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Review Article

AURORA KINASES-THE KEY MITOTIC REGULATORS

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ABSTRACT

Aurora kinases have exploded on the scene in the past ten years, and are now recognized as leading players in the orchestration of mitotic events. Aurora-A kinases are particularly important for regulation of microtubule nucleation at spindle poles, and are subject to a complex network of controls that include phosphorylation, association with TPX2 and destruction by the APC/C. Aurora B kinases are essential for chromosome condensation, kinetochore function, cytokinesis and the proper function of the spindle-assembly checkpoint when spindle tension is perturbed.

Their regulation involves association with the chromosomal passenger proteins INCENP and survivin, which are important both for targeting and activation of the kinases. Little is known about Aurora-C kinases, which are expressed at high levels only in the testis, and comprise a particularly interesting subject for future studies.

The single Aurora kinases of the budding and fission yeasts are particularly important for kinetochore– microtubule attachments and spindle-assembly checkpoint function, which are activities that are most closely associated with Aurora-B kinases. However, in a study in which kinase domains were swapped, only the kinase domain of Aurora A and not that of Aurora B could substitute for Ipl1 in budding yeast, indicating that Ipl1 is probably required for both Aurora-A and -B functions. Adding to the interest in these kinases is the fact that Aurora kinase over expression has been observed in cancer, and Aurora A can function as a bonafide oncogene. Aurora-A has long been regarded as an oncogene, as a result of its over expression and amplification in several human cancers. Yet, Aurora-A is unlikely to be a bonafide oncoprotein, because of its over expression which neither transforms primary cells nor leads to tumour formation. Nonetheless, their powerful roles in cell cycle regulation and suitability for inhibition by small molecule antagonists make both Aurora-A and Aurora-B promising anti cancer therapy targets.

The Auroras are 'journeyman kinases' that travel from location to location in the cell to do their work. The auxiliary factors also provide rich targets for regulatory activities, and we predict that deciphering the regulation of their movements will prove to be essential for the complete understanding of Aurora kinase activity. Clearly much new territory remains to be explored in the world of Aurora kinases.

Keywords:

INTRODUCTION

Kinase enzymes that catalyze the reversible addition of phosphate groups to proteins are involved in many critical biological signalling pathways. The protein kinases [1], responsible for the phosphorylation of tyrosine, threonine and serine residues in other proteins. They are the most extensively studied gene families [2, 3].The seminal work of Manning *et al* had defined and categorized the human 'kinome' space which consists of 518 kinases. Multidisciplinary research involving biology, medicine, chemistry and informatics is rapidly advancing the need of the function, disease relevance, drug ability and inter-relationships of the kinases. [4-8].

On April 13, 2003 the human Genome Project announced the completion of the DNA reference sequence of Homo sapiens [9].This event as well as the advancements in biological testing and increased accessibility of X-ray structures[10] provide a unique opportunity to dramatically improve the understanding of kinase targets for drug development.

The human protein kinases may be broadly classified into two major families, the serine/theronine protein kinases and the tyrosine protein kinases according to substrate preferences. **(Fig.1)** Sequence analysis and comparisons have been used to further subdivide each major family into smaller subfamilies. [11]. Similarity of protein sequences has been used to establish the relationship of kinases within the super- family, which has facilitated the understanding of kinase properties using an intuitive graphical representation. [12].

In mammalian cells, Aurora has been classified into three related kinases known as Aurora-A, Aurora-B, and Aurora-C. These kinases are over expressed in a number of human cancers. The transfection studies have established Aurora-A as a bone fide oncogene [13, 14, and 15].The bonafide oncogene activity and the amplification of Aurora-A in tumours [16, 17] were also observed and it has been highlighted as a drug target [18].

AURORA BIOLOGY AND EVOLUTION

The auroras have been conserved throughout eukaryotic evolution and members of this family have been extensively studied in a range of different model organisms. Where as the genomes of budding and fission yeast only encode a single Aurora kinase, Ipl 1 and Ark 1 respectively, larger eukaryotes express two or more ---- three have been identified in mammalian cells. They are known by plethora of different names in the literature. (Table-1).But it has now been simplified with the agreement to designate the family members Aurora A, B and C [19].

The phylogenetic tree **(Fig2)** shows the relationship between the Aurora proteins from budding yeast (Ipl 1), fission yeast (Ark 1), *Caenorhabditis elegans* (Ce), *Drosophila melanogaster* (Dm)[19], *Xenopus laevis* (Xl), rat (Rn),mouse(Mm) and human(Hs).As expected,a branch separates the single fungal Auroras from those expressed by multi cellular animals. In addition, Aurora-A (red) and Aurora-B(green) from *C. elegans* and *Drosophila* form separate branches, indicates an ancient duplication event in early metazoans[20,21,22,23]. The vertebrate Auroras seem to have arisen from only one of this gene. As noticed the Xenopus Auroras diverge from their mammalian counterparts.

The Aurora-A paralogues is layed on a separate branch. The Aurora-B and-C (yellow) paralogues seem to share a more closely related ancestor. One explanation for these relationships is that although an ancient duplication event yielded two Aurora genes in animal cells, one of these was lost from the early vertebrate ancestor. The rests of the gene then duplicated, giving rise to the vertebrate Aurora-A and Aurora-B paralogues. Sometimes a duplication event might also have yielded Aurora-C. The high degree of similarity between Aurora-B

and –C in the carboxy terminal region indicates that a recombination event could have occurred between Aurora-B and Aurora-C.

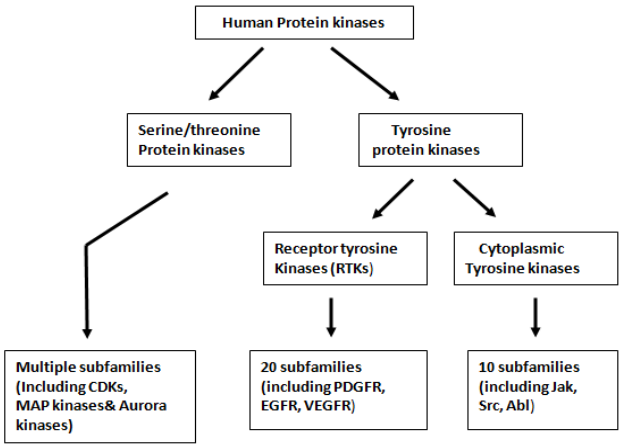

Fig. 1: Major families and subfamilies of human protein kinases.

INCENP, inner centromere protein; TACC 1, transforming acidic coiled-coil containing protein.

This phylogenetic analysis shows the relationships between the kinase domains of various aurora kinases. The diagram shows that the subfamilies A and B are very well defined in vertebrates, but the differences are not so obviously shown in invertebrates.

The three mammalian aurora paralogues are very similar in sequence. In particular within the carboxy-terminal catalytic domain, the human aurora A and B share 71% identity.

However, the three auroras differ in the length and sequence of the amino-terminal domain [24].The structure of the catalytic domain of human aurora A was recently solved [25, 26].The high degree of sequence similarity between human aurora A and B in this region is highlighted in **Fig 3**. The protein structure of the Aurora-A is based on a variable amino terminal regulatory domain, with three putative Aurora boxes (A-box I, II and III), and a conserved carboxyl terminal catalytic domain, with an activation motif and a destruction box [27].

The functional significance of the three A-boxes is not fully understood but there is some evidence that they may be related to sub cellular localization or substrate recognitions. Aurora-A is a serine–threonine kinase which requires phosphorylation in order to become activated. The presence of three phosphoric groups, respectively, at residues serine 51, threonine 288 and serine 342 of the activation motif is particularly important for the function of this kinase. The serine 51 residue is involved in controlling the timing of Aurora-A destruction process during mitotic exit while the threonine 288 is relevant for the kinase activity. The T288D mutation, in fact, which mimics a constitutive phosphorylation status, gives rise to the presence of a constitutively active Aurora kinase.

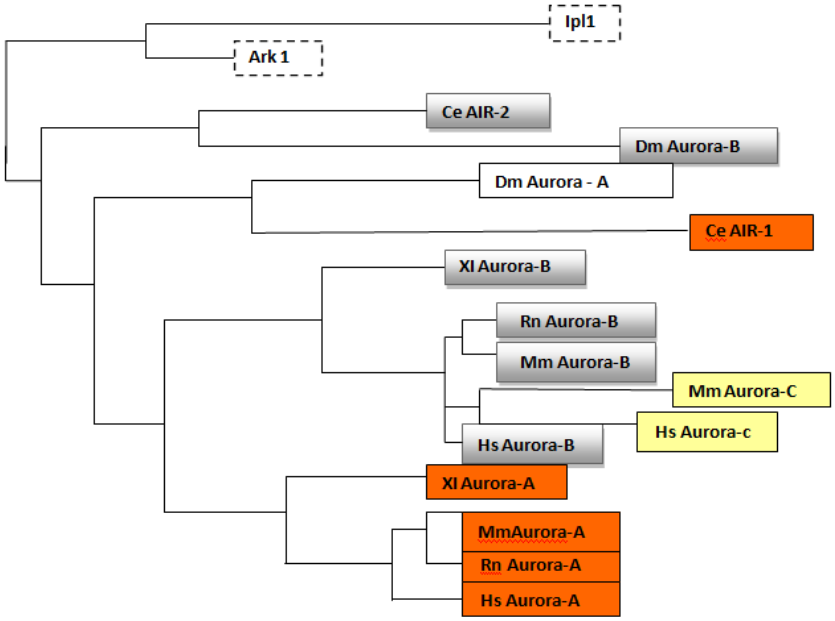

Fig. 2: The Phylogenetic Tree.

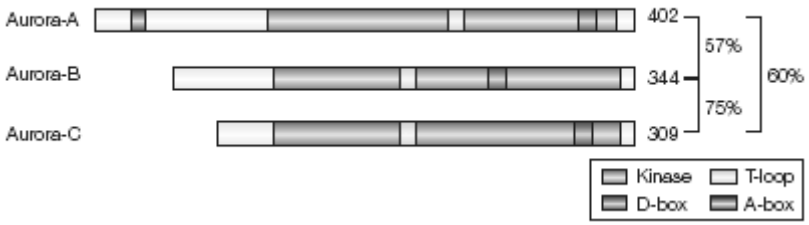

Fig. 3: Schematic representation of human Aurora-A, -B and -C.

The numbers on the right indicate their sizes in amino acids and their percentage sequence identities. Also shown are the relative positions of the catalytic kinase domains (green) and the activating T-loops (yellow). Two sequences in Aurora-A mediate its degradation at the end of mitosis — the destruction box (D-box, blue) and the D-box activating domain (DAD, or A-box, red). Although Aurora-B and -C have putative D-boxes, they lack A-boxes and their D-boxes are not targeted for proteolysis during mitotic exit. Figure modified from Ref. [3].

Source: http://www.medscape.com/viewarticle/495344_2

Finally, the serine 342 residue is principally involved in the maintenance of its conformational three-dimensional structure [27].Although the catalytic domains of the auroras are highly conserved, these proteins show different sub cellular localizations **(Fig: 4).**

Repression of Aurora-A expression by RNA interference (RNAi) delays mitotic entry in human cells [27] and over expression of the wild type kinase can compromise spindle- checkpoint function [28] as well as inhibit cytokinesis [29].Aurora-A is also involved in regulating meiotic maturation in *Xenopus oocytes*[30]. In contrast to aurora-A, aurora-B is a chromosomal passenger protein. It localizes to the centromeric regions of chromosomes in the early stages of mitosis. At the onset of ANAPHASE, aurora-B relocates from the centromeres to the microtubules that interdigitate at the spindle equator [31].This spindle elongates and the cell undergoes cytokinesis and aurora-B accumulates in the spindle midzone. The cell cortex at the site of cleavage furrow ingression before finally concentrating at the midbody.

Aurora-B kinases form a complex with two other proteins, inner centromere protein(INCENP) and surviving and behave as chromosomal passenger proteins[32].

Aurora-C is also a chromosomal passenger protein and co localizes with Aurora-B. Unlike Aurora-B, Aurora-C is specifically expressed in the testis where it functions in spermatogenesis and regulation of cilia and flagella. [33].Although Aurora-c has been shown to localize to spindle poles in late stages of mitosis [33], a recent report [34] indicates it is a chromosome passenger. The different localizations and functions of the three mammalian Aurora kinases are shown in **(fig: 5).**

AURORA A: the polar aurora

The main characteristic of the Aurora-A subfamily is its association with centrosomes and regions of microtubules that are proximal to the Centro some [35 and 36]. Aurora A associates with the centrosomes that are separating during late S/early G2. This localization is dynamic and the protein exchanges continuously with a cytoplasmic pool (FIG. 5); [37].

Low levels of Aurora A have also been reported on the spindle midzone and midbody late in mitosis [38, 39]. The association with the centrosome is directed independently both by the amino-terminal region and the carboxy-terminal catalytic domain, but does not require kinase activity [40, 41]. TPX2 (targeting protein for XKLP2), which has been implicated in Aurora-A activation is required for the localization of the kinase to spindle microtubules. This does not indulge to spindle poles [42]. Human Aurora-A is located at chromosome 20q13.2, which is commonly amplified in several tumoural tissues [43, 44].

The Aurora-A protein in mitotic events

During the late-G2 to M phase, the Aurora-A levels and kinase activity increase in order to be able to perform the role of 'guardian of the poles'. By means of the phosphorylation of different substrates, Aurora-A regulates the correct development of the various phases of mitosis, including centrosome maturation and separation, mitotic entry, bipolar spindle assembly, chromosome alignment on the metaphase plate and cytokinesis [45] **(Fig 6).**

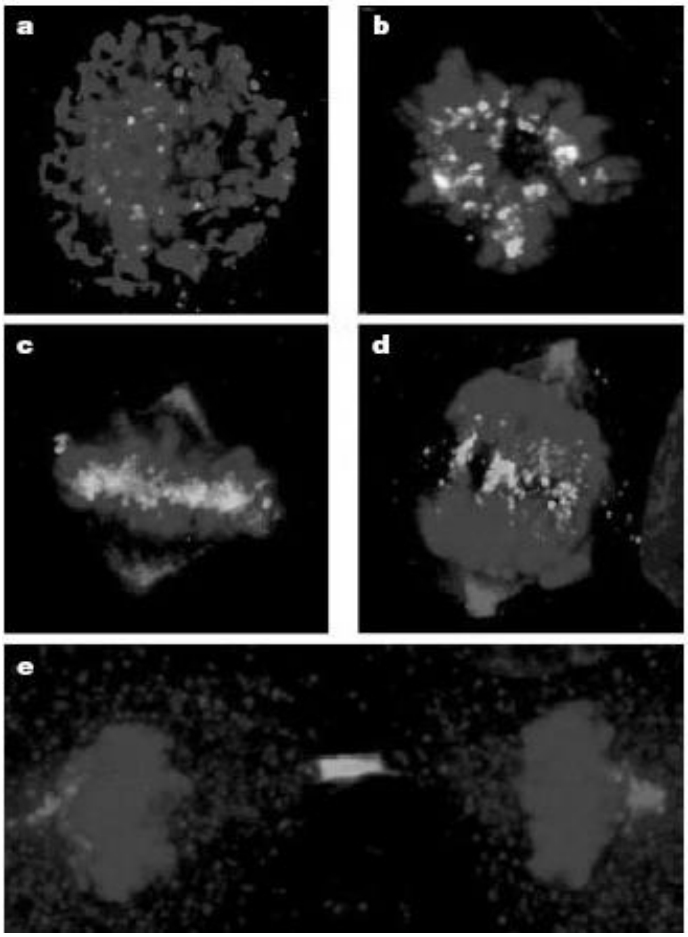

Fig. 4: Aurora-A and -B localize to key mitotic structures.

Sub cellular localization of Aurora-A (red) and Aurora-B (green) relative to the chromosomes (blue) during (a) prophase, (b) prometaphase, (c) metaphase, (d) anaphase and (e) telophase. During prophase, Aurora-A localizes to the centrosomes, whereas in later stages of mitosis it is at the spindle poles (c, d and e) and also extends up the spindle. During prometaphase and metaphase (a and b), Aurora-B localizes to the centromeres. After anaphase (d), however, Aurora-B localizes to the spindle midzone, and finally accumulates at the midbody during telophase (e).

Source http://www.medscape.com/viewarticle/495344_2

In human cell lines, Aurora-A depletion results in the inhibition of both centrosome maturation and centriole pairs separation [46]. The commitment of cells to mitosis in the late G2 phase involves the activation of both Aurora-A and CDK1–cyclin B. This activation is a kind of feedback mechanism in which the Aurora-A activation requires the CDK1–cyclin B activation [47] and the CDK1–cyclin B complex is activated by the Aurora-A-dependent phosphorylation of CDC25B at serine353, the phosphatase involved in cyclin-dependent activation.

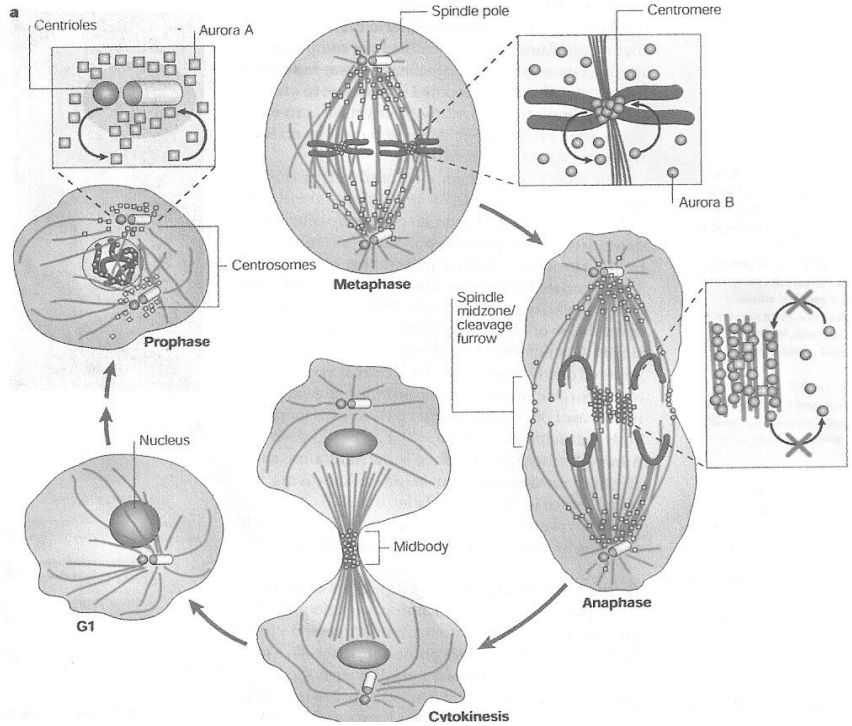

Fig. 5: Localization of Aurora kinases. | The relative localization of Aurora A and Aurora B in mitotic cells is shown.

The level of both kinases is substantially reduced in G1 cells. By prophase, Aurora A (boxes) is concentrated around the centrosomes, whereas Aurora B (circles) is nuclear. In metaphase, Aurora A is on the microtubules near the spindle poles, whereas Aurora B is located in the inner Centro mere. In anaphase, most Aurora A is on the polar microtubules, but some might also be located in the spindle midzone. Aurora B is concentrated in the spindle midzone and at the cell cortex at the site of cleavage-furrow ingression. In cytokinesis, both kinases are concentrated in the midbody

Source: http://www.nature.com/nrm/journal/v4/n11/fig_tab/nrm1245_F3.html

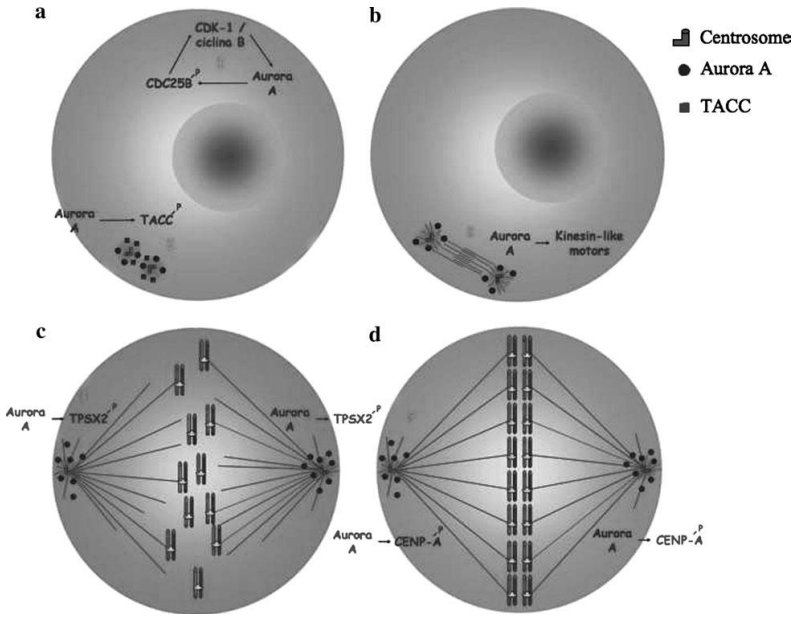

Fig. 6: (A) Aurora-A is first detected in late G2 phase at the centrosome,

Where, it is involved in the commitment to mitosis (1) and in maturation of centrosome through the phosphorylation of TACC (2). (B) Aurora-A is required for the separation of centrosomes in prometaphase through the activation of the kinesin-like motors (3). (C) For the bipolar spindle assembly (4). (D) Aurora-A cooperates with Aurora-B in the activation and maintenance of CENP-A (5), allowing a correct chromosome alignment on the metaphase plate.

Experiments conducted singly on Aurora-A and TPX2 depletion, in fact, have shown in both these, the formation of multipolar spindles [27, 48]. Several data reported in literature have shown that the chromosome alignment on the metaphase plate is principally regulated by the Aurora-B protein [49]. Recent studies [50] have shown that both Aurora-A and Aurora-B are involved in this step by means of the phosphorylation at the serine 7 residue of the CENP-A, the protein responsible for the interaction between microtubules and the kinetochore. More specifically, Aurora-A is responsible for the first CENP-A phosphorylation and activation while Aurora-B is responsible for maintaining this activation status from the late prophase to the metaphase.A perfect timing of Aurora-A activation and destruction is necessary for a proper cytokinesis. Both Aurora-A over expression and inhibition, in fact, lead to multinucleated cell formation [51].

AURORA-A –role in centrosome separation and maturation:

This was supported by ultrastructural analysis of *Drosophila* cells after they were treated with double-stranded Aurora-A DNA for RNA INTERFERENCE (RNAi). This showed the presence of spindles with no centrioles at one pole and several centrioles at the other. A second live-cell analysis of Aurora-A RNAi treatment in *C. elegans* showed that centrosomes first separate and then collapse back together [52].

Loss-of-function studies established some time ago that Aurora-A is required for multiple steps during mitosis. Perturbing Aurora-A leads to defective Centro some separation and maturation in a wide variety of experimental model systems[53,54] Cell cycle progression, mitotic spindle pole organization and MT stability are also often compromised in the absence of Aurora-A [55,56,57].In the absence of Aurora A, recruitment of several components of the pericentriolar material including γ-tubulin to the centrosome is deficient. The microtubule mass of spindles is decreased by about 60% [37, 43].

Spindle assembly

A recent report has shown a link between Ran–GTP and Aurora A in spindle assembly [58]. Ran–GTP is a small GTPase that is required for the polarity of nuclear transport, nuclear-envelope assembly and mitotic-spindle assembly in *Xenopus* extracts [59-61].In mitosis, Ran–GTP releases TPX2 The liberated TPX2 then binds Aurora A at the centrosome and targets it to the microtubules proximal to the pole [60]. TPX2 also regulates the kinase activity of Aurora A, both by counteracting the activity of the protein phosphatase PP1 and stimulating Aurora-A autophosphorylation at Thr295 which is a residue in the activation loop of Aurora A that is essential for kinase activity [62].

Regulation of aurora A activity.

Regulation of Aurora A is complex and involves both phosphorylation/dephosphorylation and degradation [63, 64, and 65]. Phosphorylation stimulates kinase activity. Three phosphorylation sites have been identified in *Xenopus* Aurora A by mass spectrometry [66, 67]. The phosphatase PP1 negatively regulates the Aurora kinases. The counteracting effect of PP1, which was first described for yeast Ipl1 [68] has also been shown in *Xenopus* and human cell lines [62, 67, 69, 70].

The activation of Aurora A by TPX2 is at least partly due to antagonism of PP1 [79, 83].The recently identified Aurora-A-kinase-interacting protein (AIP), a negative regulator of Aurora A, is a conserved nuclear protein that interacts with the kinase *in vivo* [71].AIP was isolated as a dosage-dependent suppressor of Aurora A that was ectopically over expressed in budding yeast. In mammalian cells, AIP might down regulate Aurora through proteasome-dependent degradation.

THE CHROMOSOMAL PASSENGERS: INCENP, SURVIVIN AND AURORA-B

The equatorial Aurora, Human Aurora B was first identified in a polymerase chain reaction screen for kinases that were over expressed in tumours [15]. The first chromosomal passenger protein to be described, INCENP, attracted interest because it was seen to move from centromeres to the spindle and then to the cleavage furrow as cells traverse mitosis [72, 73].INCENP is required for the correct targeting of aurora-B during mitosis.

Aurora-B, the second chromosomal passenger is related to a protein kinase. It was first identified in *Drosophila melanogaster* in a search for genes that regulate the structure and function of the mitotic spindle. Mitosis in aurora-mutant cells was characterized by monopolar spindles with duplicated centrosomes that leads to the fact that this kinase is required for centrosome separation.

Survivin, the third chromosomal passenger is an IAP. (IAP: inhibitor of apoptosis) IAPs, which were first discovered in baculovirus, are defined by the presence of one or more zinc-binding motifs termed the BIR (baculovirus IAP) [74, 75]. A recent study has reported that survivin is centromeric at metaphase, associates with the spindle midzone at anaphase, and concentrates in the intercellular bridge at cytokinesis [76]. In human cells, these subunits are Survivin, the inner centromere protein (INCENP), and Borealin/Dasra-B77];**Fig.7.**

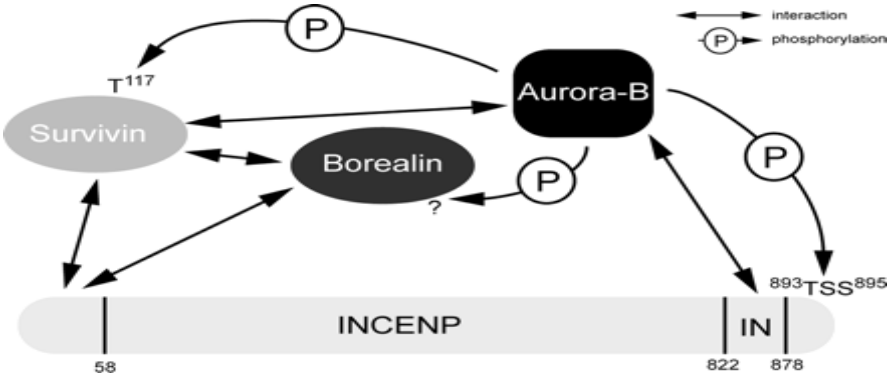

Fig. 7: Interactions within the CPC. Schematic representation of direct interactions between CPC proteins and phosphorylations of Aurora-B within the CPC. Survivin and Borealin interact with the NH_2 terminus of INCENP, whereas Aurora-B binds the COOH-terminal IN-box in INCENP. Mapped Aurora-B phosphorylation sites are indicated.

Source: http://jcb.rupress.org/content/173/6/833.full

The chromosomal-passenger localization of Aurora B was originally shown by indirect immunofluorescence in mammalian cells, *C. elegans* and *Drosophila* [47, 77, 78].A more recent analysis of the distribution of exogenous green fluorescent protein (GFP)-tagged Aurora B in living mammalian cells showed that the association of the kinase with centromeres during metaphase is dynamic: the protein exchanges continuously with the surrounding cytoplasmic pool [79]. Once the kinase associates with central spindle microtubules during anaphase (which requires kinase activity), its mobility is highly reduced.

Aurora B in chromosome biorientation.

Aurora B seems to have an important role in regulating kinetochore–microtubule interactions in higher eukaryotes. Interference with its function by RNAi microinjection of function-blocking antibodies [80] or treatment with small-molecule inhibitors [81,82] all cause defects in chromosome CONGRESSION. One study found a significant increase in the frequency of syntelic attachments after treatment with an inhibitor [83]. The mammalian kinetochore-specific histone-H3 variant CENP-A is a substrate of Aurora B in mammalian cells [84]. Phosphorylation of CENP-A by Aurora B peaks in prometaphase. Surprisingly, phosphorylation- site mutants show a delay in the late stages of cytokinesis.

Aurora B and the spindle-assembly checkpoint.

Aurora kinases are required for stable activation of the checkpoint as a result of a loss of spindle tension. This was first shown in budding yeast, in which Ipl1 was required to arrest the mitotic cycle when spindle tension was absent, but not in response to the lack of microtubules[85].Similar results have been seen in mammalian cultured cells after expression of a kinase-inactive dominant-negative form of Aurora B [78]microinjection of function-blocking anti-Aurora B antibodies[79]; treatment of cells with newly isolated Aurora-B inhibitors[80,81]; or after RNAi-mediated knockdown of the Aurora-binding partner survivin [86,87]. In *S. pombe*, loss of Ark1 inactivates the checkpoint altogether [88].

ASSOCIATION OF AURORA KINASES WITH CANCER

The genes encoding the three human Aurora kinases map to regions that are affected by chromosomal abnormalities in different cancer types. This over expression of each of the three human Auroras has been detected in tumour cell lines [15, 32, 89, 90].

Aurora A

To date, most interest has focused on Aurora A, which fits the criteria to be classified as a bona fide oncogene. The role of Aurora-A, both in normal cellular physiology and tumorigenesis, has been comprehensively reviewed by Marumoto *et al* Human Aurora A maps to chromosomal region 20q13.2, which is amplified in a number of cancer cell lines and primary tumours [91, 92].

Furthermore, mouse NIH-3T3 cells transfected with Aurora A give rise to tumours when injected into nude mice [15, 66, 91]. This requires the catalytic activity of the kinase. For instance, unlike normal cells, in tumour cells Aurora-A expression may be detected diffusely in all the cytoplasm [93], giving rise to aberrant phosphorylated cytoplasmic proteins. A large number of studies taking into consideration the kinase activity of the protein have reported a relationship between Aurora-A, the p53 tumour suppressor protein and cancer progression [94,95]. Aurora-A, in fact, phosphorylates p53 at the serine 215 residue, inducing an inactivation of transactivation activity, and at the serine 315 residue, facilitating MDM2-mediated p53 degradation. Moreover, an association has been shown between Aurora-A over expression p53 mutational status and a worse prognosis in patients affected by hepatocellular carcinomas [96]. Finally, cells with Aurora-A over expression and with a non-functional post mitotic G1 checkpoint are usually tetraploid. With regard to the predictive role of Aurora-A, it has been shown that its over expression disrupts the spindle checkpoint activated by paclitaxel (Taxol) or nocodazole treatment. Thus inducing the cells to become resistant to these drugs [97].

Two recent studies indicate that over expression of Aurora A is unlikely to trigger centrosome amplification directly, but instead leads to mitotic abnormalities that culminate in the failure of cytokinesis and the production of tetraploid cells [28, 29]. Aurora A is not unique in this regard, as over expression of Aurora B or Polo-like kinase (Plk1) also causes cytokinesis failure and centrosome duplication [87, 29]. Over expression of Aurora A has been shown to perturb the spindle-assembly checkpoint [29]. This raises the possibility that abnormal spindle arrangements caused by excessive kinase activity that would normally trigger checkpoint activation are, in this case, unable to cause a mitotic arrest, with the consequences that cells exit mitosis with chromosomal and spindle arrangements that preclude successful cytokinesis.

Aurora-induced mitotic abnormalities are exacerbated in cells that lack p53 [29]. This is partly because p53 can bind to Aurora A and directly inactivate its kinase function [98]. In addition, cells that fail in cytokinesis normally arrest in the G1 phase of the next cell cycle as the result of a p53-dependent checkpoint that seems to detect tetraploidy and block cell-cycle progression [99,100]. It could be, therefore, that in the absence of p53, cells in which overexpression of Aurora kinases has led to cytokinesis failure can then proceed through the cell cycle, undergo subsequent error-prone mitosis, and generate aneuploid progeny..

In fact both aurora-A&B, can phosphorylate histone H3 at S10 [101] and Aurora A has been shown to bind survivin in a ternary complex with the GTPase-activating protein RasGAP [102] One attractive possibility is that over expressed Aurora A might compete with Aurora B for substrates and/or regulators

Aurora B

Aurora B has also been implicated in cancer. CHO cells over expressing Aurora B show elevated levels of phosphorylated histone H3 and defects in chromosome segregation and cytokinesis [103]. The progeny of these cells are aneuploid and can produce aggressive tumours in mice. Increased levels of phosphorylation of histone H3 were also shown to correlate with overexpression of Aurora B in some human colorectal tumour cell lines. these cells are aneuploid and can produce aggressive tumours in mice. Increased levels of phosphorylation of histone H3 were also shown to correlate with overexpression of Aurora B in some human colorectal tumour cell lines [103].

CONCLUDING REMARKS

Aurora kinases have exploded on the scene in the past five years, and are now recognized as leading players in the orchestration of mitotic events. Aurora-A kinases are particularly important for regulation of microtubule nucleation at spindle poles, and are subject to a complex network of controls that include phosphorylation, association with TPX2 and destruction by the APC/C. Aurora B kinases are essential for chromosome condensation, kinetochore function, cytokinesis and the proper function of the spindle-assembly checkpoint when spindle tension is perturbed.

Their regulation involves association with the chromosomal passenger proteins INCENP and survivin, which are important both for targeting and activation of the kinase [104,105,106]. Little is known about Aurora-C kinases, which are expressed at high levels only in the testis, and comprise a particularly interesting subject for future studies.

The single Aurora kinases of the budding and fission yeasts are particularly important for kinetochore– microtubule attachments and spindle-assembly checkpoint function, which are activities that are most closely associated with Aurora-B kinases. However, in a study in which kinase domains were swapped, only the kinase domain of Aurora A and not that of Aurora B could substitute for Ipl1 in budding yeast[31], indicating that Ipl1 is probably required for both Aurora-A and -B functions. Adding to the interest in these kinases is the fact that Aurora kinase overexpression has been observed in cancer, and Aurora A can function as a bona fide oncogene. Aurora-A has long been regarded as an oncogene, as a result of its overexpression and amplification in several human cancers. Yet, Aurora-A is unlikely to be a bona fide oncoprotein, because of its overexpression which neither transforms primary cells nor leads to tumour formation. Nonetheless, their powerful roles in cell cycle regulation and suitability for inhibition by small molecule antagonists make both Aurora-A and Aurora-B promising anti-cancer therapy targets. [107]

The Auroras are 'journeyman kinases' that travel from location to location in the cell to do their work. In addition to promoting kinase activation, INCENP/survivin and TPX2 also direct the location of their respective Aurora kinases in the cell [42, 45,108,109,110]. This

provides a very powerful means of regulation, and might be essential to the ability of these kinases to choreograph mitotic events. If the auxiliary factors were essential for both function and targeting, this would enable the kinase activity to be moved from place to place within the mitotic cell with great temporal and spatial precision [111,112,113] The auxiliary factors also provide rich targets for regulatory activities, and we predict that deciphering the regulation of their movements will prove to be essential for the complete understanding of Aurora kinase activity. Clearly,much new territory remains to be explored in the world of Aurora kinases.

Table 1: Showing the Lists of Aurora kinases and its characteristics

ORGANISM	NAME	ALTERNATIVE NAMES	BINDING PARTNERS	LOCALIZATION
Saccharomyces cerevisiae	Ipl 1	----------	Sli 15,Bir 1	Kinetochore
Schizosaccharomyces pombe	Ark 1	----------	Pic 1,Bir 1	Kinetochore
Caenorhabditis elegans	Aurora-A	AIR-1		Centrosome
	Aurora-B	AIR-2	CeINCENP, BIR1	Chromosome passenger
Drosophila melanogaster	Aurora-A	DmAurora		Centrosome
	Aurora-B	IAL	DmINCENP,survivin	Chromosome passenger
Xenopus lavies	Aurora-A	Eg2	TPX2	Centrosome
	Aurora-B	XAIRK2		Chromosome passenger
Mammals	Aurora-A	Aurora2, AIRK1,ARK1,BTAK,STK6, STK15,AYK1,IAK 1	TPX2,TACC 1	Centrosome
	Aurora-B	Aurora 1,AIRK2,ARK2, IAL 1,AIK2,STK12,AIM 1	INCENP,Borealin[17], Survivin, TACC 1	Chromosome passenger
	Aurora-C	Aurora 3, AIRK3, AIE2,STK13, AIE 1,AIK3		Spindle pole or Chromosome passenger

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