Chapter 11
Regulation of Centrosomes by Cyclin-Dependent Kinases

Rose Boutros

Abstract In eukaryotic cells, each cell division cycle involves two distinct replication cycles. These are the chromosomal DNA replication and the centrosome replication cycles. Progression through the cell division cycle is regulated by the activities of the cyclin–cyclin-dependent kinase complexes. These enzymes control both DNA replication and centrosome replication and ensure that the two cycles occur in synchrony.

11.1 CDK-Cyclins and Cell Cycle Progression

Cyclin-dependent kinases (CDKs) are a large family of serine/threonine protein kinases. The founding member, Cdc2 was identified in genetic screens from yeast as a mutant that caused cell division cycle defects (Russell and Nurse 1986). The human homologue (CDK1) was subsequently identified by its ability to rescue the yeast Cdc2 mutants (Lee and Nurse 1987). There are now 11 known genes that encode CDKs and nine genes that encode CDK-like proteins in mammalian cells (Malumbres and Barbacid 2005). The protein products of the best characterised CDKs control progression through the cell division cycle, in complex with their regulatory subunits, the cyclins (Fig. 11.1). Binding of a cyclin to a CDK induces a conformational change within the active site of the CDK and allows the kinase to become activated (Bourne et al. 1996; De Bondt et al. 1993). Thus, cell cycle

R. Boutros (✉)
Children's Medical Research Institute, The University of Sydney,
214 Hawkesbury Road, Westmead, NSW 2145, Australia
e-mail: rboutros@cmri.org.au

H. Schatten (ed.), *The Centrosome*, DOI: 10.1007/978-1-62703-035-9_11,

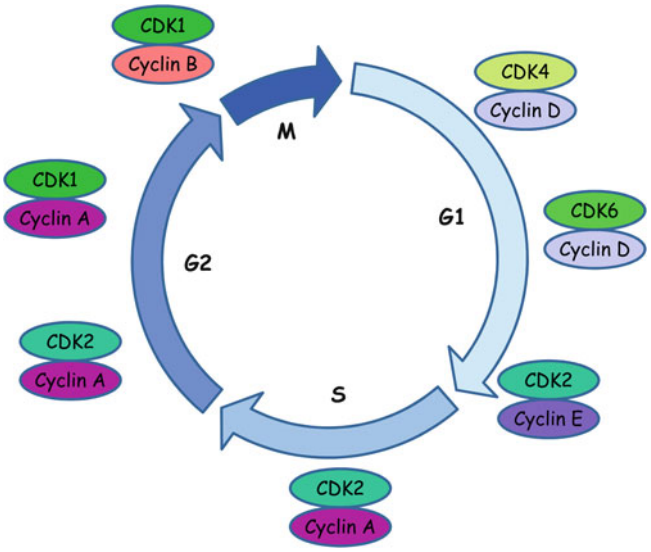

Fig. 11.1 Progression through the cell division cycle is controlled by the activities of specific CDK-cyclin complexes at each phase

progression is believed to be driven primarily by combinations of these CDKs and their cyclin partners.

Cyclins are a diverse family of proteins, all of which contain a stretch of 150 amino acids termed the 'cyclin box' (Malumbres and Barbacid 2005). They were first identified in marine invertebrates as proteins whose abundance oscillated during the cell cycle (Evans et al. 1983). There are at least 29 genes encoding cyclins in human cells, although not all have known CDK partners (Malumbres and Barbacid 2005). Those cyclins that do have known CDK partners and that regulate progression through the cell cycle fall into four major classes: D, E, A, and B type cyclins (Satyanarayana and Kaldis 2009). The D type cyclins bind CDK4 and CDK6 in G1 phase, the E type cyclins bind CDK2 at the G1–S phase transition, the A type cyclins bind CDK2 during S phase and CDK1 during G2 phase and the B type cyclins bind CDK1 during the G2–M transition and early mitosis (Satyanarayana and Kaldis 2009) (Fig. 11.1).

11.1.1 Regulation of CDK-Cyclin Activities

The catalytic activities of CDKs are tightly regulated in a strict spatio-temporal manner by a number of complementary mechanisms, including cyclin binding, changes in cyclin levels (determined by gene expression and proteolysis), protein phosphorylation and dephosphorylation, binding to CDK inhibitors, and subcellular localisation (Morgan 1995; King et al. 1996; Booher et al. 1989).

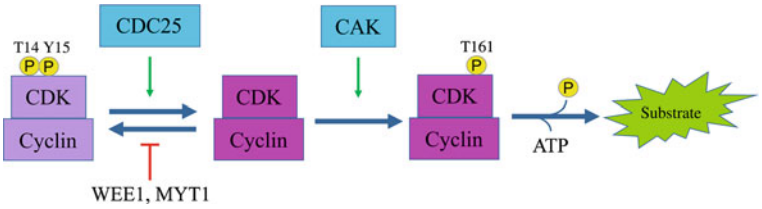

Fig. 11.2 Regulation of CDK-cyclin activity by phosphorylation. Phosphorylation of CDK on T14 and Y15 by the Wee1 and Myt1 kinases keeps the complex inactive. Dephosphorylation of these two residues by the CDC25 phosphatases activates the complex. Phosphorylation of one further residue, T161 within the activation loop of CDK is required for full activation of the complex. Once activated, CDK-cyclins can phosphorylate and activate their downstream substrates

Successive oscillations of cyclin levels throughout cell division control the overall activity of a given CDK-cyclin complex during each cell cycle phase. Cyclin protein levels are regulated by a balance between gene expression and protein degradation. Cyclin E for example, is expressed during a very narrow window at the G1-S transition. It becomes rapidly expressed in late G1 phase and then degraded very soon after forming a complex with CDK2, by ubiquitin-mediated proteolysis (Clurman et al. 1996; Won and Reed 1996). In contrast, Cyclin A is more stable throughout the cell cycle. It is expressed from early S phase and its protein levels continue to increase throughout S and G2 phase, during which the proteins complexes with CDK2 and CDK1, respectively. Cyclin A is then rapidly degraded during prometaphase (Hunt et al. 1992; Pines and Hunter 1990). Cyclins have also been reported to contribute to the substrate specificity of each CDK-cyclin complex (Peeper et al. 1993).

Phosphorylation of both CDK and cyclin subunits has been shown to regulate the level of activity of CDK-cyclin complexes. Phosphorylation of three critical residues (corresponding to T161, T14 and Y15 in mammalian cells) regulate CDK activity (Morgan 2007) (Fig. 11.2). T14 and Y15 phosphorylation by the Wee1 and Myt1 kinases keep the complex in an inactive form (Malumbres and Barbacid 2005). The opposing activities of the CDC25 protein phosphatases, which dephosphorylate CDK on these two residues, activate the complex (Fig. 11.2). Three CDC25 isoforms exist in mammalian cells (CDC25A, B and C), all of which co-operate to regulate the activities of the various CDK-cyclin complexes throughout cell division (Boutros et al. 2006, 2007), and all of which are found at the centrosome (Schmitt et al. 2006; Bonnet et al. 2008; Shreeram et al. 2008). Phosphorylation of T161 on CDK by CDK-activating kinase (CAK) is required for full activation of the kinase (Kaldis 1999) (Fig. 11.2).

CDK activities are also regulated by CDK inhibitors. These bind to and inactivate CDKs, either prior to the requirement of their activity or in response to cellular stress signals, such as DNA damage. Mammalian cells have a number of CDK inhibitors, including p21, p27 and p57, which inhibit CDK2 and p15, p16, p18 and p19 which inhibit CDK4 and CDK6 (Morgan 2007).

Some cyclins contain sequences that target them and their CDK partner to specific subcellular localisations. For example, cyclin B1 encodes a cytoplasmic retention sequence whose phosphorylation triggers the nuclear localisation of CDK1-cyclin B1. This is essential for phosphorylation of nuclear lamina A which triggers the breakdown of the nuclear envelope in prophase (Li et al. 1997). Recently, the A and E type cyclins have been found to encode centrosome localisation sequences that target these proteins to the centrosome (Matsumoto and Maller 2004; Pascreau et al. 2010).

11.2 CDK Control of the Centrosome

Each cell inherits a single centrosome at the end of cell division and a single copy of DNA. In order for accurate chromosome segregation during the next cell division, both the chromosomal DNA and the centrosome must replicate, once. Centrosome replication thus commences with DNA replication at the G1-S phase transition. CDK2-cyclin E in the nucleus initiates DNA replication through phosphorylation of the Retinoblastoma (Rb) protein and activation of the E2F transcription factor (Stevaux and Dyson 2002). Similarly, CDK2-cyclin E at the centrosome is believed to initiate centrosome replication by phosphorylation of its centrosome substrates, such as nucleophosmin (Hinchcliffe and Sluder 2002).

11.2.1 CDK2-Cyclin E/Cyclin A Control of Centrosome Replication

The first step in centriole replication is centriole disorientation—the loss of orthogonal association between the mother and daughter centrioles—in late G1 phase. This process was shown to be dependent on CDK2-cyclin E. Centriole disorientation was found to occur in late G1 phase in isolated mammalian cells that were incubated with control Xenopus egg extracts containing normal CDK2-cyclin E activity but not in extracts that had been treated with the CDK2-cyclin E inhibitors p21 or p27 (Lacey et al. 1999).

Centriole disorientation is followed in early S phase, by the appearance of small procentriole structures oriented at right angles to the original centrioles, that elongate during S phase. Under normal cell cycle conditions, only one procentriole forms perpendicular to each existing centriole (Tsou and Stearns 2006). However, if cells are arrested in S phase for prolonged periods, by inhibitors of DNA or protein synthesis for example, multiple procentrioles can form next to each existing centriole through repeated cycles of centrosome replication (Balczon et al. 1995). This experimental uncoupling of centrosome replication from DNA replication was exploited in a series of reports in 1999 that demonstrated that the

formation of procentrioles in S phase is dependent on the activity of CDK2. The Sluder laboratory used Xenopus egg extracts and sperm nuclei to demonstrate that cells incubated with control egg extracts could form multiple centrosomes following S phase arrest with the DNA polymerase inhibitor aphidicolin. However, cells incubated with egg extracts containing recombinant Xic-1^{p27}, a CDK2–cyclin E inhibitor, did not undergo repeated rounds of centrosome replication (Hinchcliffe et al. 1999). The Stearns lab used S phase-arrested Xenopus embryos in which individual blastomeres were microinjected with p21 or p27. Compared to control non-injected blastomeres that underwent multiple rounds of centrosome doubling, repeated centrosome doubling was not observed in blastomeres from the same embryo that had been microinjected with the CDK2 inhibitors (Lacey et al. 1999). Similar observations were made in mammalian cells. Nishida and colleagues demonstrated that Chinese hamster ovary (CHO) cells that were arrested in S phase by hydroxyurea treatment had high levels of CDK2 and could undergo repeated centrosome replication, whilst cells arrested in G1 phase by mimosine treatment had low levels of CDK2 and could not undergo multiple rounds of centrosome replication (Matsumoto et al. 1999). In addition, blocking CDK2 activity in S phase-arrested cells by treatment with roscovitine or butyrolactone or expression of p21 significantly inhibited the formation of extra centrioles (Matsumoto et al. 1999). The Nigg laboratory used hydroxyurea-arrested CHO cells to demonstrate a role for the Retinoblastoma (Rb)-E2F transcription factor pathway in centrosome reduplication (Meraldi et al. 1999). They found that CDK2 in complex with cyclin A, rather than cyclin E, was necessary for centrosome reduplication in this system (Meraldi et al. 1999).

More recent evidence for a requirement for CDK2 in centrosome replication came from a study on p53−/− CHO cells, which formed multiple centrin foci following G1/S arrest with hydroxyurea. These centrin foci were found to represent procentrioles that could mature into functional centrosomes and were dependent on the presence of active CDK2 (Prosser et al. 2009). We have also found that overexpression of the CDK-cyclin activator CDC25B in G1/S-arrested U2OS cells results in multiple centrosomes formed within a single S phase (Boutros et al. 2007). We found that centrosome re-replication in these cells could be blocked by specific inhibition of CDK2 but not CDK1 activity (R Boutros, unpublished data).

CDK2 in complex with cyclin E and/or cyclin A therefore appears to be required for the initiation of centrosome replication. However, the exact mechanism for this is unclear. And the findings that CDK2 knockout mice are viable suggest that other kinases, most likely CDK1, can take on the role of CDK2 in both centrosome replication and DNA replication (Berthet et al. 2003; Ortega et al. 2003). Nonetheless, a number of kinase targets for CDK2–cyclins E/A in centrosome replication have been identified to date, which suggest that CDK2 exerts its effects on centrosome replication through the timely phosphorylation of its substrates. The polo kinase 4 (PLK4), also essential for centrosome replication, functions in co-operation with CDK2 (Habedanck et al. 2005).

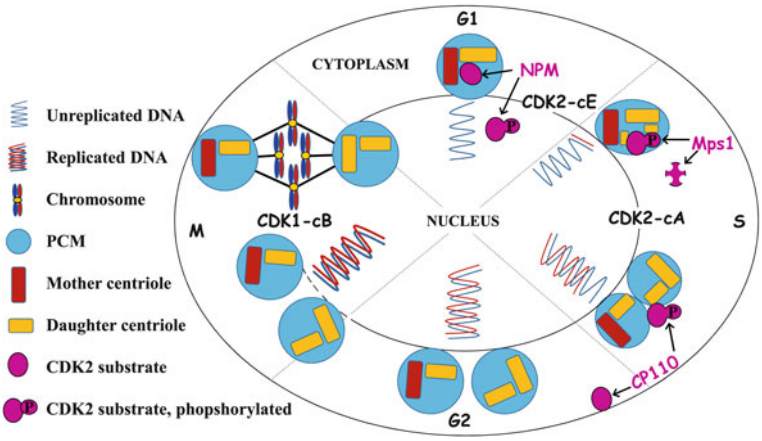

Fig. 11.3 The centrosome and DNA replication cycles. Both are initiated by the activity of CDK2-cyclin E at G1/S and maintained by CDK2-cyclin A in S/G2 phases. CDK1-cyclin B coordinates centrosome maturation with nuclear envelope breakdown and chromosome condensation at G2/M. Known centrosomal CDK2 substrates NPM, Mps1 and CP110 are shown (*pink*)

11.2.2 CDK2 Centrosomal Substrates

Once the importance of CDK2-cyclin E in centrosome replication was established, efforts turned to identifying its centrosomal targets. At least three centrosome proteins have been found to be directly phosphorylated by CDK2 in complex with cyclin E and/or cyclin A. These are Nucleophosmin (NPM) (Okuda et al. 2000), Monopolar spindle 1 (Mps1) (Fisk and Winey 2001), and Centrosome Protein of 110 kDa (CP110) (Chen et al. 2002) (Fig. 11.3).

11.2.2.1 NPM

To identify centrosomal CDK2-cyclin E targets, the Fukasawa laboratory performed an *in vitro* kinase reaction using centrosomes isolated from quiescent 3T3 mouse fibroblast cells, as substrate (Okuda et al. 2000). A single protein in the centrosome prep was found to be phosphorylated by CDK2-cyclin E and was identified as NPM (Okuda et al. 2000), also known as B23, a previously identified component of nucleolar granules (Yung et al. 1985). NPM was found to be recruited to the centrosomes during mitosis and remained at the unreplicated centrosome in early G1 phase, but was then lost following centrosome replication (Okuda et al. 2000). Microinjection of antibodies to NPM or overexpression of either a deletion mutant (NPMΔ186-239) or a non-phosphorylable mutant (NPM-T199A) of NPM blocked centrosome replication (Okuda et al. 2000; Tokuyama et al. 2001). The NPM-T199A mutant also remained associated with the centrosomes throughout the cell cycle and resulted in the formation of monopolar spindles in mitosis (Tokuyama et al. 2001).

NPM localises between the centriole pair of the mother centrosome in G1 phase to negatively regulate centrosome replication (Okuda et al. 2000; Grisendi et al. 2005). In late G1 phase, NPM is phosphorylated by CDK2–cyclin E on T199. This triggers its dissociation from the centrosome and its relocalisation to the nucleus and the start of centrosome replication (Tokuyama et al. 2001) (Fig. 11.3). NPM phosphorylation by CDK2–cyclin E therefore functions as a licensing factor for centrosome replication (Okuda et al. 2000). CDK2-cyclin A can also phosphorylate NPM on T199 *in vitro*, suggesting that NPM phosphorylation continues through S phase and may ensure that centrosome replication is not initiated a second time once cyclin E has been degraded (Tokuyama et al. 2001).

CDK1-cyclin B was shown to phosphorylate NPM on two alternative sites (T234 and T237) *in vitro* and it is possible that phosphorylation of these are involved in the recruitment of NPM to the centrosomes during mitosis, in preparation for the centrosome replication during the next cell division cycle (Tokuyama et al. 2001).

11.2.2.2 Mps1

The Mps protein kinases were first identified in yeast as temperature-sensitive mutants that were defective in the replication of the spindle pole, thus resulting in the formation of monopolar spindles during mitosis (Winey et al. 1991). Rather than arresting in metaphase, these mutants were found to continue cycling and segregate their DNA inappropriately, thus identifying a second role for Mps in the mitotic spindle assembly checkpoint (SAC) (Weiss and Winey 1996; Abrieu et al. 2001).

In addition to its mitotic roles, mammalian Mps1 was subsequently found to play a role in centrosome replication (Fisk and Winey 2001). Mouse Mps1 (mMps1) was found to localise to the centrosome in interphase as well as during mitosis. Overexpression of mMps1 caused centrosome re-replication in S phase arrested NIH3T3 cells and overexpression of a kinase-dead form (mMps1-KD) blocked centrosome replication (Fisk and Winey 2001). Initial functional analyses of human Mps1 (hMps1) did not support a direct role for this kinase in centrosome replication (Stucke et al. 2002). However, subsequent studies in human cells revealed that overexpression of hMps1 in S phase-arrested U2OS cells results in centrosome re-replication, while overexpression of a hMps1-KD blocked centrosome replication in a number of human cell lines (Fisk et al. 2003; Kanai et al. 2007). Recently, hMps1 overexpression was found to promote centrosome replication through phosphorylation of the structural centriole component centrin 2 (Yang et al. 2010). Mps1 phosphorylation of centrin 2 on three threonine residues (T45, T47, T118) stimulates the formation of new centrioles (Yang et al. 2010).

Mps1 itself is regulated by phosphorylation. Inhibition of CDK2 activity in S phase by treatment with chemical inhibitors of CDK2, resulted in loss of the centrosomal localisation of Mps1 and blocked centrosome re-replication induced by S phase arrest (Fisk and Winey 2001). Further examination of the role of CDK2 in Mps1 regulation at the centrosome revealed that CDK2 functions to promote the

stability of Mps1 protein (Fisk and Winey 2001). A deletion mutant of Mps1 (Mps1Δ12/13, deletion of exons 12 and 13) was found to remain at the centrosome after CDK2 inhibition, suggesting that CDK2 phosphorylation of Mps1 within the region coded by exons 12–13 is responsible for regulation of its protein stability (Kasbek et al. 2007). Three phosphorylation sites were identified within this region (S436, T453, T468), which are regulated by the activities of both CDK2–cyclin E and CDK2–cyclin A kinases (Kasbek et al. 2007). A non-phosphorylable mutant of Mps1 (Mps1T468A) resulted in a loss in accumulation of Mps1 at the centrosome, suggesting that CDK2–cyclin A mediated phosphorylation of Mps1 at the centrosome protects the protein from proteasome-mediated degradation (Kasbek et al. 2007) (Fig. 11.3). Preventing the degradation of Mps1 at the centrosome, in the absence of CDK2 activity, was found to be sufficient to cause centrosome re-replication in S phase arrested cells. Thus, phosphorylation of Mps1 by CDK2 controls the level of Mps1 protein at the centrosome and restricts the number of centrosome replication cycles during each cell division cycle (Kasbek et al. 2007).

11.2.2.3 CP110

CP110 was identified as a CDK substrate during a screen of a human cDNA expression library with a dominant negative form of CDK2-cyclin E (Chen et al. 2002). It was found to be phosphorylated by CDK2-cyclin E, CDK2-cyclin A and CDK1-cyclin B *in vitro*. CP110 was subsequently found to be a centrosomal protein, which specifically co-localised with centrin to the centrioles (Chen et al. 2002). Similarly to NPM and Mps1, CP110 depletion was found to suppress centrosome re-replication in S phase arrested U2OS cells. Expression of a CP110 phosphorylation site mutant caused premature centrosome separation, which resulted in unscheduled mitotic entry and subsequent accumulation of polyploid cells (Chen et al. 2002). Phosphorylation of CP110 by CDK2 therefore suppresses premature centrosome separation, thereby regulating the timing of mitotic entry (Chen et al. 2002) (Fig. 11.3).

CP110 has also been shown to play a number of roles at the centrosome which are independent of phosphorylation by CDK-cyclins. CP110 contributes to the regulation of centriole elongation, by localising to the distal end of both the mother and daughter centrioles and functioning as a cap to limit centriole length (Schmidt et al. 2009). CP110 also plays a role in cytokinesis, through interactions with the proteins centrin 2 and calmodulin (Tsang et al. 2006).

11.2.3 CDK1-Cyclin B Control of Spindle Assembly and Mitosis

The G2-M transition is regulated by CDK1 in complex with cyclin B (Fig. 11.1). CDK1-cyclin B becomes activated in prophase by the CDC25 phosphatases (Gavet and Pines 2010), first at the centrosome and then in the nucleus (Jackman et al. 2003). Once activated, CDK1-cyclin B phosphorylates many mitotic substrates,

resulting in massive architectural changes to the cell, such as centrosome maturation and separation, chromosome condensation and nuclear envelope breakdown. For example, CDK1-mediated phosphorylation of motor proteins, such as the kinesin-like protein Eg5, regulates centrosome separation and transformation into the bipolar spindle (Blangy et al. 1995). Nuclear CDK1-cyclin B phosphorylates other proteins, such as condensin, which results in chromosome condensation (Kimura et al. 1998; Kimura and Hirano 1997) and lamins, which cause nuclear membrane breakdown (Peter et al. 1990). However, CDK1 is not solely responsible for driving mitosis, as other kinases, such as the polo-like and aurora kinase families, also play key roles in regulating mitotic progression (Glover et al. 1998; Eyers and Maller 2003).

11.3 Conclusions

Centrosome replication is largely controlled by the activity of CDK2 in complex with cyclins E/A. Three CDK2 centrosome substrates have been identified to date and together, these are involved in all stages of centrosome replication—initiation, elongation and separation. In addition, phosphorylation of all three CDK substrates appears to control their local protein concentration at the centrosome. Dissociation of NPM and CP110 from the centrosome cause a decrease and protection of Mps1 from degradation causes an increase in centrosomal protein levels. Misregulation of any one of these can cause centrosome re-replication, resulting in abnormal centrosome numbers and abnormal mitotic spindles. Such defects are found in most human cancers and may contribute to tumourigenesis.

References

Russell P, Nurse P (1986) Cell 45:781–782
Lee MG, Nurse P (1987) Nature 327:31–35
Malumbres M, Barbacid M (2005) Trends Biochem Sci 30:630–641
Bourne Y, Watson MH, Hickey MJ, Holmes W, Rocque W, Reed SI, Tainer JA (1996) Cell 84:863–874
De Bondt HL, Rosenblatt J, Jancarik J, Jones HD, Morgan DO, Kim SH (1993) Nature 363:595–602
Evans T, Rosenthal ET, Youngblom J, Distel D, Hunt T (1983) Cell 33:389–396
Satyanarayana A, Kaldis P (2009) Oncogene 28:2925–2939
Morgan DO (1995) Nature 374:131–134
King RW, Deshaies RJ, Peters JM, Kirschner MW (1996) Science 274:1652–1659
Booher RN, Alfa CE, Hyams JS, Beach DH (1989) Cell 58:485–497
Clurman BE, Sheaff RJ, Thress K, Groudine M, Roberts JM (1996) Genes Dev 10:1979–1990
Won KA, Reed SI (1996) EMBO J 15:4182–4193
Hunt T, Luca FC, Ruderman JV (1992) J Cell Biol 116:707–724
Pines J, Hunter T (1990) Nature 346:760–763
Peeper DS, Parker LL, Ewen ME, Toebes M, Hall FL, Xu M, Zantema A, van der Eb AJ, Piwnica-Worms H (1993) EMBO J 12:1947–1954

Morgan DO (2007) The cell cycle: principles of control. Oxford University Press, Oxford
Boutros R, Dozier C, Ducommun B (2006) Curr Opin Cell Biol 18:185–191
Boutros R, Lobjois V, Ducommun B (2007a) Nat Rev Cancer 7:495–507
Schmitt E, Boutros R, Froment C, Monsarrat B, Ducommun B, Dozier C (2006) J Cell Sci 119:4269–4275
Bonnet J, Coopman P, Morris MC (2008) Cell Cycle 7:1991–1998
Shreeram S, Hee WK, Bulavin DV (2008) Mol Cell Biol 28:7442–7450
Kaldis P (1999) Cell Mol Life Sci 55:284–296
Li J, Meyer AN, Donoghue DJ (1997) Proc Natl Acad Sci U S A 94:502–507
Matsumoto Y, Maller JL (2004) Science 306:885–888
Pascreau G, Eckerdt F, Churchill ME, Maller JL (2010) Proc Natl Acad Sci U S A 107: 2932–2937
Stevaux O, Dyson NJ (2002) Curr Opin Cell Biol 14:684–691
Hinchcliffe EH, Sluder G (2002) Oncogene 21:6154–6160
Lacey KR, Jackson PK, Stearns T (1999) Proc Natl Acad Sci U S A 96:2817–2822
Tsou MF, Stearns T (2006) Curr Opin Cell Biol 18:74–78
Balczon R, Bao L, Zimmer WE, Brown K, Zinkowski RP, Brinkley BR (1995) J Cell Biol 130:105–115
Hinchcliffe EH, Li C, Thompson EA, Maller JL, Sluder G (1999) Science 283:851–854
Matsumoto Y, Hayashi K, Nishida E (1999) Curr Biol 9:429–432
Meraldi P, Lukas J, Fry AM, Bartek J, Nigg EA (1999) Nat Cell Biol 1:88–93
Prosser SL, Straatman KR, Fry AM (2009) Mol Cell Biol 29:1760–1773
Boutros R, Lobjois V, Ducommun B (2007b) Cancer Res 67:11557–11564
Berthet C, Aleem E, Coppola V, Tessarollo L, Kaldis P (2003) Curr Biol 13:1775–1785
Ortega S, Prieto I, Odajima J, Martin A, Dubus P, Sotillo R, Barbero JL, Malumbres M, Barbacid M (2003) Nat Genet 35:25–31
Habedanck R, Stierhof YD, Wilkinson CJ, Nigg EA (2005) Nat Cell Biol 7:1140–1146
Okuda M, Horn HF, Tarapore P, Tokuyama Y, Smulian AG, Chan PK, Knudsen ES, Hofmann IA, Snyder JD, Bove KE, Fukasawa K (2000) Cell 103:127–140
Fisk HA, Winey M (2001) Cell 106:95–104
Chen Z, Indjeian VB, McManus M, Wang L, Dynlacht BD (2002) Dev Cell 3:339–350
Yung BY, Busch RK, Busch H, Mauger AB, Chan PK (1985) Biochem Pharmacol 34: 4059–4063
Tokuyama Y, Horn HF, Kawamura K, Tarapore P, Fukasawa K (2001) J Biol Chem 276: 21529–21537
Grisendi S, Bernardi R, Rossi M, Cheng K, Khandker L, Manova K, Pandolfi PP (2005) Nature 437:147–153
Winey M, Goetsch L, Baum P, Byers B (1991) J Cell Biol 114:745–754
Weiss E, Winey M (1996) J Cell Biol 132:111–123
Abrieu A, Magnaghi-Jaulin L, Kahana JA, Peter M, Castro A, Vigneron S, Lorca T, Cleveland DW, Labbe JC (2001) Cell 106:83–93
Stucke VM, Sillje HH, Arnaud L, Nigg EA (2002) EMBO J 21:1723–1732
Fisk HA, Mattison CP, Winey M (2003) Proc Natl Acad Sci U S A 100:14875–14880
Kanai M, Ma Z, Izumi H, Kim SH, Mattison CP, Winey M, Fukasawa K (2007) Genes Cells 12:797–810
Yang CH, Kasbek C, Majumder S, Yusof AM, Fisk HA (2010) Mol Biol Cell 21:4361–4372
Kasbek C, Yang CH, Yusof AM, Chapman HM, Winey M, Fisk HA (2007) Mol Biol Cell 18:4457–4469
Schmidt TI, Kleylein-Sohn J, Westendorf J, Le Clech M, Lavoie SB, Stierhof YD, Nigg EA (2009) Curr Biol 19:1005–1011
Tsang WY, Spektor A, Luciano DJ, Indjeian VB, Chen Z, Salisbury JL, Sanchez I, Dynlacht BD (2006) Mol Biol Cell 17:3423–3434
Gavet O, Pines J (2010) Dev Cell 18:533–543
Jackman M, Lindon C, Nigg EA, Pines J (2003) Nat Cell Biol 5:143–148

Blangy A, Lane HA, d'Herin P, Harper M, Kress M, Nigg EA (1995) Cell 83:1159–1169
Kimura K, Hirano M, Kobayashi R, Hirano T (1998) Science 282:487–490
Kimura K, Hirano T (1997) Cell 90:625–634
Peter M, Nakagawa J, Doree M, Labbe JC, Nigg EA (1990) Cell 61:591–602
Glover DM, Hagan IM, Tavares AA (1998) Genes Dev 12:3777–3787
Eyers PA, Maller JL (2003) Cell Cycle 2:287–289