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Review

Aurora kinases orchestrate mitosis; who are the players?

Annie Molla

INSERM, U823, Centre de Recherche Albert Bonniot, Mécanisme d'assemblage et de régulation de l'appareil génétique, La Tronche, F-38706 France; Université Joseph Fourier, BP 170, Grenoble Cedex 9, F-38042 France

e-mail: annie.molla@ujf-grenoble.fr

Abstract

The Aurora are a conserved family of serine/threonine kinases with essential functions in cell division. In mitosis, Aurora kinases are required for chromosome segregation, condensation and orientation in the metaphase plate, spindle assembly, and the completion of cytokinesis. This review presents the Aurora kinases, their partners and how their interactions impact on the different mitotic functions.

Keywords: Aurora kinase; Aurora-A kinase; Aurora-B kinase; chromosomal passenger complex; cytokinesis; mitosis; mitotic spindle.

Introduction

Aurora kinases are key players in mitosis and are proposed as attractive targets in cancer therapy. Moreover, they are over-expressed in a wide range of human cancers (1, 2).

The Aurora kinase family is composed of three members in mammals, Aurora-A, Aurora-B, and Aurora-C whereas for other metazoans, including the frog, fruit fly and nematode, only Aurora-A and Aurora-B kinases are known (3). The fungi, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, have a single Aurora kinase, known as increase-in-ploidy 1 (Ipl1) and Aurora-related kinase 1 (Ark1), respectively. Furthermore, whereas the Aurora-A family is ubiquitous among all vertebrates, the Aurora-B and Aurora-C families arose from a gene duplication event in mammals. *Dictostelium* Aurora kinase has properties of both kinases A and B and might represent the ancestral kinase (3).

Aurora-A and -B are ubiquitous key players in mitosis whereas Aurora-C function is less documented and seems to be testis specific (4).

Aurora kinases: structure/function

Aurora kinases are monomeric enzymes of approximately 40 kDa constituting large oligomers with specific partners. Three domains compose each protein kinase: a divergent N-terminal domain, a large conserved catalytic domain and a short C terminal sequence. Aurora kinases are short-lived proteins degraded by the proteasome via the anaphase-promoting cyclosome complex (APC/c) pathway (5, 6). Both Aurora-A and -B kinases encompass degradation boxes in their sequences. However, the C-terminal D-box (RXXL) of Aurora-A is required for its destruction but the KEN box is not (5). Conversely, the degradation of Aurora-B does not depend on its D-boxes (RXXL), but it does require intact KEN boxes and A-boxes (QRVL) located within the first 65 amino acids (6). The similarities and complementarities of kinases A and B were illustrated recently by mutational approaches when simultaneously Hans et al. (7) and Fu et al. (8) showed that a single amino acid change (G128N) within the catalytic domain converts Aurora-A into Aurora-B-like kinase in terms of partner specificity and cellular function. Formerly, the equivalent residue in *Xenopus* Aurora-A (G205) was described as a key determinant of both intrinsic activity and regulation by TPX2 (9).

Despite their structural similarities, the two proteins A and B have unique spectra of binding partners and of phosphorylation substrates (Table 1).

Function and localization of Aurora-A

Aurora-A kinase, also known as Aik, BTAK, or STK15, is suspected to be an oncogenic kinase and its gene is located at 20q13, a region that is frequently amplified in cancer. Aurora-A kinase expression rises during G2 and peaks in early mitosis [reviewed in (44)]. Aurora-A localizes to the centrosomes in G2 and is also present on the mitotic spindle in mitosis. Moreover, Aurora-A null mouse embryos show severe defects at 3.5 d.p.c. (days post-coitus) morula/blastocyst stage and lethality before 8.5 d.p.c (45). Null embryos at 3.5 d.p.c. reveal growth retardation with cells in mitotic disarray manifesting disorganized spindle, misaligned and lagging chromosomes as well as micronucleated cells. This study provides the unequivocal genetic evidence for an essential physiological role of Aurora-A in normal mitotic spindle assembly, chromosome alignment segregation and maintenance of viability in mammalian embryos (45). Actually, Aurora-A mediates all these complex functions through its interactions with partners and by cross-talk with other kinases (Figure 1 and Table 1A and B). In G2 and early mitosis, Aurora-A strictly localizes on centrosomes and its targeting requires centrosomal kinases, such as Pak1, Plk-1

Table 1 Aurora-A and -B partners.

	Substrate	Interactor	Co-factors	Function
Part A	Aurora-A(T288)	TPX2		Maximal activity of Aurora-A (10)
		AurKAIP1	GSK-3β	Degradation of Aurora-A (11)
		HEF1		Activation of Aurora-A (centrosome amplification) (12)
	TPX2	TPX2 (Ser 204)	Plk1	Localization of Aurora-A to centrosome (13) Activation of Aurora-A (14) Spindle length/MT nucleation from chromosome
	Plk1 (T210)	Bora	Bora	G2/M entry activation of Cdk1, liberation of Aurora-A and recruitment of TPX2 (15)
	Xl-p53 (S129/190)	TPX2		Stabilization of p53 (Met II meiosis) (16)
	H-p53 (S315)			Ubiquitination by Mdm2 and proteolysis (17)
		Cyclin B1		Stabilization of Cyclin B (prevents APC interaction) (18)
	Cdc25B (S553)			Activation cdk1-cyclin B1/G2-M transition (19)
	Lats 2 (S83)			Centrosomal localization Lats 2 kinase (20)
	Hs-TACC3/ maskin (S558)		MAP215	Interaction microtubule-associated-proteins (dynamic of spindle pole MT) (21)
	D-TACC1(S863)			Stabilization of centrosome-associated microtubules (22)
	HDAC6	HEF 1/Cas-L (NEDD9)		Primary cilium disassembly (microtubule deacetylation) (23)
	D-Par 6		Numb	Neuronal polarity/asymmetric division (24) Spindle orientation
Part B				
Aurora kinase A	CenP-A (S7)			Localization of Aurora-B (prerequisite for Aurora-B phosphorylation) (25)
Aurora kinase B	CenP-A (S7)			Mitosis ongoing/cytokinesis completion (26)
Aurora kinase A		INCENP		γ-Tubulin nucleation (27)
Aurora kinase B	INCENP (TSS893-895)	CPC		Localization of Aurora-B (28) Activation of Aurora-B, checkpoint function
Aurora kinase A	MCAK (Xl-S196, Xl-S719)			Spindle bipolarity (29)
Aurora kinase B	MCAK (Xl-S196, Xl-T95)			Kinetochore microtubule dynamic/ recruitment of MCAK on chromatin (30)
Aurora kinase A	EB3 (S176)		SIAH1 complex	Microtubule dynamics (31) EB3 stabilization
Aurora kinase B	EB3 (S176)		SIAH1 complex	Microtubule dynamics (31) EB3 stabilization
Part C	Aurora-B (T232)	INCENP	CPC	Maximal activity (32)
	Histone H3 (S10)			Chromosome alignment (33)
	Survivin (T117)	CPC	Sgo2	Anaphase onset and cytokinesis (34, 35)
	Op18/stathmin (S16)			Spindle assembly (36)
		TD60	Microtubules	CPC localization/haspin activation (37)
		Ce-Tousled kinase		Chromosome segregation (38)
	Ndc80 (S55, S62)		Mis12 complex	Correction improper kinetochore-microtubule connections (39)
	Hs-Mis13 (S100-S109)			Kinetochore function/recruitment of Ndc80/Hec1 (40)
	MgcRacGap (S387)		Kinesin 6	Cytokinesis (41)
	Kinesin 6: Zen4/ MKLP1 (S708)		MgcRacGap	Cytokinesis completion (42)
		TACC1		Cytokinesis (43)

The list is not exhaustive and only major interacting proteins and substrates are listed; those identified only *in vitro* are omitted. For each partner, the main corresponding functions as well as their potential co-factors are indicated. Interactors: interact directly with the kinase whereas co-factors are indirect players. The phosphorylated residue is indicated when clearly identified.

Part A: Exclusive Aurora-A partners. TPX2, microtubule associated protein; AurKAIP1, Aurora-A kinase interacting protein 1; HEF1, focal adhesion scaffolding protein; Plk1 polo-like kinase 1, Lats2, a novel serine/threonine kinase, member of the Lats kinase family that includes the *Drosophila* tumour suppressor lats/warts; TACC, transforming acidic coiled-coil; MAP, microtubule associated protein; HDAC, histone deacetylase; NEDD9, neural precursor cell expressed, developmentally down-regulated 9; Par-6, partitioning defective 6 homolog alpha, a regulatory subunit of atypical protein kinase C (aPKC); Xl: *Xenopus laevis*; D, *Drosophila* and Hs, *Homo sapiens*.

Table 1 (*Continued*)

Part B: Aurora-A and -B partners. CenP-A, Centromeric Protein A; CPC, Chromosomal Passenger Complex; INCENP, INer CENtromeric Protein; MCAK, Mitotic Centromere-associated Kinesin; EB3, microtubule plus-end tracking protein; SIAH-1, ubiquitin-protein isopeptide ligase.

Part C: Exclusive Aurora-B partners. Sgo2, shugoshin 2; TD60, telophase disc-60 kDa, a member of the RCC1 family; Ndc 80, complex composed of Ndc80/H-Hec, Nuf2, Spc24, and Spc25 and is an essential core element of kinetochores; Mis 12 and Mis13, MIND kinetochore complex component; Mis12, Ndc80/Hs-Hec and KNL-1 form the KMN network, the core microtubule-binding site of the kinetochore; MgcRacGap, Rac GTPase activating protein; TACC1, transforming, acidic coiled-coil containing protein 1.

and Cdk-11 (13, 46, 47). Aurora-A functions as an anchor protein for the recruitment of additional pericentriolar proteins such as chTOG/MAP215, γ-tubulin, TACC3 and Lats 2 (20–22). During G2, the main cofactor is hBora; Aurora-A, in complex with hBora, phosphorylates Plk1 at Thr-210 and Cdc25B at Ser-353 (15, 19). Activated Plk1 phosphorylates Cdc25C and Wee1 and in turn, promotes mitotic entry [Table 1; (15)]. Plk1 and Aurora-A signalling functions are mutually dependent in G2 during recovery from DNA damage (13, 48).

During mitosis, Bora interacts with phospho-Plk1, liberates Aurora-A and the free Aurora-A kinase recruits TPX2, a microtubule interacting protein. TPX2 is the best known coactivator of Aurora-A, inducing the active conformation of the kinase, its targeting to the mitotic spindle while inhibiting its inactivation by PP1 (13, 49). In human cells, the interaction between TPX2 and Aurora-A is required for microtubule nucleation from chromosomes and therefore for building a spindle of the correct length (50, 51). The suppression of Aurora-A by small interfering RNA or its inhibition by antibodies caused multiple events to fail in mitosis, such as incorrect separation of centriole pairs, misalignment of chromosomes on the metaphase plate, and incomplete cytokinesis (52). Huck et al. have shown that inhibition of Aurora-A resulted in both apoptosis and senescence in tumour cells (53).

Function and localization of Aurora-B

Aurora-B with INner CENtromere Protein (INCENP), Survivin and Borealin form the chromosomal passenger complex (CPC) [reviewed in (54)]. Chromosomal passenger proteins are mostly absent in the interphase. They are present, in the nucleus, in late G2 phase and their expression peaks in G2/M. The CPC is characterized by a peculiar localization during mitosis (Figure 1). In prophase, passenger proteins associate along the length of the condensing chromosomes and gradually concentrate at centromeres. At prometaphase and metaphase, CPC accumulates in the inner centromere. At anaphase onset, it leaves the chromosomes and is transferred to the central spindle in association with microtubules. Finally, passenger proteins are concentrated in the midbody during cytokinesis (Figure 1). Impairment of any CPC unit leads to similar behaviour: failure of localization of the other CPC and mitotic delay; The functional interdependence is explained by the intertwined structural interactions described by Jeyaprakash et al. (55). Within the complex, Aurora-B kinase is the only enzymatic member.

During mitosis, Aurora-B phosphorylates several substrates including chromosomal proteins such as CENP-A and Histone H3 (26, 32), microtubules associated proteins (MCAK, Stathmin; MKPL-1, etc.) as well as its partners within the CPC (see Table 1B and C). Both Survivin and INCENP are substrates of Aurora-B and in turn, they activate the kinase (56–58). For example, INCENP binds to Aurora-B and induces an intermediate state of activation by stabilizing an open conformation of the catalytic site of the kinase. INCENP becomes phosphorylated and phospho-INCENP generates the fully active kinase (58). Borealin is also an activator through its phosphorylation by Mps-1 (59). However, the localization and the activity of Aurora-B depend on a functional CPC. Furthermore, microtubules and TD60, a RCC1 guanine nucleotide exchange factor, are also described as co-factors (36) and, the presence of TLK-1 [Tousled Kinase 1; (38)] and the activation of Chk1 (60) modulate the activity of Aurora-B (Figure 1 and Table 1B and C). By contrast, MST1 (mammalian sterile 20 like kinase 1) limits the activity of Aurora-B to promote stable kinetochore-microtubule attachment (61).

In cells, the inhibition of Aurora-B kinase or the invalidation of any passenger protein leads to similar phenotypes (37, 62): delay in mitotic progression and kinetochore-spindle mis-attachments (Figure 1). Chromosomes fail to align on the mitotic plate owing to improper chromosome spindle attachments and cells exit from mitosis by premature silencing of the spindle checkpoint. Aurora-B kinase controls thus the establishment of the mitotic spindle, kinetochore tension and the activation of the spindle checkpoint. At the metaphase to anaphase transition the relocation of Aurora-B kinase and the CPC from centromeres to the central spindle require both the kinesin MKlp2 and Aurora-B activity (63, 64). On the central spindle Aurora kinase contributes to proper cytokinesis through phosphorylation of MgcRacGAP and kinesin 6 (40, 41). Recently Aurora-B kinase and the CPC were found to participate to a checkpoint called NoCut that prevents abscission until all chromosomes are pulled out of the cleavage plane (65).

Cells treated with Aurora inhibitors progressed through mitosis with misaligned chromosomes and exited without cytokinesis. Upon such a mitotic abortion, cells are polyploid and exhibit irregular lobed nuclei (66). Therefore passenger protein inhibition prevents at least cell expansion. Cells with

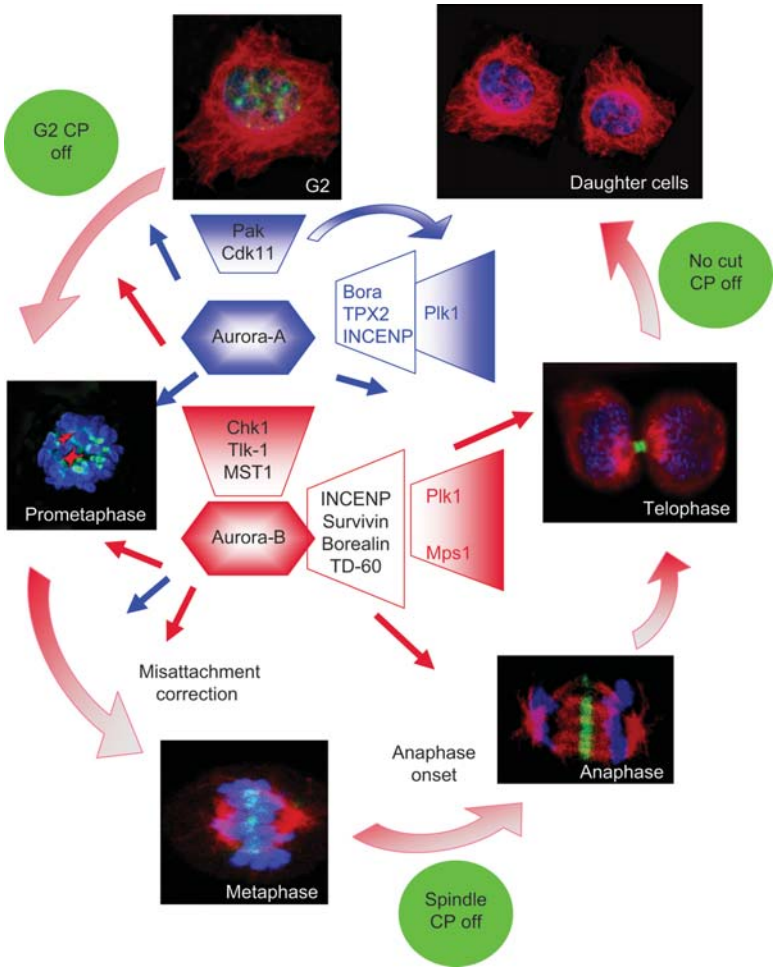

Figure 1 Involvement of Aurora kinases and their partners in mitosis.
The different phases of mitosis are represented by immunofluorescent images. Aurora-B is portrayed in green, Tubulin in red and DNA in blue. The involvement of each kinase in the different phases is portrayed by colour arrows: blue for Aurora-A and red for Aurora-B. Aurora-A interacts with Bora, is regulated by Pak and Cdk11, and, phosphorylates Plk1 inducing in turn, mitosis onset. Then, Aurora-A drives maturation of the centrosomes, interacts with TPX2 and participates in the formation of the mitotic spindle. By contrast, Aurora-B in the inner centromere within the chromosomal passenger proteins (INCENP, Survivin and Borealin) participates in chromosome congression, corrects microtubule mis-attachments and allows chromosome alignment on the metaphasic plate. Aurora-B is regulated by the presence of TD-60, microtubules and the kinases Chk1, Tlk-1 and MST1; A cross-talk exists indirectly with Plk1 that phosphorylates INCENP and with Mps 1 which modifies Borealin. Finally, the CPC is transferred to the central spindle and concentrates on the midbody. For mitosis progression, cells have to turn off several checkpoints (CP): (1) the G2 CP controlling genome integrity and preventing entry in mitosis with DNA damage; (2) the spindle CP that controls tension across kinetochores; and finally (3) NoCut ensures that cytokinesis completes only after all chromosomes have migrated to the poles. The three CP indicated by green lights are under the control of Aurora kinases.

intact checkpoint function arrest with 4N DNA content, those with compromised checkpoint function are more likely to undergo endoreduplication followed by eventual apoptosis. The integrity of the p53-p21Waf1/Cip1–dependent postmitotic checkpoint governs thus the response to Aurora kinase inhibition (67).

Regulation of the Aurora-B kinase activities and consequences for the CPC

Although Aurora kinases and their partners are well described, and their key roles in mitosis undisputable, the modulation of activities are poorly documented. Aurora kinases belong to the AGC kinase group but their architecture and regulatory mechanisms are only partly described (58). It is established that both Aurora-A, -B kinases are autophosphorylated (Table 1A and C) and, that their accurate localizations depend on their activity (10, 66, 68). In the presence of inhibitors or dominant negative kinase Aurora-B localized on centromere but progressively fused on the whole chromatin as revealed by time-lapse experiments (66, 68, 69).

In the past, a main question was to elucidate the interrelation between Aurora-B kinase activity and tension across kinetochores. Recently, Liu et al. have elegantly solved this

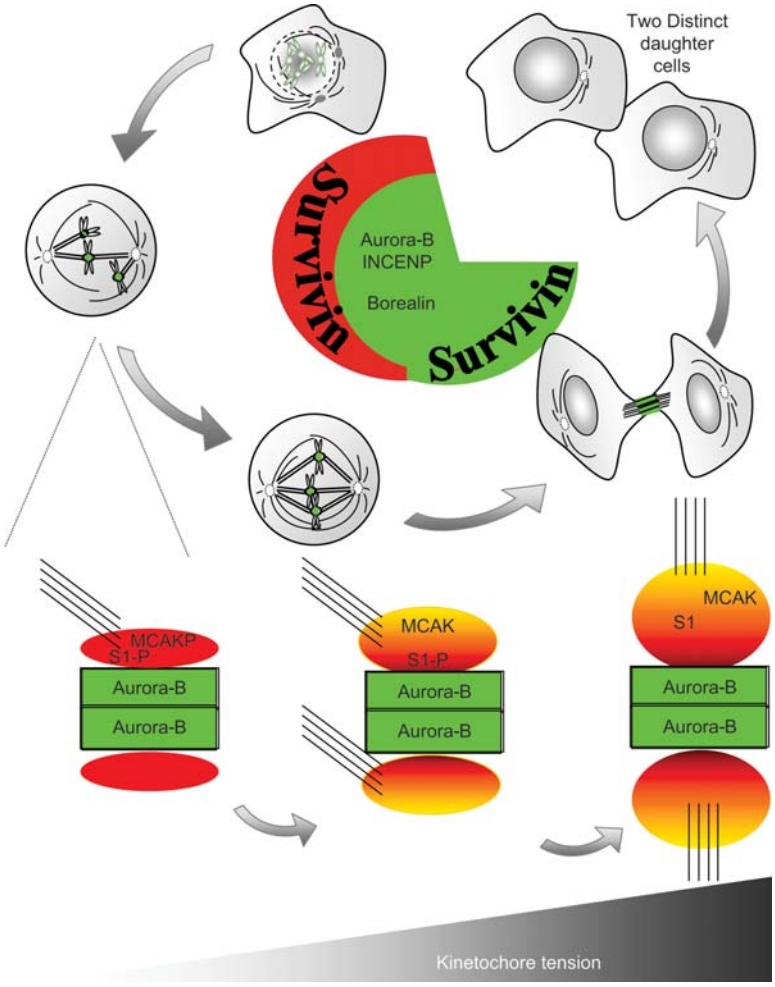

Figure 2 Aurora-B kinase is immobilized in the inner centromere.
In the upper part of the figure, the expression and localization of the CPC are illustrated in green. The results of dynamic experiments, in live cells, are indicated in the centre (33, 71). The proteins found immobile by FRAP are represented in green whereas the mobile counterpart is in red. Survivin is mobile on the chromosome and then immobile on microtubules whereas other CPC members are always found to be immobile. The lower part of the figure demonstrates the tension across centromeres and the progressive separation of the sticky kinase from its substrates (72); the consequence probably being the establishment of a gradient of phosphorylation of Aurora-B substrates.

question (70). By using FRET-based bio-sensors and playing with the targeting of Aurora-B, these authors have established that the spatial separation of Aurora-B kinase from kinetochore substrates senses chromosome bi-orientation. In the absence of tension, kinetochore substrates such as MCAK in the vicinity of the kinase are phosphorylated and have therefore low affinity for microtubules (Figure 2). Kinetochore-microtubules attachments are thus destabilized. Conversely, when tension is exerted, kinetochore substrates are pulled away from the kinase, their phosphorylation decreases and microtubules are stabilized around kinetochores (Figure 2). In line with this, Aurora-B kinase activity does not require any modulation and can remain maximal during mitosis but, its localization is essential for its correct function. Our study of CPC by FRAP (fluorescent recovery after photobleaching) reveals that Aurora-B and its docking partner INCENP are fully immobile in prometaphase and metaphase [Figure 2; (34, 71, 72)]. Although these data are controversial, the immobilization of the kinase in the inner centromere fits perfectly with this spatial regulation of its function (71, 73, 74). Other conclusions that could be drawn from FRAP experiments are the peculiar role of Survivin within the CPC and the existence of different conformation for the complex. Survivin is mobile until anaphase onset and then is stuck to its partners when the complex is transferred to microtubules (72). The binding of INCENP to microtubule might either induce a conformational change within the CPC or recruit a new partner that prevents Survivin movements. The structure of the core CPC complex reveals that the helical domain of Survivin forms a tight three helical bundle with Borealin and INCENP (55). This situation might reflect the microtubule bound CPC because specific residues for spindle localization were noted at the molecular surface of the crystal and could thus account for the immobilization of Survivin.

Importance of Aurora kinase on cell cycle checkpoints

Aurora kinases interfere directly or indirectly with three cell cycle checkpoints from G2 to mitosis exit (Figure 1). As described before, Aurora kinase A is involved in mitosis entry through Bora and Plk1 and it was also reported that both Aurora kinases A and B are inhibited upon DNA damage (75, 76); they therefore participate at least indirectly to the G2/M checkpoint (13). Aurora-B kinase is a main regulator of the spindle assembly checkpoint (SAC) that triggers anaphase onset and protects cells from aneuploidy. The SAC is turned on until all the chromosomes are bi-oriented to the two different poles (77). A new checkpoint, named NoCut Checkpoint was recently described (65, 78, 79). It delays the completion of cytokinesis in response to anaphase defects. NoCut was first identified in yeast and depends on both Aurora-B kinase and the anillin-related proteins Boi1 and Boi2 that act as abscission inhibitors (78). NoCut monitors clearance of chromatin from the midzone to ensure that cytokinesis completes only after all chromosomes have migrated to the poles (79) and Aurora-B is part of a sensor that responds to unsegregated chromatin at the cleavage site (65). The direct or indirect control of the three checkpoints by Aurora kinases is an additional proof of the huge importance of these kinases during the cell cycle.

Which Aurora kinase is the better drug target?

This question is still open because the interrelations between Aurora-A and -B are complicated and not well understood (80). During cycle progression, A is implicated first, in G2, and then B is involved upon mitosis entry. However, the inhibitors exhibiting a broad specificity indicate an Aurora-B inhibition phenotype, in the cells (66, 81). Moreover, the Aurora-A inhibition phenotype is still not observed with these inhibitors, in the Aurora-B mutant cells (81). In fact, cells resistant to ZM447439 were selected and although the resistance was unambiguously attributed to Aurora-B, these cells were also found to be resistant to pan-Aurora inhibitors (81). Several explanations could be proposed; among them might be an Aurora-A function partially disconnected from its catalytic activity, the misidentification of the real target for some of these inhibitors or the prerequisite of Aurora-B inhibition for A impairments. Therefore, the balance for targeting is mostly in favour of Aurora-B but this point will be solved in the near future because several drugs are under clinical trials [for reviews see (82, 83)]. It is too early to evaluate the impact of this targeting and to draw conclusions whether specificity among Aurora kinases is a benefit or a drawback. Some of the molecules have already been used successfully in leukaemia-resistant tumours but the benefit could be accredited to the inhibition of off-targets such as mutated bcr-Abl (84). Preclinical data report that the classical cancer treatment (paclitaxel, radiation, topoisomerase poison) enhances the effect of Aurora-B kinase inhibitors (85). These inhibitors represent, therefore, a real hope in cancer therapy. However, taking into account the identification of Aurora-like homologues in various organisms (fungi, plants, *Trypanosoma brucei*, etc.) broader applications could be considered (86).

Importance of Aurora kinases in germinal lineages

In addition to their mitotic functions, the three kinases are involved in germinal cells and seems crucial during meiosis. Aurora-A localizes to the spindle poles during meiosis I and II whereas Aurora-B associates with chromosomes after germinal vesicle breakdown, is concentrated on kinetochores at metaphase I and on the spindle midzone at late anaphase I (87, 88). In mouse oocytes, Aurora kinase A is a crucial component of MTOC (microtubule organizing centres) involved in resumption of meiosis, MTOC multiplication, spindle formation as well as metaphase I to II transition. Aurora kinase C expression appears to be testis specific (4). Remarkably, Aurora-C null mice are viable but the males exhibit compromise fertility. These recent descriptions shed light on the importance of Aurora kinase in the fertilization process. In fact, Aurora-B expression is altered in aged oocytes and, in humans, a homozygous mutation of Aurora kinase C yields large-headed polyploid spermatozoa and causes male infertility (89). A functional Aurora-C protein is necessary for male meiotic cytokinesis whereas its absence (Aurora-C c.144delC mutation) does not impair oogenesis (90).

In conclusion, Aurora kinases have a key role in both mitosis and meiosis. In this review, their direct partners are described, but Aurora kinases are also included in complex structures such as the centrosome (Aurora-A) and the inner centromere (Aurora-B). Numerous proteins are present in these structures and their arrangement is not fully resolved. In the near future, the definition of the interfaces between inner and outer centromeres and centromere/kinetochore and so on is expected to progress with high-resolution fluorescent microscopy techniques.

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References

1. Vader G, Lens SM. The Aurora kinase family in cell division and cancer. Biochim Biophys Acta 2008; 1786: 60–72.

2. Carmena M, Ruchaud S, Earnshaw WC. Making the Auroras glow: regulation of Aurora A and B kinase function by interacting proteins. Curr Opin Cell Biol 2009; 21: 796–805.
3. Li H, Chen Q, Kaller M, Nellen W, Gräf R, De Lozanne A. Dictyostelium Aurora kinase has properties of both Aurora A and Aurora B kinases. Eukaryot Cell 2008; 7: 894–905.
4. Kimmins S, Crosio C, Kotaja N, Hirayama J, Monaco L, Höög C, van Duin M, Gossen JA, Sassone-Corsi P. Differential functions of the Aurora-B and Aurora-C kinases in mammalian spermatogenesis. Mol Endocrinol 2007; 21: 726–39.
5. van Leuken R, Clijsters L, van Zon W, Lim D, Yao X, Wolthuis RM, Yaffe MB, Medema RH, van Vugt MA. Polo-like kinase-1 controls Aurora A destruction by activating APC/C-Cdh1. PLoS One 2009; 4: e5282.
6. Nguyen HG, Chinnappan D, Urano T, Ravid K. Mechanism of Aurora B degradation and its dependency on intact KEN and A-boxes: identification of an aneuploidy-promoting property. Mol Cell Biol 2005; 25: 4977–92.
7. Hans F, Skoufias DA, Dimitrov S, Margolis RL. Molecular distinctions between Aurora A and B: a single residue change transforms Aurora A into correctly localized and functional Aurora B. Mol Biol Cell 2009; 20: 3491–502.
8. Fu J, Bian M, Liu J, Jiang Q, Zhang C. A single amino acid change converts Aurora-A into Aurora-B-like kinase in terms of partner specificity and cellular function. Proc Natl Acad Sci USA 2009; 106: 6939–44.
9. Eyers PA, Churchill ME, Maller JL. The Aurora A and Aurora B protein kinases: a single amino acid difference controls intrinsic activity and activation by TPX2. Cell Cycle 2005; 4: 784–9.
10. Walter AO, Seghezzi W, Korver W, Sheung J, Lees E. The mitotic serine/threonine kinase Aurora2/AIK is regulated by phosphorylation and degradation. Oncogene 2000; 19: 4906–16.
11. Lim SK, Gopalan G. Aurora-A kinase interacting protein 1 (AURKAIP1) promotes Aurora-A degradation through an alternative ubiquitin-independent pathway. Biochem J 2007; 403: 119–27.
12. Pugacheva EN, Golemis EA. The focal adhesion scaffolding protein HEF1 regulates activation of the Aurora-A and Nek2 kinases at the centrosome. Nat Cell Biol 2005; 7: 937–46.
13. Macůrek L, Lindqvist A, Lim D, Lampson MA, Klompmaker R, Freire R, Clouin C, Taylor SS, Yaffe MB, Medema RH. Polo-like kinase-1 is activated by aurora A to promote checkpoint recovery. Nature 2008; 455: 119–23.
14. Macurek L, Lindqvist A, Medema RH. Aurora-A and hBora join the game of Polo. Cancer Res 2009; 69: 4555–8.
15. Seki A, Coppinger JA, Jang CY, Yates JR, Fang G. Bora and the kinase Aurora a cooperatively activate the kinase Plk1 and control mitotic entry. Science 2008; 320: 1655–8.
16. Pascreau G, Eckerdt F, Lewellyn AL, Prigent C, Maller JL. Phosphorylation of p53 is regulated by TPX2-Aurora A in Xenopus oocytes. J Biol Chem 2009; 284: 5497–505.
17. Katayama H, Sasai K, Kawai H, Yuan ZM, Bondaruk J, Suzuki F, Fujii S, Arlinghaus RB, Czerniak BA, Sen S. Phosphorylation by aurora kinase A induces Mdm2-mediated destabilization and inhibition of p53. Nat Genet 2004; 36: 55–62.
18. Qin L, Tong T, Song Y, Xue L, Fan F, Zhan Q. Aurora-A interacts with Cyclin B1 and enhances its stability. Cancer Lett 2009; 275: 77–85.
19. Dutertre S, Cazales M, Quaranta M, Froment C, Trabut V, Dozier C, Mirey G, Bouché JP, Theis-Febvre N, Schmitt E, Monsarrat B, Prigent C, Ducommun B. Phosphorylation of CDC25B by Aurora-A at the centrosome contributes to the G2-M transition. J Cell Sci 2004; 117: 2523–31.
20. Toji S, Yabuta N, Hosomi T, Nishihara S, Kobayashi T, Suzuki S, Tamai K, Nojima H. The centrosomal protein Lats2 is a phosphorylation target of Aurora-A kinase. Genes Cells 2004; 9: 383–97.
21. Kinoshita K, Noetzel TL, Pelletier L, Mechtler K, Drechsel DN, Schwager A, Lee M, Raff JW, Hyman AA. Aurora A phosphorylation of TACC3/maskin is required for centrosome-dependent microtubule assembly in mitosis. J Cell Biol 2005; 170: 1047–55.
22. Conte N, Delaval B, Ginestier C, Ferrand A, Isnardon D, Larroque C, Prigent C, Séraphin B, Jacquemier J, Birnbaum D. TACC1-chTOG-Aurora A protein complex in breast cancer. Oncogene 2003; 22: 8102–16.
23. Pugacheva EN, Jablonski SA, Hartman TR, Henske EP, Golemis EA. HEF1-dependent Aurora A activation induces disassembly of the primary cilium. Cell 2007; 129: 1351–63.
24. Wirtz-Peitz F, Nishimura T, Knoblich JA. Linking cell cycle to asymmetric division: Aurora-A phosphorylates the Par complex to regulate Numb localization. Cell 2008; 135: 161–73.
25. Kunitoku N, Sasayama T, Marumoto T, Zhang D, Honda S, Kobayashi O, Hatakeyama K, Ushio Y, Saya H, Hirota T. CENP-A phosphorylation by Aurora-A in prophase is required for enrichment of Aurora-B at inner centromeres and for kinetochore function. Dev Cell 2003; 5: 853–64.
26. Zeitlin SG, Shelby RD, Sullivan KF. CENP-A is phosphorylated by Aurora B kinase and plays an unexpected role in completion of cytokinesis. J Cell Biol 2001; 155: 1147–57.
27. Katayama H, Sasai K, Kloc M, Brinkley BR, Sen S. Aurora kinase-A regulates kinetochore/chromatin associated microtubule assembly in human cells. Cell Cycle 2008; 7: 2691–704.
28. Adams RR, Eckley DM, Vagnarelli P, Wheatley SP, Gerloff DL, Mackay AM, Svingen PA, Kaufmann SH, Earnshaw WC. Human INCENP colocalizes with the Aurora-B/AIRK2 kinase on chromosomes and is overexpressed in tumour cells. Chromosoma 2001; 110: 65–74.
29. Zhang X, Ems-McClung SC, Walczak CE. Aurora A phosphorylates MCAK to control ran-dependent spindle bipolarity. Mol Biol Cell 2008; 19: 2752–65.
30. Andrews PD, Ovechkina Y, Morrice N, Wagenbach M, Duncan K, Wordeman L, Swedlow JR. Aurora B regulates MCAK at the mitotic centromere. Dev Cell 2004; 6: 253–68.
31. Ban R, Matsuzaki H, Akashi T, Sakashita G, Taniguchi H, Park SY, Tanaka H, Furukawa K, Urano T. Mitotic regulation of the stability of microtubule plus-end tracking protein EB3 by ubiquitin ligase SIAH-1 and Aurora mitotic kinases. J Biol Chem 2009; 284: 28367–81.
32. Yasui Y, Urano T, Kawajiri A, Nagata K, Tatsuka M, Saya H, Furukawa K, Takahashi T, Izawa I, Inagaki M. Autophosphorylation of a newly identified site of Aurora-B is indispensable for cytokinesis. J Biol Chem 2004; 279: 12997–3003.
33. Hans F, Dimitrov S. Histone H3 phosphorylation and cell division. Oncogene 2001; 20: 3021–7.
34. Delacour-Larose M, Thi MN, Dimitrov S, Molla A. Role of survivin phosphorylation by aurora B in mitosis. Cell Cycle 2007; 6: 1878–85.
35. Wheatley SP, Barrett RM, Andrews PD, Medema RH, Morley SJ, Swedlow JR, Lens SM. Phosphorylation by aurora-B negatively regulates survivin function during mitosis. Cell Cycle 2007; 6: 1220–30.
36. Gadea BB, Ruderman JV. Aurora B is required for mitotic chro-

matin-induced phosphorylation of Op18/Stathmin. Proc Natl Acad Sci USA 2006; 103: 4493–8.
37. Rosasco-Nitcher SE, Lan W, Khorasanizadeh S, Stukenberg PT. Centromeric Aurora-B activation requires TD-60, microtubules, and substrate priming phosphorylation. Science 2008; 319: 469–72.
38. Han Z, Riefler GM, Saam JR, Mango SE, Schumacher JM. The C-elegans Tousled-like kinase contributes to chromosome segregation as a substrate and regulator of the Aurora B kinase. Curr Biol 2005; 15: 894–904.
39. Cheeseman IM, Chappie JS, Wilson-Kubalek EM, Desai A. The conserved KMN network constitutes the core microtubule-binding site of the kinetochore. Cell 2006; 127: 983–97.
40. Cimini D. Detection and correction of merotelic kinetochore orientation by Aurora B and its partners. Cell Cycle 2007; 6: 1558–64.
41. Minoshima Y, Kawashima T, Hirose K, Tonozuka Y, Kawajiri A, Bao YC, Deng X, Tatsuka M, Narumiya S, May WS Jr, Nosaka T, Semba K, Inoue T, Satoh T, Inagaki M, Kitamura T. Phosphorylation by aurora B converts MgcRacGAP to a RhoGAP during cytokinesis. Dev Cell 2003; 4: 549–60.
42. Guse A, Mishima M, Glotzer M. Phosphorylation of ZEN-4/MKLP1 by aurora B regulates completion of cytokinesis. Curr Biol 2005; 15: 778–86.
43. Delaval B, Ferrand A, Conte N, Larroque C, Hernandez-Verdun D, Prigent C, Birnbaum D. Aurora-B-TACC1 protein complex in cytokinesis. Oncogene 2004; 23: 4516–22.
44. Barr AR, Gergely F. Aurora-A: the maker and breaker of spindle poles. J Cell Sci 2007; 120: 2987–96.
45. Sasai K, Parant JM, Brandt ME, Carter J, Adams HP, Stass SA, Killary AM, Katayama H, Sen S. Targeted disruption of Aurora A causes abnormal mitotic spindle assembly, chromosome misalignment and embryonic lethality. Oncogene 2008; 27: 4122–7.
46. Zhao ZS, Lim JP, Ng YW, Lim L, Manser E. The GIT-associated kinase PAK targets to the centrosome and regulates Aurora-A. Mol Cell 2005; 20: 237–49.
47. Petretti C, Savoian M, Montembault E, Glover DM, Prigent C, Giet R. The PITSLRE/CDK11p58 protein kinase promotes centrosome maturation and bipolar spindle formation. EMBO Rep 2006; 7: 418–24.
48. De Luca M, Lavia P, Guarguaglini G. A functional interplay between Aurora-A, Plk1 and TPX2 at spindle poles: Plk1 controls centrosomal localization of Aurora-A and TPX2 spindle association. Cell Cycle 2006; 5: 296–303.
49. Satinover DL, Leach CA, Stukenberg PT, Brautigan DL. Activation of Aurora-A kinase by protein phosphatase inhibitor-2, a bifunctional signaling protein. Proc Natl Acad Sci USA 2004; 101: 8625–30.
50. Bird AW, Hyman AA. Building a spindle of the correct length in human cells requires the interaction between TPX2 and Aurora A. J Cell Biol 2008; 182: 289–300.
51. Sardon T, Peset I, Petrova B, Vernos I. Dissecting the role of Aurora A during spindle assembly. EMBO J 2008; 27: 2567–79.
52. Marumoto T, Honda S, Hara T, Nitta M, Hirota T, Kohmura E, Saya H. Aurora-A kinase maintains the fidelity of early and late mitotic events in HeLa cells. J Biol Chem 2003; 278: 51786–95.
53. Huck JJ, Zhang M, McDonald A, Bowman D, Hoar KM, Stringer B, Ecsedy J, Manfredi MG, Hyer ML. MLN8054, an inhibitor of Aurora A kinase, induces senescence in human tumor cells both in vitro and in vivo. Mol Cancer Res 2010; 8: 373–84.
54. Ruchaud S, Carmena M, Earnshaw WC. Chromosomal passengers: conducting cell division. Nat Rev Mol Cell Biol 2007; 8: 798–812.
55. Jeyaprakash AA, Klein UR, Lindner D, Ebert J, Nigg EA, Conti E. Structure of a Survivin-Borealin-INCENP core complex reveals how chromosomal passengers travel together. Cell 2007; 131: 271–85.
56. Bolton MA, Lan W, Powers SE, McCleland ML, Kuang J, Stukenberg PT. Aurora B kinase exists in a complex with survivin and INCENP and its kinase activity is stimulated by survivin binding and phosphorylation. Mol Biol Cell 2002; 13: 3064–77.
57. Bishop JD, Schumacher JM. Phosphorylation of the carboxyl terminus of inner centromere protein (INCENP) by the Aurora B kinase stimulates Aurora B kinase activity. J Biol Chem 2002; 277: 27577–80.
58. Sessa F, Mapelli M, Ciferri C, Tarricone C, Areces LB, Schneider TR, Stukenberg PT, Musacchio A. Mechanism of Aurora B activation by INCENP and inhibition by hesperadin. Mol Cell 2005; 18: 379–91.
59. Jelluma N, Brenkman AB, van den Broek NJ, Cruijsen CW, van Osch MH, Lens SM, Medema RH, Kops GJ. Mps1 phosphorylates Borealin to control Aurora B activity and chromosome alignment. Cell 2008; 132: 233–46.
60. Zachos G, Black EJ, Walker M, Scott MT, Vagnarelli P, Earnshaw WC, Gillespie DA. Chk1 is required for spindle checkpoint function. Dev Cell 2007; 12: 247–60.
61. Oh HJ, Kim MJ, Song SJ, Kim T, Lee D, Kwon SH, Choi EJ, Lim DS. MST1 limits the kinase activity of aurora B to promote stable kinetochore-microtubule attachment. Curr Biol 2010; 20: 416–22.
62. Ruchaud S, Carmena M, Earnshaw WC. The chromosomal passenger complex: one for all and all for one. Cell 2007; 131: 230–1.
63. Gruneberg U, Neef R, Honda R, Nigg EA, Barr FA. Relocation of Aurora B from centromeres to the central spindle at the metaphase to anaphase transition requires MKlp2. J Cell Biol 2004; 166: 167–72.
64. Xu Z, Ogawa H, Vagnarelli P, Bergmann JH, Hudson DF, Ruchaud S, Fukagawa T, Earnshaw WC, Samejima K. INCENP-aurora B interactions modulate kinase activity and chromosome passenger complex localization. J Cell Biol 2009; 187: 637–53. Erratum in: J Cell Biol 2010; 188: 611.
65. Steigemann P, Wurzenberger C, Schmitz MH, Held M, Guizetti J, Maar S, Gerlich DW. Aurora B-mediated abscission checkpoint protects against tetraploidization. Cell 2009; 136: 473–84.
66. Hoang TM, Favier B, Valette A, Barette C, Nguyen CH, Lafanechère L, Grierson DS, Dimitrov S, Molla A. Benzo[e]pyridoindoles, novel inhibitors of the aurora kinases. Cell Cycle 2009; 8: 765–72.
67. Gizatullin F, Yao Y, Kung V, Harding MW, Loda M, Shapiro GI. The aurora kinase inhibitor VX-680 induces endoreduplication and apoptosis preferentially in cells with compromised p53-dependent postmitotic checkpoint function. Cancer Res 2006; 66: 7668–77.
68. Ditchfield C, Johnson VL, Tighe A, Ellston R, Haworth C, Johnson T, Mortlock A, Keen N, Taylor SS. Aurora B couples chromosome alignment with anaphase by targeting BubR1, Mad2, and Cenp-E to kinetochores. J Cell Biol 2003; 161: 267–80.
69. Honda R, Körner R, Nigg EA. Exploring the functional interactions between Aurora B, INCENP, and survivin in mitosis. Mol Biol Cell 2003; 14: 3325–41.

70. Liu D, Vader G, Vromans MJ, Lampson MA, Lens SM. Sensing chromosome bi-orientation by spatial separation of aurora B kinase from kinetochore substrates. Science 2009; 323: 1350–3.
71. Delacour-Larose M, Vu HL, Molla A. Aurora B kinase, an immobile passenger! Cell Cycle 2009; 8: 3600–1.
72. Delacour-Larose M, Molla A, Skoufias DA, Margolis RL, Dimitrov S. Distinct dynamics of Aurora B and Survivin during mitosis. Cell Cycle 2004; 3: 1418–26.
73. Murata-Hori M, Wang YL. Both midzone and astral microtubules are involved in the delivery of cytokinesis signals: insights from the mobility of aurora B. J Cell Biol 2002; 159: 45–53.
74. Ahonen LJ, Kukkonen AM, Pouwels J, Bolton MA, Jingle CD, Stukenberg PT, Kallio MJ. Perturbation of Incenp function impedes anaphase chromatid movements and chromosomal passenger protein flux at centromeres. Chromosoma 2009; 118: 71–84.
75. Cazales M, Schmitt E, Montembault E, Dozier C, Prigent C, Ducommun B. CDC25B phosphorylation by Aurora-A occurs at the G2/M transition and is inhibited by DNA damage. Cell Cycle 2005; 4: 1233–8.
76. Monaco L, Kolthur-Seetharam U, Loury R, Murcia JM, de Murcia G, Sassone-Corsi P. Inhibition of Aurora-B kinase activity by poly(ADP-ribosyl)ation in response to DNA damage. Proc Natl Acad Sci USA 2005; 102: 14244–8.
77. Kallio MJ, McCleland ML, Stukenberg PT, Gorbsky GJ. Inhibition of aurora B kinase blocks chromosome segregation, overrides the spindle checkpoint, and perturbs microtubule dynamics in mitosis. Curr Biol 2002; 12: 900–5.
78. Norden C, Mendoza M, Dobbelaere J, Kotwaliwale CV, Biggins S, Barral Y. The NoCut pathway links completion of cytokinesis to spindle midzone function to prevent chromosome breakage. Cell 2006; 125: 85–98.
79. Mendoza M, Norden C, Durrer K, Rauter H, Uhlmann F, Barral Y. A mechanism for chromosome segregation sensing by the NoCut checkpoint. Nat Cell Biol 2009; 11: 477–83.
80. Cochran AG. Aurora A: target invalidated? Chem Biol 2008; 15: 525–6.
81. Girdler F, Sessa F, Patercoli S, Villa F, Musacchio A, Taylor S. Molecular basis of drug resistance in aurora kinases. Chem Biol 2008; 15: 552–62.
82. Cheung CH, Coumar MS, Hsieh HP, Chang JY. Aurora kinase inhibitors in preclinical and clinical testing. Expert Opin Investig Drugs 2009; 18: 379–98.
83. Vu HL, Hoang TMN, Favier B, Molla A. Aurora kinases and passenger proteins as targets for cancer therapy: an up-date. Curr Enzyme Inhibition 2010; 6: 19–25.
84. Giles FJ, Cortes J, Jones D, Bergstrom D, Kantarjian H, Freedman SJ. MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation. Blood 2007; 109: 500–2.
85. Shimomura T, Hasako S, Nakatsuru Y, Mita T, Ichikawa K, Kodera T, Sakai T, Nambu T, Miyamoto M, Takahashi I, Miki S, Kawanishi N, Ohkubo M, Kotani H, Iwasawa Y. MK-5108, a highly selective Aurora-A kinase inhibitor, shows antitumor activity alone and in combination with docetaxel. Mol Cancer Ther 2010; 9: 157–66.
86. Jetton N, Rothberg KG, Hubbard JG, Wise J, Li Y, Ball HL, Ruben L. The cell cycle as a therapeutic target against Trypanosoma brucei: Hesperadin inhibits Aurora kinase-1 and blocks mitotic progression in bloodstream forms. Mol Microbiol 2009; 72: 442–58.
87. Saskova A, Solc P, Baran V, Kubelka M, Schultz RM, Motlik J. Aurora kinase A controls meiosis I progression in mouse oocytes. Cell Cycle 2008; 7: 2368–76.
88. Yamamoto TM, Lewellyn AL, Maller JL. Regulation of the Aurora B chromosome passenger protein complex during oocyte maturation in Xenopus laevis. Mol Cell Biol 2008; 28: 4196–203.
89. Dieterich K, Soto Rifo R, Faure AK, Hennebicq S, Ben Amar B, Zahi M, Perrin J, Martinez D, Sèle B, Jouk PS, Ohlmann T, Rousseaux S, Lunardi J, Ray PF. Homozygous mutation of AURKC yields large-headed polyploid spermatozoa and causes male infertility. Nat Genet 2007; 39: 661–5.
90. Dieterich K, Zouari R, Harbuz R, Vialard F, Martinez D, Bellayou H, Prisant N, Zoghmar A, Guichaoua MR, Koscinski I, Kharouf M, Noruzinia M, Nadifi S, Sefiani A, Lornage J, Zahi M, Viville S, Sèle B, Jouk PS, Jacob MC, Escalier D, Nikas Y, Hennebicq S, Lunardi J, Ray PF. The Aurora Kinase C c.144delC mutation causes meiosis I arrest in men and is frequent in the North African population. Hum Mol Genet 2009; 18: 1301–9.