THE CELLULAR GEOGRAPHY OF AURORA KINASES

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Aurora is the name given to a family of highly conserved protein kinases with essential roles in many aspects of cell division. Yeasts have a single Aurora kinase, whereas mammals have three: Aurora A, B and C. During mitosis, Aurora kinases regulate the structure and function of the cytoskeleton and chromosomes and the interactions between these two at the kinetochore. They also regulate signalling by the spindle-assembly checkpoint pathway and cytokinesis. Perturbation of Aurora kinase expression or function might lead to cancer.

CENTROSOME
The main microtubule-organizing centre of cells.

CHROMOSOME CONDENSATION
On entry into mitosis, chromosomes become compacted or 'condensed'. This is especially apparent in higher eukaryotes.

KINETOCHORE
A proteinaceous structure that connects each chromatid to the spindle microtubules.

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Aurora is the name given to a family of serine/threonine protein kinases that regulate many processes during cell division. Aurora kinases are involved in the control of the CENTROSOME and nuclear cycles, and have essential functions in mitotic processes such as CHROMOSOME CONDENSATION, spindle dynamics, KINETOCHORE–MICROTUBULE interactions, chromosome orientation and establishment of the metaphase plate. They are also required for the proper completion of cytokinesis.

The original *aurora* allele was identified in a screen for *Drosophila melanogaster* mutants that were defective in spindle-pole behaviour, and was named after the aurora, a phenomenon of the night sky in the polar regions[1]. (Another kinase identified in the same screen was given the Spanish name for pole — Polo[2].) Increase-in-ploidy 1 (Ipl1; REF. 3), the single essential Aurora kinase of *Saccharomyces cerevisiae*, was identified in a genetic screen for mutants that were defective in chromosome segregation. *Schizosaccharomyces pombe* also has a single Aurora called Aurora-related kinase (Ark1; REFS 4,5) which was isolated as a gene that, when present in a multicopy plasmid, suppressed the deleterious effects of overexpressing *Xenopus* Aurora A in *S. pombe*[4]. Metazoans have several Aurora kinases, with two PARALOGUES known in *D. melanogaster*, *Caenorhabditis elegans* and *Xenopus*, and three in mammals. Because the kinases were identified independently many times, the nomenclature became unwieldy, but it has now been simplified with the agreement to designate the family members Aurora A, B, and C[6,7]. The original *Drosophila* Aurora is now classified as Aurora A. A phylogenetic analysis showing the relationships between the kinase domains of various Aurora kinases is shown in FIG. 1. This diagram shows that the subfamilies A and B are very well defined in vertebrates, but the differences are not so obvious in invertebrates.

The three mammalian Aurora paralogues are very similar in sequence, in particular within the carboxy-terminal catalytic domain, in which human Aurora A and B share 71% identity. However, the three Auroras differ in the length and sequence of the amino-terminal domain[8,9]. The structure of the catalytic domain of human Aurora A was recently solved[10,11]. The high degree of sequence similarity between human Aurora A and B in this region is highlighted in FIG. 2, in which sequence conservation has been mapped on the surface of the Aurora-A catalytic domain. This high degree of conservation must be taken into account when considering the specificity of Aurora kinase substrates and inhibitors (see below).

Surprisingly, given this level of similarity, the three mammalian Aurora kinases have very distinct localizations and functions (FIG. 3). Aurora-A kinases are associated with the centrosome from the time of centrosome duplication through to mitotic exit, and are also associated with regions of microtubules proximal to centrosomes in mitosis. Aurora-B kinases form a complex with two other proteins, inner centromere protein (INCENP) and survivin, and behave as chromosomal 'passenger' proteins[12]. Passenger proteins associate with centromeric

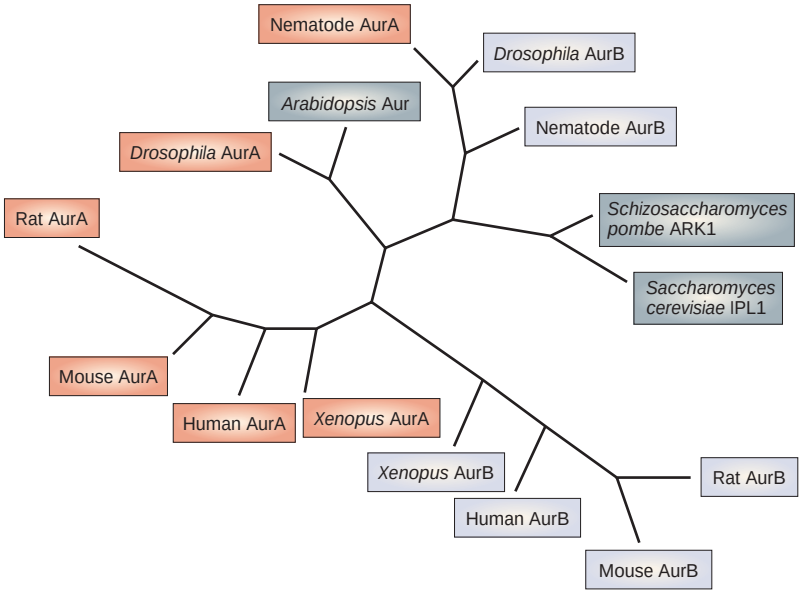


Figure 1 | **The relationships between the kinase domains of the Aurora kinases**. The vertebrate A- and B-type Aurora kinases (Aur) are readily distinguished, but the relationships between the invertebrate and plant enzymes are less clear-cut. The phylogenetic tree was calculated by maximum parsimony. The confidence estimate of the topology assignment was obtained by bootstrapping (randomized substitutions).

MICROTUBULE
A hollow tube, 25 nm in diameter, that is formed by the lateral association of 13 protofilaments, which are themselves polymers of α- and β-tubulin subunits.

PARALOGUES
Genes with related structure and function within the same species.

HETEROCHROMATIN
A condensed form of chromatin containing few expressed genes and often rich in repeated DNA elements. It is commonly, but not exclusively, found around the centromere.

MIDBODY
A dense bundle of microtubules embedded in an electron-dense matrix. This is derived from the central spindle during late telophase and is localized within the intercellular bridge during cytokinesis.

SPINDLE MIDZONE
Organized bundles of antiparallel microtubules that form during anaphase and telophase. Signals from the central spindle are thought to be important for signalling the location of the cleavage furrow.

HETEROCHROMATIN early in mitosis (see BOX 1), transfer to the central spindle in anaphase and are amongst the first proteins to localize at the cell cortex where the contractile ring subsequently forms. Chromosomal passenger proteins remain associated with the MIDBODY during cytokinesis. The dramatic movements of passenger proteins during mitosis led to the proposal that they might have a role in the coordination of chromosomal and cytoskeletal events during the cell cycle[12]. Less is known about Aurora-C kinases, which are specifically expressed at high levels in the testis and show centrosomal localization from anaphase to telophase[13–16]. One challenge for the future will be to dissect out the features that define the substrate specificity, regulation and localization of each of the Aurora kinases.

The expression levels of human Auroras and some of their associated polypeptides are elevated in certain types of cancer, and overexpression of Aurora A can induce transformation. These observations have lent new interest to this family of kinases as potential drug targets for the development of new anti-cancer therapies.

Aurora A: the polar aurora

The defining characteristic of the Aurora-A subfamily has been its association with centrosomes and regions of microtubules that are proximal to the centrosome[1,17–19]. 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. 3; REF. 20). Low levels of Aurora A have also been reported on the SPINDLE MIDZONE and midbody late in mitosis[19,21,22]. 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[23,24]. TPX2 (targeting protein for XKLP2), which has been implicated in Aurora-A activation (see below), is required for the localization of the kinase to spindle microtubules, but not to SPINDLE POLES[25].

Aurora A in centrosome separation and maturation. The high frequency of monopolar MITOTIC FIGURES in certain *Drosophila aurora* mutants indicated a potential role for the kinase in centrosome separation[1]. 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[24]. By contrast, centrosome duplication and separation seemed normal in one study using Aurora-A RNAi in *C. elegans*[17]. However, a second live-cell analysis of Aurora-A RNAi treatment in *C. elegans* showed that centrosomes first separate and then collapse back together[26].

In order to become fully functional after they duplicate and separate, centrosomes must recruit a number of different proteins in a process known as maturation. In the absence of Aurora A, recruitment of several components of the PERICENTRIOLAR MATERIAL — including γ-TUBULIN — to the centrosome is deficient, and the microtubule mass of spindles is decreased by about 60% (REFS 20,26). Furthermore, the morphology of the astral microtubule array is also aberrant. This might partly reflect an impaired function of factors that regulate microtubule dynamics, such as *Drosophila* transforming-acidic-coiled-coil protein (D-TACC; this seems to be the orthologue of TACC3 in humans), and/or Eg5, a kinesin-like protein that is involved in spindle assembly. Both of these proteins are substrates of Aurora A *in vitro*[24,27].

Spindle assembly. A recent report has shown a link between Ran–GTP and Aurora A in spindle assembly[28]. 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[29–31]. In mitosis, Ran–GTP releases TPX2 (and other centrosome-associated proteins such as nuclear-mitotic-apparatus protein (NuMA)) from IMPORTIN-α and importin-β (FIG. 4). The liberated TPX2 then binds Aurora A at the centrosome and targets it to the microtubules proximal to the pole[25]. 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 — a residue in the ACTIVATION LOOP of Aurora A that is essential for kinase activity[28,32]. Whether or not this activation requires microtubules is presently debated. So a Ran–GTP gradient is converted into a gradient of active Aurora A, and this is important for spindle assembly *in vitro*.

Meiotic maturation and metaphase I spindle orientation. Xenopus oocytes are arrested in prophase of the first meiotic division. Progesterone induces the activation of M-phase promoting factor (MPF; cyclin-dependent-kinase-1–cyclin-B–CKS1) and extracellular

signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK), which transform the oocyte into a mature egg. Aurora A was identified as a component of the progesterone-induced signalling pathway in a screen for proteins that were modified in response to progesterone stimulation[33]. Aurora-A activation is an early event after progesterone activation, and its activity results in ERK/MAPK signalling.

The ERK/MAPK cascade is initiated by translational upregulation of Mos, a MAPK kinase kinase. Translation of Mos messenger RNA requires polyadenylation and is dependent on cytoplasmic-polyadenylation-element binding protein (CPEB), a protein that binds within 3′ untranslated sequences. Aurora A is responsible for the early phosphorylation of CPEB and consequent upregulation of Mos[34]. A later wave of CPEB phosphorylation depends on MPF. *Xenopus* Aurora A is also required downstream of MPF for extrusion of the first POLAR BODY, meiotic-spindle positioning and exit from metaphase I (REFS 35,36). (Aurora B is required for polar-body extrusion in *C. elegans*[37].) The Eg5 kinesin (an Aurora-A substrate) is involved in the Aurora-mediated exit from metaphase I by an as-yet-unknown mechanism[38]. Aurora-A phosphorylation of CPEB also has an essential role in cell-cycle regulation in *Xenopus* early embryos, by upregulating the translation of cyclin B1.

Regulation of Aurora A activity. Regulation of Aurora A is complex and involves both phosphorylation/dephosphorylation and degradation. Phosphorylation stimulates kinase activity. Three phosphorylation sites have been identified in *Xenopus* Aurora A by mass spectrometry[39]. Phosphorylation of Thr295 (Thr288 in human Aurora A) in the activation loop is essential for kinase activity[40]. This residue is in a protein kinase A (PKA) consensus motif, and PKA can phosphorylate and activate Aurora A *in vitro*[40]. However, this site also fits the consensus phosphorylation sequence that has been defined for *S. cerevisiae* Ipl1 ((R/K)X(T/S)(I/L/V); REF. 41) and the equivalent residue (Thr260) in yeast Aurora has indeed been identified as an autophosphorylation site[41]. Ser53 in the amino-terminal A Box is phosphorylated during M phase and might have a role in the regulation of Aurora-A degradation (see below). Although the third phosphorylation site to be identified — Ser349 — is not essential for catalytic activity, S349D mutants block kinase activation, which indicates a possible structural or regulatory role for this modification[39].

The phosphatase PP1 negatively regulates the Aurora kinases. The counteracting effect of PP1, which was first described for yeast Ipl1 (REF. 42), has also been shown in *Xenopus* and human cell lines[33,40,43,44]. The activation of Aurora A by TPX2 is at least partly due to antagonism of PP1[28,32].

Aurora A is degraded in late mitosis/early G1 by the Cdh1/Fizzy-related form of the anaphase-promoting complex/cyclosome (APC/C; the APC/C with Cdh1/Fizzy-related as a substrate recognition subunit[45,46]). Aurora A has a silent carboxy-terminal D-box (destruction box; FIG. 2), which is also present in Aurora B[47,48], but which is only functional in the presence of an amino-terminal A-box (also called the D-box-activating-domain (DAD))[47]. The A-box/DAD is absent from Aurora B and C, and their D-boxes are not targeted by the APC/C during mitotic exit. Phosphorylation of the A-box seems to make the Aurora A resistant to APC/C-mediated degradation. Interestingly, the D-box is recognized by both the Cdh1/Fizzy-related and Cdc20/Fizzy forms of the APC/C, but Aurora A is only targeted by the former.

The recently identified Aurora-A-kinase-interacting protein (AIP), a negative regulator of Aurora A, is a conserved nuclear protein that interacts with the

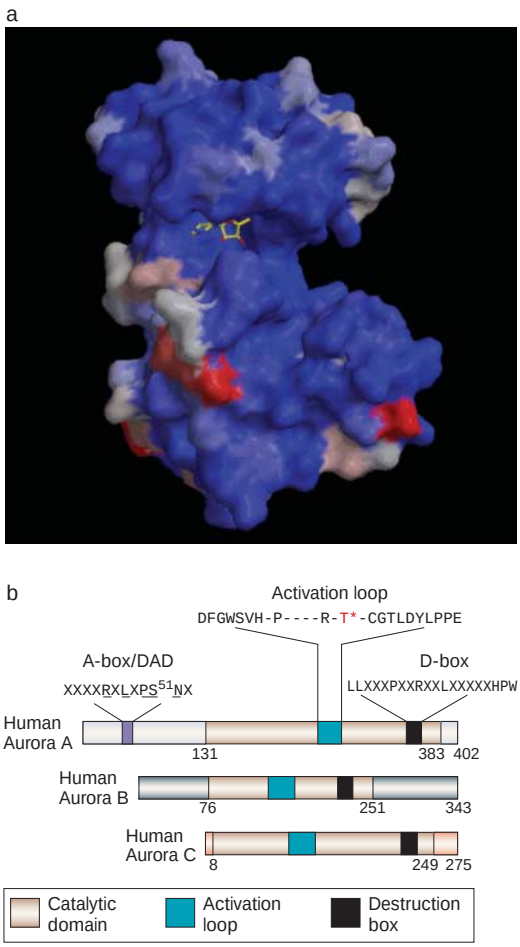


Figure 2 | **Structure of the Aurora kinases. a** | The region of Aurora A and B surrounding the catalytic cleft is remarkably conserved. The figure shows the crystal structure of the kinase domain of Aurora A. The GRASP programme was used to obtain the surface representation of Aurora A. Surface mapping of amino-acid conservation was obtained with the Cosurf programme. A linear colour ramp represents the average conservation of each amino acid, ranging from 0.5 (red, divergent) to 1.0 (blue, conserved). **b** | The organization of human Aurora-A, -B and -C kinases. The position of the A-box/D-box-activating domain (DAD) and the D-box is shown, as is the position of the activation loop. These features have been characterized most thoroughly in Aurora A, and the boxes shown for Aurora B and C are approximations only.

SPINDLE POLE
The region at the end of the mitotic spindle where minus ends of the microtubules are clustered together as a result of the action of various microtubule motor proteins. In most animal cells, the spindle pole is centered around a centrosome. Plant spindles in somatic cells, however, lack focused centrosomes.

MITOTIC FIGURES
A term used by cytologists to describe mitotic cells visualized under the microscope.

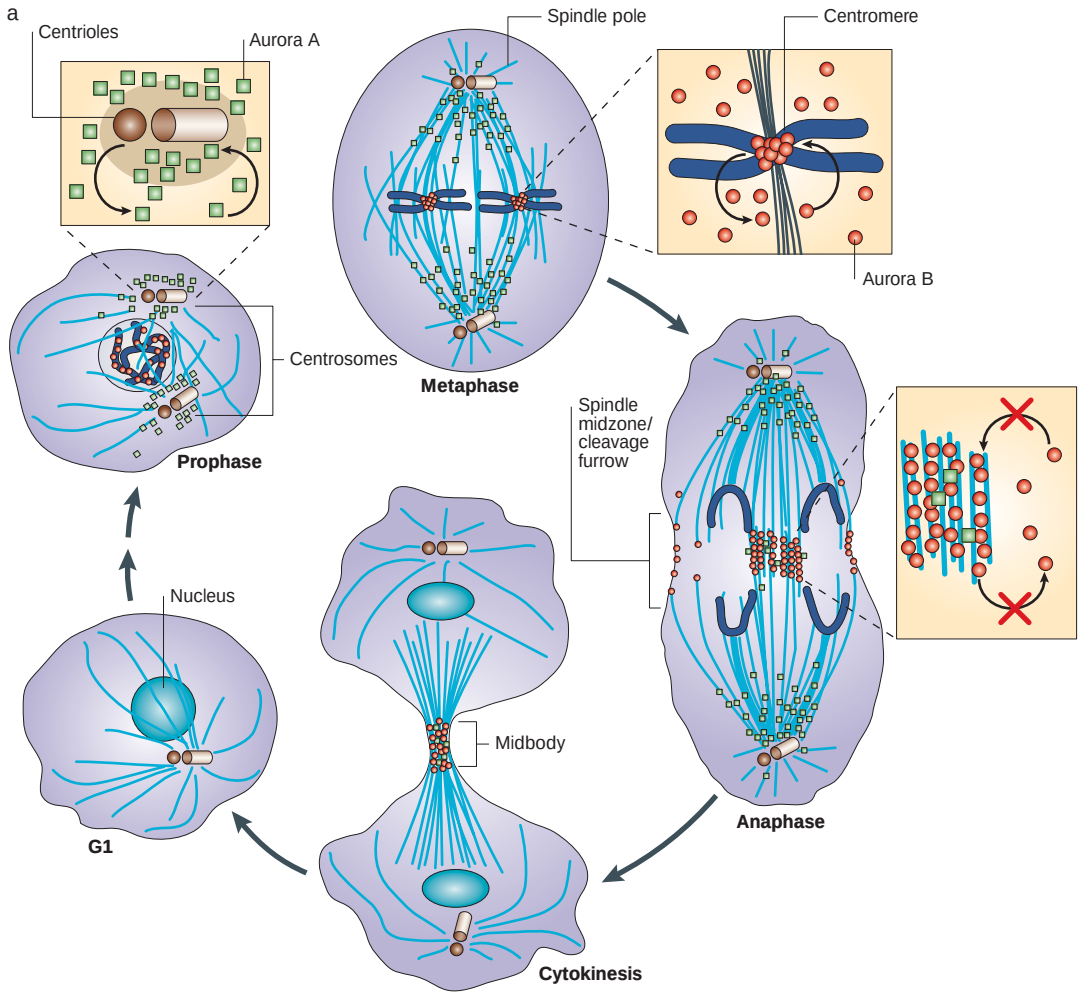
RNA INTERFERENCE
(RNAi). A form of post-transcriptional gene silencing in which expression or transfection of double-stranded RNA induces degradation — by nucleases — of the homologous endogenous transcripts, mimicking the effect of the reduction, or loss, of gene activity.

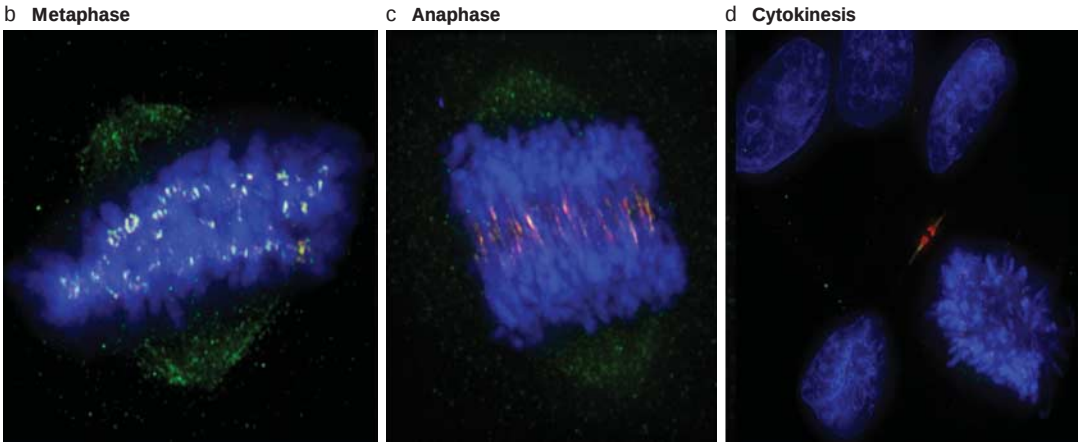
CENTRIOLE
A cylindrical array of 9 bundles of microtubules (usually triplets in animal cells) with other specialized appendages. Two centrioles, referred to as mother and daughter, are found in the centre of centrosomes in animal cells.

PERICENTRIOLAR MATERIAL
Region of the cytoplasm surrounding the two centrioles in the centrosome. This is the region where microtubule assembly is initiated by γ-tubulin.

γ-TUBULIN
A specialized isoform of tubulin that, together with several associated proteins, forms a ring-like complex that directs the initiation of microtubule assembly.

IMPORTINS
A class of protein discovered because of the ability of the members to act as adaptors and carriers during the import (and export) of proteins across the nuclear envelope. Importins are now known to have a second role in regulating the assembly of the mitotic spindle.





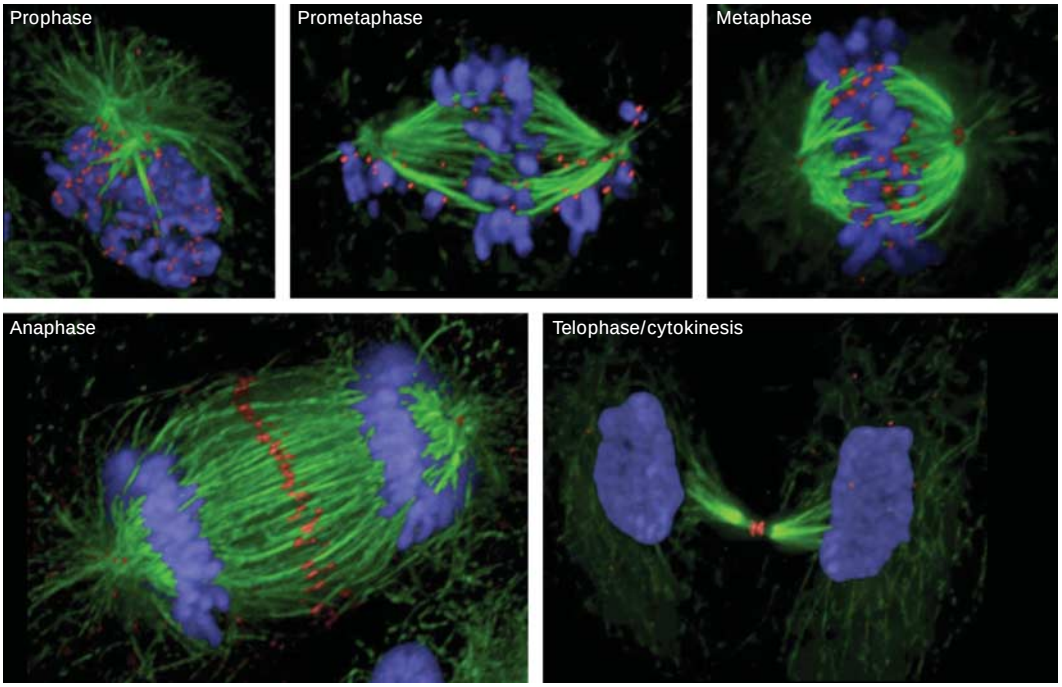
ACTIVATION LOOP
A conserved structural motif in kinase domains, which needs to be phosphorylated for full activation of the kinase.

MPF
(Maturation-promoting factor/M-phase promoting factor). The complex of a B-type cyclin Cks1, and cyclin-dependent kinase 1, which is also referred to as Cdc2 or p34, depending on the species. This is the main enzyme that is responsible for entry into M phase in both meiosis and mitosis.

POLAR BODY
Either of the two small cells, each being formed during the successive divisions of meiosis, that forms as a result of division of a primary oocyte during its development to a mature ovum. The cytoplasm divides unequally during each division — the polar body is much smaller than the developing oocyte. Polar bodies eventually degenerate.

Figure 3 | **Localization of Aurora kinases. a** | 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 (green boxes) is concentrated around the centrosomes, whereas Aurora B (red circles) is nuclear. In metaphase, Aurora A is on the microtubules near the spindle poles, whereas Aurora B is located in the inner centromere. 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. The inset boxes show the results of fluorescence recovery after photobleaching (FRAP) studies, and indicate that Aurora A and B are dynamic at centrosomes and centromeres, respectively, but that Aurora B becomes immobile when targeted to the spindle midzone. Restoration microscopy of Aurora B (red staining), inner centromere protein (INCENP; green staining), and DNA (blue staining) in mitotic HeLa cells in (**b**) metaphase, (**c**) anaphase and (**d**) cytokinesis. Some background staining of INCENP on the spindle is seen in this experiment.

Box 1 | A brief primer of mitosis



Mitosis begins with prophase (see figure), as chromosomes condense within the intact nuclear envelope and the replicated centrosomes begin to separate. The centrosomes undergo a process termed maturation, and begin to nucleate two asters of dynamic microtubules. Prometaphase (see figure) begins with nuclear-envelope breakdown, which allows the kinetochores to bind to microtubules. Chromosomes that have successfully attached to microtubules emanating from both poles of the spindle move to the spindle midzone, forming a highly dynamic METAPHASE PLATE. During metaphase (see figure), all chromosomes have achieved an alignment at the spindle midzone. The degradation of key mitotic regulators begins, culminating in the activation of the anaphase-promoting complex/cyclosome (APC/C). Action of the APC/C ultimately leads to activation of a protease, known as separase, that cleaves a key regulator of sister-chromatid pairing. This triggers the onset of anaphase — the coordinated separation of sister chromatids to opposite poles of the spindle (see figure). During anaphase, the spindle midzone gradually becomes organized into bundles of microtubules that will ultimately have an important role in specifying the formation of the cleavage furrow. During telophase, the nuclear envelope reforms on the surface of the separated masses of sister chromatids, and during cytokinesis (see figure), the cortex constricts under the action of an actomyosin ring. Ultimately, the remnant of the spindle is left as a bundle of microtubules passing through an intercellular bridge and embedded in a dense matrix at the midbody. The figures show chromosomes (blue), microtubules (green), and centromere protein E (CENP-E; red) — a marker for kinetochores, the central spindle, and midbody.

METAPHASE PLATE
The dynamic group of chromosomes positioned roughly midway between spindle poles prior to the onset of anaphase. These chromosomes have formed proper bipolar attachments (that is, their sister chromatids are connected to opposite spindle poles).

PROTEASOME
Protein complex responsible for degrading intracellular proteins that have been tagged for destruction by the addition of ubiquitin.

ASTRAL MICROTUBULES
Microtubules that extend in a radial array outwards from the spindle poles, excluding those microtubules that attach to kinetochores or form part of the organized spindle midzone.

kinase *in vivo*[49]. AIP was isolated as a dosage-dependent suppressor of Aurora A that was ectopically overexpressed in budding yeast. In mammalian cells, AIP might downregulate Aurora through PROTEASOME-dependent degradation[49]. Its normal function is not known.

Aurora B: the equatorial Aurora

Human Aurora B was first identified in a polymerase chain reaction screen for kinases that were overexpressed in tumours[8]. Rat Aurora B was identified in a screen to find kinases that affected *S. cerevisiae* proliferation when they were overexpressed[50]. Aurora-B kinases are chromosomal passenger proteins that are essential for a number of processes during mitosis. Aurora-B expression and activity in proliferating tissues are cell-cycle regulated: expression peaks at the G2–M transition, and kinase activity is maximal during mitosis[8,50].

The chromosomal-passenger localization of Aurora B was originally shown by indirect immunofluorescence in mammalian cells, *C. elegans* and *Drosophila*[37,50,51]. 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[52]. Once the kinase associates with central spindle microtubules during anaphase (which requires kinase activity), its mobility is highly reduced. A subpopulation of the tagged Aurora also seems to be transported by ASTRAL MICROTUBULES to the equatorial cell cortex[52].

Aurora B in chromosome biorientation. After nuclear-envelope breakdown, prometaphase chromosomes rapidly establish attachments to a nearby spindle pole,

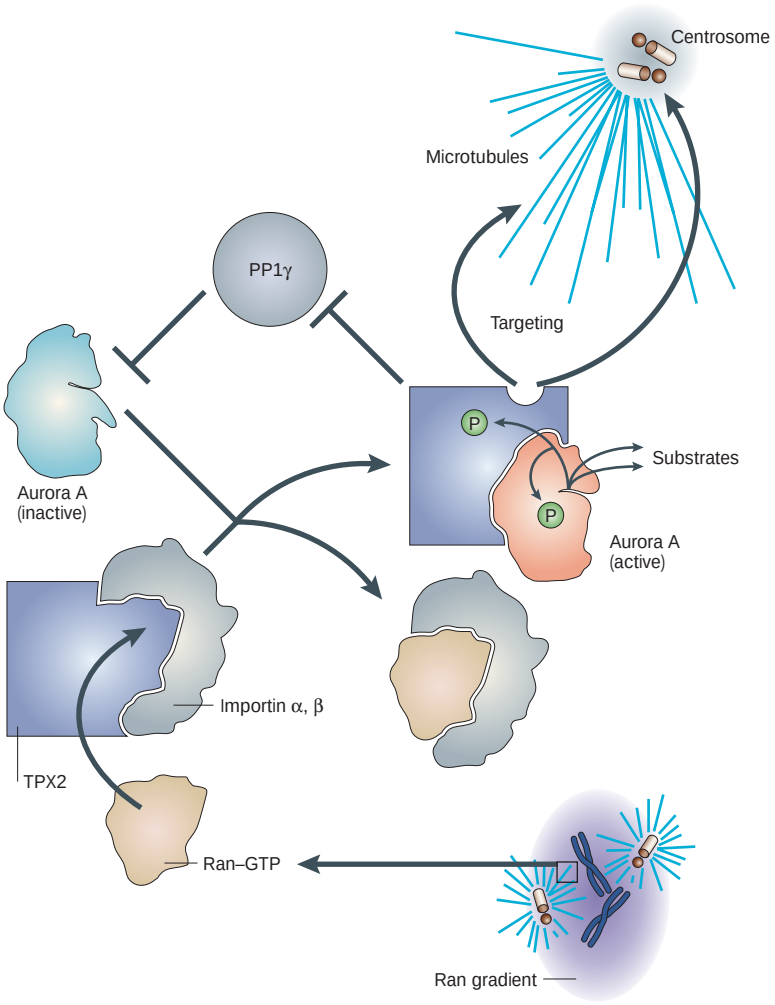


Figure 4 | **Regulation of Aurora-A activity by Ran–GTP and TPX2.** As cells enter mitosis, targeting protein for XKLP2 (TPX2) is in a complex with importins α or β. A gradient of Ran–GTP surrounding chromosomes (lower right) promotes the release of TPX2 from the importin. TPX2 then binds to Aurora A, which has been kept in an inactive state by protein phosphatase 1 γ (PP1γ). TPX2 interferes with PP1 action, enabling the kinase to autophosphorylate and activate itself and other substrates, including TPX2. TPX2 then also targets the kinase to microtubules proximal to the centrosome. Note that the kinase might not require continued association with TPX2 to phosphorylate other substrates.

creating a 'monotelic' attachment (one sister kinetochore attached, the other one free; see FIG. 5). Eventually, the free kinetochore captures a microtubule from the opposite pole, yielding a bipolar (amphitelic) attachment that ultimately results in the positioning of the chromosome midway between the spindle poles at a metaphase plate. If both sister kinetochores attach to the same pole (syntelic attachment) the chromosome is unable to congress to the metaphase plate. Classic studies of meiotic cells by Nicklas and co-workers showed that tension within the spindle stabilizes amphitelic attachment[53], and seems to correlate with silencing of a phospho-epitope on one or more kinetochore proteins that is recognized by the 3F3/2 monoclonal antibody[54].

In yeast, Ipl1 has been proposed to promote amphitelic kinetochore attachment to microtubules by destabilizing syntelic attachments of SISTER CHROMATIDS[55]. This might be especially important in *S. cerevisiae*, in which chromosomes are attached to nuclear microtubules for most of the cell cycle and replicated sister kinetochores enter mitosis attached to the same spindle-pole body. How the kinase recognizes syntelic attachments is not clear, but it has been proposed that tension between amphitelically oriented sister kinetochores stretches them apart enough to separate microtubule-binding sites from Aurora B that is sequestered in the inner centromere, which thereby limits the accessibility of the kinase to its substrate[55].

Aurora B also seems to have an important role in regulating kinetochore–microtubule interactions in higher eukaryotes. Interference with its function by RNAi[51], microinjection of function-blocking antibodies[56] or treatment with small-molecule inhibitors[57,58] all cause defects in chromosome CONGRESSION. One study found a significant increase in the frequency of syntelic attachments after treatment with an inhibitor[58]. Expression of a dominant-negative catalytically inactive version of Aurora B in NRK (normal rat kidney) cells disrupts microtubule attachment and causes a loss of dynein and centromere protein E (CENP-E) from kinetochores[59]. These motor proteins are thought to be involved in kinetochore binding to microtubules and also in signalling kinetochore attachment to the spindle-assembly checkpoint.

Kinetochore targets of Aurora kinases are best known in budding yeast, in which the essential kinetochore protein Ndc10 was shown to be a substrate of Ipl1 (REF. 60; see FIG. 6). Other kinetochore-associated targets of Ipl1 phosphorylation include Ipl1 itself; its targeting/activating factor Sli15, which is the yeast homologue of INCENP; Dam1, a member of a protein complex the association of which with the outer kinetochore seems to be regulated by Ipl1; and Cse4, a kinetochore-specific histone-H3 variant[41,61–63]. On the basis of these studies, a consensus phosphorylation site for Ipl1, as mentioned above, has been defined as ((R/K)X(T/S)(I/L/V); REF. 41). The consensus sequence for metazoan Aurora B is likely to be similar, but where phosphoacceptor sites have been mapped, they are preceded by two basic residues[64].

The mammalian kinetochore-specific histone-H3 variant CENP-A is a substrate of Aurora B in mammalian cells[65]. Phosphorylation of CENP-A by Aurora B peaks in prometaphase[65]. Surprisingly, phosphorylation-site mutants show a delay in the late stages of cytokinesis. Why a kinetochore protein should show defects in completion of cytokinesis, a cytoskeleton/membrane event, is unclear. Furthermore, INCENP and Aurora-B localization is perturbed in the CENP-A phosphomimetic mutant S7E for reasons that remain unclear.

Aurora B in chromosome condensation and cohesion? Aurora-B kinases are responsible for one of the classic modifications of chromatin in mitosis — phosphorylation of histone H3 on S10 (REF. 66). This modification, which is conserved from yeast to vertebrates, is carried

SISTER CHROMATIDS
Chromosomes that have been duplicated during S phase. Sister chromatids are held together by cohesins until metaphase.

CONGRESSION
The movement of correctly attached mitotic chromosomes to the metaphase plate at the midzone of the mitotic spindle.

out by Ipl1 in budding yeast[67] and Aurora B in metazoans[44,51,67–71]. Aurora B is also responsible for histone-H3 phosphorylation on S28 from prophase to metaphase[72,73]. In living NRK cells undergoing prophase, Aurora-B–GFP was seen all over the chromatin, although it was enriched on centromeres[52]. It had long been predicted that these histone modifications might help to drive mitotic chromatin condensation; however, when this was measured, the degree of histone-H3 S10 phosphorylation was found not to correlate with the level of chromatin condensation[51].

Defects in chromosome structure and compaction are observed in Aurora-B-depleted *Drosophila* cells[51,74], but the underlying mechanism is not known. One possibility is that Aurora activity might be required for CONDENSIN function. However, the relationship between the kinase and condensin is unclear. The condensin complex[75] does not localize properly to chromosomes in *Drosophila* cells that lack active Aurora B (REF. 74) or in *S. pombe* that lacks Ark1 (REF. 76). In *C. elegans*, condensin activity is independent of Aurora B in prometaphase, but becomes dependent on the kinase in metaphase[77,78]; in *Xenopus* extracts, Aurora B is not required for condensin binding or chromosome condensation[71]. Furthermore, in cells treated with the Aurora-B inhibitor hesperadin[58] (see BOX 2), in which Aurora B localizes properly but is enzymatically inactive, the condensin complex localizes normally. There is no evidence so far that any of the condensin subunits is a substrate of Aurora B.

In metaphase I of *C. elegans* meiosis, Aurora B has been shown to localize to the paired arms of the homologous chromosomes distal to the CHIASMATA[77,79]. It is the selective release of cohesion in this region that permits terminalization of chiasmata and releases homologous chromosomes for proper segregation to the spindle poles in anaphase I. Aurora B could regulate this process by phosphorylating Rec8, a meiosis-specific subunit of the COHESIN complex[77,79]. Interestingly, the centromeric localization of the Aurora-B binding partners INCENP and survivin (see below) has been shown to depend on cohesin function in chicken DT40 B lymphocytes[80].

Aurora B is essential for cytokinesis. Overexpression of a catalytically inactive form of rat Aurora B (which was previously known as Aim1) prevents the last steps of cytokinesis in a number of cell lines[50]. A similar phenotype is produced by exogenous expression of a dominant mutant of the chromosomal passenger INCENP (see below) that lacks the Aurora-B-binding domain (IN-box) and delocalizes the kinase[81,82].

Depletion of Aurora B by RNAi in *Drosophila* tissue-culture cells and in *C. elegans* confirmed a role for the kinase in the late stages of cytokinesis[51,69,83,84]. In some cases, inactivation of Aurora B was associated with delocalization of the kinesin-like protein Pavarotti/CHO1/MKLP1/ZEN4 (CHO1, Chinese hamster ovary monoclonal antibody 1; MKLP1, mitotic kinesin-like protein 1; ZEN4, zygotic enclosure defective), which is essential for establishment of the central spindle during anaphase[69,83,84]. However, in one study, Pavarotti was correctly localized after depletion of Aurora B in cells in which cytokinesis failed[51].

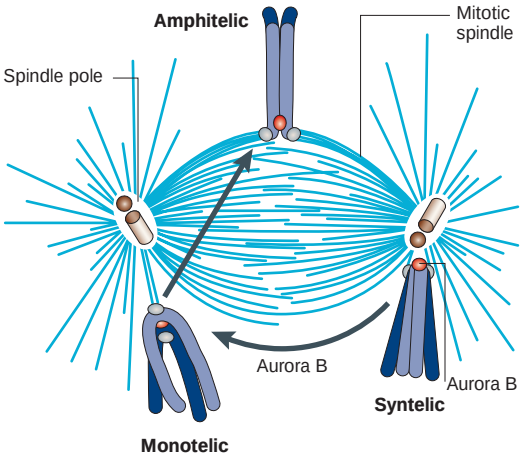


Figure 5 | **Role of Aurora B in promoting chromosome bi-orientation on the mitotic spindle.** Normally, the first attachment of chromosomes to the spindle microtubules (blue) is monotelic (one kinetochore bound, one kinetochore free). If both kinetochores attach to the same spindle pole (syntelic attachment), Aurora B in the inner centromere (red) promotes release of the bound microtubules, which therefore promotes the formation of monotelic attachments. Eventually, chromosomes become attached to both spindle poles (amphitelic attachment).

Other specific targets of Aurora B in the CLEAVAGE FURROW include myosin II regulatory light chain[85], vimentin[86], desmin, and glial fibrillary acidic protein (GFAP; REF. 87; FIG. 6). Although many of the phosphorylation sites in desmin and GFAP are also targeted by Rho kinase, one phosphorylation site in desmin is specifically phosphorylated by Aurora B. Phosphospecific antibodies showed that this phosphorylation occurs specifically at the cleavage furrow. Because phosphorylation has a dramatic effect on the stability of INTERMEDIATE FILAMENTS, it was suggested that desmin phosphorylation by Aurora B could contribute to the destabilization of intermediate filaments that is essential in the later stages of cytokinesis[87].

Aurora B also phosphorylates S387 of MgcRacGAP (which is known in *C. elegans* as Cyk4; REF. 88) in the midbody[89]. This phosphorylation significantly changes the specificity of MgcRacGAP from an activating protein for the small GTPase Rac to an activator of RhoA. Phosphorylated MgcRacGAP colocalizes with Rho in the contractile ring. RhoA regulates actin polymerization and is essential for completion of cytokinesis[90,91]. In cells expressing a non-phosphorylatable form of MgcRacGAP, cleavage-furrow ingression proceeds to a late stage but finally reverts without separation of the daughter cells[89], which indicates that any failure of Aurora B to phosphorylate MgcRacGAP would probably have the same effect.

Aurora B and the spindle-assembly checkpoint. Aurora B and its associated proteins INCENP and survivin (see below) have recently emerged as important factors for the spindle-assembly checkpoint, a biochemical circuit that delays mitotic progression until all chromosomes

CONDENSIN
A complex of two SMC (structural maintenance of chromosomes) proteins and three auxiliary subunits that can bind to and supercoil DNA. Condensin directs the binding of other non-histone proteins to mitotic chromosomes, and although not essential for mitotic chromatin condensation, it is essential for the structural integrity of mitotic chromosomes.

CHIASMATA
Connections formed between homologous chromosomes that are thought to be the point of the interchange that is involved in crossing over.

COHESIN
A protein complex that tethers sister chromatids together from the time they are created (during DNA replication) until cohesin cleavage at the onset of anaphase.

CLEAVAGE FURROW
A region of the plasma membrane in higher eukaryotic cells that ingresses to separate the two daughter cells at cytokinesis; contraction in this region is driven by actin and myosin filament interaction.

INTERMEDIATE FILAMENT
A cytoskeletal filament, typically 10 nm in diameter, that occurs in higher eukaryotic cells. The protein composition of intermediate filaments varies between cell types. Examples of intermediate filament proteins are keratins, vimentin and desmin.

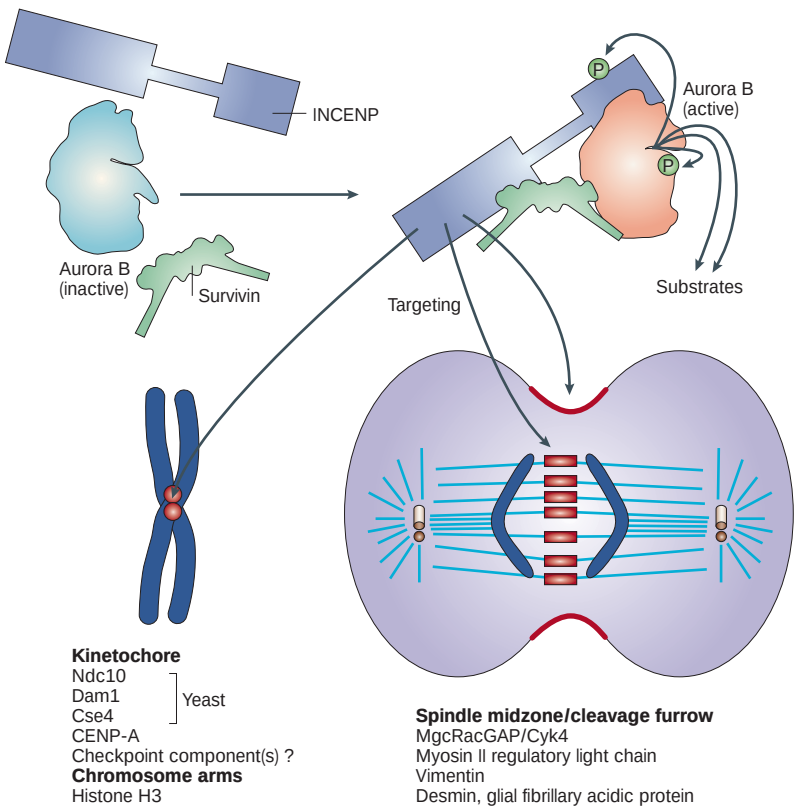


Figure 6 | **Some of the known Aurora-B substrates in mitotic cells.** Aurora B forms a complex — the chromosomal passenger complex — with inner centromere protein (INCENP) and survivin. Aurora-B phosphorylation of INCENP in turn promotes Aurora-B activity, as does survivin binding. INCENP targets the complex to centromeres (lower left part of figure) early in mitosis, and the spindle midzone and cleavage furrow late in mitosis (lower right part of figure). Some of the known substrates of Aurora B are shown — in particular, those that influence kinetochores, chromosome arms and the spindle midzone/cleavage furrow. CENP-A, centromere protein A.

have achieved a proper bipolar orientation on the mitotic spindle. The checkpoint is triggered by kinetochores that lack bound microtubules, and also by a lack of tension in the spindle, although the mechanism by which the latter triggers the checkpoint is controversial. On the one hand, the checkpoint might be directly activated by a lack of tension at the kinetochores. On the other, it has been suggested that the lack of tension promotes the generation of free kinetochores that then activate the 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[92]. Similar results have been seen in mammalian cultured cells after expression of a kinase-inactive dominant-negative form of Aurora B (REF. 52); microinjection of function-blocking anti-Aurora B antibodies[56]; treatment of cells with newly isolated Aurora-B inhibitors[57,58]; or after RNAi-mediated knockdown of the Aurora-binding partner survivin (see below)[93,94]. In *S. pombe*, loss of Ark1 inactivates the checkpoint altogether[76].

Aurora B's fellow travellers, INCENP and survivin. In addition to being regulated by phosphorylation[95], Aurora B is also regulated by association with at least two other proteins, INCENP and survivin. Together, these three proteins are referred to as the chromosomal-passenger complex[6]. This complex is conserved from vertebrates to budding yeast and the proteins involved are Ipl1, Sli15 and Bir1[41,61]. In vertebrates it has now clearly been shown that each component of the complex is required for the proper localization of the two others[82,83,93,96,97]. So, INCENP and survivin apparently function to target the kinase, and the movement of the passenger complex from centromeres, to central spindle, to midbody, presumably reflects movement of the kinase to act on different substrates.

Both INCENP and survivin have a role in activating the kinase. INCENP is a microtubule-binding protein[98] that has a non-conserved amino-terminal region that is important for targeting the protein to chromosomes and centromeres[99], and a highly conserved carboxy-terminal motif, the IN-box, that is responsible for binding Aurora B (REFS 64,100). INCENP is both a substrate and a positive regulator of the kinase. It is phosphorylated by Aurora B in the IN-box[41,64,101] and this phosphorylation enhances the activity of the kinase. Although the mechanism is not yet known, recent results indicate that INCENP phosphorylation might alter the protein structure in the region of the IN-box, and this might somehow contribute to the stimulation of kinase activity[64].

Survivin is a small protein containing a BIR (baculovirus inhibitor of apoptosis (IAP) repeat) domain, a Zn^{2+}-finger motif that is found in the IAP proteins, which are important regulators of the apoptotic pathway[102]. Evidence concerning whether survivin has an important role in apoptosis regulation is controversial, but genetic experiments in mice[103] and RNAi studies indicate that the primary role of the protein is in mitosis, in which it is required for the localization of both Aurora B and INCENP[93]. *Xenopus* survivin binds to Aurora B and enhances its activity *in vitro*[97], although human survivin does not stimulate the kinase activity in similar assays[64]. Treatment of cells with survivin antisense RNA results in decreased Aurora-B activity and mislocalization of the kinase[104]. The *S. pombe* survivin homologue Cut17/Bir1 is required for Ark1 localization[105] and activity[76].

Three other chromosomal passengers have recently been characterized. One of them — TD-60 — which colocalizes exactly with INCENP in cells[106], is apparently a guanine nucleotide exchange factor[107]. This raises the possibility that a small G-protein — probably Rac1 — might be involved in the regulation of the activity of the passenger complex that contains Aurora-B kinase. The second passenger, inner centromere KinI stimulator (ICIS), is an inner centromere protein that seems to regulate the microtubule-disassembly activity of mitotic centromere-associated kinesin (MCAK)[108]. It is possible that ICIS is a substrate of Aurora B. Genetic analysis in *C. elegans* has recently identified an additional component of the chromosomal passenger

Box 2 | New inhibitors of Aurora-B kinase

Two recent studies using small-molecule inhibitors of Aurora kinases have opened new possibilities for the study of the function of these kinases.

ZM447439 inhibits Aurora A and B with IC_{50}s of 0.11 and 0.13 μM, respectively[57]. The IC_{50} for most other kinases tested was >10 μM, but lymphocyte-specific protein tyrosine kinase (LCK) was inhibited at 0.88 μM. Phosphorylation of histone H3 is abolished in human cells treated with ZM447439. Furthermore, although a normal bipolar spindle forms and kinetochores attach to microtubules, chromosomes do not align properly at a metaphase plate. Although drug treatment does not affect the localization of Aurora A, Aurora B or survivin, it substantially reduces the levels of BubRI, Mad2 and centromere protein E (CENP-E) at kinetochores and compromises the spindle-assembly checkpoint. Effects on cytokinesis were not examined in detail. These phenotypes resemble those seen after RNA interference (RNAi)-mediated suppression of Aurora B, but not Aurora A, although the Aurora-B RNAi phenotype is more severe. Why the cells do not show the phenotypes that are expected for inhibition of Aurora A (for example, failure of centrosome maturation) is not known.

Hesperadin, a structurally distinct inhibitor, produces similar effects in a variety of cell types[58]. In addition to Aurora B, hesperadin at 1 μM also significantly inhibits at least six other kinases, including checkpoint kinase 1 (CHK1), LCK, mitogen-activated protein kinase (MAPK)-associated protein kinase 1 (MAPKAP-K1), MAPK kinase 1 (MKK1), phosphorylase kinase (PHK) and AMP-activated protein kinase (AMPK). The authors argue that the drug is specific for Aurora B because, at 0.2–1 μM, its effects on cultured cells resemble those seen after Aurora-B RNAi treatment. Like ZM447439, hesperadin inhibits the spindle-assembly checkpoint response to Taxol, but not nocodazole (at least over a 3-hour period), as expected, given the involvement of Aurora B in the tension-sensitive arm of the spindle-assembly-checkpoint pathway. A detailed analysis of microtubule attachments in cycling and hesperadin-treated cells showed that the drug causes a significant increase in the number of syntelic chromosome attachments seen, apparently at the cost of monotelic attachments. Overall, the data support a model in which the target of hesperadin (presumably Aurora B) helps promote normal chromosome alignment in mitosis by destabilizing syntelic attachments, as had been previously proposed for Ipl1 in budding yeast[55].

complex — chromosome segregation and cytokinesis defective (CSC-1; REF. 109). CSC-1 binds to *C. elegans* BIR-1/survivin and can form a four-way complex with INCENP and Aurora B. The role of CSC-1 in this complex is not known. To date, CSC-1 has not been detected in species other than nematodes.

Aurora kinases and cancer

Aurora kinases are of great interest for cancer researchers. The genes encoding the three human Aurora kinases map to regions that are affected by chromosomal abnormalities in different cancer types, and overexpression of each of the three human Auroras has been detected in tumour cell lines[8,15,110,111].

Aurora A. To date, most interest has focused on Aurora A, which fits the criteria to be classified as a bona fide oncogene (FIG. 7). Human Aurora A maps to chromosomal region 20q13.2, which is amplified in a number of cancer cell lines and primary tumours[8,112,113]. Furthermore, mouse NIH-3T3 cells transfected with Aurora A give rise to tumours when injected into nude mice[8,39,112]. This requires the catalytic activity of the kinase[8].

How might the inappropriate expression of Aurora A transform cells? One possibility is that the kinase somehow uncouples centrosome duplication from the cell cycle, thereby causing centrosome amplification. It is now almost 100 years since the proposal by Boveri that cancer might be caused by centrosomal abnormalities[114]. The relationship between such abnormalities and cancer has now been clearly shown[115], and considerable efforts have been focused on determining whether the centrosomal phenotypes are a cause or consequence of the cancerous transformation.

Two recent studies indicate that overexpression 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[116,117]. Aurora A is not unique in this regard, as overexpression of Aurora B or Polo-like kinase (Plk1) also causes cytokinesis failure and centrosome duplication[110,116]. Remarkably, this phenotype did not require that the two Aurora kinases be catalytically active — catalytically inactive mutants were as capable as, and in some cases more capable than, the kinase-active forms of inducing cytokinesis failure and centrosome amplification[116]. The mechanism of this cytokinesis failure is not known, but overexpression of Aurora A has been shown to perturb the spindle-assembly checkpoint[117]. 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 (REF. 116). This is partly because p53 can bind to Aurora A and directly inactivate its kinase function[118]. 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[119–123]. 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

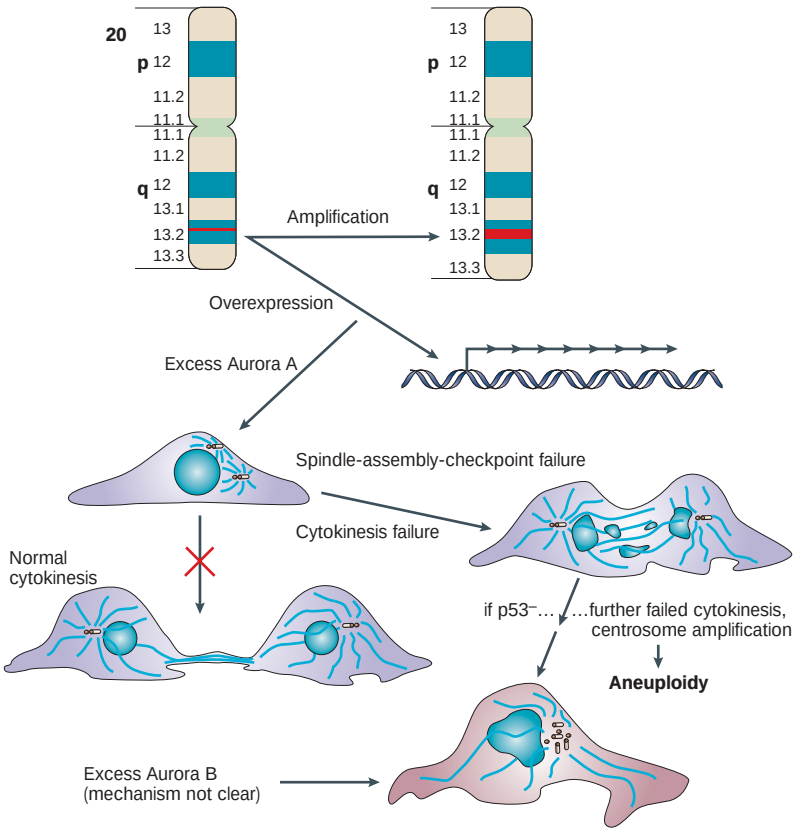


Figure 7 | **Aurora A and cancer.** Overexpression of Aurora A, either as a consequence of gene amplification or by other means, disrupts mitotic progression, apparently by blocking the ability of chromosomes to achieve a normal orientation on the spindle. Despite the difficulties with chromosome alignment, these cells exit mitosis because Aurora-A overexpression also inactivates the spindle-assembly checkpoint. The cells ultimately fail in cytokinesis, producing tetraploid progeny. If the cells also lack p53 ($p53^-$), they continue through subsequent cell cycles, ultimately becoming polyploid and, eventually, aneuploid, with amplified centrosomes. Aurora A could also potentially contribute to carcinogenesis in other ways that are not shown here. Dysregulation of Aurora-B kinase might also lead to ANEUPLOIDY and cancer (lower left), but the mechanism is much less explored than that for Aurora A.

mitosis, and generate aneuploid progeny. Whether cytokinesis failures represent the only route to centrosome amplification is a very important topic for future experimentation.

Why should the overexpression of Aurora A perturb mitosis and produce an effect that actually resembles that seen with a dominant-negative catalytically inactive Aurora-B mutant[50]? As described above, the two kinases share a high degree of homology in the kinase domain. In fact, both can phosphorylate histone H3 at S10 (REF. 70), and Aurora A has been shown to bind survivin in a ternary complex with the GTPase-activating protein RasGAP (REF. 124). One attractive possibility is that overexpressed Aurora A might compete with Aurora B for substrates and/or regulators.

Aurora B. Aurora B has also been implicated in cancer. CHO cells overexpressing Aurora B show elevated levels of phosphorylated histone H3 and defects in chromosome segregation and cytokinesis[125]. 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[125].

The Aurora theme: location, location, location

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. 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[8], 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.

The best known cell-cycle regulatory kinases are cyclin-dependent kinases (CDKs), so named because they require the association of a cyclin subunit for catalytic activity[126,127]. Binding of the cyclin subunit to the CDKs changes the kinase structure, preparing it for activation by CDK-activating kinase (CAK) and promoting the binding of substrates[128].

It now seems that the Aurora kinases are similar, but different, to CDKs. Bacterially expressed Aurora A and B are catalytically active, so they do not absolutely require the binding of associated subunits for activity. However, they are much more active when associated with auxiliary factors. In the case of Aurora B (and the yeast Auroras), these factors are INCENP and survivin[61,97,101]. In the case of Aurora A, TPX2 is one such factor[28,32]. Significantly, the homology with CDKs breaks down when the role of these auxiliary subunits is considered. Aurora A does not absolutely require an external activating kinase, although PKA and MSK1 (mitogen- and stress-activated protein kinase) can do this[32]. In fact, TPX2 seems to enable Aurora A to activate itself and to resist inactivation by PP1 (REF. 32). It will be important to demonstrate in the future whether a similar mechanism operates for Aurora B and INCENP/survivin.

ANEUPLOIDY
The ploidy of a cell refers to the number of sets of chromosomes that it contains. Aneuploid karyotypes are those whose chromosome complements are not a simple multiple of the haploid set.

Interestingly, both TPX2 and INCENP are substrates of their respective kinases[61,97,101,129] and INCENP phosphorylation has been shown to be required for the stimulation of kinase activity[101].

If the role of INCENP/survivin and TPX2 in kinase activation is considered further, a picture emerges of the Auroras as '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[25,28,82,83,96]. 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. For example, Aurora B moves from the entire chromosome, to the centromere, to the central spindle and equatorial cortex as cells traverse mitosis[50,82]. 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.

1. Glover, D. M., Leibowitz, M. H., McLean, D. A. & Parry, H. Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles. *Cell* **81**, 95–105 (1995).
2. Sunkel, C. E. & Glover, D. M. Polo, a mitotic mutant of *Drosophila* displaying abnormal spindle poles. *J. Cell Sci.* **89**, 25–38 (1988).
3. Chan, C. S. & Botstein, D. Isolation and characterization of chromosome-gain and increase-in-ploidy mutants in yeast. *Genetics* **135,** 677–691 (1993).
4. Petersen, J., Paris, J., Willer, M., Philippe, M. & Hagan, I. M. The *S. pombe* aurora-related kinase Ark1 associates with mitotic structures in a stage dependent manner and is required for chromosome segregation. *J. Cell Sci.* **114**, 4371–4384 (2001).
5. Leverson, J. D., Huang, H. K., Forsburg, S. L. & Hunter, T. The *Schizosaccharomyces pombe* Aurora-related kinase Ark1 interacts with the inner centromere protein Pic1 and mediates chromosome segregation and cytokinesis. *Mol. Biol. Cell* **13**, 1132–1143 (2002).
6. Adams, R. R., Carmena, M. & Earnshaw, W. C. Chromosomal passengers and the (Aurora) ABCs of mitosis. *Trends Cell Biol.* **11**, 49–54 (2001).
7. Nigg, E. A. Mitotic kinases as regulators of cell division and its checkpoints. *Nature Rev. Mol. Cell. Biol.* **2**, 21–32 (2001).
8. Bischoff, J. R. *et al.* A homologue of *Drosophila* aurora kinase is oncogenic and amplified in human colorectal cancers. *EMBO J.* **17**, 3052–3065 (1998).
Provides one of the first insights into the link between Aurora kinases and carcinogenesis.
9. Giet, R. & Prigent, C. Aurora/Ipl1p-related kinases, a new oncogenic family of mitotic serine-threonine kinases. *J. Cell Sci.* **112**, 3591–3601 (1999).
10. Cheetham, G. M. *et al.* Crystal structure of aurora-2, an oncogenic serine/threonine kinase. *J. Biol. Chem.* **277**, 42419–42422 (2002).
11. Nowakowski, J. *et al.* Structures of the cancer-related Aurora-A, FAK, and EphA2 protein kinases from nanovolume crystallography. *Structure* **10**, 1659–1667 (2002).
12. Earnshaw, W. C. & Bernat, R. L. Chromosomal passengers: towards an integrated view of mitosis. *Chromosoma* **100**, 139–146 (1990).
13. Bernard, M., Sanseau, P., Henry, C., Couturier, A. & Prigent, C. Cloning of STK13, a third human protein kinase related to *Drosophila* aurora and budding yeast Ipl1 that maps on chromosome 19q13.3-ter. *Genomics* **53**, 406–409 (1998).
14. Tseng, T. C., Chen, S. H., Hsu, Y. P. & Tang, T. K. Protein kinase profile of sperm and eggs: cloning and characterization of two novel testis-specific protein kinases (AIE1, AIE2) related to yeast and fly chromosome segregation regulators. *DNA Cell Biol.* **17**, 823–833 (1998).
15. Kimura, M., Matsuda, Y., Yoshioka, T. & Okano, Y. Cell cycle-dependent expression and centrosome localization of a third human aurora/Ipl1-related protein kinase, AIK3. *J. Biol. Chem.* **274**, 7334–7340 (1999).
16. Hu, H. M., Chuang, C. K., Lee, M. J., Tseng, T. C. & Tang, T. K. Genomic organization, expression, and chromosome localization of a third aurora-related kinase gene, Aie1. *DNA Cell Biol.* **19**, 679–688 (2000).
17. Schumacher, J. M., Ashcroft, N., Donovan, P. J. & Golden, A. A highly conserved centrosomal kinase, AIR-1, is required for accurate cell cycle progression and segregation of developmental factors in *Caenorhabditis elegans* embryos. *Development* **125**, 4391–4402 (1998).
18. Roghi, C. *et al.* The *Xenopus* protein kinase pEg2 associates with the centrosome in a cell cycle-dependent manner, binds to the spindle microtubules and is involved in bipolar mitotic spindle assembly. *J. Cell Sci.* **111**, 557–572 (1998).
19. Sugimoto, K. *et al.* Molecular dynamics of aurora-A kinase in living mitotic cells simultaneously visualized with histone H3 and nuclear membrane protein importinα. *Cell Struct. Funct.* **27**, 457–467 (2002).
20. Berdnik, D. & Knoblich, J. A. *Drosophila* Aurora-A is required for centrosome maturation and actin-dependent asymmetric protein localization during mitosis. *Curr. Biol.* **12**, 640–647 (2002).
This describes a role for Aurora A in asymmetric cell division and examines the dynamics of Aurora-A association with centrosomes.
21. Wittmann, T., Wilm, M., Karsenti, E. & Vernos, I. TPX2, a novel *Xenopus* MAP involved in spindle pole organization. *J. Cell Biol.* **149**, 1405–1418 (2000).
22. Gruss, O. J. *et al.* Chromosome-induced microtubule assembly mediated by TPX2 is required for spindle formation in HeLa cells. *Nature Cell Biol.* **4**, 871–879 (2002).
23. Giet, R. & Prigent, C. The non-catalytic domain of the *Xenopus laevis* aurora A kinase localises the protein to the centrosome. *J. Cell Sci.* **114**, 2095–2104 (2001).
24. Giet, R. *et al. Drosophila* Aurora A kinase is required to localize D-TACC to centrosomes and to regulate astral microtubules. *J. Cell Biol.* **156**, 437–451 (2002).
RNAi analysis confirms a role for Aurora A in centrosome maturation and separation.
25. Kufer, T. A. *et al.* Human TPX2 is required for targeting Aurora-A kinase to the spindle. *J. Cell Biol.* **158**, 617–623 (2002).
26. Hannak, E., Kirkham, M., Hyman, A. A. & Oegema, K. Aurora-A kinase is required for centrosome maturation in *Caenorhabditis elegans*. *J. Cell Biol.* **155**, 1109–1116 (2001).
27. Giet, R., Uzbekov, R., Cubizolles, F., Le Guellec, K. & Prigent, C. The *Xenopus laevis* aurora-related protein kinase pEg2 associates with and phosphorylates the kinesin-related protein XlEg5. *J. Biol. Chem.* **274**, 15005–15013 (1999).
28. Tsai, M. Y. *et al.* A Ran signalling pathway mediated by the mitotic kinase Aurora A in spindle assembly. *Nature Cell Biol.* **5**, 242–248 (2003).
This study shows that TPX2 activates Aurora-A kinase, and proposes that Aurora A might be an important downstream target of Ran–GTP in promoting mitotic spindle assembly.
29. Wilde, A. & Zheng, Y. Stimulation of microtubule aster formation and spindle assembly by the small GTPase Ran. *Science* **284**, 1359–1362 (1999).
30. Kalab, P., Pu, R. T. & Dasso, M. The ran GTPase regulates mitotic spindle assembly. *Curr. Biol.* **9**, 481–484 (1999).
31. Carazo-Salas, R. E. *et al.* Generation of GTP-bound Ran by RCC1 is required for chromatin-induced mitotic spindle formation. *Nature* **400**, 178–181 (1999).
32. Eyers, P. A., Erikson, E., Chen, L. G. & Maller, J. L. A novel mechanism for activation of the protein kinase aurora a. *Curr. Biol.* **13**, 691–697 (2003).
This study shows that TPX2 activates Aurora-A kinase in part by blocking the inactivation of the kinase by protein phosphatase 1.
33. Andresson, T. & Ruderman, J. V. The kinase Eg2 is a component of the *Xenopus* oocyte progesterone-activated signaling pathway. *EMBO J.* **17**, 5627–5637 (1998).
34. Mendez, R. *et al.* Phosphorylation of CPE binding factor by Eg2 regulates translation of c-mos mRNA. *Nature* **404**, 302–307 (2000).
This describes the involvement of Aurora A in cell-cycle regulation by regulating poly(A)-dependent translation.
35. Frank-Vaillant, M. *et al.* Progesterone regulates the accumulation and the activation of Eg2 kinase in *Xenopus* oocytes. *J. Cell Sci.* **113**, 1127–1138 (2000).
36. Maton, G. *et al.* Cdc2–Cyclin B triggers H3 kinase activation of Aurora-A in *Xenopus* oocytes. *J. Biol. Chem.* **278**, 21439–21449 (2003).
37. Schumacher, J. M., Golden, A. & Donovan, P. J. AIR-2: An Aurora/Ipl1-related protein kinase associated with chromosomes and midbody microtubules is required for polar body extrusion and cytokinesis in *Caenorhabditis elegans* embryos. *J. Cell Biol.* **143**, 1635–1646 (1998).
38. Castro, A., Mandart, E., Lorca, T. & Galas, S. Involvement of Aurora A kinase during meiosis I–II transition in *Xenopus* oocytes. *J. Biol. Chem.* **278**, 2236–2241 (2003).
39. Littlepage, L. E. *et al.* Identification of phosphorylated residues that affect the activity of the mitotic kinase Aurora-A. *Proc. Natl Acad. Sci. USA* **99**, 15440–15445 (2002).
Systematic analysis of the residues that are relevant for regulation of Aurora-A kinase.
40. Walter, A. O., Seghezzi, W., Korver, W., Sheung, J. & Lees, E. The mitotic serine/threonine kinase Aurora2/AIK is regulated by phosphorylation and degradation. *Oncogene* **19**, 4906–4916 (2000).
41. Cheeseman, I. M. *et al.* Phospho-regulation of kinetochore-microtubule attachments by the Aurora kinase Ipl1p. *Cell* **111**, 163–172 (2002).
This is the most thorough study yet of the protein targets of the Aurora kinase Ipl1.
42. Francisco, L., Wang, W. & Chan, C. S. Type 1 protein phosphatase acts in opposition to IpL1 protein kinase in regulating yeast chromosome segregation. *Mol. Cell. Biol.* **14**, 4731–4740 (1994).
43. Katayama, H., Zhou, H., Li, Q., Tatsuka, M. & Sen, S. Interaction and feedback regulation between STK15/BTAK/Aurora-A kinase and protein phosphatase 1 through mitotic cell division cycle. *J. Biol. Chem.* **276**, 46219–46224 (2001).
44. Murnion, M. E. *et al.* Chromatin-associated protein phosphatase 1 regulates Aurora-B and histone H3 phosphorylation. *J. Biol. Chem.* **276**, 26656–26665 (2001).
45. Honda, K. *et al.* Degradation of human Aurora2 protein kinase by the anaphase-promoting complex-ubiquitin-proteasome pathway. *Oncogene* **19**, 2812–2819 (2000).
46. Castro, A. *et al.* APC/Fizzy-Related targets Aurora-A kinase for proteolysis. *EMBO Rep.* **3**, 457–462 (2002).
47. Castro, A. *et al.* The D-Box-activating domain (DAD) is a new proteolysis signal that stimulates the silent D-Box sequence of Aurora-A. *EMBO Rep.* **3**, 1209–1214 (2002).
48. Littlepage, L. E. & Ruderman, J. V. Identification of a new APC/C recognition domain, the A box, which is required for the Cdh1-dependent destruction of the kinase Aurora-A during mitotic exit. *Genes Dev.* **16**, 2274–2285 (2002).
References 46 and 48 do a good job of dissecting the complexities of Aurora-A regulation by the APC/C.
49. Kiat, L. S., Hui, K. M. & Gopalan, G. Aurora-A kinase interacting protein (AIP), a novel negative regulator of human Aurora-A kinase. *J. Biol. Chem.* **277**, 45558–45565 (2002).
50. Terada, Y. *et al.* AIM-1: a mammalian midbody-associated protein required for cytokinesis. *EMBO J.* **17**, 667–676 (1998).
One of the first reports showing the requirement of Aurora B for cytokinesis.

51. Adams, R. R., Maiato, H., Earnshaw, W. C. & Carmena, M. Essential roles of *Drosophila* inner centromere protein (INCENP) and Aurora-B in histone H3 phosphorylation, metaphase chromosome alignment, kinetochore disjunction, and chromosome segregation. *J. Cell Biol.* **153**, 865–880 (2001).
52. Murata-Hori, M., Tatsuka, M. & Wang, Y. L. Probing the dynamics and functions of Aurora B kinase in living cells during mitosis and cytokinesis. *Mol. Biol. Cell* **13**, 1099–1108 (2002).
Examines the dynamic behaviour of Aurora-B kinase *in vivo* using green-fluorescent-protein-labelled protein.
53. Nicklas, R. B. & Staehly, C. A. Chromosome micromanipulation. I. The mechanics of chromosome attachment to the spindle. *Chromosoma* **21**, 1–16 (1967).
54. Nicklas, R. B., Wards, S. C. & Gorbsky, G. J. Kinetochore chemistry is sensitive to tension and may link mitotic forces for a cell cycle checkpoint. *J. Cell Biol.* **130**, 929–939 (1995).
55. Tanaka, T. U. *et al.* Evidence that the Ipl1–Sli15 (Aurora kinase–INCENP) complex promotes chromosome bi-orientation by altering kinetochore-spindle pole connections. *Cell* **108**, 317–329 (2002).
This paper was the first to propose that Ipl1 might be involved in the resolution of syntelic chromsome attachments.
56. Kallio, M. J., McCleland, M. L., Stukenberg, P. T. & Gorbsky, G. J. Inhibition of aurora B kinase blocks chromosome segregation, overrides the spindle checkpoint, and perturbs microtubule dynamics in mitosis. *Curr. Biol.* **12**, 900–905 (2002).
Antibody injection is used to identify some of the many functions of Aurora B in mammalian cells.
57. Ditchfield, C. *et al.* Aurora B couples chromosome alignment with anaphase by targeting BubR1, Mad2 and Cenp-E to kinetochores. *J. Cell Biol.* **161**, 267–280 (2003).
This description of a small-molecule inhibitor of Aurora B identifies a role for the kinase in the spindle-assembly checkpoint when the checkpoint is activated in the presence of microtubules by altering tension within the spindle.
58. Hauf, S. *et al.* The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint. *J. Cell Biol.* **161**, 281–294 (2003).
This description of a second small-molecule inhibitor of Aurora B provides the best evidence to date that the kinase is involved in the resolution of syntelic chromosomal attachments during prometaphase.
59. Murata-Hori, M. & Wang, Y. The kinase activity of Aurora B is required for kinetochore–microtubule interactions during mitosis. *Curr. Biol.* **12**, 894–899 (2002).
60. Biggins, S. *et al.* The conserved protein kinase Ipl1 regulates microtubule binding to kinetochores in budding yeast. *Genes Dev.* **13**, 532–544 (1999).
61. Kang, J. *et al.* Functional cooperation of Dam1, Ipl1, and the inner centromere protein (INCENP)-related protein Sli15 during chromosome segregation. *J. Cell Biol.* **155**, 763–774 (2001).
62. Buvelot, S., Tatsutani, S. Y., Vermaak, D. & Biggins, S. The budding yeast Ipl1/Aurora protein kinase regulates mitotic spindle disassembly. *J. Cell Biol.* **160**, 329–339 (2003).
63. Shang, C. *et al.* Kinetochore protein interactions and their regulation by the Aurora kinase Ipl1p. *Mol. Biol. Cell* **14**, 3342–3355 (2003).
64. Honda, R., Korner, R. & Nigg, E. A. Exploring the functional interactions between Aurora B, INCENP, and survivin in mitosis. *Mol. Biol. Cell* **14**, 3325–3341 (2003).
A thorough study of the regulation of Aurora-B kinase activity by INCENP and survivin.
65. Zeitlin, S. G., Shelby, R. D. & Sullivan, K. F. CENP-A is phosphorylated by Aurora B kinase and plays an unexpected role in completion of cytokinesis. *J. Cell. Biol.* **155**, 1147–1157 (2001).
66. Gurley, L. R., D'Anna, J. A., Barham, S. S., Deaven, L. L. & Tobey, R. A. Histone phosphorylation and chromatin structure during mitosis in Chinese hamster cells. *Eur. J. Biochem.* **84**, 1–15 (1978).
67. Hsu, J. Y. *et al.* Mitotic phosphorylation of histone H3 is governed by Ipl1/aurora kinase and Glc7/PP1 phosphatase in budding yeast and nematodes. *Cell* **102**, 279–291 (2000).
68. Speliotes, E. K., Uren, A., Vaux, D. & Horvitz, H. R. The survivin-like *C. elegans* BIR-1 protein acts with the Aurora-like kinase AIR-2 to affect chromosomes and the spindle midzone. *Mol. Cell* **6**, 211–223 (2000).
69. Giet, R. & Glover, D. M. *Drosophila* Aurora B kinase is required for histone H3 phosphorylation and condensin recruitment during chromosome condensation and to organize the central spindle during cytokinesis. *J. Cell Biol.* **152**, 669–681 (2001).
70. Crosio, C. *et al.* Mitotic phosphorylation of histone H3: spatio-temporal regulation by mammalian Aurora kinases. *Mol. Cell. Biol.* **22**, 874–885 (2002).
71. MacCallum, D. E., Losada, A., Kobayashi, R. & Hirano, T. ISWI remodeling complexes in *Xenopus* egg extracts: identification as major chromosomal components that are regulated by INCENP-aurora B. *Mol. Biol. Cell* **13**, 25–39 (2002).
72. Goto, H. *et al.* Identification of a novel phosphorylation site on histone H3 coupled with mitotic chromosome condensation. *J. Biol. Chem.* **274**, 25543–25549 (1999).
73. Goto, H., Yasui, Y., Nigg, E. A. & Inagaki, M. Aurora-B phosphorylates Histone H3 at serine28 with regard to the mitotic chromosome condensation. *Genes Cells* **7**, 11–17 (2002).
74. Giet, R. & Prigent, C. The *Xenopus laevis* aurora/Ip11p-related kinase pEg2 participates in the stability of the bipolar mitotic spindle. *Exp. Cell Res.* **258**, 145–151 (2000).
75. Hirano, T. The ABCs of SMC proteins: two-armed ATPases for chromosome condensation, cohesion, and repair. *Genes Dev.* **16**, 399–414 (2002).
76. Petersen, J. & Hagan, I. M. *S. pombe* Aurora kinase/survivin is required for chromosome condensation and the spindle checkpoint attachment response. *Curr. Biol.* **13**, 590–597 (2003).
This study uses yeast genetics to show a role for Aurora B and its associated protein survivin in the spindle-assembly checkpoint.
77. Kaitna, S., Pasierbek, P., Jantsch, M., Loidl, J. & Glotzer, M. The Aurora B kinase AIR-2 regulates kinetochores during mitosis and is required for separation of homologous chromosomes during meiosis. *Curr. Biol.* **12**, 798–812 (2002).
78. Hagstrom, K. A., Holmes, V. F., Cozzarelli, N. R. & Meyer, B. J. *C. elegans* condensin promotes mitotic chromosome architecture, centromere organization, and sister chromatid segregation during mitosis and meiosis. *Genes Dev.* **16**, 729–742 (2002).
79. Rogers, E., Bishop, J. D., Waddle, J. A., Schumacher, J. M. & Lin, R. The aurora kinase AIR-2 functions in the release of chromosome cohesion in *Caenorhabditis elegans* meiosis. *J. Cell Biol.* **157**, 219–229 (2002).
This provides important insights into the role of Aurora B in chromosome segregation in meiosis.
80. Sonoda, E. *et al.* Scc1/Rad21/Mcd1 is required for sister chromatid cohesion and kinetochore function in vertebrate cells. *Dev. Cell* **1**, 759–770 (2001).
81. Mackay, A. M., Ainsztein, A., Eckley, D. M. & Earnshaw, W. C. A dominant mutant of inner centromere protein (INCENP), a chromosomal protein, disrupts prometaphase congression and cytokinesis. *J. Cell Biol.* **140**, 991–1002 (1998).
82. Adams, R. R. *et al.* INCENP binds the aurora-related kinase AIRK2 and is required to target it to chromosomes, the central spindle and cleavage furrow. *Curr. Biol* **10**, 1075–1078 (2000).
83. Kaitna, S., Mendoza, M., Jantsch-Plunger, V. & Glotzer, M. Incenp and an Aurora-like kinase form a complex essential for chromosome segregation and efficient completion of cytokinesis. *Curr. Biol.* **10**, 1172–1181 (2000).
84. Severson, A. F., Hamill, D. R., Carter, J. C., Schumacher, J. & Bowerman, B. The aurora-related kinase AIR-2 recruits ZEN-4/CeMKLP1 to the mitotic spindle at metaphase and is required for cytokinesis. *Curr. Biol.* **10**, 1162–1171 (2000).
85. Murata-Hori, M. *et al.* Myosin II regulatory light chain as a novel substrate for AIM-1, an aurora/Ipl1p-related kinase from rat. *J. Biochem. (Tokyo)* **128**, 903–907 (2000).
86. Goto, H. *et al.* Aurora-B regulates the cleavage furrow-specific vimentin phosphorylation in the cytokinetic process. *J. Biol. Chem.* **278**, 8526–8530 (2003).
87. Kawajiri, A. *et al.* Functional significance of the specific sites phosphorylated in desmin at cleavage furrow: Aurora-B may phosphorylate and regulate Type III intermediate filaments during cytokinesis coordinatedly with Rho-kinase. *Mol. Biol. Cell* **14**, 1489–1500 (2003).
88. Jantsch-Plunger, V. *et al.* CYK-4: A Rho family GTPase activating protein (GAP) required for central spindle formation and cytokinesis. *J. Cell Biol.* **149**, 1391–1404 (2000).
89. Minoshima, Y., *et al.* Phosphorylation by Aurora B converts MgcRacGAP to a RhoGAP during cytokinesis. *Dev. Cell* **4**, 549–560 (2003).
An elegant study that identifies a new substrate for Aurora B and shows how the kinase might participate in the regulation of cytokinesis.
90. Kishi, K., Sasaki, T., Kuroda, S., Itoh, T. & Takai, Y. Regulation of cytoplasmic division of *Xenopus* embryo by rho p21 and its inhibitory GDP/GTP exchange protein (rho GDI). *J. Cell Biol.* **120**, 1187–1195 (1993).
91. Mabuchi, I. *et al.* A rho-like protein is involved in the organisation of the contractile ring in dividing sand dollar eggs. *Zygote* **1**, 325–331 (1993).
92. Biggins, S. & Murray, A. W. The budding yeast protein kinase Ipl1/Aurora allows the absence of tension to activate the spindle checkpoint. *Genes Dev.* **15**, 3118–3129 (2001).
93. Carvalho, A., Carmena, M., Sambade, C., Earnshaw, W. C. & Wheatley, S. P. Survivin is required for stable checkpoint activation in taxol-treated HeLa cells. *J. Cell Sci.* **116**, 2987–2998 (2003).
94. Lens, S. M. A. *et al.* Survivin is required for a sustained spindle checkpoint arrest in response to lack of tension. *EMBO J.* **22**, 2934–2947 (2003).
References 93 and 94 use RNAi technology to show that survivin is required for the spindle-assembly checkpoint in the presence of microtubules, and for BubR1 targeting to the kinetochore.
95. Sugiyama, K. *et al.* Aurora-B associated protein phosphatases as negative regulators of kinase activation. *Oncogene* **21**, 3103–3111 (2002).
96. Wheatley, S. P., Carvalho, A., Vagnarelli, P. & Earnshaw, W. C. INCENP is required for proper targeting of survivin to the centromeres and the anaphase spindle during mitosis. *Curr. Biol.* **11**, 886–890 (2001).
97. Bolton, M. A. *et al.* 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* **13**, 3064–3077 (2002).
A thorough study of the regulation of Aurora-B kinase activity by INCENP and survivin.
98. Wheatley, S. P., Kandels-Lewis, S. E., Adams, R. R., Ainsztein, A. M. & Earnshaw, W. C. INCENP binds directly to tubulin and requires dynamic microtubules to target to the cleavage furrow. *Exp. Cell. Res.* **262**, 122–127 (2001).
99. Ainsztein, A. M., Kandels-Lewis, S. E., Mackay, A. M. & Earnshaw, W. C. INCENP centromere and spindle targeting: identification of essential conserved motifs and involvement of heterochromatin protein HP1. *J. Cell Biol.* **143**, 1763–1774 (1998).
100. Terada, Y., Katayama, H., Tatsuka, M. & Kuriyama, R. AIM-1 regulates onset of cytokinesis by targeting INCENP to midzone and midbody. *Mol. Biol. Cell* **11S**, 343a (2000).
101. Bishop, J. D. & Schumacher, J. M. Phosphorylation of the carboxyl terminus of inner centromere protein (INCENP) by the Aurora B kinase stimulates Aurora B kinase activity. *J. Biol. Chem.* **277**, 27577–27580 (2002).
Provided a clear demonstration that INCENP phosphorylation by Aurora B is part of a feedback loop that stimulates kinase activity.
102. Deveraux, Q. L. & Reed, J. C. IAP family proteins — suppressors of apoptosis. *Genes Dev.* **13**, 239–252 (1999).
103. Uren, A. G. *et al.* Survivin and the inner centromere protein INCENP show similar cell-cycle localization and gene knockout phenotype. *Curr. Biol.* **10**, 1319–1328 (2000).
104. Chen, J. *et al.* Survivin enhances Aurora-B kinase activity and localizes Aurora-B in human cells. *J. Biol. Chem.* **278**, 486–490 (2003).
105. Morishita, J. *et al.* Bir1/Cut17 moving from chromosome to spindle upon the loss of cohesion is required for condensation, spindle elongation and repair. *Genes Cells* **6**, 743–763 (2001).
106. Martineau-Thuillier, S., Andreassen, P. R. & Margolis, R. L. Colocalization of TD-60 and INCENP throughout G2 and mitosis: evidence for their possible interaction in signalling cytokinesis. *Chromosoma (Berl.)* **107**, 461–470 (1998).
107. Mollinari, C. *et al.* The mammalian passenger protein TD-60 is an RCC1 family member with an essential role in prometaphase to metaphase progression. *Dev. Cell* **5**, 295–307 (2003).
108. Ohi, R., Coughlin, M. L., Lane, W. S. & Mitchison, T. J. An inner centromere protein that stimulates the microtubule depolymerizing activity of a KinI kinesin. *Dev. Cell* **5,** 309–321 (2003).
109. Romano, A. *et al.* CSC-1: a subunit of the Aurora B kinase complex that binds to the survivin-like protein BIR-1 and the incenp-like protein ICP-1. *J. Cell Biol.* **161**, 229–236 (2003).
110. Tatsuka, M. *et al.* Multinuclearity and increased ploidy caused by overexpression of the aurora- and Ipl1-like midbody-associated protein mitotic kinase in human cancer cells. *Cancer Res.* **58**, 4811–4816 (1998).
111. Takahashi, T. *et al.* Centrosomal kinases, HsAIRK1 and HsAIRK3, are overexpressed in primary colorectal cancers. *Jpn. J. Cancer Res.* **91**, 1007–1014 (2000).
112. Zhou, H. *et al.* Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. *Nature Genet.* **20**, 189–193 (1998).
113. Tanner, M. M. *et al.* Frequent amplification of chromosomal region 20q12-q13 in ovarian cancer. *Clin. Cancer Res.* **6**, 1833–1839 (2000).
114. Boveri, T. *Zur Frage der Entstehung maligner Tumoren* (Fischer Verlag, Jena, 1914).

115. Doxsey, S. Duplicating dangerously: linking centrosome duplication and aneuploidy. *Mol. Cell* **10**, 439–440 (2002).
116. Meraldi, P., Honda, R. & Nigg, E. A. Aurora-A overexpression reveals tetraploidization as a major route to centrosome amplification in p53$^{-/-}$ cells. *EMBO J.* **21**, 483–492 (2002).
Presents data indicating that centrosome amplification in response to Aurora kinase overexpression arises as a result of failures in cytokinesis.
117. Anand, S., Penrhyn-Lowe, S. & Venkitaraman, A. R. AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol. *Cancer Cell* **3**, 51–62 (2003).
118. Chen, S. S., Chang, P. C., Cheng, Y. W., Tang, F. M. & Lin, Y. S. Suppression of the STK15 oncogenic activity requires a transactivation-independent p53 function. *EMBO J.* **21**, 4491–4499 (2002).
119. Minn, A. J., Boise, L. H. & Thompson, C. B. Expression of Bcl-xL and loss of p53 can cooperate to overcome a cell cycle checkpoint induced by mitotic spindle damage. *Genes Dev.* **10**, 2621–2631 (1996).
120. Lanni, J. S. & Jacks, T. Characterization of the p53-dependent postmitotic checkpoint following spindle disruption. *Mol. Cell. Biol.* **18**, 1055–1064 (1998).
121. Khan, S. H. & Wahl, G. M. p53 and pRb prevent rereplication in response to microtubule inhibitors by mediating a reversible G1 arrest. *Cancer Res.* **58**, 396–401 (1998).
122. Casenghi, M. *et al.* p53-independent apoptosis and p53-dependent block of DNA rereplication following mitotic spindle inhibition in human cells. *Exp. Cell Res.* **250**, 339–350 (1999).
123. Andreassen, P. R., Lohez, O. D., Lacroix, F. B. & Margolis, R. L. Tetraploid state induces p53-dependent arrest of nontransformed mammalian cells in G1. *Mol. Biol. Cell* **12**, 1315–1328 (2001).
124. Gigoux, V., L'Hoste, S., Raynaud, F., Camonis, J. & Garbay, C. Identification of Aurora kinases as RasGAP Src homology 3 domain-binding proteins. *J. Biol. Chem.* **277**, 23742–23746 (2002).
125. Ota, T. *et al.* Increased mitotic phosphorylation of histone H3 attributable to AIM-1/Aurora-B overexpression contributes to chromosome number instability. *Cancer Res.* **62**, 5168–5177 (2002).
126. Gautier, J., Norbury, C., Lohka, M., Nurse, P. & Maller, J. Purified maturation-promoting factor contains the product of a *Xenopus* homolog of the fission yeast cell cycle control gene cdc2+. *Cell* **54**, 433–439 (1988).
127. Lohka, M., Hayes, M. K. & Maller, J. L. Purification of maturation-promoting factor, an intracellular regulator of early mitotic events. *Proc. Natl Acad. Sci. USA* **85**, 3009–3013 (1988).
128. Pavletich, N. P. Mechanisms of cyclin-dependent kinase regulation: structures of Cdks, their cyclin activators, and Cip and INK4 inhibitors. *J. Mol. Biol.* **287**, 821–828 (1999).
129. Kufer, T. A. *et al.* Human TPX2 is required for targeting Aurora-A kinase to the spindle. *J. Cell Biol.* **158**, 617–623 (2002).

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