Introduction

Cell division is a highly complex process that has intrigued scientists for over a century. Underneath the striking structural rearrangements lies a complex regulatory network of kinases and phosphatases that maintain the accuracy of cell division. One such kinase is Aurora-A, a member of the evolutionary conserved Aurora serine/threonine kinase family. Whereas there is only one Aurora protein in yeast (the founding member of the family Ipl1 in Saccharomyces cerevisiae and Ark1 in Schizosaccharomyces pombe), metazoans have at least two aurora genes: aurora-a and aurora-b (reviewed in Andrews et al., 2003). A third member of the family, aurora-c, is specifically expressed during meiosis in the mammalian testis, where it behaves similarly to Aurora-B (Bernard et al., 1998; Kimmins et al., 2007; Kimura et al., 1999; Tang et al., 2006; Tseng et al., 1998). The catalytic domain of the Aurora kinases is highly conserved; sequences outside this region are more divergent. Members of the Aurora kinase family play important but distinct roles in maintaining genome stability. Whereas Aurora-B is required for chromosome bi-orientation and cytokinesis (reviewed in Vagnarelli and Earnshaw, 2004), Aurora-A has emerged as a major regulator of mitotic centrosomes and spindle assembly.

Centrosomes consist of a pair of centrioles surrounded by a pericentriolar matrix (PCM), the site of microtubule (MT) assembly. To form the poles of the bipolar spindle, centrosomes must undergo a series of tightly controlled events including duplication, separation and maturation (for details see Fig. 1) (for reviews, see Nigg, 2007; Azimzadeh and Bornens, 2007). Loss-of-function studies established some time ago that Aurora-A is required for multiple steps during mitosis. Perturbing Aurora-A leads to defective centrosome separation and maturation in a wide variety of experimental model systems (Fig. 1 and Table 1) (Berdnik and Knoblich, 2002; Girdler et al., 2006; Glover et al., 1995; Hannak et al., 2001; Marumoto et al., 2003; Mori et al., 2007; Schumacher et al., 1998; Terada et al., 2003). Cell cycle progression, mitotic spindle pole organisation and MT stability are also often compromised in the absence of Aurora-A (Hachet et al., 2007; Hirotà et al., 2003; Liu and Ruderman, 2006; Marumoto et al., 2002; Peset et al., 2005; Portier et al., 2007; Schumacher et al., 1998).

The human aurora-a gene maps to 20q13, a region frequently amplified in breast cancers, and is also overexpressed in several tumours (Bischoff et al., 1998; Sen et al., 1997; Zhou et al., 1998). It has also been identified as a low-penetrance cancer susceptibility gene in colorectal tumours (Ewart-Toland et al., 2003). Ectopic expression of Aurora-A leads to centrosome amplification, aneuploidy and chromosome instability (Anand et al., 2003; Kufer et al., 2002; Zhou et al., 1998), illustrating the potential of Aurora-A to drive cancer progression. However, the molecular mechanisms responsible for the transforming nature of Aurora-A overexpression remain elusive (Keen and Taylor, 2004).

The expression and localisation of Aurora-A is consistent with its function as a mitotic centrosomal kinase. During G1/S phase, its levels are low, but, in G2 phase, the levels of Aurora-A mRNA and protein kinase activity all rise rapidly, reaching a peak in early mitosis (Bischoff et al., 1998; Kimura et al., 1997; Zhou et al., 1998). The cdk1-activated anaphase-promoting complex/cyclosome (APC) initiates Aurora-A degradation in anaphase B but only completes it in G1 phase (Honda et al., 2000; Lindon and Pines, 2004; Taguchi et al., 2002). Aurora-A kinase is present on duplicated centrosomes from late S phase until early G1 phase and it is also detectable on spindle MTs during mitosis (Fig. 2). The rapid turnover of Aurora-A both in the centrosome and on the mitotic spindle argues for a signalling rather than a structural role for the kinase at these locations (Stenoien et al., 2003). This is not surprising, because as well as playing a significant role in organising the mitotic MT network, the centrosome also acts as an important signalling platform (Azimzadeh and Bornens, 2007). Thus the Aurora-A kinase at the centrosome is clearly in prime position to coordinate mitotic events.

The Aurora-A consensus phosphorylation site was defined in budding yeast as [KR][TS][ILV] (Cheeseman et al., 2002).
**Fig. 1.** The centrosome cycle. At the beginning of G1 phase, cells contain a single centrosome with two perpendicularly aligned, closely associated centrioles. The two centrioles are not identical at this stage. The daughter centriole originates from the previous cell cycle, whereas the mother centriole (centriole with black cap) assembled at least two cell cycles ago. During G1 phase, the tight link (purple bar) between the centrioles is dissolved (centriole disengagement), but centrioles remain connected by a loose fibrous structure. Centriole disengagement is a prerequisite for centrosome duplication. In S phase, the centrosome duplicates simultaneously with DNA replication. Duplication involves the assembly of two new centrioles perpendicularly to the existing centrioles. Note that at this point there are three different types of centriole in the cell: two newly formed centrioles, the daughter and the mother centriole. Next, the daughter centriole finally acquires the same molecular characteristics as the mother centriole and the fibrous tether between the mother and daughter centrioles is severed. Due to the tight link (purple bars) between the old centrioles and the newly formed ones, the two centrosomes are now engaged and prevented from further replication. In late G2 phase, the two centrosomes undergo maturation by recruiting additional PCM (grey circle) components to prepare for their role as spindle poles. The centrosomes then separate and move to the opposite side of the nucleus. Here, we show this as simultaneous with nuclear envelope breakdown (NEBD) and mitotic commitment; however, separation can be completed before or after NEBD (see text). Also, the timing and ordering of these events vary between cell types and organisms. After NEBD, the centrosomes start nucleating MT asters that capture chromosomes and form a bipolar spindle structure. The bipolar nature of mitosis ensures that each daughter cell inherits one centrosome. In dark-purple text, we list the experimental systems in which there is evidence for Aurora-A involvement in a particular step of the centrosome cycle (for more details, see Table 1).

**Table 1. Phenotypes of Aurora-A mutants and knockdowns**

| Organism | Gene name | Phenotype | References |
|----------|-----------|-----------|------------|
| *X. laevis* | eg2 | Monopolar or short bipolar spindles in egg extracts | (13) Liu and Ruderman, 2006 |
| | | Partially decondensed chromatin | (14) Peset et al., 2005 |
| | | Failure in meiosis I to meiosis II transition in oocytes | (15) Castro et al., 2003 |
| | | Defects in CPEB-dependent translational regulation during oocyte maturation | (16) Sarkissian et al., 2004 |
| *D. melanogaster* | aurora-a | Monopolar spindles | (7) Glover et al., 1995 |
| | | Short astral MTs | (8) Giet et al., 2002 |
| | | Defective centrosome maturation | (9) Terada et al., 2003 |
| | | Loss of asymmetric localisation of Numb in sensory organ precursors and neuroblasts | (10) Berdnik and Knoblich, 2002 |
| | | Abnormal-looking centrosomes | (11) Wang et al., 2006 |
| | | Aneuploidy and embryonic lethality | (12) Lee et al., 2006 |
| *C. elegans* | air-1 | Monopolar spindles (centrosomes collapse after NEBD) | (1) Hannak et al., 2001 |
| | | Weak astral MTs | (2) Motegi et al., 2006 |
| | | Ectopic cortical furrowing during late mitosis | (3) Srayko et al., 2005 |
| | | Decrease in centrosomal MT levels | (4) Portier et al., 2007 |
| | | Defective centrosome maturation | (5) Hachet et al., 2007 |
| | | Delay in mitotic entry | (6) Schumacher et al., 1998 |
| | | Delay in NEBD | (1) Schumacher et al., 1998 |
| | | Abnormal-looking centrosomes | (9) Terada et al., 2003 |
| | | Aneuploidy and embryonic lethality | (10) Berdnik and Knoblich, 2002 |
| *H. sapiens* | aurora-a | Monopolar spindles | (17) Girdler et al., 2006 |
| | | Delay in mitotic entry | (18) Hirota et al., 2003 |
| | | Defective centrosome maturation | (19) De Luca et al., 2006 |
| | | Misaligned chromosomes in metaphase | (20) Marumoto et al., 2002 |
| | | | (21) Marumoto et al., 2003 |
This motif has now been confirmed in higher eukaryotes as a genuine Aurora-A-phosphorylation site in the proteins TACC, CDC25B and in NDEL1 (Barros et al., 2005; Dutertre et al., 2004; Giet et al., 2002; LeRoy et al., 2007; Peset et al., 2005). The kinase activity of Aurora-A is regulated by autocatalytic phosphorylation of Thr288 in its activatory T-loop (Bischoff et al., 1998; Littlepage et al., 2002; Walter et al., 2000). This autocatalytic activity of Aurora-A is facilitated by cofactors such as Bora, Ajuba, PAK1 and Tpx2 (Table 2) (Eyers et al., 2003; Hirota et al., 2003; Hutterer et al., 2006; Zhao et al., 2005). The mechanism of cofactor-mediated Aurora-A activation is best understood in the case of Tpx2. Co-crystallisation revealed that binding of Tpx2 to Aurora-A not only induces it to adopt an active conformation but also prevents dephosphorylation of Thr288 by protein phosphatase 1 (PP1) (Bayliss et al., 2003). Importantly, the latter is not due to competition, because the binding sites for PP1 and Tpx2 on Aurora-A do not overlap (Katayama et al., 2001). Tpx2, Bora and Ajuba are also substrates of the kinase (Hirota et al., 2003; Hutterer et al., 2006; Kufer et al., 2002).

Below, we will describe how the Aurora-A kinase, together with its cofactors and substrates, coordinates early mitotic events in and outside the centrosome.

**Aurora-A: parenting the centrosome to maturity**

MT numbers and dynamics are carefully controlled during the cell cycle. The centrosome, or more specifically the PCM, is the predominant site for MT nucleation in proliferating cells. Mitotic centrosomes nucleate up to sevenfold more MTs than their interphase counterparts (Piehl et al., 2004). This increase in nucleation capacity is at least partially brought about by centrosome maturation in late G2 phase and prophase, when the PCM expands by recruiting additional components, such as the γ-tubulin ring complex (γ-TuRC), *Drosophila* centrosomin (CNN) or *Caenorhabditis elegans* CeGrip (Hannak et al., 2001; Khodjakov and Rieder, 1999; Megraw et al., 1999).

An evolutionarily conserved role for Aurora-A in this process has been established in several organisms, including *C. elegans*, *Drosophila* and humans (Berdnik and Knoblich, 2002; Hannak et al., 2001; Hirota et al., 2003; Mori et al., 2007; Terada et al., 2003). In Aurora-A-depleted *C. elegans* embryos, γ-tubulin fails to accumulate at the centrosome prior to mitosis, which results in a 60% decrease in centrosomal MT levels (Hannak et al., 2001). Similarly, centrosomes of *aurora-a* mutant sensory organ precursor cells in *Drosophila* display no increase in γ-tubulin levels upon mitotic entry (Berdnik and Knoblich, 2002). By contrast, no major change can be detected in the levels of centrosomal γ-tubulin and CNN in *aurora-a* mutant neuroblasts or in Aurora-A-depleted *Drosophila* S2 cells (Giet et al., 2002). This raises the question of how general a role Aurora-A plays in centrosome maturation in *Drosophila*.

Targeting of Aurora-A to centrosomes requires Polo-like kinase 1 (Plk-1), which is also implicated in centrosome maturation (Lane and Nigg, 1996; Sunkel and Glover, 1988). Factors that lie upstream of Aurora-A and regulate its role in centrosome maturation include two additional kinases, CDK11 (Petretti et al., 2006) and PAK1 (Zhao et al., 2005). When CDK11 levels are reduced, neither Plk-1 nor Aurora-A accumulates at the centrosome and centrosome maturation consequently fails. Likewise, inhibiting the activity of PAK1 delays centrosome maturation. PAK1 is a cofactor of Aurora-A, but it can also phosphorylate the kinase. PAK1 has a well-established role in focal adhesion turnover, and therefore it could provide a link between mitotic events and focal adhesion dynamics (Zhao et al., 2005). Interestingly, the focal adhesion scaffolding factor Hef1 also plays a role in Aurora-A activation and centrosome maturation (Pugacheva and Golemis, 2005). Another cofactor of Aurora-A that has been implicated in centrosome maturation is Tpx2 (De Luca et al., 2006). As well as promoting its autophosphorylation and kinase activity (Bayliss et al., 2003; Eyers et al., 2003; Tsai and Zheng, 2005), Tpx2 also targets Aurora-A to the mitotic spindle MTs (Kufer et al., 2002). Moreover, Tpx2 plays an important role in spindle assembly (see below). Centrosome maturation in *Drosophila* sensory precursor cells requires a third Aurora-A cofactor, Bora (Hutterer et al., 2006). Bora is evolutionarily conserved, but its function in centrosome maturation has not yet been explored. Interestingly, in *C. elegans* embryos, Bora is not required for viability (Kamath et al., 2003; Sonnichsen et al., 2005).

So far, only a few downstream targets of Aurora-A have been found to affect centrosome maturation. One such factor is LATS2, a serine-threonine kinase present at mitotic centrosomes that is phosphorylated by Aurora-A (Abe et al., 2006; Toji et al., 2004). When LATS2 levels are knocked down

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**Table 2. Aurora-A substrates and cofactors and their involvement in Aurora-A-mediated processes**

| Aurora-A substrate | Process |
|--------------------|---------|
| CDC25B             | Mitotic entry (through activation of cyclin-B1–Cdk1) |
| CPEB               | Translational control of cell cycle regulators |
| Eg5                | Centrosome separation, mitotic spindle assembly |
| LATS2              | Centrosome maturation |
| NDEL1              | Centrosome maturation, mitotic entry, centrosome separation |
| TACC               | Astral MT stability, mitotic spindle assembly |

| Aurora-A cofactor | Process |
|------------------|---------|
| Ajuba            | Centrosome maturation |
| Bora             | Centrosome maturation, asymmetric cell division |
| PAK1             | Centrosome maturation |
| Tpx2             | Centrosome maturation, mitotic spindle assembly |
Commitment phobia: immature centrosomes in mitotic entry

In addition to centrosome maturation, Aurora-A also regulates cell cycle progression – in particular, entry into mitosis. Human cells display severe delays in mitotic entry when Aurora-A function is disrupted (Hirota et al., 2003; Marumoto et al., 2002; Marumoto et al., 2003). Similar defects are observed in Aurora-A-depleted C. elegans embryos (Hannak et al., 2001) and in human cells treated with Plk-1 inhibitors (Lenart et al., 2007).

In most cells, chromosomes start condensing in G2 phase or early prophase, which requires the activity of cyclin-A–Cdk1. Later stages of chromosome condensation, however, rely on the chief mitotic kinase, cyclin-B1–Cdk1. Cyclin-B1–Cdk1 complexes are activated in late prophase and this activation triggers mitotic entry by initiating NEBD. At this point, cells become committed to mitosis and they proceed into prometaphase, even if stressed (reviewed in Pines and Rieder, 2001). For mitotic entry to occur with normal timing, the concerted activity of several kinases is required. In addition to Aurora-A and cyclin-B1–Cdk1, Plk-1 and NIMA have also been implicated in this process (reviewed in Nigg, 2001). Several of these factors reside at the centrosome, which effectively compartmentalises their activity. For instance, cyclin-B1–Cdk1 complexes appear at the centrosome during prophase, prior to the major wave of cyclin-B1–Cdk1 activation elsewhere in the cell (De Souza et al., 2000; Jackman et al., 2003), and this initial activation appears to be important for normal timing of mitotic entry (Kramer et al., 2004). The centrosomal targeting of cyclin-B1–Cdk1 requires Aurora-A and occurs at the same time as centrosome maturation (Hirota et al., 2003). Moreover, Aurora-A phosphorylates CDC25B, which in turn activates cyclin-B1–Cdk1 at the centrosome (Cazales et al., 2005; Dutertre et al., 2004). This may facilitate the local activation of cyclin-B1–Cdk1 and hence promote mitotic entry. A positive feedback loop between Aurora-A and cyclin-B1–Cdk1 involves the inactivation of PP1 by cyclin-B1–Cdk1 at the centrosome (Katayama et al., 2001; Marumoto et al., 2002).

Until recently, it was widely believed that the role of Aurora-A in mitotic entry was linked to its centrosomal function, but new experimental evidence suggests otherwise. In Xenopus egg extracts, Aurora-A regulates the timing of mitotic entry in a centrosome- and chromatin-independent way (Liu and Ruderman, 2006). Here, the effect of Aurora-A is dose dependent; its overexpression accelerates G2/M progression, whereas its depletion delays, but does not block, mitosis. Both centrosomes and Aurora-A are required for timely mitotic entry in C. elegans embryos (Hachet et al., 2007; Portier et al., 2007). Importantly, however, inhibiting centrosome assembly delays NEBD to a lesser extent than depleting Aurora-A, which further supports a centrosome-independent role of the kinase in mitotic entry. The mechanism employed by Aurora-A to

by small interfering RNA (siRNA) in mammalian cells, centrosome maturation fails. Aurora-A-mediated phosphorylation has been suggested to target LATs2 to the centrosome (Toji et al., 2004). LATs2 interacts with and phosphorylates a fourth Aurora-A cofactor, Ajuba, which also plays a role in centrosome maturation in mammalian cell culture (Abe et al., 2006; Hirota et al., 2003). LATs2, however, neither is required for Ajuba-dependent autoactivation of Aurora-A nor affects the targeting of Aurora-A to centrosomes. As yet, the significance of the phosphorylation of Ajuba by LATs2 for Aurora-A function is unclear, as is the molecular pathway by which LATs2 induces centrosome maturation (Fig. 3). Also, the finding that the Ajuba-knockout mouse is viable raises the question of whether Ajuba is essential for Aurora-A function in an intact organism (Pratt et al., 2005).

Another protein downstream of Aurora-A that has a role in centrosome maturation is NDEL1 (Mori et al., 2007). NDEL1 is phosphorylated by Aurora-A in late G2/prophase. This phosphorylation is required to recruit NDEL1 to the centrosome and subsequently leads to the ubiquitylation and degradation of NDEL1. Expression of a phosphomimetic version of NDEL1 partially restores centrosome maturation in the absence of Aurora-A function and is equally proficient at rescuing other defects characteristic of Aurora-A-depleted cells, such as failures in centrosome separation and mitotic entry. NDEL1 is therefore required for several of the Aurora-A-driven processes and is not specific for centrosome maturation (Table 2). Likewise, depleting cells of Ajuba leads not only to defective centrosome maturation but also to severely delayed mitotic entry (Hirota et al., 2003). These examples highlight the problem of teasing apart centrosome maturation and concomitant or subsequent mitotic events, such as mitotic commitment, nuclear envelope breakdown (NEBD), centrosome separation and spindle assembly, that could all potentially be perturbed by a previous failure in centrosome maturation.
control mitotic progression, however, seems to differ between experimental systems. In *Xenopus* egg extracts and human cells, Aurora-A inhibition delays both chromosome condensation and NEBD, indicating a failure of cyclin-B1–Cdk1 activation (Hirotta et al., 2003; Liu and Ruderman, 2006; Marumoto et al., 2002). By contrast, global Cdk1 activity seems less affected in *C. elegans*, because although NEBD onset is delayed, chromosome condensation occurs with normal timing (Hachet et al., 2007; Hannak et al., 2001; Portier et al., 2007). These findings suggest that the role of Aurora-A in mitotic entry can only be partially explained by its contribution to cyclin-B1–Cdk1 activation at the centrosome. An additional level of regulation could exist, involving an unestablished centrosome-independent mechanism. Aurora-A may also be directly involved in nuclear envelope permeabilisation, which could be important for proper timing of mitotic entry (Portier et al., 2007).

Aurora-A seems to employ a surprisingly different mechanism to control cell cycle progression in *Xenopus* oocytes, which do not normally contain centrosomes. Here, oocyte maturation is induced by Aurora-A-mediated phosphorylation of the cytoplasmic polyadenylation element binding factor (CPEB), which binds to the 3’ untranslated region of regulatory mRNA molecules (Mendez et al., 2000a; Mendez et al., 2000b; Sarkissian et al., 2004). This requirement for Aurora-A does not seem to be unique to frogs, because post-mitotic neurons also employ Aurora-A phosphorylation to regulate the activity of CPEB (Huang et al., 2002) and mouse oocytes require Aurora-A for cyclin-B1 translation during maturation (Tay et al., 2000).

**Centrosome separation requires Aurora-A**

In centrosome-containing cells, the formation of a bipolar spindle depends on the correct duplication and separation of centrosomes. Although Aurora-A does not seem to play a role in duplication (Meraldi et al., 2002), it is clearly important for centrosome separation. Here, we use the term ‘separation’ to describe the movement of the centrosomes following maturation (see Fig. 1).

A role for Aurora-A in centrosome separation was first described in *Drosophila* embryos, where embryos carrying a mutation in the *aurora-A* gene display monopolar spindles (Glover et al., 1995). Monopolar spindles are also apparent in Aurora-A-depleted *C. elegans* embryos and *Xenopus* egg extracts (Hannak et al., 2001; Liu and Ruderman, 2006; Roghi et al., 1998) and in human cells treated with either Aurora-A inhibitors (Girdler et al., 2006) or siRNA (Marumoto et al., 2003). However, in some cases, spindles are disorganised but still bipolar when Aurora-A function is disrupted (Peset et al., 2005; Schumacher et al., 1998). This inconsistently is likely to stem from the fact that centrosome separation can occur by at least two distinct pathways: a nuclear-envelope-dependent (prior to NEBD) pathway and a nuclear-envelope-independent one (after NEBD). Evidence suggests that these alternative separation pathways co-exist within a single cell culture dish (Rattner and Berns, 1976; Rosenblatt et al., 2004; Whitehead et al., 1996). Careful studies of Aurora-A-depleted *C. elegans* embryos revealed that, whereas prior to NEBD, centrosome separation proceeds normally, at the onset of NEBD, the two centrosomes collapse into a monopole (Hannak et al., 2001). Therefore, Aurora-A plays an active role in the execution and/or maintenance of centrosome separation after NEBD. Because centrosome separation precedes maturation in *C. elegans* embryos, the separation pathway prior to NEBD must be independent of maturation. The role of Aurora-A in maintaining spindle pole separation, however, could be linked to its function in maturation. The molecular mechanism by which Aurora-A controls separation is still unclear, but there are two possibilities, which we discuss below.

The BimC-like kinesin Eg5 has an evolutionarily conserved role in spindle pole separation during mitosis (Harborth et al., 2001; Mayer et al., 1999; Walczak et al., 1998). Eg5 can slide antiparallel MTs and tether MT plus-ends (Kapitein et al., 2005), which led to the proposal that it maintains centrosome separation by generating a force to push overlapping MTs apart. Because Eg5 is phosphorylated by Aurora-A (Giet et al., 1999), it is tempting to speculate that it is through this kinase that Aurora-A regulates centrosome separation. As yet, however, there is no experimental evidence to suggest that phosphorylation of Aurora-A is required for Eg5 function. It is also simplistic to think that centrosome separation depends solely on overlapping MTs. For instance, in early prometaphase, before chromosomes assume bipolar attachments, centrosomes continue to migrate despite the apparent lack of antiparallel MTs between the two asters (Rieder and Alexander, 1990). This implies that the mechanism of centrosome separation must be intrinsic to each aster (Waters et al., 1993). If so, how is the force for this movement generated? Spindle poles are linked to the cell cortex by a subgroup of MTs, called astral MTs, that are exclusively nucleated by the centrosome. The importance of the cortex in centrosome positioning has emerged from the finding that disabling cortical myosin-II function does not disrupt initial centrosome movement but blocks centrosome migration following NEBD (Rosenblatt et al., 2004). Because astral MTs are sparse and short when Aurora-A function is disabled (Giet et al., 2002), we can speculate that centrosome separation defects are caused by inadequate attachments between the spindle poles and the cortex.

**The role of Aurora-A in centrosomal MT organisation**

Mitotic spindles are grossly abnormal when Aurora-A function is disrupted (Glover et al., 1995; Hannak et al., 2001; Schumacher et al., 1998). Although, arguably, such defects are to be expected when centrosome maturation is perturbed, growing evidence supports a more direct role of Aurora-A in spindle organisation. A strong contender to link centrosomal Aurora-A function to mitotic MT dynamics is the highly conserved transforming acidic-coiled-coil-containing (TACC) family of proteins (reviewed in Gergely, 2002). The TACC proteins share a conserved, 200-residue, coiled-coil ‘TACC’ domain at their C-terminus that targets the protein to the mitotic spindle and centrosome (Gergely et al., 2000). Only one TACC protein has been identified in *C. elegans* (Tac-1) (Bellanger and Gonczy, 2003; Le Bot et al., 2003; Snyakyo et al., 2003), *Drosophila* (D-TACC) (Gergely et al., 2000) and *Xenopus* (Maskin) (Stebbins-Boaz et al., 1999), whereas there are three in humans (TACC1, TACC2 and TACC3) (reviewed in Gergely, 2002).

The first evidence for a link between TACC and Aurora-A came from the observation that centrosomal recruitment of TACC is compromised in *aurora-A* mutant *Drosophila*...
syncitial embryos and larval neuroblasts (Giet et al., 2002). Subsequently, the Aurora-A consensus site was mapped to a highly conserved stretch of amino acids in Drosophila and Xenopus TACC and in human TACC3 (Barros et al., 2005; Kinoshita et al., 2005; Peset et al., 2005). The TACC proteins interact with members of the highly conserved ch-TOG/XMAP215 family of centrosomal proteins that stabilise MTs and control their plus-end dynamics. TACC has been proposed to modulate the activity of ch-TOG/XMAP215 at the centrosome, perhaps by loading it onto spindle MTs (Lee et al., 2001; Gergely et al., 2003; Kinoshita et al., 2005).

It is clear that Aurora-A can phosphorylate TACC, but what role does this phosphorylation play? Is it required for the interaction of TACC with ch-TOG/XMAP215? Data from Drosophila and Xenopus argue against this, because both phosphorylatable and non-phosphorylatable TACCs can proficiently bind to ch-TOG/XMAP215 (Barros et al., 2005; Kinoshita et al., 2005). Could phosphorylation of TACC instead be required for its centrosomal targeting? This possibility is supported by several reports. First, antibodies against phosphorylated TACC stain the centrosome but not spindle MTs in Drosophila, Xenopus and human cells (Barros et al., 2005; Kinoshita et al., 2005). Second, TACC is displaced from the centrosome in both aurora-a mutant fly embryos and human cells subjected to Aurora-A inhibitors (Giet et al., 2002; LeRoy et al., 2007). We cannot, however, exclude that mismarking of TACC is caused by abnormal centrosome maturation in these two cases. A more direct role for Aurora-A in targeting TACC has been established by experiments in which all three conserved phosphorylation sites of Xenopus TACC are disrupted. This non-phosphorylatable TACC protein fails to localise to the centrosome in egg extracts (Kinoshita et al., 2005). Yet, surprisingly, a mutant form of D-TACC, in which the conserved Aurora-A-phosphorylation site is disrupted, still localises to the centrosome in d-tacc mutant embryos. This inconsistency will be resolved if D-TACC turns out to contain other, less conserved, Aurora-A-target sites that are sufficient for its localisation (Barros et al., 2005). Alternatively, phosphorylation of D-TACC by Aurora-A might not be essential for centrosomal targeting. Indeed, there is evidence that in human cells another Aurora-A substrate, NDEL1, is required for recruitment of TACC to the centrosome (Mori et al., 2007). NDEL1 interacts with TACC3 and its phosphorylation by Aurora-A precedes that of TACC3.

Clearly, phosphorylation of TACC by Aurora-A affects its localisation, but does it modulate its function? Several lines of evidence favour this idea. Expression of a transgene encoding a non-phosphorylatable form of D-TACC in d-tacc mutant embryos does not rescue the embryonic lethality normally associated with this mutation. Unlike wild-type D-TACC, non-phosphorylatable D-TACC fails to concentrate on minus ends of MTs around the centrosome (Barros et al., 2005). Moreover, similarly to Aurora-A mutants, D-TACC-mutant embryos display a reduced number of astral MTs, and this is not rescued by non-phosphorylatable D-TACC. Likewise, when non-phosphorylatable TACC protein is added to TACC-depleted Xenopus mitotic egg extract, it does not fully restore centrosomal MT nucleation (Kinoshita et al., 2005; Peset et al., 2005). Phosphorylation of TACC by Aurora-A thus appears to be required to stabilise centrosome-nucleated MTs, particularly astral MTs, by loading TACC or TACC-XMAP215 complexes onto MT minus-ends.

One of the main functions of ch-TOG/XMAP215 is to counter the activity of a MT-destabilising kinesin, MCAK/XKCM1, and this requires the TACC protein (Kinoshita et al., 2001; Kinoshita et al., 2005). Because the TACC proteins do not bind MTs directly, phosphorylation of TACC could indirectly regulate ch-TOG/XMAP215 activity at the centrosome (Lee et al., 2001). We can therefore speculate that the phosphorylation of TACC by Aurora-A serves to target ch-TOG/XMAP215 to MT minus-ends, where it can protect them against MCAK/XKCM1 activity (Fig. 4) (Barros et al., 2005). Given that phosphorylated TACC is only detected at the centrosomes, this transfer onto MTs potentially involves the dephosphorylation of TACC. Such a mechanism would ensure that, during mitotic spindle formation, TACC and ch-TOG/XMAP215 selectively stabilise centrosome-associated MTs, hence making the centrosome the preferred site of MT assembly. Note that, through its regulation of astral MTs, Aurora-A also plays an important role positioning the cleavage furrow in C. elegans embryos in preparation for cytokinesis (Motegei et al., 2006). It remains to be seen whether this involves the TACC proteins.

The pole maker: Aurora-A and centrosome-independent spindle assembly

In most animal cells, two independent spindle assembly pathways exist (O’Connell and Khodjakov, 2007). The first one relies on centrosome-dependent nucleation of MTs that

![Fig. 4](image_url)
become stabilised upon contact with kinetochores, whereas the second pathway involves the nucleation, stabilisation and focusing of MTs that assemble around chromatin. The relative contributions of these two pathways are likely to vary between cell types and organisms. For instance, oocytes of many animal species contain no centrosomes and therefore rely solely on the chromatin-driven pathway for spindle assembly (reviewed in Compton, 2000). More recently, it was revealed that certain in vitro systems can display bipolar spindle formation even in the absence of centrosomes and chromatin, which indicates that mitotic MTs have an intrinsic capacity to form bipolar spindle-like structures (reviewed in Karsenti and Vernos, 2001).

Bipolar spindle assembly in the absence of centrosomes, or indeed centrosomes and chromatin, requires the activity of the small GTPase Ran (reviewed in Budde and Heald, 2003; Joseph, 2006; Karsenti and Vernos, 2001). In intact cells, Ran controls nucleocytoplasmic transport as well as promoting MT polymerisation and stability (reviewed in Harel and Forbes, 2004). Ran-GTP regulates spindle assembly by prompting the release of spindle assembly proteins from their association with nuclear import factors (e.g. importins) at the onset of mitosis (Gruss et al., 2001; Nachury et al., 2001; Wiese et al., 2001). The Aurora-A cofactor Tpx2 is regulated in this manner; it is nuclear during interphase but, once released by Ran-GTP activity, it binds to MTs and centrosomes. Tpx2 is an essential factor for Ran-GTP-dependent MT nucleation around chromatin in frog egg extracts (Gruss et al., 2001; Wittmann et al., 2000). This raises the question of whether Aurora-A kinase is involved in Ran-dependent spindle assembly.

A biochemical screen aimed at identifying components of this Ran-dependent pathway revealed an essential requirement for Aurora-A activity. Here the role of the kinase is to promote the assembly of a protein complex (EXTAH) comprising Eg5, XMAP215, Tpx2, Aurora-A and a novel MT-binding protein, HURP (Koffa et al., 2006; Sauer et al., 2005). Moreover, studies show that Aurora-A-coated beads are able to promote MT assembly in Xenopus egg extracts lacking both chromatin and centrosomes (Tsai and Zheng, 2005). Strikingly, unlike chromatin-coated beads, which promote MT assembly in their vicinity, Aurora-A-coated beads act like microtubule-organising centres (MTOCs); they nucleate MTs and form the poles of bipolar spindles. This behaviour depends on both γ-tubulin and Tpx2. In light of these data, we can speculate that the EXT AH complex might be responsible for Aurora-A-dependent bipolar spindle assembly (Fig. 5). The finding that XMAP215-coated beads fail to promote bipolarity indicates that MT stabilisation alone is not sufficient for bipolarity (Tsai and Zheng, 2005). Moreover, despite being a component of EXT AH, unlike Aurora-A, XMAP215 can neither activate nor recruit the complex.

Aurora-A thus has a direct role organising a spindle pole in the absence of centrosomes, probably by concentrating γ-tubulin at the poles and regulating the assembly of EXT AH. EXT AH is an excellent candidate to organise bipolar spindles from adjacent asters (see Fig. 5), because it contains a combination of MT stabilisers (e.g. XMAP215), MT-bundling proteins (e.g. HURP) (Koffa et al., 2006) and MT-crosslinking proteins (e.g. Eg5 or Tpx2) (Kapitein et al., 2005; Manning and Compton, 2007). To what extent this system reflects the in vivo situation remains to be seen, but the use of Xenopus egg extracts clearly provides a way to tease apart the role of Aurora-A in centrosome maturation from its function in spindle assembly, which is inherently difficult in intact somatic cells. Also, although the Ran-dependent pathway is not essential for bipolarity when centrosomes are present, it is clearly an important factor during spindle assembly (Kalab et al., 2006; Koffa et al., 2006). Moreover, several members of EXT AH are required for bipolar spindle formation in human somatic cells. Disrupting Tpx2 or XMAP215 function causes multipolarity, inhibition of Eg5 or Aurora-A leads to monopolar spindle formation, and reduced levels of HURP destabilise kinetochore-associated MTs (Cassimeris and Morabito, 2004; Garrett et al., 2002; Gergely et al., 2003; Girdler et al., 2006; Hannak et al., 2001; Harborth et al., 2001; Koffa et al., 2006; Liu and Ruderman, 2006; Peset et al., 2005; Sillje et al., 2006).

**Fig. 5.** Aurora-A coordinates centrosome- and chromatin-independent spindle assembly. Aurora-A-coated beads assemble bipolar spindles in Xenopus egg extracts in the absence of chromatin and centrosomes, in combination with the EXT AH complex. Aurora-A (Aur) phosphorylates Tpx2, which in turn leads to the autophosphorylation of Aurora-A and hence activation of its kinase activity (in orange). Activation of Aurora-A kinase recruits other proteins of the EXT AH complex, which are required for MT nucleation (γTuRC), MT stabilisation (XMAP215) and MT bundling (HURP). Eg5 may provide motor activity, which, in combination with the MT activities mentioned, could slide apart, cross-link and stabilise MTs emanating from adjacent Aurora-A-coated beads. Once a bipolar spindle is formed, members of the EXT AH complex may help maintain the stability of this structure.

**Aurora-A in asymmetric cell division and cell fate determination**

Aurora-A is also involved in a more specialised version of mitosis, asymmetric cell division. Mutations in Aurora-A...
were isolated in a genetic screen aimed at identifying genes required for external sensory organ function in *Drosophila* (Berdnik and Knoblich, 2002). A non-allelic mutant from the same genetic screen replicated the same phenotypes, and these mutations map to the *bora* gene. Bora binds to and activates Aurora-A and plays a role in both centrosome maturation (see above) and the establishment of polarity during asymmetric cell division (Hutterer et al., 2006). It is nuclear throughout interphase, but in prophase it moves to the cytoplasm in a cyclin-B1–Cdk1-dependent manner. Because Aurora-A requires cyclin-B1–Cdk1 for its activation (Marumoto et al., 2002; Maton et al., 2003), it was proposed that cyclin-B1–Cdk1 could control Aurora-A activity by modulating the localisation of Bora (Hutterer et al., 2006). Indeed, in embryos in which cyclin-B1–Cdk1 is inactive, Bora fails to accumulate in the cytoplasm.

In addition, two recent studies describe an essential function of Aurora-A in self-renewal of larval neuroblasts in *Drosophila* (Lee et al., 2006; Wang et al., 2006). Importantly, this does not appear to be linked to the centrosome, because *unu* mutant neuroblasts that lack centrosomal Aurora-A do not have defects in neuroblast self-renewal. Instead, Aurora-A functions in the cytoplasm to asymmetrically localise Numb, a cell fate determinant (Berdnik and Knoblich, 2002; Lee et al., 2006; Wang et al., 2006). Interestingly, *aurora-a* mutants display a marked increase in the number of neuroblasts at the expense of neurons within their brain, which indicates a tumour-suppressor-like role for Aurora-A in this context.

**Conclusions**

Despite some inconsistencies, studies so far unequivocally argue that Aurora-A drives early mitotic events. The picture is by no means complete, however. Challenges ahead include the identification of factors downstream of Aurora-A that are directly linked to the recruitment of γ-tubulin to the PCM during vertebrate centrosome maturation. Interestingly, the early emphasis on the role of Aurora-A at the centrosome has now shifted to include centrosome-independent functions such as those in mitotic entry and spindle assembly. Considering the complexity of these biological processes, one could assume that Aurora-A kinase is a master regulator that phosphorylates multiple targets that in turn take care of one or more aspects of the diverse downstream effects. Despite much effort, however, only a few such substrates have been identified. We cannot yet exclude the possibility that there are several effectors out there waiting to be identified. Equally possible is that Aurora-A is similar to its kinetochore-residing sibling, Aurora-B, in that it is not a ‘lone’ kinase. Through its association with activatory cofactors, Aurora-A may be essential for the formation of protein complexes in a similar fashion to how Aurora-B regulates the chromosome passenger complex. Aurora-A could help assemble such complexes not only by phosphorylation but also by acting as a structural component. Recent findings implicating Aurora-A in the EXTAH complex support such a scenario.

Aurora-A has long been regarded as an oncogene, as a result of its overexpression and amplification in several human cancers (reviewed in Giet et al., 2005). Yet, Aurora-A is unlikely to be a bona fide oncoprotein, because its overexpression neither transforms primary cells nor leads to tumour formation in mice (Anand et al., 2003; Zhang et al., 2004). 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 first generation of antagonists developed inhibited the activity of all three Aurora kinases, albeit to varying degrees. For instance, cellular phenotypes caused by inhibitors Hesperadin and ZM447439 are more reminiscent of Aurora-B inhibition than Aurora-A inhibition (Girdler et al., 2006) (reviewed in Keen and Taylor, 2004). Second-generation inhibitors with specificity for a single Aurora kinase have only become available recently. Early results are promising: an Aurora-A-specific antagonist shows significant anti-tumour activity in a xenograft model and has entered phase I clinical trials (Manfredi et al., 2007). Nonetheless, it will be vital to explore the role of Aurora-A in asymmetric stem cell division and cell fate determination in mammalian systems if Aurora-A inhibitors are to become widely used in anti-cancer therapy.

Considering the diversity of the pathways in which Aurora-A participates, targeting downstream factors responsible for specific aspects of its function may in the future become a preferable therapeutic approach to inhibiting the kinase itself. For example, proteins required for mitotic entry and spindle assembly could be better suited for drug targeting than those involved in astral MT stability or asymmetric cell division. However, unless effectors of Aurora-A turn out to be kinases themselves, this will take some time, because small molecule targeting of protein-protein interfaces is still in its infancy. Finally, regardless of whether Aurora-A antagonists succeed as anti-cancer therapies, they represent powerful tools to tease apart the direct and indirect consequences of Aurora-A inhibition. Dissecting the hierarchy of Aurora-A-regulated events presents one of the greatest challenges ahead.

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