1-DRP1 complex effectively regulates mitochondrial fission [43].

Construction and control of a bipolar spindle

A critical mitotic role of Aurora-A is in supporting appropriate function of the centrosome as a microtubule-organizing center (MTOC) in mitosis. In all metazoans assessed, mutation or depletion of Aurora-A causes formation of spindles with abnormally organized poles, including characteristic monopolar structures, and weak, sparse, or short astral microtubules [5, 7, 22, 44–47]. Aurora-A control of the mitotic spindle has been the target of intense study, and a number of critical effectors have been identified.

Transforming, acidic coiled-coil (TACC) family proteins are evolutionarily conserved, lack known catalytic activity, and feature a 200 amino acid coiled coil motif at their C-terminus to promote protein interactions; their role in association with Aurora-A in formation and action of a bipolar spindle is exhaustively discussed in [48]. Briefly, Aurora-A expression is correlated with that of TACC1, TACC2, and TACC3, and Aurora-A forms complexes with TACCs 1 and 3 [49–51]. TACC proteins interact with proteins of the highly conserved ch-TOG/XMAP215 family, to stabilize microtubules at centrosomes, in part by binding to the minus ends of microtubules and thus opposing the activity of a microtubule-destabilizing kinesin, mitotic centromere associated kinesin (MCAK/XKCM1) [49, 52]. In Drosophila *aurora* mutant cells, or after RNAi depletion of *aurora*, the abnormal organization of the spindle poles and abnormally short arrays of astral microtubules, correlate with the loss of the Drosophila D-TACC from centrosomes [7]. Aurora-A also influences formation of bipolar spindles by directly phosphorylating MCAK on S196, regulating its activity on mitotic asters, and on S719, promoting its association with spindle poles [53]; together, these events induce conversion of mitotic asters to a fully developed bipolar spindle.

Besides its role in regulated M phase entry, Aurora-A inhibits an additional activity of the BRCA1 ubiquitin ligase in negative regulation of centrosomal microtubule nucleation, working in tandem with protein phosphatase 1α (PP1α) [42, 54]; however, essential targets of BRCA1 relevant to mitotic MTOC activity for the spindle pole are not known. Centrosomal LIMK1 has ben proposed to support spindle formation through modulating a dialog with the actin filament system [55, 56]. Aurora-A phosphorylates LIMK1 on S307, with this phosphorylation important for maintaining mitotic colocalization of the two proteins, and hence directed LIMK1 activity.

The first defined mitotic target of Aurora-A phosphorylation was the kinesin-related, evolutionarily conserved protein XlEg5 of Xenopus [57], with this phosphorylation important for spindle assembly and stability [57]. Subsequent studies suggested a model in which Aurora-A control of Eg5 influenced centrosomal separation by influencing Eg5 specification of microtubule sliding, i.e. by directly forcing apart centrosomes [48]. A more recent study has focused on the interaction between Aurora-A/Eg5 and a kinetochore-based spindle assembly pathway, involving the protein Mcm21R, which uses poleward microtubule flux to help push centrosomes apart [58].

Spindle nucleation arises from the centrosome, from chromatin, or in the absence of either given an appropriate initiating cue [59]. While most attention focuses on the Aurora-A role at centrosomes in formation of the spindle aster, Aurora-A is capable of inducing formation of spindle-like asters in the absence of the nucleating function of centrosome or chromatin [60]; TPX2, by contrast, promotes microtubule polymerization. This activity involves interaction between Aurora-A and TPX2, and a group of proteins including HURP [61],

XMAP215, and Eg5 [62]. Under physiological conditions, these interactions and Aurora-A activation are stimulated by Ran-GTP, which is enriched in the vicinity of the kinetochore and chromatin (pathway reviewed extensively in [63]). Aurora-A phosphorylates a single conserved residue close to the motor domain of another kinesin, centromere protein A (CENP-E/kinesin-7), which is a major mitotic regulator of bipolar spindle dynamics. A PP1 binding site overlaps this phosphorylation site; Aurora-A phosphorylation disrupts PP1 binding to CENP-E. This Aurora-A/PP1 phosphorylation switch is required not only for congression of polar chromosomes through modulation of of CENP-E motor activity, but also for CENP-E-dependent delivery of PP1 to the kinetochore, which is important for stable biorientation of chromosomes [64]. CENP-A is a variant of histone H3 that is a component of the nucleosome core of centromeric chromatin at the kinetochore. Aurora-A phosphorylates S7 of CENP-A, an essential step for the attachment of microtubules to the kinetochore, and consequently for chromosome alignment and segregation [65, 66].

Another Aurora-A partner, RASSF1A, is a tumor suppressor that binds microtubules to arrest cell growth in M-phase [67]. Aurora-A phosphorylation of RASSF1A interrupts its microtubule binding activity, and also relieves RASSF1A-dependent inhibition of the APC/Cdc20 complex, permitting M-phase progression [67, 68]. Aurora-A also coordinates chromosome segregation and anaphase microtubule dynamics later in mitosis. Aurora-A propagates from the centrosome to the spindle and then to the midzone, before much of the protein is degraded at the midbody [69]. Aurora-A has recently been found to be mitotically SUMOylated, which may contribute to localization control [70]. Rather than simply passively trafficking, Aurora-A also contributes actively to the ability of the APC/Cdh1 complex to form a robust spindle midzone in late mitosis [69]. SAF-A (scaffold-attachment factor A) is required for chromosome segregation, in part through association with the Aurora-A-TPX2 complex. An essential function of SAF-A is to recruit Aurora-A to the spindle microtubules [71]; together, SAF-A, Aurora-A, and TPX-2 influence chromosome congression, kinetochore-microtubule attachments, and stability of kinetochore microtubules.

III. Control of Aurora-A activation and degradation in mitosis

Activation of Aurora-A

Activation of Aurora-A as cells enter mitosis involves spatially and temporally constrained interactions with multiple partner proteins. Proteins regulating this process are indicated in Table 1, and Figure 2. Littlepage et al first defined mitotic phosphorylation of Aurora-A incubated with metaphase-arrested frog oocytes, on the residues S53, T295, and S349 (equivalent to S51, T288, and S342 of human Aurora-A) [72]. Activating interactions that induce Aurora-A autophosphorylation at T288 (in human Aurora-A; T295 in *Xenopus* Aurora-A) in the kinase activation loop have been most studied. Relevant partner proteins for this phosphorylation include TPX2 (target protein for *Xenopus* kinesin-like protein 2), Ajuba/JUB, NEDD9 (also known as HEF1 and CasL), and BORA; in addition, PAK1 (p21-activating kinase 1) has been reported to activate Aurora-A via transphosphorylation of T288 [73].

Among these, the structural basis of the TPX2 [74] interaction has been most intensively studied. Activation of the GTPase Ran at nuclear envelope breakdown GTP stimulates spindle assembly by releasing the spindle assembly factor TPX2 from an importin-α/β inhibitory complex. The liberated TPX2 binds to Aurora-A kinase, promoting a conformational change that activates auto-phosphorylation, and moves the activation loop to a central position from which it is protected from de-phosphorylation by the negative regulatory factor PP1, providing access for Aurora-A substrates [75–81]. Phosphorylation of

TPX2 by Plx1 increases its ability to activate Aurora-A [82]. The TPX2 interaction also helps target Aurora-A to mitotic spindles, proximal to substrates [51, 78].

Ajuba (JUB) is a scaffolding protein, containing multiple LIM domains, that was described as an interactor and activator of Aurora-A in 2003 [83]. Both Aurora-A and Ajuba are phosphorylated by Aurora-A during their interaction; this interaction was shown to be important for activation of the cyclin-B/CDK1 complex, and committing cells to mitosis [83]. No studies of this activating interaction have subsequently been reported in humans. However, one recent study in *Drosophila* sheds potential light on the Aurora-A/Ajuba interaction [84]. *Drosophila jub* (*ajuba*) mutants die in larval-pupal transition. Jub localizes to the centrosomes of neural stem cells; Mutation of *jub* led to centrosome separation defects and abnormal mitotic spindles. Surprisingly, in *jub* mutants Aurora-A activity was not perturbed, but Aurora-A recruitment and maintenance at the centrosome was defective. The authors of this study proposed that a major function of Jub in Drosophila is to restrict active Aurora-A to centrosome during mitosis, but not to activate Aurora-A. This failure of Jub to regulate Aurora-A might also reflect a difference in the way Aurora-A is regulated between vertebrates and invertebrates [84]; more investigation is required.

Aurora-A directly interacts with another scaffolding protein, NEDD9, also known as CASL and HEF1 [85–87]. Identification of NEDD9 as an Aurora-A activator was initially surprising, given a predominant role for this protein at focal adhesions in regulation of cell migration and invasion [88–91]. However, NEDD9 was subsequently found to accumulate at the centrosome as cells move into G2 and M phase [21, 92]. Depletion of NEDD9 does not affect Aurora-A accumulation at the centrosome, but blocks the T288 phosphorylation and activation of Aurora-A at mitotic entry, and leads to accumulation of cell with monopolar spindles and cleavage furrow regression. Overexpression of NEDD9 induces Aurora-A hyperactivation, and produces cells with multipolar spindles and supernumerary centrosomes, and failure of cytokinesis [21, 93]. Interestingly, a protein closely related to NEDD9, p130Cas/BCAR1, has been shown to bind directly to Ajuba [94]; potentially, NEDD9 and Ajuba similarly interact during Aurora-A activation.

The serine/threonine kinase Pak1 is also well known for functions in proliferation and cell migration signaling that moonlights with additional roles in cell cycle, including control of centrosome number and mitotic progression. Zhao et al defined interactions between Pak1 and a centrosomal adaptor protein, PIX/GIT, that leads to centrosomal activation of Pak1: PAK1, or two related PAK kinases, PAK2 and PAK3, each bind Aurora-A, and can phosphorylate Aurora-A on the T288 activation loop site or an alternative site, S342, in vitro [73]. Like Pak1, LIM kinase 1 (LIMK1) is better known as a regulator of the actin cytoskeleton through phosphorylation of substrates such as cofilin. However, a pool of LIMK1 colocalizes with γ-tubulin and Aurora-A at the centrosome between early prophase through anaphase, and phosphorylates Aurora-A; the target of LIMK1 is not the well-defined T288 motif, but has otherwise not been determined [56].

Mutations in the Drosophila *borealis* (*bora*) gene phenocopy Aurora-A mutations. Cdc2-dependent nuclear exclusion of Bora releases the protein to the cytoplasm, where it binds and activates Aurora-A [20]. Part of the function of Bora in promoting Aurora-A activity may involve binding to substrates as a co-factor with Aurora-A, increasing phosphorylation site availability [30]. However, two independent studies suggested that Plk1 phosphorylation of Bora leads to β-TrCP-dependent degradation of Bora, with one study indicating that human Bora competed with TPX2 for Aurora-A binding, limiting Aurora-A activation [32, 95]. The kinase Plk1 is known to be required for Aurora-A association with centrosomes, important during centrosome maturation [42, 61]. Overexpressed cytoplasmic hBora, found during Plk1 inhibition, was conjectured to titrate away Aurora-A from relevant substrates

necessary for spindle assembly, providing a separate means of controlling activity, and linking the function of Aurora-A with a second important mitotic kinase.

Arpc1b is another upstream activator of Aurora-A kinase, better known as a component of the Arp2/3 actin regulatory complex. Overexpression of Arpc1b leads to abnormal centrosomal amplification, while depletion of Arpc1b drastically reduced the ability of cells to enter the cell cycle; this was accompanied by failure to accumulate active Aurora-A at the centrosome at G2/M transition. Coupled in vitro experiments demonstrated Arpc1b interaction with the N-terminal domain of Aurora-A activated Aurora-A activity [96].

The centrosomal proteins CEP192 is also important for bipolar spindle assembly. Direct interactions between CEP192 and Aurora-A were shown to help concentrate Aurora-A at the centrosome, allowing the protein to form homodimers and homo-oligomers. This interaction supported Aurora-A activation and microtubule assembly, via a different mechanism from that described for TPX2 and the other activators [19].

As early as 1994, the activity of protein type 1 phosphatase was shown to oppose that of IPL1 kinase in mitosis [97], and IPL1 mutations found to be suppressed by overexpression of Glc8, an ortholog of phosphatase inhibitor 2 (I-2, Inh-2) [98]. In humans, protein phosphatase 1 (PP1) dephosphorylation of T288 limits Aurora-A activity [99], and I-2/Inh-2 opposes this activity [98]. The opposition involved direct binding of I-2/Inh-2 to Aurora-A, was not additive with TPX2 activation, and interestingly, did not involve increased activation-loop phosphorylation [98]. A subsequent evolutionary analysis of I-2/Inh-2 proteins demonstrated that vertebrate (human and Xenopus) but not *Drosophila*, *C. elegans*, or yeast orthologs of the group possessed this activation activity [60]. More recently, the protein phosphatase 6 (PP6) holoenzyme has been described as the major negative regulator of Aurora-A activation-loop phosphorylation, inhibiting stability of the Aurora-A/TPX2 complex [100].

Aurora-A interacts with nucleophosmin/B23 (NPM). Although NPM is best known as a nucleolar protein, it also accumulates with Aurora-A at the centrosome in G2 cells, and coimmunoprecipitates with the protein. Interestingly, although NPM strongly induces Aurora-A activity in in vitro kinase assays with canonical substrates, it neither induces T288 phosphorylation on Aurora-A, nor protects T288-phosphorylated Aurora-A from dephosphorylation by PP1 [101]. Instead, this activation was associated with and depends on S89-phosphorylation of Aurora-A. These data suggest a third, independent means of activating Aurora-A, together with the mechanisms associated with TPX2 and Cep192 (also see [102], and the discussion of Ca^{2+}/CaM, above, for a fourth mechanism that has been described in interphase cells); we note, recent work by Dodson and Bayliss also supports the idea of Aurora-A activation without obligate T288 phosphorylation [80].

Littlepage et al found that S349A-mutated *Xenopus* Aurora-A had modestly reduced kinase activity, but that a S349D phosphomimic completely blocked kinase activation [72]. Sarkissian et al extended this work, finding glycogen synthase kinase 3 (GSK3) phosphorylation of Aurora-A on S290/S291 subsequently induces Aurora-A autophosphorylation on S349, which is inhibitory [103]. S290 and 291 are just prior to T295 of the activation loop in Xenopus Aurora-A, while S349 is on the αG helix of the C-terminal domain (see below). The equivalent residues in human Aurora-A are S283, S284, T288 and S342. They also found that mutation of these sites to non-phosphorylatable alanines (S349A, S290A/S291A) results in a constitutively active form of the kinase. Interestingly, this group inspected immature versus matured Xenopus oocytes, and found that activity of Aurora-A correlated with loss of S349 phosphorylation, rather than changes in the level of T295 phosphorylation (equivalent to T288 in humans) [103].

Another Aurora-A binding protein, PUM2, has been identified as promoting in vitro activation of Aurora-A; to date, the mechanism of action involved is unknown [104]. Similarly, the Aurora-A partner and substrate RASSF1A activates Aurora-A through an undefined mechanism [105]. It is likely that there are additional regulators of Aurora-A activity that have not yet been defined. For example, recently Aurora-A was identified as proximal target of a mitotic checkpoint associated with Golgi fragmentation, which inhibited Aurora-A recruitment to centrosomes and Aurora-A activation [106], The molecular basis of this checkpoint requires further study.

Aurora-A degradation in late mitosis

Destruction of Aurora-A is also regulated via interactions with partner proteins (Table 1, Figure 2). Aurora-A is degraded by the proteasome at the end of mitosis [107–109], with inhibition of the proteasome in cycling cells leading to the accumulation of ubiquitinated forms of Aurora-A [107–109]. Aurora-A is targeted for proteasomal degradation via interaction with the anaphase promoting complex/cyclosome (APC/C, [110]), and particularly with phosphorylation- and protein partner-controlled association with the APC/C co-activator subunits, Cdc20 and Cdh1 [111]. Aurora-A kinase contains two different sequences, an A-box and a D-box, that must both be present for Cdh1-dependent protein destruction. The N-terminal A-box (residues 47–59, in Xenopus) encompasses short sequence, Q^{47}RILGPSNVPQRV, which is highly conserved in vertebrate forms of Aurora-A (hence the name). The A-box is contained in the N-terminal disordered region of Xenopus Aurora-A (residues 1–128). The E3 ubiquitin ligase Chfr (checkpoint protein with forkhead and ring domain) directly targets Aurora-A for ubiquitination and degradation, interacting with an N-terminal region (res 1–61) containing the A-box [112]. This region also includes the Xenopus S53 (human S51), phosphorylated during mitosis. Although S53A mutation does not block destruction, an S53D phosphomimic mutation completely blocks Cdh1-induced destruction, results interpreted as suggesting that S53 phosphorylation might negatively regulate Aurora-A destruction until the last stages of mitotic exit [113]. In support of this idea, protein phosphatase 2A (PP2A) associates with Aurora-A at the spindle poles in mitosis, and dephosphorylates S51; inhibition of PP2A reduces the destruction of Aurora-A at the end of mitosis [77, 114]. The C-terminus of Aurora-A contains a functional destruction box (D-box, residues 378–381) [111]. The translational regulator PUM2 binds to the D-box of Aurora-A, preventing its ubiquitination and enhancing protein stability [104]. Aurora-A also contains a KEN box (residues 6–9), which is known to be required for the degradation of other mitotic proteins (Nek2 and B99); however, this is not crucial for Aurora-A degradation [113, 115]. The USP2a (ubiquitin-specific cysteine protease 2a) stabilizes mitotic Aurora-A through the direct protein interaction of deubiquitination; it appears that multiple interaction motifs mediate the association of the two proteins. [116].

Other studies have indicated an additional, ubiquitin-independent pathway of Aurora-A degradation. Aurora-A kinase interacting protein 1 (AURKAIP1 or AIP), promotes degradation of Aurora-A in a proteasome-dependent but ubiquitin-independent manner [117]. AURKAIP1 acts upstream of antizyme 1 (Az1), a well-studied mediator of ubiquitin-independent protein degradation, and has been proposed to enhance the binding affinity of Az1 to Aurora-A to promote proteasomal targeting [118, 119]. AURKAIP1, Aurora-A, and GSK-3β colocalize at the spindle poles in metaphase. Further, depletion of AURKAIP1 stabilizes and activates Aurora-A in early mitotic phase, causing mitotic cell arrest. AURKAIP1 phosphorylation by GSK-3β decreases its ability to downregulate Aurora-A, suggesting GSK-3β positively regulates Aurora-A expression in early mitosis [120]. This opposes the effect of GSK-3β phosphorylation on Aurora-A discussed above, in which phosphorylation on S290/291 negatively regulates kinase activity [103], suggesting either a delicate and potentially dynamic balance between Aurora-A, AURKAIP1, and GSK-3β at

different phases of mitosis (or alternatively, differences between assay systems. GSK-3β also regulates the F-box protein FBXW7 to induce degradation of Aurora-A; this process is impaired in cancer, after loss of the tumor suppressor PTEN causes inhibition of AKT and GSK-3β [121].

IV. Non-mitotic activation and signaling of Aurora-A

While the main focus on Aurora-A has been its actions in mitosis or cancer, it is increasingly apparent that the protein has important functions in non-transformed, non-mitotic cells. Better-defined examples include influence on microtubule dynamics, cell migration, and polarity, particularly in the context of neurite extension [22, 26, 27, 122–126], induction of disassembly of cilia [127], and regulation of intracellular calcium signaling [128]. Given the elaborate spatial and temporal assembly of the Aurora-A activation machinery described above to support the high level and sustained activation of Aurora-A in mitosis, an important question linked to these observed non-mitotic activities is linked to activity control in the absence of the machinery. Although this field is much less mature, the emerging answers appear to indicate the existence of alternative means of Aurora-A activation [101, 102], and also to indicate that some Aurora-A activities may not depend on protein activity, as opposed to scaffolding function provided by inactive Aurora-A [129]. We note, there is very clear evidence for multiple additional activities of Aurora-A during interphase in cancer cell lines, generally in cases in which the protein is overexpressed. As it is not yet clear whether these activities occur in untransformed cells, albeit at lower levels, or are specific to the transformed environment, they are discussed in the following section on Aurora-A in cancer.

Aurora-A in microtubule dynamics and cell polarity control: emphasis on neurite extension

In interphase human cells, the majority of Aurora-A is localized to the centrosome, although a smaller pool of the protein is also found in the cytoplasm and nucleus [124]. The centrosome nucleates microtubular networks throughout all phases of cell cycle, helping organize cell structure, polarity, and migration [92]. Chemical inhibition of Aurora-A in interphase mammalian cells significantly disrupts interphase microtubule dynamics, suggesting at least some of the protein is in an active form and in a non-centrosomal compartment [122]. It is also possible that the accumulating pool of inactive Aurora-A serves some functional role in regulating interphase microtubular dynamics; a kinase-independent stabilizing role for Aurora-A in stabilizing spindle microtubules was very recently reported for Aurora-A in *C. elegans* [129], but a possible similar function has not been investigated in interphase cells.

As noted above, studies of mitotic functions of Aurora-A demonstrated that Aurora-A bound and phosphorylated NDEL1 and TACC3 as part of the completion of centrosomal maturation, and that expression of an NDEL1 phosphorylation-mimetic can compensate for loss of Aurora-A activity in allowing mitotic entry [26]. In a fascinating extension of their initial work, Mori and coworkers pursued the observation that NDEL1 is an important binding partner of LIS1, the first gene identified as a target of mutation in the severe neuronal developmental disorder lissencephaly, to ask if Aurora-A might contribute to NDEL1 function in this second context [126]. This study found that Aurora-A was abundantly expressed in post-mitotic neurons, and was colocalized with and phosphorylated by atypical PKC (aPKC) on T287 of the activation loop, with this activating phosphorylation essential for the microtubule-dependent process of neurite extension (Figure 3A). Although the TPX2-Aurora-A interaction leading to T288-phosphorylation was observed in these cells, and collaborated with the aPKC-Aurora-A-NDEL1 pathway, the latter was particularly important for the microtubule reorganization that supported neurite elongation [126].

aPKC interacts with two partner proteins, Par-3 and Par-6, in an evolutionarily conserved complex that governs asymmetric cell division at mitosis and regulates cell polarity [123, 130]. Interestingly, Aurora-A had previously been defined as promoting aPKC activation in mitosis, with Aurora-A phosphorylation of Par-6 derepressing aPKC activity [6]. Activity of the PP2A protein phosphatase opposes this activation of aPKC in neuroblasts [130]; studies of Aurora-A in mitotic cells demonstrated PP2A dephosphorylation of Aurora-A residue S51 promote Aurora-A degradation [114]. To date, the extent to which Aurora-A mitotic interactions with PP2A, Par-3, and Par-6 are maintained in post-mitotic functions such as neurite extension remains relatively unexplored; however, given recent identification of roles for Par-3 at the centrosome in the polarization of other post-mitotic populations, such as intestinal epithelial cells [131], it seems likely that this is a fertile area for investigation.

Aurora-A in ciliary disassembly, calcium regulation, and PKD

One of the more surprising activities to emerge recently for Aurora-A was based on genetic studies of a very distant Aurora-A ortholog, the CALK protein of the green algae *Chlamydomonas reinhardtii* [132, 133]. *Chlamydomonas* utilize organelles termed flagella for environmental sensing, mating responses, and movement, and resorb or shed flagella during mating response to pheromone and transient ionic shock, with CALK activated during and required for flagellar loss [133]. In mammals, most cells have a single, non-motile cilium – a structure paralogous to a flagellum – protruding as an antenna from the cell surface, acting as a receiver for mechanical and chemical cues from fluid flow or the extracellular matrix (Figure 3B). The cilia extends from a perimembrane basal body: this basal body differentiates from the centrosome in quiescent cells, but redifferentiates to a centrosome as cells return to cycle, paralleled by a cell cycle related protrusion and resorption cycle for cilia [134]. Defects in cilia are associated with numerous clinically important syndromes, with “ciliopathies” including polycystic kidney disease (PKD), nephronopthisis (NPHP), Joubert Syndrome (JS), Bardet-Biedl Syndrome (BBS), and others [29]. Signaling systems dependent on or influenced by intact cilia include Hedgehog, Notch, Wnt, Par3-aPKC, and PDGFa, and predictably, links are increasing between ciliary signaling defects and both developmental disorders and cancer.

In 2007, in studies modeled on those in *Chlamydomonas*, it was demonstrated that serum growth factors induce Aurora-A activation at the basal body of the cell cilium in non-cycling G0/G1 mammalian cells, with this activation necesssary and sufficient for ciliary resorption [127]. Activation of Aurora-A in ciliary resorption was preceded by and dependent on upregulation of its mitotic activating partner NEDD9. Both cilia and flagella are organized around a cytoskeletal core (the axoneme) composed of 9 microtubule doublets arranged in a ring; acetylation of the tubulin subunits stabilizes the axonemal structure [29]. During ciliary disassembly, Aurora-A specifically phosphorylated the tubulin deacetylase HDAC6, increasing in HDAC6 deacetylase activity. Inhibition of HDAC6 activity by the small molecule inhibitor tubacin or interference of HDAC6 by siRNA, in each case, resulted in cilium stabilization. Interestingly, HDAC6 has been reported to associate with PP1 [135], which binds microtubules and dephosphorylates and inactivates Aurora-A in pre-mitotic cells [99]. Similar feedback may limit Aurora-A activation in cilia. Pitchfork (PIFO) also localizes to the base of the cilia, and is required for Aurora-A activation during the disassembly process; as yet, the mechanism is not known [136].

Further work in *Chlamydomonas* has suggested increasing intraflagellar Ca^{2+} concentrations during the mating response [137], shortly before the activation of the CALK kinase, while a separate study indicated rapid spatiotemporal patterning of Ca^{2+} distribution as a critical signal for flagellar excision [138]. An indirect association between Aurora-A and Ca^{2+} in vertebrates was provided by an analysis of oocyte maturation in Xenopus, which indicated that inhibition of Ca^{2+} signaling led to eventual failure to accumulate and activate Aurora-A

[139]. In a direct investigation of a Ca^{2+}–Aurora-A interaction, Plotnikova et al demonstrated that numerous stimuli that transiently increase cytoplasmic Ca^{2+} (including arginine vasopressin (AVP), histamine, or thapsigargin) induce Aurora-A activation with extremely rapid kinetics. Ca^{2+}–induced Aurora-A activity peaked within 1 minute of stimulation, returned to baseline within 2–5 minutes, and depended on a direct interaction between the N-terminal unstructured domain of Aurora-A with Ca^{2+}/calmodulin (CaM) [102]. In vitro, incubation of Ca^{2+}/CaM with Aurora-A resulted in robust autophosphorylation of Aurora-A on S51 or S53, as well as additional phosphorylations on S66 or S67, and S98. The S51/S53 phosphorylation is suggestive that this method of Aurora-A activation may also be relevant to mitotic activation of the kinase [102], discussed below, and to the activation of the protein in post-mitotic neurons.

These studies had been performed in renal cells because of the previously defined critical interaction between cilia, Aurora-A, and the function of the heterodimeric complex between polycystins 1 and 2, encoded by the PKD1 and PKD2 genes, which serves as a cilia-localized transmembrane Ca^{2+} channel: mutations in these genes are responsible for the most clinically prevalent of the ciliopathies, PKD [140]. Plotnikova et al determined that Aurora-A is abundant and active in a subset of normal, quiescent renal cells, is overexpressed and hyperactivated in human PKD specimens [102]. Moreover, in reciprocal action, Aurora-A bound and phosphorylated the polycystin 2/PKD2 protein, limiting PKD2 activity during rapid Ca^{2+} signaling responses [128]. These findings suggest Aurora-A activity changes may be relevant to the pathology of PKD.

V. Aurora-A protein structure

Human Aurora-A is a protein of 403 amino acids, with a canonical kinase domain comprising residues 133 to 383. The first experimental structure of Aurora-A was determined in 2002 (PDB entry 1MQ4) [141], and still remains the highest-resolution crystal structure of the human kinase. There are now 57 crystal structures of human Aurora-A in complex with ATP, ADP, ANP (an analog of ATP), and various inhibitors. Three of these structures are in complex with the Aurora-A binding activator protein TPX2 [142–144]. In addition, there are 8 structures of mouse Aurora-A, and 5 structures of *Xenopus laevis* Aurora B. The majority of human Aurora-A structures contain coordinates only for residues 127–388, regardless of whether the proteins crystallized were longer on either or both ends. The first 123 amino acids of Aurora-A is predicted to be intrinsically disordered, as are the C-terminal 16 amino acids acids [145]. The experimental structures confirm the disorder predictions, since even in those structures of protein constructs consisting of residues 100–403, the first ordered residue in any structure is S123 and the last ordered residue is Q394.

The Aurora-A kinase domain shares the common structural features of other protein kinases. The N-terminal part of this domain consists of a five-stranded β-sheet and an α-helix termed the “C-helix”; Aurora-A also has a short α-helix called the “B-helix”, seen in some kinases, that is just prior and perpendicular to the C-helix. The C-terminal part of the kinase domain consists of seven α-helices and a two-stranded β-sheet, and contains the catalytic aspartic acid of the HRD motif (sequence His-Arg-Asp at positions 254–256) and the mobile activation loop, whose position and conformation determine whether a kinase is active or inactive. The Aurora-A activation loop spans residues 274 to 299, beginning with a DFG sequence motif and ending with an APE motif (sequence PPE in Aurora-A). Active forms of Aurora-A are phosphorylated on T287 and T288 by PAK [73] and PKA [109], and on T287 by atypical protein kinase C [126].

A given kinase may have many different conformations depending on the binding of activators or inhibitors and phosphorylation of various sites. These conformations vary

primarily in the position of the activation loop as well as the position of the C-helix or the entire N-terminal domain relative to the C-terminal domain. Kornev and Taylor have recently provided an analysis of protein kinases in terms of two "spines" of interacting residues that span the two domains [146]. These spine residues are not contiguous in sequence but form stacks of contacts in active kinases that are disrupted in inactive or inhibited kinases. We have identified the spine residues in Aurora-A structures using sequence and structure alignments of Aurora-A to PKA, based on a detailed analysis of PKA by Kornev and Taylor [146]. The so-called regulatory spine consists of Q185, L196, H254 (of the HRD motif), and F275 (of the DFG motif). These residues correspond to PKA residues L95, L95, Y164, and F185. The catalytic spine consists of V147, A160, V218, L262, L263, L264, L318, and F322 (corresponding to PKA residues V57, A70, M128, L172, L173, L174, L227, and M231 respectively).

The integrity of the regulatory spine is dependent on the position of the DFG motif, such that in an active kinase, the F275 residue of DFG points into the kinase domain and sits under the C-helix. Twenty-nine Aurora-A structures contain this motif in this so-called "DFGin" position. As discussed below, Aurora-A is activated by phosphorylation and by binding of the mitotic spindle protein TPX2 [78]. There are three structures of Aurora-A with TPX2 bound (PDB entries 1OL5, 3E5A, and 3HA6), and only one of these has ADP bound (1OL5) [142], while the other two contain small molecule inhibitors. An image of active Aurora-A kinase with ADP and TPX2 is shown in Figure 4A. A closeup of the active site residues is shown in Figure 4B. This structure is phosphorylated on T287 and T288 (marked "TPO" in the figures). Binding of TPX2 alters the conformation of the Aurora-A activation loop [142], bringing phosphorylated T288 into a position where it forms a salt-bridge with R255 of the HRD motif, forming an active kinase. In the absence of TPX2, pT288 faces out and the activation loop is more extended than it is in the TPX2-bound state. In addition, in the active conformation with TPX2 bound, the side chain of T292 forms a hydrogen bond with the active site D254 of the HRD motif. In other DFGin structures without TPX2, neither of these interactions is formed. As discussed above, the regulatory spine of Aurora-A kinase consists of H252, F275, Q185, and L196. In an active kinase, these residues form a column with each residue in the spine in contact with its neighbors. The van der Waals surfaces of these residues are shown in Figure 4B.

Most protein kinases exhibit an inactive conformation referred to as "DFGout." Looking at the active site as shown in Figure 4A,B, the Phe of DFG in DFGout structures sits underneath the ADP rather than under the C-helix. None of the Aurora-A kinase structures is in a DFGout conformation. Besides the DFGin conformations, many Aurora-A crystal structures contain an unusual conformation of the DFG loop, referred to by Dodson et al. as "DFGup" [141]. In the DFGup conformation, the F275 points upwards into the N-terminal domain and is wedged between the C-helix and the N-terminal domain β-sheet. A superposition of several DFGup structures of Aurora-A kinase is shown in Figure 4C. This position disrupts a salt bridge between K162 of the β-sheet and E181 of the C-helix that is formed in active Aurora-A, as are the equivalent residues in other kinases. Aurora-A kinase with the Aurora-specific inhibitor MLN8054 bound and a DFGup conformation of the activation loop is shown in Figure 4D.

Bibby et al. observed three somatic mutations of Aurora-A associated with cancer [147]. One of these, S155R, occurs in the interface between Aurora-A and TPX2. Mutation to Arg would disrupt this interaction by replacing a small polar residue with a large positively charged residue in the interface. This residue is shown in Figure 4A. A second somatic mutation is V174M occurs at the junction of the B-helix and the C-helix in the N-terminal domain. This mutation leads to constitutive activation of Aurora-A, probably by altering the interaction of the N and C terminal domains. This residue is also shown in Figure 4B.

As noted above, PAK1 phosphorylated S342 of human Aurora-A while mutation of the equivalent residue, S349, in Xenopus Aurora-A to Ala and Asp leads to less active and inactive kinase respectively. This serine residue is shown in Figure 4A in an active kinase structure. In this conformation, S342 forms a hydrogen bond to E302, which is in a segment just after the activation loop of Aurora-A (residues 274–299). Phosphorylation of S342 or mutation of S342 to Asp would be expected to break this interaction, potentially altering the conformation or dynamics of the activation loop. Phosphorylation may destabilize the conformation of the activation loop such that it may extend away from the kinase domain in a manner suitable for autophosphorylation in trans, thus leading to activation. Subsequent dephosphorylation of S342 may be required for an active monomeric kinase. Mutation to D242 would lead to permanent inactivation due to the repulsive interaction with E302. One recent report has identified a SUMOylation event on residue K249 of mouse Aurora-A (K258 in human Aurora A). Mutation of this residue to a non-SUMOylatable Arg results in defective and multipolar spindles, abnormal localization to the mitotic spindle, but normal kinase activity [70]. This residue (K258), shown in Figure 4B, is located two residues C-terminal of D256 of the HRD motif, and forms hydrogen bonds with the side chains of D256 and T292 of the activation loop.

VI. Aurora-A and cancer

Phenotype and mechanism

In 1998, two independent studies for the first time identified significant upregulation of Aurora-A as a common feature of multiple classes of common solid cancers, including colorectal, breast, ovarian, prostate, neuroblastoma and cervical, in both primary tumor tissue and cell lines [148, 149]. Aurora-A is situated on chromosome 20q13.2, a locus that is frequently amplified in solid tumors, accounting for some of the elevated expression. However, in some cases Aurora-A protein was increased in the absence of DNA rearrangements, based on changes of gene expression or protein stabilization. Aurora-A transcription is regulated by the ERK-responsive Ets pathway, by STAT5a, by estrogen/GATA3 [150, 151], by HIF1 [152], and by additional pathways that are frequently elevated in cancer (also see review in [153]). A number of Aurora-A interacting and/or activating proteins are themselves elevated in cancer, and through their enhanced interactions stabilize Aurora-A from protein degradation. Examples of these include NEDD9/HEF1 [21, 87], IQGAP1 [154], and TPX2 [76, 155]; as with Aurora-A, overexpression of each of these interactors is oncogenic. Conversely, some proteins known to take place in degradation of Aurora-A during cell cycle, such as Chfr, are commonly downregulated via promoter hypermethylation or other means in cancer [156].

The pathological function of Aurora-A has been frequently reviewed, and the protein has attracted much interest as a therapeutic target [10, 157–162]. There are a number of phenotypes consistently associated with Aurora-A overexpression. These include the presence of supernumerary centrosomes associated with multipolar spindles; aneuploidy; increased resistance to apoptosis; and deficient cell cycle checkpoint functions (Figure 5). A number of these phenotypes arise from the failure of cytokinesis in cells with overexpressed Aurora-A, resulting in initial accumulation of centrosomes [11, 149]. How Aurora-A mediates these effects involves altered interaction with numerous partners and substrates, although surprising, even over-expression of a kinase-dead form of Aurora-A can induce centrosomal amplification [11], indicating both that non-catalytic activities of the protein may be particularly important, and also that cancer treatment strategies based on inhibiting Aurora-A kinase activity may be problematic. Upon overexpression, Aurora-A is readily detected in cells in all stages of cell cycle, and in both cytoplasmic and nuclear compartments. Hence, a major and open question has been whether the predominant oncogenic activities of Aurora-A arise from newly acquired interactions with partners with

which it does not normally associate, or from constitutive, enforced interactions replacing normally transient or cyclical functions.

One early focus of attention has been the dialog between Aurora-A and loss of p53 in tumorigenesis. The aneuploidy associated with overexpression of Aurora-A (or of Aurora-A-stabilizing proteins such as NEDD9/HEF1) results in triggering of mitotic checkpoints and rapid clearance of a large part of the cell population due to subsequent apoptosis [11, 21, 92]. Loss of p53 eliminates these checkpoints, alleviating the clearance associated with Aurora-A overexpression [11]. In a model for mouse mammary tumors, Aurora-A was unable to induce tumorigenesis except in a p53-deficient background, because of the induction of cellular senescence and p16 expression [163]. Suggestively, genomic instability and supernumerary centrosomes also characterize the phenotype of cells or primary tumors that lack p53 [164, 165]. Subsequent work demonstrated that Aurora-A and p53 are involved in a tightly regulated negative feedback loop that is lost in cancer. Aurora-A phosphorylation of S315 on p53 increases MDM2-dependent degradation of p53 [166]. Reciprocally, interaction of the p53 with the Aurora-A A-box inhibits Aurora-A kinase activity and potential for transformation [167]. This homeostatic relationship is deregulated in cancer. p53+/− mice develop tumors with elevated Aurora-A levels, but tumors derived from p53−/− mice often have Aurora-A elevation in normal tissue, but gene deletion in lymphomas [168]. A genome-wide expression array screen of human breast tumors similarly indicated correlation of loss of p53 expression and Aurora-A mRNA levels [168]. As one explanation for this functional interaction, loss of p53 in tumors is also associated with loss of heterozygosity (LOH) or mutation of the FBXW7/Cdc4 gene, encoding a ubiquitin ligase that degrades Aurora-A [168, 169]. Latent infection with Kaposi's sarcoma herpesvirus (KSHV) is predisposing for cancer. KSHV encodes a latency-associated nuclear antigen (LANA) that induces Aurora-A transcription; the elevated Aurora-A causes phosphorylation of p53 on S315 and a second residue, S215, creating a binding site for a cellular ubitiquitin ligase complex that degrades p53 [170, 171]. Elevated Aurora-A in tumors also targets the inactivation of the p53-related protein p73, contributing to the loss of mitotic checkpoint by disrupting the CDC20-MAD2 complex, and promoting apoptosis resistance [172].

Overexpressed Aurora-A also influences the activity of numerous transcription factors relevant for cancer progression, binding and promoting degradation of the AP-2α tumor suppressor [173], and phosphorylating S32 and S36 of IκBα, leading to degradation of this protein [174] [175]. Loss of IκBα activates its partner, the transcription factor NF-κB, which has wide action in promoting tumor growth and survival. Aurora-A phosphorylation also activates the prosurvival kinase AKT [176], and potentiates the signaling of oncogenic Ras by activating its interphase effector RALA [177, 178]. Figure 6 is a current summary of proteins known to interact with Aurora-A either directly (physically) or functionally; there are almost certainly more that have not yet been determined. In addition, two recent extensive peptide scanning and phosphoproteomics studies have both refined understanding of previously defined Aurora-A targets, and identified still more candidates for Aurora-A regulation [86, 91]. For each, increased Aurora-A action in cancer has the potential to alter functionality.

Predictive value of Aurora-A amplification and overexpression

For effective clinical management of cancer, one goal has been to better understand how presence of Aurora-A amplification and/or overexpression impacts the likely course of the disease: whether it predicts greater or lesser aggression, or response to specific classes of drugs. At present, the scientific literature tends to associate elevated Aurora-A expression with a poorer outcome in tumors, although some studies contradict the trend. Particularly in cases in which Aurora-A levels are increased based on genomic amplification, it is difficult to conclusively assign results to contributions of Aurora-A, in part because the Aurora-A

amplicon on chromosome 20 frequently causes the enhanced expression of multiple. We here summarize a number of studies regarding Aurora-A and prognosis in several common cancers.

Increased Aurora-A DNA copy number or chromosome 20 aneuploidy are common in ovarian cancer [179–181]. Six clinical studies of Aurora-A reported various conclusions on prognosis [182–187]. For instance, Lassmann et al have shown that high Aurora-A expression is associated with improved overall survival in patients with stage III ovarian cancer receiving taxol/carboplatin therapy, but significantly worse survival in patients who received the carboplatin-based treatment without taxol [186]. A second group found increased overall and progression-free survival (PFS) in patients with Aurora-A positive tumors in comparison with the patients whose tumors did not express Aurora-A [187]. In contrast, Kulkarni et al found that expression of Aurora-A strongly predicted shorter disease-free survival in early stage ovarian carcinomas, but not in advanced stage tumors; three other groups also correlated high expression with aggressive disease and poor outcome [183–185]. Interestingly, some recent work has identified a negative correlation between expression of BRCA2 and Aurora-A that more strongly predicts prognosis in patients with ovarian cancer. In these studies, the nuclear accumulation of BRCA2 was significantly associated with good overall survival and disease-free survival in patients with high-grade ovarian carcinoma, whereas strong expression of Aurora-A was significantly associated with poor outcome [188, 189].

Increased copy number of Aurora-A is often associated with progression from a colonic polyp to an invasive malignancy in colon cancer [190], and is one of the most common copy number alterations in cancer. A number of genes involved in cell cycle regulation are part of Aurora-A amplicon including TPX2 [191]: overexpression of Aurora-A and TPX2 correlated by immunohistochemistry. In a multivariate analysis, Aurora-A protein overexpression was associated with chromosomal instability (identified as loss of heterozygosity in 2p, 5q, 17q and 18q) but did not correlate with clinical outcomes [192]. In a second study, higher Aurora-A expression was associated with recurrence in stage II and III in a large, homogenous cohort of colon cancer patients [193]. In a third study, Aurora-A was most commonly detected in well or moderately differentiated, versus poorly differentiated tumors [194]. In another study, elevated Aurora-A copy number correlated with increased PFS and overall survival, but only in the context of a wild type Ras allele [195]. An Aurora-A F31I polymorphism is associated with increased aneuploidy in colon tumors, and has been described as a low penetrance cancer susceptibility allele affecting multiple cancer types [196, 197]. A rare S155R somatic mutation associated with colon cancer has been suggested to promote aneuploidy by reducing the interactions between Aurora-A and TPX2 [147].

High expression of Aurora-A overexpression is very strongly linked to decreased survival in primary breast tumors, and associated with high expression of HER2 and progesterone receptor [198]. Correlated expression of Aurora-A, PR, and estrogen receptor (PR) was found in an independent study [184]. In investigations of the codon 31 polymorphism, the F/I and I/I genotypes were associated with increased risk of breast cancer, particularly in overweight women; in analysis of a second polymorphism, V57I, the 57V allele was associated with an increased risk of invasive breast cancer [199–201]. Overexpression of Aurora-A localized to the perimembrane compartment was associated with decreased 5-year survival in non-small cell lung cancer (NSCLC) was associated with poor survival prognosis [202]. Aurora-A mRNA and protein are overexpressed in poorly or moderately differentiated lung cancer [203]. In lung cancer, a large case control study of codon 31 polymorphisms found that the I/I genotype reduced odds for lung cancer, but only in men [204]. A novel protein, SLAN (suppressed in lung cancer), has recently been identified as

binding and inactivating Aurora-A, and is frequently down-regulated in lung cancer tissues overexpressing Aurora-A; prognostic value of SLAN expression is not known [205]. Patients with head and neck carcinoma and elevated Aurora-A mRNA had a shorter disease-free and overall survival [206].

VII. Aurora-A Inhibitors in the clinic

Based on the information summarized above, Aurora-A has been of high interest as a drug target, with drug development and assessment effort much reviewed (e.g. [158, 207]). Numerous candidate drugs have undergone preclinical testing in vitro and in animal models. As of 2012, compounds that had made it through pre-clinical testing into Phase I or II trials include MK-0457 and MK-5108 (Merck), AZD1152 (Astra Zeneca), AT9283 (Astex Therapeutics), PF-03814735 (Pfizer), AS703569 (EMD Serono), PHA-739358 (Nerviano), and MLN8054 and MLN8237 (Millennium). Many of these compounds have activity against multiple structurally related kinases including ABL, SRC, JAK2, VEGFR2, FLT3, and FGFR1, which has influenced the clinical development of these drugs towards certain tumor types with relevance to their off-target activity. For example, one such application has been in chronic myeloid leukemia (CML) where inhibitors of Aurora kinase have been active against ABL kinase with a T315I resistance mutation [208].

Overall, the clinical testing of Aurora kinase inhibitors has so far produced little evidence for anti-cancer activity in a broad range of hematological and solid tumors primarily seen as disease stabilization in a minority of patients. For example, a selective orally administered inhibitor of Aurora-A kinase, MLN8054, has recently completed three Phase I studies which identified useful clinical biomarkers coupled with promising early indications of antitumor activity measured by durable partial or minor responses [209–211]. A number of phase II trials are ongoing using a second-generation related compound, MLN8237 (ClinicalTrials.gov identifiers NCT00830518, NCT00500903, NCT01091428, and others). Toxicities consisted mainly of reversible neutropenia along with mucositis and somnolence, with neutropenia as the dose-limiting toxicity The predominant toxicities of MLN8237 reflect the mechanism of action in highly proliferating tissues (bone marrow, GI epithelium, and hair follicles). The somnolence was unexpected, and remains unexplained; it is interesting to speculate that the recently detected interphase activities of Aurora-A in regulation of Ca^{2+} signaling, cilia, and in the function of post-mitotic neurons may be relevant.

The reasons for the overall modest clinical effect are also unclear, and contrast sharply with the results obtained in cell lines and xenografts discussed above. One possibility for such discrepancy might be the existence of redundant signaling pathways in tumor cells allowing for bypass signaling (i.e., drug-selected activation of Aurora-A partners or effectors) to drive cellular proliferation despite the blockade of Aurora-A kinase. In a large-scale screen in breast cancer cell lines, high Aurora-A copy number conferred resistance to GSK1070916, an inhibitor of Aurora-B/C [212], thus suggesting a bypass mechanism between functionally related Aurora-A paralogs. Practical considerations in regard to allowable dose and schedule of drug administration may also play a role in limiting efficacy; significant neutropenia is the main dose-limiting toxicity of Aurora inhibition, thus preventing prolonged Aurora-A signaling inhibition. Dose-escalation studies [213] demonstrated a trend toward higher anti-tumor activity when neutropenia was prevented by administration of growth factors.

In spite of all the biological properties discussed above, it remains unresolved if Aurora kinase A is a true oncogenic driver in human cancers. As noted above, the Aurora-A locus at 20q13 is frequently amplified as part of large chromosomal amplicons, or even the entire arm or chromosome copy number is increased. The relationship of the Aurora copy number,

its kinase activity to the sensitivity to its specific inhibitors is presently unknown. The Aurora gene copy number may have differential interaction with the treatment drugs. Suggestively, in some studies, a higher level of AURKA expression was noted in low-grade, less aggressive tumors [194, 208]. Alternatively, increased AURKA gene copy number may be an oncogenic driver, but simultaneously render cells more susceptible to chemotherapy due to enhancement of a "mutator phenotype" [214] associated with abnormal cell divisions and genomic instability in cells with hyperactive Aurora A kinase.

Abundant preclinical data provide support for combining Aurora-A inhibitors with a wide variety of existing agents targeting the Aurora-A partners and effectors discussed above, or with less specific anti-mitotic agents such as microtubular poisons or ionizing radiation [215]. For the last possibility, one rationale is based on the known activity of Aurora-A in enhancing tumor radioresistance [216] through p53 phosphorylation and increased Akt activity [166, 176]. In practice, inhibition of Aurora-A sensitizes cancer cells to radiation therapy (RT), even in tumors such as head and neck carcinomas that contain p53-inactivating mutations [158]. Moving further afield, we have previously identified synergy in combining inhibitors targeting Aurora-A and members of core proliferation and survival pathways such as EGFR [217] and SRC [218]; EGFR and SRC inhibition each independently enhance RT; future strategies may combine Aurora-A inhibition with EGFR inhibitors such as cetuximab or SRC inhibitors such as dasatinib to improve clinical efficacy. If there is one consistent lesson emerging from the field of systems biology, it is that inhibition of a single target, no matter how promising, is likely to be insufficient for cancer therapy except in the most unusual cases.

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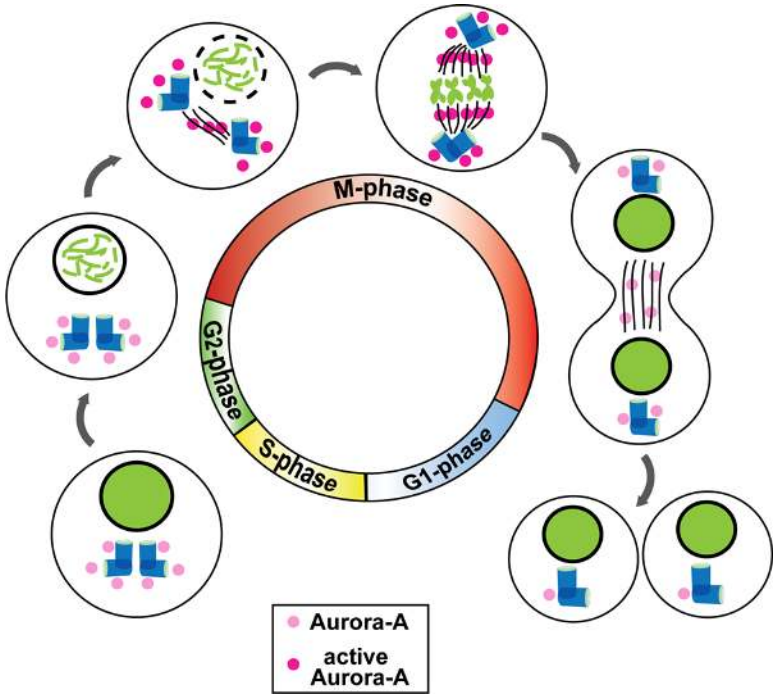

Figure 1. Aurora-A in cell cycle

Aurora-A begins to accumulate significantly at centrosomes in S phase, and is activated at the boundary between G2 and M phase. Active Aurora-A propagates along the mitotic spindle to the midzone, with most of the protein inactivated and degraded before cytokinesis, with only low levels detectable in early G1 cells.

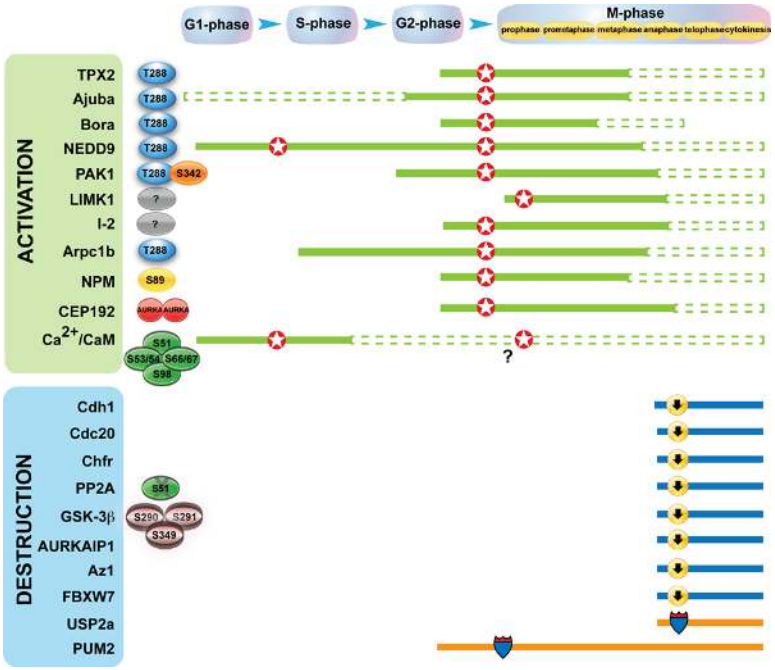

Figure 2. Aurora-A interaction with partners regulating activation and destruction

Proteins interacting with Aurora to promote activation (green line, star), promote destruction (blue line, arrow), or protect from destruction (orange line, shield) are indicated in context of phases of cell cycle in which they associate with Aurora-A. When interaction involves specific phosphorylations on Aurora-A, these are indicated in circle at left of drawing.

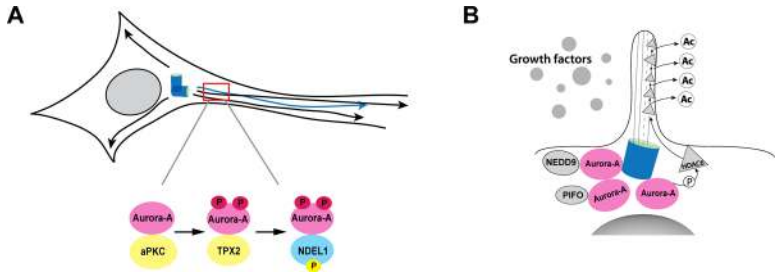

Figure 3. Active Aurora-A in non-cycling cells

A. aPKC activates Aurora-A, which interacts NDEL1 to induce microtubule-based extension of post-mitotic neurons. **B**. NEDD9 and PIFO activate Aurora-A at the basal body of cilia in quiescent cells, leading to Aurora-A dependent activation of HDAC6, and ciliary resorption.

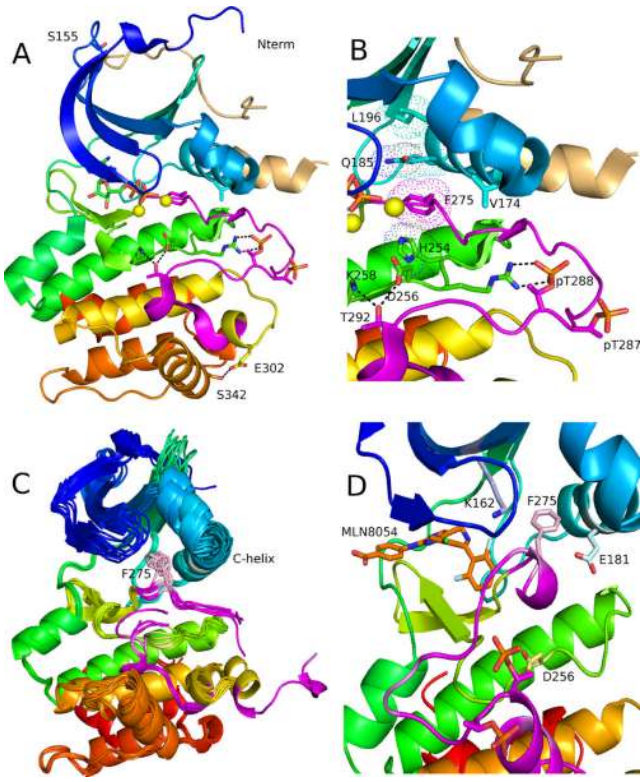

Figure 4.

A. Ribbon diagram of the ADP-bound structure of human Aurora A from PDB entry 1OL5. The chain is colored from blue (N-terminus) to red (C-terminus). The activation loop is shown in magenta and the activator TPX2 is colored beige. Aurora A in this structure is phosphorylated on T287 and T288, and the DFG motif at the beginning of the activation loop is in the "DFG-in" position, such that the F275 of the DFG motif (magenta sticks) is located under the C-helix (cyan). **B.** Close-up of the active site of Aurora A from PDB entry 1OL5. Hydrogen bonds are shown in dotted black lines between pT288 and R255 of the HRD motif, T292 of the activation loop and D256 of the HRD motif and K258. The yellow spheres are active site magnesium ions. The regulatory spine of Aurora-A is shown in dots (H254, F275, Q195, and L196). **C.** Several structures in the "DFGup" conformation are shown. F275 points upwards between the C-helix and the N-terminal domain β sheet. **D.** Compound MLN8054 bound to human Aurora A from PDB entry 2WTV. F275 of the DFG motif is in a "DFGup" position, disrupting the salt-bridge interaction between E181 and K162. The activation loop is in an inactive position, in contrast to the active position in A and B.

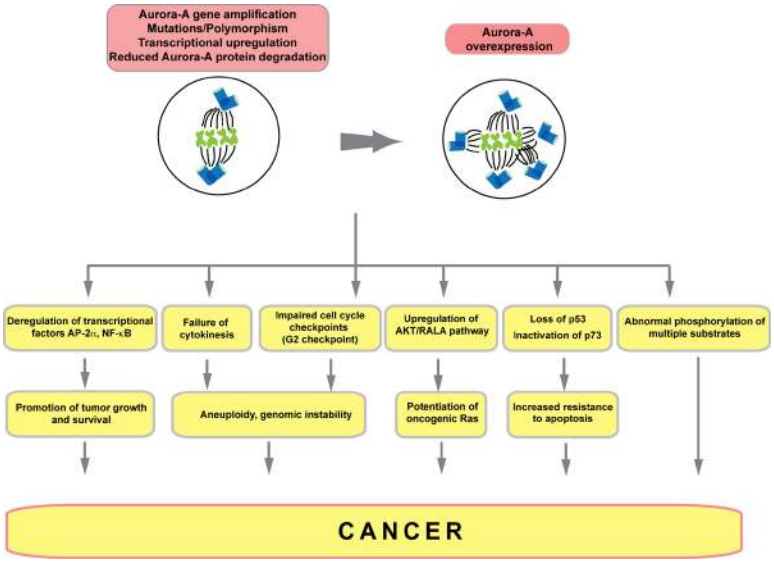

Figure 5. Aurora-A activities in cancer

Aurora-A expression is elevated based on changes in DNA copy number, transcription, and/or changes in protein stability. Overexpressed Aurora-A induces multiple categories of growth defect that promote cancer, outlined here schematically; see text for details.

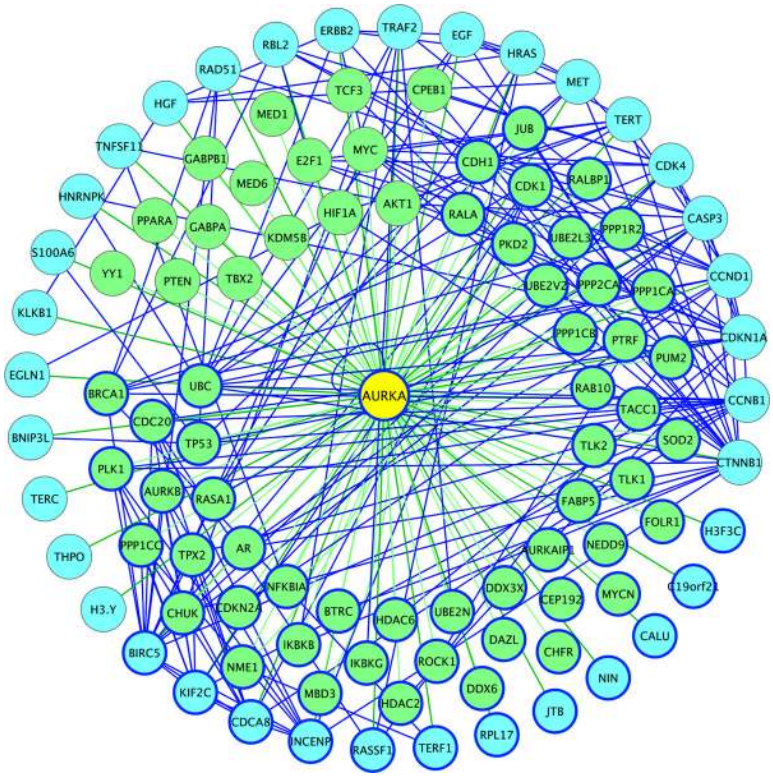

Figure 6. Extended Aurora-A interaction network

Schematic indicates proteins that known or highly likely to interact physically and/or functionally (indirect interaction) with Aurora-A/AURKA. All proteins are indicated by official gene symbol. Interaction data were collected using online databases String [229] (using medium confidence score 0.4 and excluding text mining-only results) and Ingenuity [http://www.ingenuity.com/] (extracting only experimental and high confidence predicted interactions). Data were imported, merged and visualized in Cytoscape [230]. Blue rim around protein indicates direct protein-protein interaction; lack of rim indicates indirect interaction. Green circles represent highly validated interactions generally reported in publications. Blue circles represent high confidence hits from larger screens, but are less well studied. Green lines indicate interactions with Aurora-A/AURKA; blue lines indicate interactions among proteins described as interacting with Aurora-A/AURKA.

Table 1

	Gene	Aurora-A phosphorylates	Phosphorylation on Aurora-A	Localization	Function
Activator	TPX2	ND	T288	centrosome	Activation of kinase acti targeting to microtubu
	Ajuba	ND	T288	centrosome	
	NEDD9(HEF1)	S296	T288	centrosome	Activation of kinase acti
	BORA		T288	cytoplasm	Activation
	Ca2+/Calmodulin		S51/S53/54/S66/67/S98	centrosome	Rapid activation
	Nucleophosmin B23(NPM)		S89	centrosome	Activation
	Phosphatase inhibitor (I-2)		T288 independent	centrosome	Activation
	Arpc1 b	T21	T288	centrosome	Activation
	PAK1		T288, S342	centrosome	Activation
Inhibitor	PP1		Dephosphorylate T288	?	
	p53			nucleus	
	Gadd45a				
Substrate	BRCA1	S308	-	centrosome	G2/M transition of cell c
	PLK1	T210		cytoplasm	
	CDC25B			cytoplasm	
	Centrin	S122/S170		centrosome	
	LATS2	S83	-	centrosome	
	TACC3 (human)	S34/S552/S558 (human)	-	centrosome	
	NDEL1	S251	-	centrosome	
	HDAC6	ND	-	Basal body of primary cilium	Activation of kinase acti
	Ski	ND	-	centrosome	?Mitosis ? oncogenic
	Hepatoma up-regulated protein (HURP)	S627/S725/S757/S830	-		Protein stabilization
	p53	S215/S315	-		Protein degradation
	PP1				
	TPX2	S48/S90/S94	T288	nucleus and mitotic spindle	
	Eg5		-	mitotic spindle	Centrosome maturation separation
	Histone H3	S10	-	chromosomes	
	CENP-A	S7	-	centosome	
	CENP-E	T422	-		
	CEP192		T295 (equivalent to T288 in humans)	centrosome	Activation Targeting to cent
	CPEB			cytoplasm	
	LIMK1	S307/T508	ND (not at T288)	centrosome	Activation
	LIMK2	S283/T494/T505		cytoplasm, nucleus	
	SRC	ND	ND	cytoplasm	Kinase activity enhancer

	Gene	Aurora-A phosphorylates	Phosphorylation on Aurora-A	Localization	Function
	AKT	S473	-	cytoplasm	Kinase activity enhancer
	IκBα	S32/S36	-	cytoplasm	Degradation
	Polycystin-2 (PC2)	S829		? ER, primary cilium ?	Negative regulation of pr function
Binding partners	TACC1			centrosome, spindle pole	
	Centrosomin (CNN)			spindle pole	
Destruction	Chfr			Spindle pole	Promotes Ubq-depende proteosomal degradati
	Protein phosphatase 2A (PP2A)	-	-	Spindle pole	Promotes Ubq-depende proteosomal degradati
	Cdh1			Spindle pole	Promotes Ubq-depende proteosomal degradati
	Cdc20			Spindle pole	Promotes Ubq-depende proteosomal degradati
	AURKAIP1 (AIP)	-	-	Spindle pole	Ubq-independent proteas dependent degradatio
	antizyme 1 (Az1)	-	-	Spindle pole	Ubq-independent proteas dependent degradatio
	GSK-3β	S245/S387	S290/S291/S349	Spindle pole	Promotes Ubq-independ proteasome dependent degr
	FBXW7	T217/E221 binding sites	-	Spindle pole	Promotes Ubq-independ proteasome dependent degr
	Fas-associated factor 1 (FAF1)	S289/S291		ND	Promotes Ubq-independ proteasome dependent degr
	PHLDA1	S98		cytoplasm	Promotes Ubq-dependent deg
	PUM2	-	-	centrosome	Protective against degrad
	Ubiquitin-specific cysteine protease 2a (USP2a)	-	-	centrosome	Inhibits degradation, deubiqu