Chapter 3

Regulation of Aurora Kinases and Their Activity

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Additional information is available at the end of the chapter

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Abstract

The three mitotic protein kinases Aurora-A, B and C are complementary enzymes that regulate multiple mitotic events. To do so, the different kinases must be locally activated, and the control of their activity is tightly regulated in time and space during mitosis. For instance, Aurora-A is first active at the centrosomes, then on microtubules at the spindle pole, Aurora-B is active in the nucleus, then at chromosome kinetochores and later one at the midbody. Aurora kinase activity is regulated in space and time by locally binding to regulators. Aurora kinases must bind to protein partners to be activated. Aurora-A for instance binds to targeting protein for *Xenopus* kinesin-like protein 2 (TPX2) and is activated at the spindle pole, Aurora-B and Aurora-C to INner CENtromer Protein (INCENP) and is activated on the chromosomes. These activations go through an autophosphorylation of a threonine residue in the T-loop of the kinase. Other protein partners are using different mechanisms to activate Auroras. These allow activation of the kinase at different time and location in the cell. This review is an up-to-date list of regulators of Aurora kinases. The subcellular localization of these regulators explains the presence of an active Aurora kinase. It also explains the changes in the localizations of the Aurora kinases activity observed during cell cycle progression in mitosis. Aurora kinases have been recently reported to be involved in nonmitotic events, and the identity of their activators in these events must be searched.

Keywords: Aurora kinase, regulation, posttranslational modification

1. Introduction

During the process of division, the cell goes through two main phases such as interphase and mitosis that is followed by the physical separation of the two daughter cells. During interphase, the cell duplicates its contents that will be segregated during mitosis to generate two daughter

cells. The whole process lasts about 24 h in the case of human cells during which mitosis takes only 1 h. This short phase is highly regulated by phosphorylation and dephosphorylation reactions [1]. Among the key protein kinases involved, there are cyclin-dependent kinase 1 (CDK1), polo-like kinase 1 (Plk1), NIMA-related kinase 2 (Nek2) and the Aurora kinases (Aurora-A, B and C) [2]. The three mitotic protein kinases Aurora-A, B and C are complementary enzymes that regulate multiple mitotic events [3].

During mitosis, the cell segregates its two centrosomes that migrate around the nucleus to reach opposite position. The nuclear membrane breaks down, and the chromatin starts to condense to form chromosomes. Microtubules nucleate from both the centrosomes and the chromosomes to form a bipolar spindle [4]. The force exerted by the spindle microtubules contributes to the alignment of chromosomes on the metaphase plate. This event is immediately followed by the separation of each pair of sister chromatids and the beginning of their migration to the two opposite poles of the cell. The last part of the migration is driven by the central spindle, assembled at the future site of cell division. A constriction ring is assembled around the cell at the exact same location that will contribute to the separation of two volumes corresponding to the two daughter cells [5]. The physical separation of the two cells, abscission, will occur later on during the following interphase.

Aurora-A localizes at both the centrosomes and the spindle poles. The kinase activity is required for microtubule nucleation during bipolar spindle assembly and during central spindle formation [6]. Aurora-B is part of the Chromosome Passenger Complex (CPC), it localizes at chromosome kinetochores from prophase to metaphase and at the midbody from anaphase to telophase [7]. Its kinase activity is responsible for the massive phosphorylation of the Ser10 of histone H3 in mitosis. Aurora-B corrects the wrong attachments of microtubules to kinetochores during prometaphase [8]. During exit from mitosis, Aurora-B is required for cytokinesis. Aurora-C that is mainly involved in meiosis can replace Aurora-B during mitosis [9].

In vitro, the three kinases share the same substrates, such as histone H3. *In vivo*, to fulfill their function, the three kinases are differentially localized and also locally activated, and the control of their activity is then tightly regulated in time and space during mitosis. For instance, Aurora-A is initially active in the cytoplasm and at the centrosomes in the end of G2, then on microtubules at the spindle pole during prometaphase. Aurora-B is active in the nucleus by the end of G2, then at chromosome kinetochores in prometaphase and later at the midbody during anaphase and telophase. To achieve such regulation in space and time Aurora kinases are locally activated by binding to activators.

2. Bipolar spindle assembly

2.1. Aurora-A and TPX2

Targeting protein for *Xenopus* kinesin-like protein 2 (TPX2) is the best-characterized Aurora-A activator. It is a 100-kDa protein expressed from G1/S transition to cytokinesis and then rapidly degraded [10, 11]. TPX2 was first identified as a binding partner of the plus end-directed

Xenopus kinesin-like protein 2 (Xklp2) [12]. TPX2 helps localizing Xklp2 to the spindle pole in prometaphase and metaphase [13, 14].

In interphase, from S to G2, TPX2 localizes to the nucleus where it is sequestered by importin alpha. In mitosis, TPX2 is released from the importin by RanGTP in the vicinity of the spindle. RanGTP produced by the chromosome protein RCC1 (RanGEF) is localized as a gradient around the chromosomes. It is only when the nuclear membrane breaks down that TPX2 can reach the centrosome to bind Aurora-A, to activate and re-localize Aurora-A protein on microtubules at the spindle pole [15–17].

The binding of TPX2 to Aurora-A induces a conformational change in the kinase in a way that the phosphorylated threonine of the activation loop (T288 in human) is better protected from phosphatase activity (PP1 in particular) [18]. Phosphorylation of T288 or binding to TPX2 triggers activation of Aurora-A activity independently, but both the events are synergistic [19]. Most importantly, because binding of TPX2 to Aurora-A changes the conformation of the kinase, it modifies the affinity of the substrates for the kinase as well as the affinity of kinase inhibitors [20].

2.2. Aurora-A and CEP192

Centrosomal protein of 192 kDa (Cep192) was named after a proteomic analysis of the centrosome composition [21]. Cep192 is a protein involved in centrosome maturation and bipolar spindle assembly [22]. These functions correspond to those described for Aurora-A [23, 24], and indeed, Cep192 activates Aurora-A at the centrosome to control mitotic spindle assembly [25]. The mechanism by which Cep192 activates Aurora-A is different from TPX2. Cep192 is a scaffold protein that brings together two molecules of Aurora-A. Within the dimer, each Aurora-A molecule phosphorylates its neighbor on T288, leading to the complete activation of the kinase. This activation takes place at the centrosome early in mitosis. Aurora-A is then presumably released from Cep192 to bind to TPX2 and to move on the spindle poles [25].

2.3. Aurora-A and Maskin/TACC3

Maskin is a *Xenopus laevis* protein that got its name by the fact that it regulates RNA translation. Maskin links the 5′cap and the 3′UTR of the mRNA, creating a closed structure that cannot be translated [26]. During *Xenopus laevis* oocyte maturation, phosphorylation of Maskin by Aurora-A is required for the control of sequential mRNA translation [27]. Maskin is not only a substrate of Aurora-A, but it is also an activator of its kinase activity as binding of Maskin to Aurora-A induces a sevenfold stimulation of its kinase activity [27]. Whether Maskin affects the phosphorylation of threonine in the activation loop of the kinase has not been investigated yet.

The human homologue of Maskin is transforming acidic coiled-coil containing protein 3 (TACC3) and D-TACC in *Drosophila melanogaster*. Phosphorylation of D-TACC or TACC3 by Aurora-A is required for its centrosome localization [28], microtubule nucleation during bipolar spindle assembly [29–31] and during central spindle assembly [32]. Conversely, the activation of Aurora-A by TACC3 or D-TACC has not been demonstrated yet.

2.4. Aurora-B and INCENP

INner CENtromer Protein (INCENP) participates to the chromosome passenger complex (CPC) together with Aurora-B, Survivin and Borealin [33]. The complex controls multiple events during mitosis: from chromosome condensation and segregation to cytokinesis [34]. Aurora-B is carrying the kinase catalytic activity of the CPC, while INCENP is the activator of the kinase.

Binding of INCENP to Aurora-B is essential to the function of the kinase such as chromosome segregation and cytokinesis [35, 36]. Just like binding to TPX2 triggers activation of Aurora-A through autophosphorylation of T288 in its activation loop, binding to INCENP triggers activation of Aurora-B through autophosphorylation of T232 in its activation loop [37, 38]. Both the kinases and the modes of activation are so closed that a single amino acid change (G198 to N) transforms the activator of Aurora-A from TPX2 to INCENP. The demonstration has been made in *Xenopus* [39] and human [40].

In term of evolution, it is striking to note that *Drosophila melanogaster* genome do not contain any gene coding for a TPX2. Ssp1/Mei-38 would be the closest TPX2-related protein in *Drosophila*. Ssp1/Mei-38 possesses a microtubule-binding domain but lacks the Aurora-A-binding domain, indicating that it cannot activate Aurora-A [41].

3. G2/M transition

3.1. Aurora-A and Ajuba

Ajuba means curiosity in Urdu, an Indian dialect. Ajuba is a LIM domain-containing protein that serves as a scaffold to build numerous protein complexes. The LIM domain is a Zinc finger structure [42]. Ajuba was first reported to bind to Aurora-A at the centrosome in late G2 and to trigger the kinase activation through autophosphorylation of T288. Ajuba would then participate to the activation of Aurora-A and the commitment to mitosis (**Figure 1**) [43] . It was also suggested that Ajuba interacts with the N-terminal domain of Aurora-A to release its inhibitory binding to the C-terminal catalytic domain of the kinase [43]. Aurora-A activation by Ajuba would be a two-step mechanism, binding to the N-terminal domain of the kinase and triggering autophosphorylation of T288 [44]. The activation of Aurora-A by Ajuba has not been observed In *Xenopus laevis* [45]. In *Drosophila melanogaster*, although Ajuba does not activate Aurora-A, the protein is necessary to maintain Aurora-A at the centrosome [46].

3.2. Aurora-A and Nucleophosmin

Nucleophosmin (NPM) is a nucleolar protein involved in multiple functions: histone chaperoning, ribosome biogenesis, mitotic spindle assembly, genome stability, apoptosis and cancer [47]. Like Aurora-A, NPM localizes to the centrosome where it is required for centrosome duplication [48]. Depletion of NPM leads to the formation of disorganized spindles, a phenotype observed after Aurora-A depletion [49]. NPM is also a strong interactor of Aurora-A, and

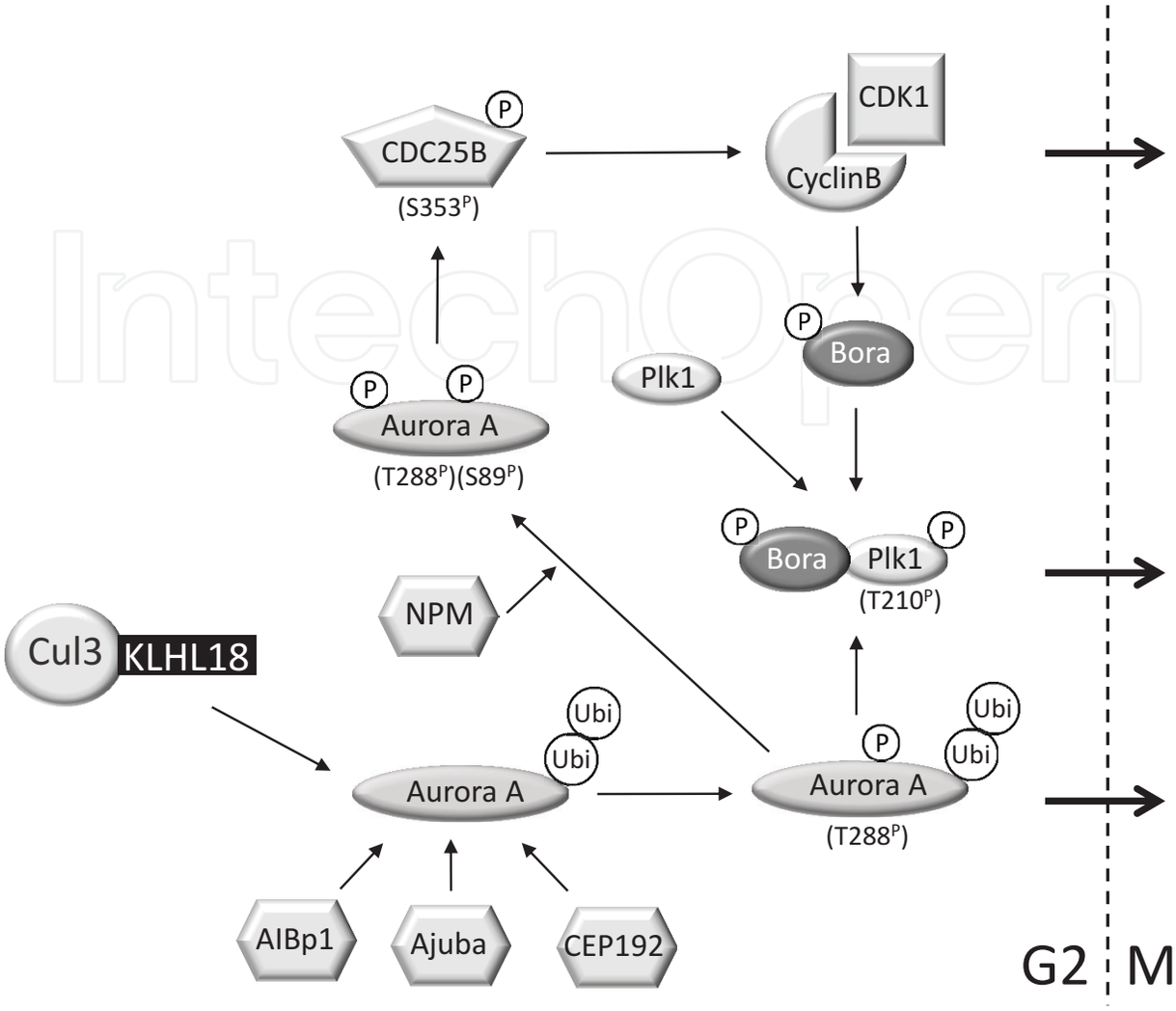

Figure 1. The three kinases CDK1/cyclinB, Plk1 and Aurora-A phosphorylate substrates required the G2/M transition. This scheme shows the pathways used by Aurora-A to activate Plk1 and CDK1/cyclinB.

both proteins interact at the centrosome late in G2. Binding of NPM triggers a phosphorylation event on the kinase. The active Aurora-A, already phosphorylated on T288, undergoes a second autophosphorylation on serine 89 which induces a very strong stimulation of its kinase activity [50]. This stimulation is required at the centrosome in particular for the phosphorylation of S353 on the phosphatase CDC25B involved in the activation of CDK1/cylin B for G2/M transition. Surprisingly, the stimulation of Aurora-A by NPM is not required for the phosphorylation of T210 that activates PLK1 in the end of G2 [50] (**Figure 1**).

3.3. Aurora-A and Bora

Bora was identified in a genetic screen setup to search for mutations affecting the development of *Drosophila melanogaster* external sensory (ES) organs [51]. The gene was named Bora for Aurora-A Borealis because the phenotypes of *Bora* and *Aurora-A* mutants were similar. Bora binds to Aurora-A *in vitro*, is phosphorylated but also activates the kinase in *Drosophila*

and human. *In vitro*, Bora can activate Aurora-A in the presence of PP1 (seven- to eightfold), suggesting that the mechanism used by Bora might be identical to TPX2 although it was not demonstrated that Bora triggers autophosphorylation of Aurora-A on threonine in the kinase activation loop [51]. However, when expressed at physiological levels, Bora does not co-immunoprecipitate with Aurora-A, and on the contrary, it immunoprecipitates with PLK1. Furthermore, depletion of Bora does not affect phosphorylation of T288 [52]. Eventually, it was demonstrated that Bora binds to the Polo-Box Domain of Plk1 (PBD) to relieve the auto-inhibition of PBD and to expose the T210 of the activation loop to Plk1-activating kinase. Aurora-A then binds to Bora, gets activated and activates Plk1 by phosphorylating T210 (**Figure 1**) [52, 53]. This activation of Plk1 by Aurora-A through the interaction with Bora occurs in G2.

3.4. Aurora-A and AlBp1

AIBp1 (AIK binding protein, AIK stands for Aurora/Ipl1-related kinase) is thus an Aurora-A binding protein but also a hNinein binding protein. Depletion of AIBp1 gives phenotypes typical of Aurora-A: bipolar mitotic spindle defects [54]. Binding of AIBp1 to Aurora-A increases its kinase activity *in vitro* [54]. *In vivo* expression of AIBp1 increases T288 phosphorylation on Aurora-A, whereas its depletion decreases T210 phosphorylation on Plk1 [55]. These data are reminiscent of the effect of Bora on both Aurora-A and Plk1 [52, 53]. It was then proposed that AIBp1 plays the same role as Bora but in a hNinein signaling pathway.

4. Actin network

4.1. Aurora-A and HEF-1/NEDD9/Cas-L

Human enhancer of filamentation 1 (HEF1) or neural precursor cell expressed, developmentally down-regulated 9 (NEDD9) or Crk-associated substrate related, lymphocyte-type (Cas-L) is a scaffolding protein that localizes to focal adhesions in interphase cells and to the mitotic spindle in M-phase. It participates in integrin-dependent signaling processes, such as cell attachments, cell migration and cell survival [56]. Cells depleted with HEF-1 show a decrease in T288 phosphorylation of Aurora-A, indicating that HEF-1 is required for activation of Aurora-A kinase *in vivo*. *In vitro* both proteins directly interact, and when increasing levels of HEF-1 are added to Aurora-A, an increase of T288 phosphorylation and its kinase activity are observed [57]. Interaction of HEF-1 with Aurora-A occurs in G2, during which the activation of Aurora-A by HEF-1 induces phosphorylation of HEF-1 and inhibition of the interaction. Interaction of HEF-1 with Aurora-A plays a critical role in primary cilia disassembly upon reentry in the cell cycle after Go arrest. In this particular case, HEF-1-activated Aurora-A phosphorylates and activates HDAC6, which in turn deacetylates the tubulin that is sufficient to provoke cilia resorption [58]. The activation of Aurora-A in the process of cilia disassembly is also dependent on Ca2+ and calmodulin (CaM) that are required for Aurora-A to bind to its activators [59].

4.2. Aurora-A and PAK-1

p21-Activated protein kinase-1 (PAK-1) regulates cell motility and morphology [60, 61] and is involved in focal adhesion disassembly through the PAK-PIX-GIT complex, PIX is a Rac

GTP exchange factor and GIT is a G-protein-coupled receptor kinase-interacting protein [62]. This complex is also active at the centrosome, and when Pak1 is activated it dissociâtes from the PIX-GIT to phosphorylate and activate Aurora-A [63]. The activation goes through phosphorylation of the T288 in the activation loop, but there was also a phosphorylation of S342 in the C terminal end of the kinase. Although T288 is known to be an activation site, S342 is rather known to inhibit Aurora-A kinase activity when phosphorylated. This has been shown in *Xenopus laevis* where the phosphorylation of S349 (human S342) downregulates Aurora-A *in vitro* [64] and *in vivo* during oocyte maturation between Metaphase I and Metaphase II of meiosis [65]. The same data have been reported in human where phosphorylation of S342 was observed in G2 upon DNA damage to inhibit Aurora-A, avoiding mitosis entry in the presence of lesions [66]. This discrepancy has not been solved yet.

4.3. Aurora-A and ILK

Integrin-linked kinase (ILK), like PKA-1, is a protein kinase involved in cell adhesion, and the kinase links the extracellular matrix to the actin cytoskeleton [67, 68]. ILK has also been observed in centrosome where it associates with TACC3/Ch-TOG, and its kinase activity is required for Aurora-A interaction with TACC3 [69]. ILK acts upstream of Aurora-A that in turn phosphorylates TACC3 on S558, to control microtubule nucleation [70, 71]. How ILK controls Aurora-A activity toward TACC3 is unknown.

4.4. Aurora-A and Arpc1b

Arpc1b is a component of the seven-subunit protein Arp2/3 complex involved in new actin filament nucleation and polymerization [72]. Arpc1b localizes on centrosome in G2 and interacts with Aurora-A only if Arpc1b has been previously phosphorylated on T21 by Pak-1. Arpc1b is also a substrate of Aurora-A, and the kinase phosphorylates wild-type Arpc1b but not the T21A mutant. This phosphorylation by Aurora-A is required for the interaction of Arpc1b with Arpc2 [73]. On the other hand, Arpc1b is an activator of Aurora-A *in vitro* and *in vivo*, and binding to Arpc1b triggers T288 autophosphorylation just like TPX2 does. Depletion of Arpc1b leads to a decrease on T288 as well as a decrease of its activity toward substrates such as PLK1 or histone H3 [73].

5. Ubiquitylation

Ubiquitination corresponds to a posttranslational modification (PTM) of proteins during which 76 amino-acid peptides are covalently linked to a protein, usually on lysine residues. It requires a multistep reaction: it needs 1) an E1 enzyme that will activate the ubiquitin, then 2) an E2 enzyme that will conjugate the ubiquitin and finally 3) an E3-ligase that will catalyze the transfer of ubiquitin peptide on the protein substrate [74].

5.1. Aurora-A and CUL3-KLHL18

The multiprotein complex E3 ubiquitin ligases of the cullin-RING-type ubiquitin ligase family include eight members in human. In the case of Cul3, the broad-complex, tramtrack and

bric-a-brac (BTB) domain-containing proteins like KLHL18 (*Kelch-like*) serve to recognize the ubiquitin substrate [75]. There are about 200 BTB proteins in human with various functions not all being Cul3 adaptors [76]. Cul3 and KLHL18 localize at the centrosome in late G2, and the depletion of each of the protein provokes a delay in the G2/M transition that has been attributed to a default in Aurora-A phosphorylation on T288 and consequently a default in the kinase activation at the centrosome [77]. The activation of Aurora-A by Cul3-KLHL18 involved a nonproteasomal ubiquitination of the kinase; however, the activation is not a direct effect of ubiquitination (**Figure 2**). Although the mechanism of activation is not fully understood, the hypothesis is that ubiquitination of Aurora-A could facilitate the interaction of the kinase with its activators in late G2, such as Ajuba or Cep192 for instance (**Figure 1**).

5.2. Aurora-B and CUL3-BTB proteins

Aurora-B unlike Aurora-A binds to three different BTB proteins KLHL9, KLHL13 and KLHL21, and all three substrate adaptors participate to Cul3 complexes that ubiquitinate Aurora-B *in vivo* and *in vitro* [78, 79]. Like for Aurora-A, the ubiquitination of Aurora-B does not lead to any degradation of the kinase, although depletion of Cul3, KLHL9 and KLHL13 mimics depletion of the 26S proteasome [78]. On the contrary, ubiquitination by Cul3-KLHL9, −KLHL13 or KLHL21 regulates the kinase localization during mitosis. In the absence of KLHL9 or KLHL13, instead of moving to the kinetochore region, Aurora-B remains on chromosome arms during

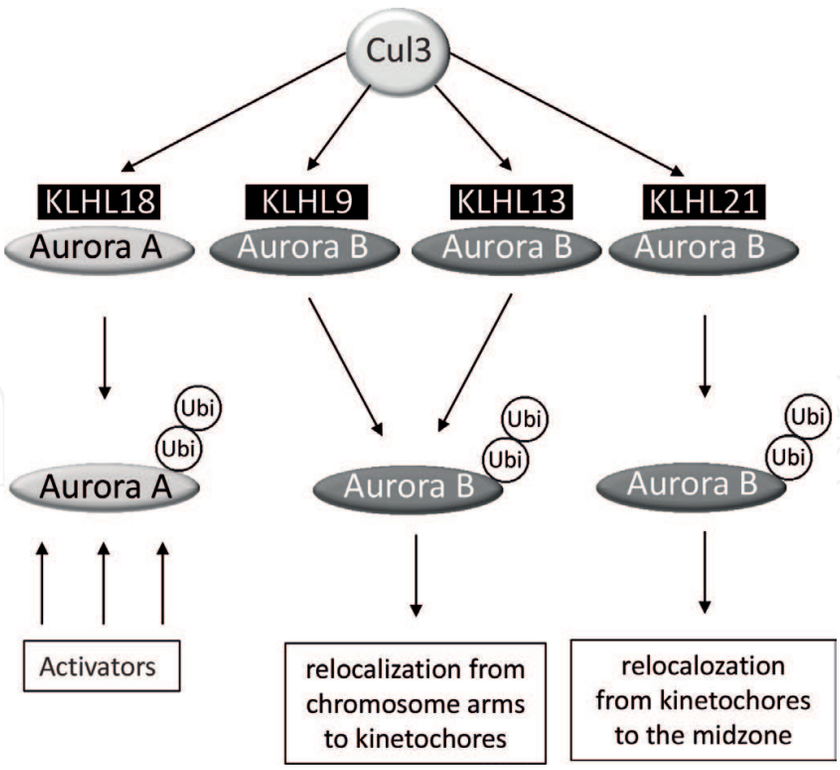

Figure 2. Cul3-dependent ubiquitination of Aurora kinases. Aurora-A is targeted by KLHL18, while Aurora-B by KLHL9, KLHL13 and KLHL21. Ubiquitination of Aurora-B localizes the protein, while ubiquitination of Aurora-A stimulates binding of the activators.

prometaphase/metaphase [78]. In the absence of KLHL21 instead of moving to the midzone, Aurora-B remains on anaphase chromosomes (**Figure 2**). In this last case, it is the whole CPC complex with Aurora-B, INCENP, Survivin and Borealin that remains on anaphase chromosomes [79].

Although KLHL9, KLHL13 and KLHL21 are substrate adaptors, their localizations do not really fit to their function. KLHL9 and KLHL13 have not been found on chromosomes for instance. On the other hand, KLHL21 does localize to the midzone where it could bring Cul3 to ubiquitinate Aurora-B, but even in this case KLHL21 should be at the kinetochore to ubiquitinate Aurora-B to target it to the midzone. The proposed hypothesis to explain this discrepancy is the high turnover of Aurora-B on its localization.

5.3. Aurora-A, Aurora-B and FBXW7

FBXW7 is an F-box protein participating to Skp, Cul1, F-box containing complex (SCF), a multiprotein E3 ubiquitin ligase complex that ubiquitinates proteins to be degraded by the proteasome. There are 69 F-box proteins coded by the human genome. Like KLHL proteins for Cul3, F-box proteins target the ubiquitin ligase complex to Cul1 substrates. FBXW7 binds to Aurora-A and Aurora-B and participates to their ubiquitination *in vivo* and *in vitro* [80, 81]. Depletions of FBXW7 stabilize both protein kinases levels *in vivo*, indicating that the FBXW7-dependent ubiquitination leads to the degradation of the kinases by the proteasome [81, 82]. F-box proteins usually recognize phosphorylated proteins, and FBXW7 for instance binds to Aurora-A previously phosphorylated by GSK3β on S245 and S387 [81] (**Figure 3**). Phosphorylation sites involved in Aurora-B/FBXW7 have not been identified, and the kinase involved is not known.

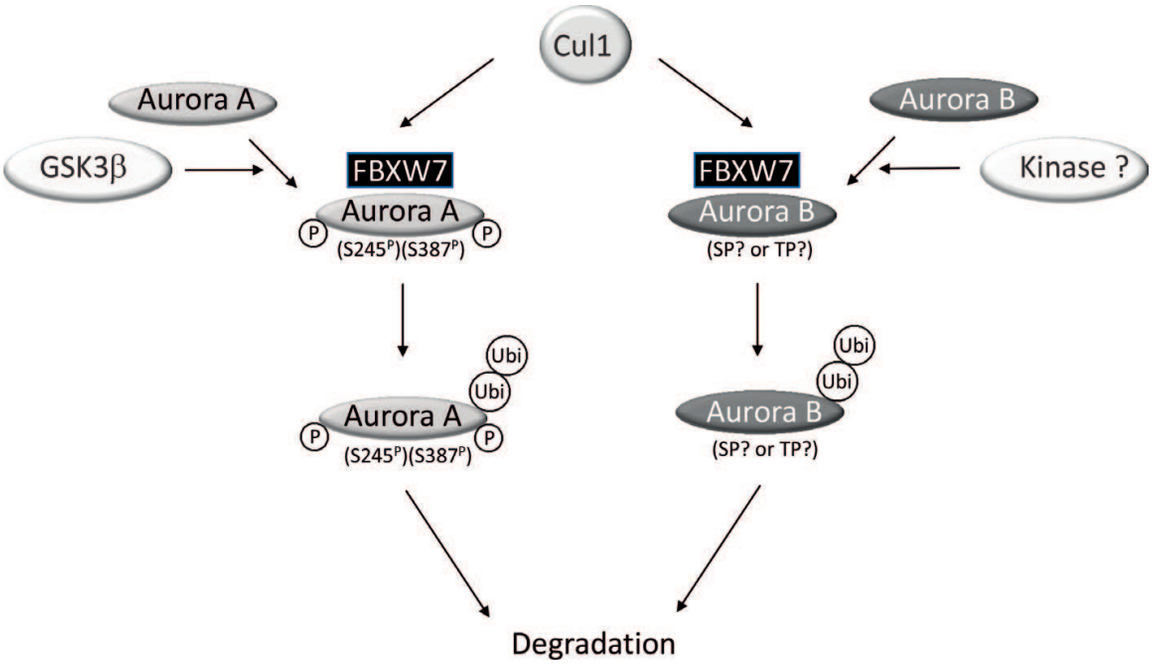

Figure 3. Cul1-dependent ubiquitination of Aurora kinases. Both Aurora-A and Aurora-B are targeted by FBXW7 F-box for ubiquitination. Aurora-A must be previously phosphorylated by GSK3β, while the kinase phosphorylating Aurora-B is unknown. Ubiquitination triggers degradation.

5.4. Aurora-A, Aurora-B and Cdh1

Cdc20-homologue 1 (Cdh1) is an activator and substrate adaptor of the E3 Ubiquitin ligase APC/C (Anaphase Promoting Complex/cyclostome). Cdh1 recognizes proteins containing a D-box (destruction box) (motif…RxxL…) and a KEN-box (motif …KEN…). All three Aurora kinases (A, B and C) contain a D-box in the carboxy end of the protein [83]. Both Aurora-A and B are ubiquitinated and degraded in a D-box-dependent manner [83, 84] although there are conflicting reports regarding Aurora-B [85]. Whether Aurora-C is degraded through its D-box remains also an open question. The Cdh1-dependent degradation of Aurora-A was demonstrated in both *Xenopus* and *human* [86, 87]. A new sequence required for the Cdh1-dependent degradation was discovered in Aurora-A from different species that was absent in Aurora-B and C. This sequence in the NH2 terminal end of the protein was named simultaneously A-box (for only in Aurora-A) [88] and DAD-box (for D-box-activating domain) (**Figure 4**) [89]. Interestingly, the A-box of Aurora-A contains a Serine at position 51 that when phosphorylated stabilizes the protein by inhibiting the functionality of the A-box [86, 90].

When tested in *Xenopus laevis* extracts Aurora-B was not found to be degraded in a Cdh1-dependent manner, it does contain a D-box but no A-Box, and only a chimera protein Aurora-A/Aurora-B containing Aurora-A A-box and Aurora-B D-box could be degraded in the extract [88, 89]. However, study in human finally revealed that Aurora-B contains also a functional D-box recognized by Cdh1 [84]. Interestingly, the same authors report that the KEN-box in

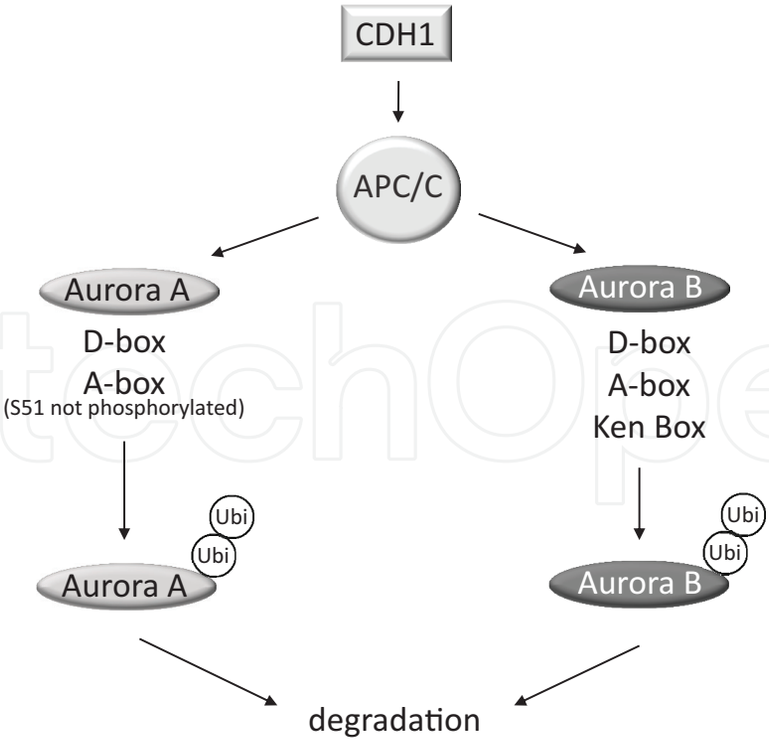

Figure 4. CDH1-dependent ubiquitination of Aurora kinases by APC/C. Both Aurora-A and Aurora-B are targeted by APC/C to be degraded. The ubiquitination required the presence A- and D-boxes in Aurora-A as well as the unphosphorylated state of S51 and the presence A- and D- and KEN-boxes in Aurora-B.

Aurora-B is required for Cdh1-dependent degradation. The discovery of a functional A-box in Aurora-B was more surprising, and since the box is not only present in Aurora-A, the name DAD-box seems now more adequate than A-box to name it. Finally, Aurora-B needs three functional boxes to be degraded in a Cdh1-dependent manner from the NH2 to the COOH end: a KEN-Box (KEN), an A-box (QRVL) and a D-box (RxxL) [85].

6. Sumoylation

Sumoylation resembles ubiquitination, and it is a posttranslational modification corresponding to a covalent attachment of a one or several SUMO proteins (100 amino acids) to a substrate. SUMOs stands for small ubiquitin-related modifiers, and there are now about ten different ubiquitin-like modifiers including ubiquitin and SUMO [91]. Like for ubiquitination, the sites of sumoylation are lysine residues, and the modification occurs also in a three-step reaction by E1, E2 and E3 ligases.

Both Aurora-A and Aurora-B are sumoylated *in vivo* on a lysine residue located in the sequence …IHDRIKPEN… conserved in all Aurora kinases [92, 93].

Aurora-A is sumoylated on K249, and expression of the Aurora-A mutant K249R that cannot be sumoylated affects spindle assembly and potentiates the oncogenic property of the kinase [93]. Aurora-B is sumoylated on lysine 207, and expression of the Aurora-B mutant K207R affects chromosome segregation and cytokinesis [92]. Interestingly enough, sumoylation of Aurora-A or Aurora-B does not affect the kinase activity in vitro indicating that sumoylation is probably playing required for the localization of the protein or for protein-protein interaction. The exact function of Aurora sumoylation remains to be found.

7. Poly(ADP-ribosyl)ation

Poly(ADP-ribosyl)ation (PARylation) is a covalent modification of protein that can be catalyzed by 16 different Poly(ADP-ribose) polymerases (PARP) that attach multiple ADP-ribose units on substrate proteins by hydrolyzing NAD+. The reverse reaction is insured by Poly(ADP-ribose) glycohydrolase (PARG) (three isoforms) and several ADP ribose hydrolases [94, 95]. Only Aurora-B is PARylated *in vivo*, and interestingly enough, the modification occurs in the presence of DNA damage [96]. PARylation of Aurora-B leads to a decrease of Serine 10 histone H3 phosphorylation, indicating a loss of Aurora-B kinase activity. The kinase directly interacts with PARP-1 and PARP-2, and both enzymes can PARylate Aurora-B and inhibit its activity [96].

8. Phosphorylation

Aurora kinases belong to a family of protein kinases that need to be phosphorylated on a threonine residue in its T-loop to be active [97]. Aurora-A must be phosphorylated on T288,

Aurora-B on T232 and Aurora-C on T198 and T202 [37, 98, 99]. These phosphorylations are autophosphorylation events that occur in the presence of an activator such as TPX2 for Aurora-A or INCENP for Aurora-B and C [16, 99]. Aurora-A has two other levels of regulation controlled by phosphorylation. The kinase activity can be upregulated by autophosphorylation of S89 in the presence of nucleophosmin, as described above [50]. Aurora-A can also be downregulated by phosphorylation of S342 [64]. *In vivo*, phosphorylation of S342 occurs in the presence of DNA damages during G2 and depends on the activation of the checkpoint kinase Chk1 [66, 100]. Is Aurora-A a direct target of Chk1 or the target of a kinase downstream of Chk1 remains an open question.

Since Aurora kinases are phosphorylated, they are obviously targeted by phosphatases. T288 in Aurora-A and T232 in Aurora-B for instance are dephosphorylated and inactivated by type 1 protein phosphatase [101, 102]. T288 is also dephosphorylated by PPP6 that specifically target Aurora-A when bound to TPX2 [103]. These dephosphorylations inactivated Aurora kinase activity.

As discussed above, Aurora-A degradation by APC/C-CDH1 depends on the presence of an A-box in the kinase and phosphorylation of S51 within the human A-box inhibits this degradation process [64]. Although the kinase responsible for this phosphorylation remains to be identified, the phosphatase PP2A insures its dephosphorylation [104].

9. Conclusion

Since their discovery, Aurora kinases have become priority targets for the development of inhibitors for cancer treatments [105]. But their regulation takes multiple forms, adding difficulties in developing the efficient drugs targeting the kinases. This review tends to report a nonexhaustive list of posttranslational modifications (PTMs) affecting the functions of the kinases. These PTMs can be used as biomarkers, like the phosphorylation of T288 in Aurora-A frequently used to measure the kinase activity *in vivo*, and this test is currently questioned [106]. More interestingly, these PTMs can be used to design original inhibitory strategies different from those targeting the kinase active site. The binding of TPX2 to Aurora-A for instance has been targeted to search for Aurora-A inhibitor [107]. This kind of approach targeting PTMs offers broad prospects for specific inhibition of Aurora kinases. Many new inhibitors should then be discovered in the coming years.

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