Carcinogenesis vol.28 no.5 pp.899–912, 2007
doi:10.1093/carcin/bgm019
Advance Access publication January 27, 2007

REVIEW

A census of mitotic cancer genes: new insights into tumor cell biology and cancer therapy

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Tumor cell proliferation is frequently associated with genetic or epigenetic alterations in key regulators of the cell cycle. Most known oncogenes and tumor suppressors target entry into the cell cycle and control the G_1/S transition. However, tumor-associated alterations in spindle formation or chromosome segregation are also frequent and may result in chromosomal instability. In fact, a few centrosomal or mitotic proteins such as aurora A, polo-like kinase 1 and PTTG1 (securin) have been reported to act as oncogenes. Some spindle checkpoint regulators such as the BUB kinases or MAD2 protect cells from aberrant chromosome segregation and may therefore function as suppressors of malignant transformation. However, few cancer-associated mutations in these or other mitotic regulators have been described thus far and many of these molecules do not fit into the classical definition of 'oncogenes' or 'tumor suppressor genes'. In some cases, both over-expression and decreased expression of these genes result in mitotic arrest. Moreover, some mitotic regulators such as MAD2 are either up- or down-regulated depending on the tumor types and, in both cases, these alterations result in chromosomal imbalances and tumor development. Minor changes in protein levels that do not compromise cell viability might therefore be sufficient to dysregulate the mitotic cycle and induce genomic instability. Despite the limited knowledge on the molecular basis of these processes, the clinical success of mitotic poisons such as taxanes reinforces the interest in these molecules, their involvement in human cancer and the therapeutic opportunities to modulate their function in cancer treatment.

Oncogenes and tumor suppressors in the cell cycle

More than 100 different diseases are included under the term 'cancer'. All these diseases share a reduced number of unique and specific properties (1). Some of these properties, such as limitless replicative proliferation, self-sufficiency in growth signals and insensitivity to growth inhibitory signals, may be a direct consequence of deregulated cell cycles (2–4). In fact, cell cycle alterations resulting in unscheduled proliferation are frequently associated with cancer. Most of these alterations target key regulators of G_1 progression and the G_1/S transition such as the components of the so-called $p16^{INK4A}$-CDK4-pRB pathway (2,4). These alterations include over-expression of cyclins (mainly D- and E-type cyclins) and cyclin-dependent kinases (CDKs) such as CDK4 and CDK6. CDK inhibitors (mainly $p16^{INK4A}$, $p15^{INK4B}$ and $p27^{KIP1}$) or CDK substrates such as the retinoblastoma protein (pRB) are also often inactivated. In most cases, dysregulation of these genes is a consequence of chromosome alterations [amplification of cyclin D1 (CCND1) or CDK4, translocation of CDK6 and deletion of the genes encoding $p16^{INK4A}$ and pRB], promoter hypermethylation (pRB, $p16^{INK4A}$ and $p15^{INK4B}$) or specific point mutations as described in the CDK4, CDK6 and $p16^{INK4A}$ genes. In other cases, inactivation of tumor suppressors such as $p27^{KIP1}$ is a consequence of genetic alterations in their proteolytic pathway. The high frequency of these alterations in human tumors suggests that dysregulation of the pathways controlling entry into the cell cycle and commitment to DNA replication are essential to allow unscheduled proliferation of cancer cells (4).

Little is known about the involvement of other cell cycle regulators in tumorigenesis. During the last few years, various mutations have been identified that do not provoke a direct increase in cell proliferation, but rather target specific cell cycle regulators involved in progression through mitosis. Although these alterations do not directly promote unscheduled proliferation, they probably induce chromosome aberrations that may contribute to a transformed phenotype. Molecular biology and genetic studies suggest that subtle alterations on the protein levels of these mitotic regulators, generally not detected by routine molecular pathology screenings, might provoke mitotic aberrations with significant consequences in malignant transformation. We will review these alterations in mitotic regulators here and will discuss how they may participate in the malignant phenotype.

Molecular regulation of mitosis

During mitosis, duplicated genetic material and centrosomes are equally distributed between the two daughter cells. The morphological changes required for this process have traditionally been used to define the different stages throughout mitosis (Figure 1). At prophase, chromatin condenses into chromosomes and the nuclear envelope breaks down. During prometaphase, a massive reorganization of the cytoskeleton results in the generation of the bipolar spindle where chromosomes are attached. In order to organize this bipolar spindle, centrosomes have been duplicated previously in a 'centrosome cycle', which parallels the 'chromatin' cell cycle and includes duplication (during S phase), segregation and maturation (at the G_2/M transition) of the centrosomes (5). These centrosomes function as a pair of microtubule-organizing centers that migrate to opposite poles of the cells and are essential for proper spindle formation. At metaphase, chromosomes are bound to the plus ends of the microtubules through their kinetochores and are aligned at the 'metaphase plate' in the center of the mitotic spindle. Segregation of the two sets of chromosomes occurs during anaphase after loss of the sister chromatid cohesion. Finally, in telophase, chromosomes decondense and the two new nuclei are formed after reconstruction of the nuclear envelope. Once the two new nuclei are separated, the cell undergoes cytokinesis to divide the cytoplasm and separate the two daughter cells (Figure 1).

Protein phosphorylation and degradation

From a molecular point of view, the majority, if not all, of mitotic regulators are present at the end of G_2 and are ready to act throughout mitosis. Their activity is primarily regulated by phosphorylation and proteolysis, although other lesser known post-translational regulatory mechanisms such as sumoylation and acetylation (6,7) are also involved. Several kinases and phosphatases have been identified that regulate the centrosomal and mitotic cycles (8,9). The CDK1 (also known as CDC2) is one of the master regulators of mitosis as it is involved in the centrosome cycle and early mitotic events. CDK1 requires binding to A- or B-type cyclins and is further regulated by phosphorylation and dephosphorylation events (8,10). CDK1 is inactivated by the inhibitory kinases WEE1 and MYT1 by phosphorylation of specific residues at its N-terminus. Activation of CDK1 requires phosphorylation at the T loop by the CDK-activating kinase, as well as elimination of the N-terminal inhibitory phosphates by CDC25

Abbreviations: APC/C, anaphase-promoting complex/cyclosome; CDK, cyclin-dependent kinase; FZR1, fizzy-related 1; PLK1, polo-like kinase 1; SAC, spindle assembly checkpoint.

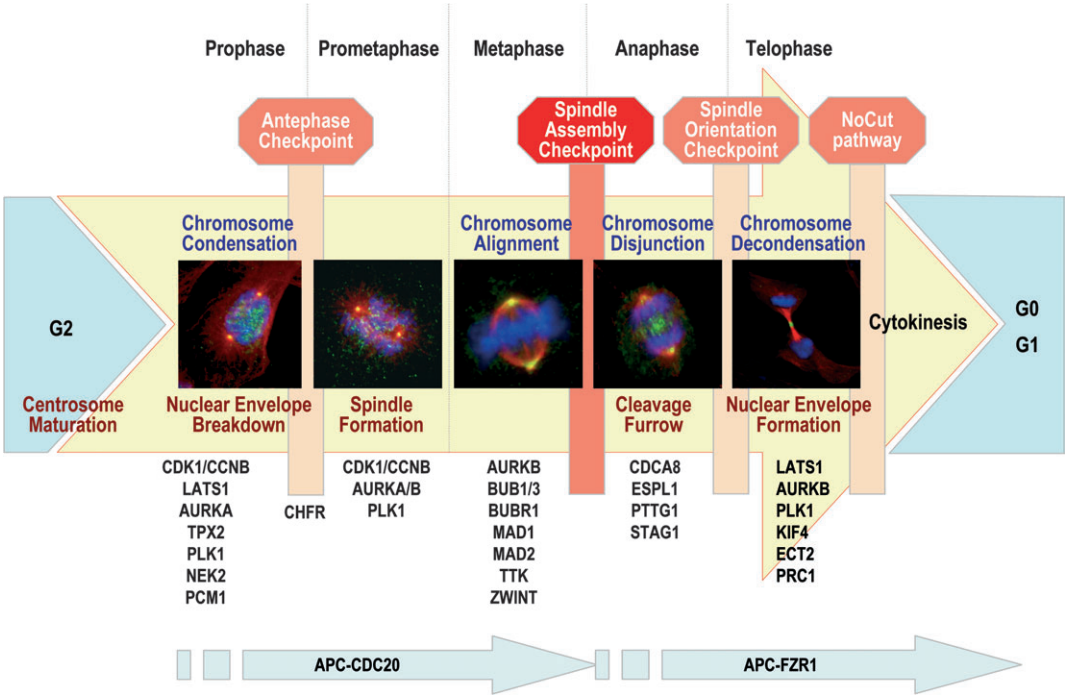

Fig. 1. A cellular and molecular view of mitosis. Major changes in chromosome and spindle structure as well as the mitotic checkpoints that regulate transition through the different stages of mitosis are indicated. Some of the representative regulators altered in human cancer are indicated. The involvement of APC/C ubiquitin ligases during different mitotic stages is also indicated with thick arrows. Pictures represent NIH 3T3 cells at different stages during mitosis. DNA is stained with 4′,6-diamino-2-phenylindole (blue); microtubules (red) and PLK1 (green) are detected using anti-α-tubulin or anti-PLK1-specific antibodies.

phosphatases. Active CDK1–cyclin complexes phosphorylate >70 substrates during G_2 and early mitosis triggering centrosome separation, Golgi dynamics, nuclear envelope breakdown and chromosome condensation among other processes (10). Additional mitotic kinases of the aurora, polo and nek protein families participate in the centrosome cycle by phosphorylating specific substrates such as Abnormal Spindle Microcephaly Associated Homolog (ASPM) and Centrosomal Nek2-associated protein 1 (CNAP1) (11–13). Similarly, proline-directed kinases such as CDK1 cooperate with aurora and polo kinases to phosphorylate various histones involved in chromosome condensation including histones H1 and H3, as well as other proteins involved in chromosome condensation such as topoisomerase II (TOP2A) and the complex known as condensin (10–12,14). The effect of phosphorylation by these kinases is counteracted by several phosphatases such as the general phosphatases PP1 and PP2 or the proline-directed phosphatases CDC14A and CDC14B (15).

The activity of cell cycle kinases and other mitotic regulators is tightly controlled by ubiquitin-mediated proteolysis (16). Progression through mitosis is intimately associated with the activity of the anaphase-promoting complex/cyclosome (APC/C), the major mitotic ubiquitin ligase that controls the timely degradation of several mitotic regulators such as mitotic cyclins or aurora and polo kinases (17,18). Substrate specificity is provided by two regulatory cofactors of the APC/C: CDC20 (also known as fizzy in *Drosophila*) and FZR1 (fizzy-related 1 or Cdh1). Whereas APC/C–CDC20 activity is controlled by the spindle assembly checkpoint (SAC) during early mitosis (see below), APC/C–FZR1 complexes are activated in late mitosis and remain active through G_1 phase (19). Once all chromosomes contact the bipolar spindle and move to the metaphase plate, APC/C–CDC20 degrades B-type cyclins and PTTG1 triggering the cleavage of cohesins by separase (ESPL1) and the separation of sister chromatids. FZR1, on the other hand, targets for degradation of additional APC/C substrates such as polo-like kinase 1 (PLK1), aurora A, survivin (also known as BIRC5), NEK2, CDC20 and SKP2 later from anaphase to the following G_1 phase. FZR1 levels are relatively constant during the cell cycle and its activity is mainly regulated by cell cycle-dependent phosphorylation. Thus, phosphorylation of FZR1 by CDKs during S, G_2 and early M phases inhibits its binding to APC/C (20,21), whereas its dephosphorylation by CDC14 in late M and G_1 phases allows binding to APC/C and activation of the complex (21,22). Other ubiquitin ligases have been shown to function in mitosis regulation. For example, CHFR seems to be critical for the early phases of mitosis since it plays an important role in the antephase checkpoint (Figure 1), which arrests the cell cycle in the presence of certain stresses before the cell commits to mitosis (23). Although it was originally proposed that CHFR establishes this checkpoint by targeting specific mitotic proteins for degradation (24,25), recent evidences show that the CHFR-dependent checkpoint requires ubiquitination but not proteasome activity (26,27).

In addition to kinases, phosphatases and proteolytic molecules, mitotic progression requires a variety of other biochemical functions including ATPase-driven motors such as dyneins, kinesins and related proteins (28). These and other microtubule-associated and kinetochore-associated proteins are involved in spindle dynamics and chromosome movements that facilitate the proper separation of DNA material into two daughter cells (29).

Mitotic checkpoints and chromosome segregation

A number of different mitotic checkpoints that arrest mitotic progression in response to cell cycle dysfunction have been described based on the existence of signaling pathways (30). A previous G_2 checkpoint does not allow mitosis entry if DNA is damaged (31,32). This cell cycle checkpoint involves sensor proteins, such as Ataxia Telangiectasia Mutated (ATM) and Ataxia Telangiectasia and RAD3 Related (ATR), which detect DNA damage and trigger a cascade of signals through the CHK1 and CHK2 kinases and the p53 pathway among others. These DNA damage signaling pathways control both G_1/S and G_2/M transitions and their involvement in human cancer is well established (31). Therefore, these checkpoints will not be further discussed here.

The major checkpoint that controls mitotic progression is known as the SAC or mitotic checkpoint (33,34). This signaling pathway ensures the proper alignment of the chromosomes at the metaphase plate prior to chromosome segregation. The SAC is activated in every cell cycle immediately upon entry into mitosis and functions to delay anaphase until

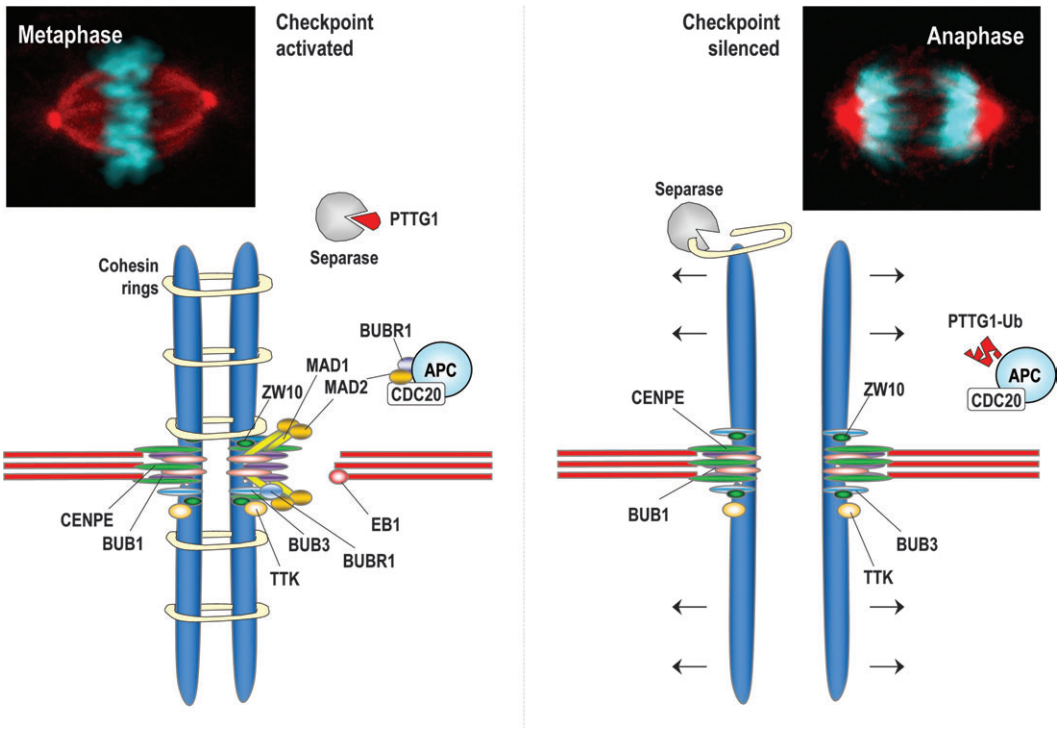

Fig. 2. Molecular players at the SAC. Sister chromatid cohesion is maintained until metaphase by cohesin complexes, whose stability is ensured by a signaling pathway that sensors unattached kinetochores. Lack of attachment is sensored by kinases such as BUB1, BUBR1 or TTK and microtubule motors such as CENPE. These proteins recruit MAD1/MAD2 heterodimers. MAD2 cycles rapidly to sequester CDC20 and inhibits APC/C activity. After microtubule attachment, MAD2 is released from APC/C–CDC20 complexes resulting in APC/C activation, ubiquitination (Ub) and destruction of PTTG1 and the subsequent activation of the protease separase that destroys cohesin complexes. Tension is then generated between the bi-oriented kinetochores resulting in sister chromatid separation during anaphase. Pictures represent NIH 3T3 cells at metaphase or anaphase. DNA (blue) and microtubules (red) are detected as described in Figure 1.

all chromosomes are properly attached at the metaphase plate (Figure 2). The inhibitory signal comes from the unattached kinetochores, and induces the recruitment of checkpoint proteins such as MAD2, BUBR1 (also known as BUB1B), BUB3 and TTK (Mps1). Although the origin of this signal is not properly understood, additional protein complexes such as the one formed by aurora B (AURKB), survivin and INCENP are known to participate by sensing tension between sister centromeres (35,36). Upon binding to the kinetochore protein CENPE, the kinase BUBR1 is activated and recruits the MAD1–MAD2 heterodimer in collaboration with HEC1 and the ZW10–ZWINT–ZWILCH complex (37,38). Activated BUB1B and/or MAD2 tightly sequester CDC20, preventing the activation of the APC/C. Upon proper chromosome alignment, MAD2 is released from the complex, resulting in the activation of APC/C–CDC20, which targets PTTG1 and cyclin B1 for degradation. The elimination of PTTG1 activates separase, which in turn cleaves the cohesin complexes that keep together sister chromatids (Figure 2). On the other hand, degradation of cyclin B1 results in CDK1 inactivation, which is required for mitotic exit (33).

In addition to the SAC, additional checkpoints that ensure proper progression throughout mitosis have been proposed (Figure 1). The antephase checkpoint, defined by CHFR, delays entry into metaphase when centrosome separation is inhibited by cellular stress (23). Two cytokinesis checkpoints that prevent cell division in response to misaligned chromosomes have also been proposed in yeast. One of them is modulated by the function of EB1, a microtubule-binding protein (39). The second cytokinesis checkpoint, known as the NoCut pathway, depends on aurora B and the anillin-related proteins Boi1 and Boi2 and delays the completion of cytokinesis in cells with spindle mid-zone defects (40). The signaling pathways that control these three checkpoints are not well understood and require further study.

Exit from mitosis and cytokinesis

The proper exit from mitosis requires the spatial and temporal coordination of several processes including inactivation of CDKs, the onset of anaphase, the disassembly of the spindle and, finally, cytokinesis. Some of the molecular mechanisms involved in these processes are included in three different pathways described in yeast: the CDC14 early anaphase release (FEAR), the mitotic exit networks and the NoCut pathway (40–43). The CDC14 phosphatase is the main player in the FEAR and mitotic exit network pathways and has a critical role in many late mitotic events in yeast (44). Although the ability of CDC14 homologs to antagonize mitotic CDK activity is probably conserved in all eukaryotes, other CDC14 functions described in yeast appear to differ significantly between species (42,44). It has been speculated that, in mammalian cells, chromosome passenger proteins such as INCENP and aurora B could function similarly to the FEAR network in coordinating accurate chromosome segregation with later mitotic events (42). Interestingly, it has been recently reported that aurora B is required for the NoCut pathway, a checkpoint-like network that prevents chromosome breakage by linking completion of cytokinesis to spindle mid-zone function (40).

The central spindle assembly, another process relevant to cytokinesis, requires the action of the microtubule-associated protein PRC1 (protein regulator of cytokinesis 1) and the centralspindlin complex (45). This complex consists of a Rho family GAP, RACGAP1 (also called MgcRacGAP) and the kinesin-like protein KIF23 (also called MKLP1). Both PRC1 and the centralspindlin complex are regulated by phosphorylation. Thus, inactivation of CDK1 at the end of mitosis activates PRC1. Aurora B and PLK1 kinases, on the other hand, associate with another kinesin-like protein, KIF20A (also called MKLP2), and seem to be required for centralspindlin function at the central spindle (46,47). During furrow positioning and initiation, which is facilitated by the central spindle, the main players seem to be aurora B and the RhoA pathway, which includes this small GTPase as well as its exchange factor, ECT2, and the downstream effector Rho-associated, coiled- coil-containing protein kinase 1 (ROCK1) (45). The contractile ring, composed of actin, myosin II, formin and septins among many other structural and regulatory proteins, is assembled

at the future cleavage site (48). Finally, contractile force is generated upon the phosphorylation of non-muscle myosin II, the principal motor responsible for cytokinesis, by ROCK1 and citron kinase (49) resulting in complete cell division into two daughter cells.

Alteration of mitotic regulators in human cancer

One century ago, Theodore Boveri predicted that chromosome alterations may be associated with cancer development and progression (50). In the last few years, a significant number of genetic alterations in mitotic regulators have been reported (Table I). As predicted, molecular studies show that these mutations induce genetic instability and, in fact, many of these alterations are associated with human tumors with a chromosome instability (CIN) phenotype (51). So far, >20 mitotic regulators have been found to be mutated in human cancer by genetic or epigenetic means (Table I). Genetic alterations include DNA amplification (such as AURKA and its regulators TPX2, FOXM1 and CENPF) and chromosomal translocations affecting the expression of particular genes (*NUMA1, CEP110, Ninein, NUP98, PCM1* and the nucleophosmin gene *NPM1*). Deletions in the *NPM1* and *LATS1* genes also occur in specific tumor types. In addition, tumor-associated point mutations have been reported in NPM1 and PLK1, as well as in several SAC regulators such as the BUB1 and BUBR1 kinases and the kinetochore proteins KNTC1 (also known as ROD), ZW10, ZWILCH, MAD1 and MAD2 (also known as MAD1L1 and MAD2L1, respectively). In some particular cases, normal expression of mitotic proteins is altered by epigenetic means as described for LATS1, LATS2, CHFR and RASSF1.

In addition to these genetic and epigenetic alterations, many more mitotic genes display cancer-associated altered expression (Table I). These molecules include proteins regulating pre-mitotic events (such as B-type cyclins, CHFR, CDK1 and FOXM1, a transcription factor that modulates the expression of many other mitotic genes), centrosome kinases (aurora A, NEK2 and PLK1), proteolysis regulatory proteins (including CDC20 and RASSF1), structural proteins (such as H2AFX, CENPF and PCM1), SAC components (BUB kinases, MAD1, MAD2 and TTK, among others) and other proteins involved in the exit from mitosis (ECT2 and PRC1). Interestingly, the SAC is the major target of mitotic alterations (Figure 3), suggesting the importance of this mitotic checkpoint in protecting cells from malignant transformation.

The signature of CIN

As mentioned above, CIN is a hallmark of many tumor types and alteration of mitotic regulators seems to be more frequent among CIN+ cancers. In fact, CIN has been proposed as a driving force in tumor initiation since it can be detected in the early stages of tumorigenesis (52). The molecular mechanisms underlying CIN were poorly understood until very recently when a CIN signature associated with cancer has been described (53). Out of the 70 genes included in that signature, 29 of them can be considered mitotic regulators according to their function. Some of these molecules participate in the dynamic structural changes required for mitosis (CKAP5, NACPH, NCAPD2 and H2AFX), although most of them regulate progression through the different mitotic stages (e.g. CDK1, FOXM1, AURKA, CDC20, PTTG1, MAD2L1, ZWINT and PRC1). Interestingly, many of these genes are involved in the regulation of the centrosome cycle (CDK1 and AURKA) or in SAC (AURKB, MAD2L1, PTTG1, ZWINT and CDC20). In fact, these genes account for more than half of the genes represented in Table I, indicating that the altered expression of mitotic genes, in general, is associated with CIN rather than cell proliferation. It is important to note that altered expression of mitotic genes does not necessarily correlate with cell proliferation indicators such as the 'mitotic index' used to quantify dividing cells in histology sections. In contrast, expression of G_1/S regulators or DNA replication molecules such as cyclin E, $p27^{KIP1}$ or MCM proteins is usually a better predictor of cell proliferation (4).

Not all human tumor types display a CIN phenotype. CIN is observed in colon, breast, lung and prostate cancer, whereas it does not appear in hematopoietic tumors such as chronic myelogenic leukemia or acute lymphoblastic leukemia. On the other hand, hematopoietic malignancies are rarely associated with alterations in mitotic regulators. Importantly, in those tumor types where CIN is present, there is a significant correlation between the CIN phenotype and poor prognosis, suggesting that chromosome imbalances might specifically contribute to aggressive or metastatic cancer (53).

Interestingly, there are some cases where both the up- and the down-regulation of specific mitotic regulators result in CIN. An example is MAD2, which is either up- or down-regulated in some specific tumor cells, provoking defective SAC and chromosomal imbalances (54). These data suggest that subtle changes in the level of expression of specific mitotic regulators might have important consequences in genomic stability. Even more importantly, either up-regulation or down-regulation of the same molecule may result in similar genomic aberrations. As these changes in expression level are not routinely detected in clinical settings, defining these proteins as having either oncogenic or tumor suppressor properties is difficult and a challenge in this area of cancer research.

Experimental evidence on mitotic deregulation and cancer

In agreement with the observed effect of mitotic dysregulation in human cancer, over-expression or down-regulation of specific mitotic regulators promotes genetic instability in cultured cells. For example, up-regulation or under-expression of PIN1 (55), NEK2 (56), auroras A and B (57–60), TPX2 (57) or FOXM1 (61), among others, leads to mitotic abnormalities including G_2/M arrest, centrosome maturation and centrosome numeric defects, lagging chromosomes, improper spindle orientation, lack of spindle checkpoint and cytokinesis failure. In some cases, over-expression of these genes induces cellular transformation in mouse fibroblasts. PLK1 over-expression results in foci formation and the resulting transformed clones grow in soft agar and, more importantly, form tumors in nude mice (62). Similar results have been obtained with aurora kinases A and B, PTTG1, TPX2, PIN1, UBC2E, BUB1 and ECT2 (63–72). On the other hand, re-expression of mitotic regulators inactivated in human cancer (RASSF1, CHFR, LATS1 and PMS2) reverts some oncogenic properties in tumor cells (9).

Mouse models: heterozygous mice make the difference

Genetically engineered mice have recently provided solid evidence of the critical role of mitotic regulators in tumorigenesis (73). Over the last few years, a number of mouse models have been generated for specific mitotic genes. Interestingly, many of them develop a cancer-associated phenotype (Table II). Over-expression of aurora A or Pin1 in the mammary gland results in breast hyperplasia or tumors accompanied with genetic instability or centrosome amplification (65,74). The tumor-associated phenotype of over-expressing aurora A is worsened in a p53+/− background (74,75), suggesting that the p53 pathway protects cells from malignant transformation by inducing apoptosis upon CIN.

In addition to these transgenic models, the function of the endogenous molecules has been investigated using gene targeting in the mouse. Ablation of some SAC proteins, such as Bub1, Bub1b, Bub3 and Mad2, results in embryonic lethality linked to massive chromosome mis-segregation, lagging chromosomes and/or apoptosis (76–80). Interestingly, partial deficiency in some of these molecules (heterozygous models) provokes a cancer-prone phenotype by themselves or in collaboration with other genetic abnormalities or tumor induction treatments. For example, *Mad2* heterozygous mice display an increased incidence of papillary lung adenocarcinomas when compared with control animals (81) and *Bub3* heterozygous mice are more susceptible to 7,12-dimethylbenzanthracene (DMBA)-induced lung adenocarcinomas than their wild-type littermates (82). However, despite accumulating aneuploid cells, these mice are not prone to spontaneous tumors even when they are crossed with *p53* or *pRb* heterozygous knockout mice (83). Similar results are observed in *Bub1b* hypomorphic mice (∼10% of normal BubR1 protein levels) as only a small percentage of mice develop spontaneous tumors (80).

Table I. Alteration of mitotic regulators in human cancer

Name (symbol)[a]	Molecular and cellular function	Cancer-associated mutation[b]	Altered expression in primary tumors[c]
Aurora kinase A (AURKA)	Ser/Thr kinase involved in centrosome maturation, microtubule formation and stabilization and chromosome segregation (117)	Amplification in different types of human cancer (69,118,119). Low-penetrance tumor-susceptibility factor in colorectal and esophageal cancer (99,100)	CIN. Over-expressed in various cancers including breast, colorectal, pancreatic, ovarian, esophageal, gastric and bladder cancers (69,119–124)
Aurora kinase B (AURKB)	This Ser/Thr kinase is a chromosomal passenger protein implicated in chromosome condensation, spindle checkpoint and cytokinesis (117)	ND	CIN. Over-expressed in astrocytomas, seminomas, prostate cancer and primary non-small lung carcinomas (69,125–128)
Baculoviral IAP repeat-containing 5, survivin (BIRC5)	Member of the chromosomal passenger complex involved in apoptosis in G_2/M (129)	ND	Over-expressed in many human tumors (130)
Budding uninhibited by benzimidazoles 1 homolog (BUB1)	Ser/Thr protein kinase involved in SAC (131)	Mutated in colon, lung and pancreatic cancer cells (132–136). Promoter hypermethylation in colon carcinoma (136)	Reduced expression in AML (137); Over-expressed in gastric and breast cancers and in non-endometrioid endometrial carcinomas (138–140)
Budding uninhibited by benzimidazoles 1 homolog beta, BUBR1 (BUB1B)	Ser/Thr protein kinase involved in SAC (141,142)	CC. Point mutations in mosaic variegated aneuploidy and premature chromatid separation syndrome (135,143,144). Promoter hypermethylation in colon carcinoma (136)	Over-expressed in gastric and breast cancers (138,140)
Budding uninhibited by benzimidazoles 3 homolog (BUB3)	Mitotic checkpoint protein that is required to localize BUB1 and BUB1B to kinetochores (145)	ND	Over-expressed in high-grade primary breast cancer and gastric carcinomas (138,140)
CDC28 protein kinase regulatory subunit 1B (CKS1B)	CDK regulator essential for their biological function including mitosis regulation (146)	Amplification in multiple myeloma (147)	Over-expression is associated with reduced levels of $p27^{Kip1}$ and with amplification linked to aggressiveness (147,148)
CDC28 protein kinase regulatory subunit 2 (CKS2)	Binds to the catalytic subunit of CDKs and is essential for their biological function (146)	ND	CIN. Over-expressed in correlation with progression and aggressiveness of bladder, prostate, cervical and colon cancer and metastasis (149–152)
Cell division cycle 2 (CDC2)/CDK1	Ser/Thr kinase with key roles in G_2/M (10)	ND	CIN. Over-expressed in a number of primary tumors, in some cases correlating with patient survival rates (153–155)
Cell division cycle 20 homolog (CDC20)	It activates and confers substrate specificity to APC/C (156)	ND	CIN. Over-expressed in head and neck, pancreatic, breast, gastric and ovarian cancer and in early stage lung adenocarcinoma (122,138, 157–159)
Cell division cycle-associated 8, borealin (CDCA8)	Component of the chromosomal passenger complex required for stability of the bipolar spindle checkpoint (160)	ND	CIN. Aberrant expression linked to poor prognosis in gastric cancer (161)
Centromere protein F, mitosin (CENPF)	Kinetochore-associated protein involved in chromosome segregation during mitosis (162)	Genetic amplification in esophageal squamous cell carcinoma cell lines (163)	Over-expression in all cases with DNA amplification and also associated with Wilms tumors, pancreatic ductal carcinomas and gliomas (163–166)
Centrosomal protein 110 kDa (CEP110)	Centrosome duplication and microtubule nucleation and organization from the centrosomes (167)	CC. Fused to the tyrosine kinase FGFR1 gene as a result of translocations in myeloproliferative disorders (168)	ND
Checkpoint with forkhead and ring finger domains (CHFR)	E3 ubiquitin–protein ligase involved in the antephase checkpoint (23)	Promoter hypermethylation and deacetylated histones in 10–50% primary cancers of various origins (169–176)	Down-regulated in colon, gastric, lung and esophageal cancers (169–176)
Cyclin B1 (CCNB1)	CDK1 activator involved in G_2/M progression (10)	ND	CIN. Over-expressed in pulmonary adenocarcinoma, gastrointestinal stromal tumors and non-small cell lung cancer (154,155,177–179)
Cyclin B2 (CCNB2)	CDK1 activator involved in G_2/M progression (10)	ND	CIN. Over-expressed in colorectal cancer and in non-endometrioid carcinomas (139)
Cytoskeleton-associated protein 5 (CKAP5/ch-TOG)	Plays a major role in organizing spindle poles (180)	ND	CIN. Over-expressed in hepatomas and colonic tumors (181)

Table I. *Continued*

Name (symbol)[a]	Molecular and cellular function	Cancer-associated mutation[b]	Altered expression in primary tumors[c]
Microtubule-associated protein RP/EB family member 1. End-binding protein 1, EB1 (MAPRE1)	Microtubule-binding protein. Also binds adenomatous polyposis coli protein. Involved in the cytokinesis checkpoint	MLL is fused to EB1 in acute lymphoblastic leukemia (182)	Over-expressed in esophageal squamous cell carcinoma (183)
Epithelial cell transforming sequence 2 oncogene (ECT2)	RHOA, RHOC and RAC guanine nucleotide exchange factor that plays a role in citokinesis (184)	ND	CIN
Extra spindle poles like 1, separase (ESPL1)	Caspase-like protease. It cleaves cohesin complexes at the onset of anaphase (185)	ND	CIN
Forkhead box M1 (FOXM1)	Transcription factor that plays an important role in the control of mitosis (61,97)	Located at chromosome 12p13, commonly amplified in carcinomas and lymphomas	CIN. Over-expressed in several tumor types, in particular in different types of aggressive carcinomas (186)
H2A histone family, member X (H2AFX)	Variant of histone H2A involved in chromosomal stability (187)	ND	CIN
Kinesin family member 4A (KIF4A)	Motor protein involved in the formation of the central spindle mid-zone and mid-body (188)	ND	CIN
Kinetochore-associated 1 (KNTC1/ROD)	Component of the complex that recruits MAD1–MAD2 to unattached kinetochores (189)	Homozygous missense change (E2199D) in colorectal cancer (190)	Over-expressed in lung, bladder and liver tumors (I.P.deC., G.deC. and M.M., unpublished observations)
Kinetochore-associated 2; highly expressed in cancer 1 (KNTC2/HEC1)	Recruits ZWINT1 and ZW10 for proper SAC function (38)	ND	Over-expressed in brain, liver and lung tumors (I.P.deC., G.deC. and M.M., unpublished observations)
Large tumor suppressor, homolog 1 (LATS1)	Ser/Thr kinase that putatively regulates G_2/M transition (191) and is involved in mitotic exit (192)	Allelic loss and hypermethylation in soft sarcomas, astrocytomas and breast cancers (94,95,193)	Soft tissue sarcomas, astrocytomas and breast cancers show reduced expression (94,95,193)
Large tumor suppressor, homolog 2 (LATS2)	Ser/Thr kinase that protects cells from centrosome amplification and genomic instability (194,195)	Hypermethylation in acute lymphoblastic leukemias, astrocytomas and breast cancers (94,193,196)	Reduced expression in acute lymphoblastic leukemias, astrocytomas and breast cancers (94,193,196)
Mitotic arrest deficient-like 1; MAD1 (MAD1L1)	Spindle checkpoint protein that directly recruits MAD2 to unattached kinetochores (131)	Mutations in cancer cells from lymphoid, pancreas, prostate, breast and lung tissues (197,198)	Reduced expression associated with carcinogenesis in human gastric cancer and poorly differentiated tumors (199,200)
Mitotic arrest deficient-like 2; MAD2 (MAD2L1)	Binds to and sequesters CDC20 inhibiting APC/C activity during SAC (145,201,202)	Rare mutations have been found in bladder and breast cancer cells (203,204)	CIN. Over-expressed in several tumor types, where it correlates with high E2F activity and poor patient prognosis (54,138)
Mps1 protein kinase (TTK)	Kinetochore-associated kinase essential for the mitotic checkpoint (205)	ND	CIN. Over-expressed in breast cancer (138)
Never in mitosis gene a-related kinase 2 (NEK2)	Ser/Thr kinase involved in centrosome separation, chromatin condensation, spindle assembly and chromosome segregation (206)	ND	CIN. Over-expressed in a range of human tumors including cervical, ovarian, breast, prostate, breast and hematopoietic tumors (207)
Ninein, GSK3β interacting protein (NIN)	Centrosomal protein involved in microtubule nucleation and centrosome maturation (167)	CC. Fused to PDGFRB in a patient with a t(5;14)(q33;q24) and an imatinib-responsive myeloproliferative disorder (208)	Deregulated expression in nasopharyngeal cancers (209)
Non-SMC condensin I complex, subunit D2 (NCAPD2/CNAP1)	Regulatory subunit of the condensin complex (210)	ND	CIN
Non-SMC condensin I complex, subunit H (NACPH/CAPH)	Regulatory subunit of the condensin complex (211)	ND	CIN
Nuclear mitotic apparatus protein 1 (NUMA1)	Multifunctional protein associated with spindle and centrosome regulation (212)	CC. Translocation with RARalpha gene in acute promyelocytic leukemia (213). Allelic variants associated with breast cancer susceptibility (104)	Over-expression in hematopoietic disorders (214)
Nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1)	Maintenance of genomic stability and the regulation DNA transcription (91)	CC. Frequently mutated, rearranged and deleted in human cancer (215)	Over-expressed in various tumors, and it has been proposed as a marker for gastric, colon, ovarian and prostate carcinomas (215)
Nucleoporin (NUP98)	Bidirectional transport across the nuclear envelop. Participates in APC/C regulation and maintains euploidy by preventing unscheduled degradation of PTTG1 (216)	CC. Translocation with HOXA9, NSD1 or PSIP1/LEDGF in different hematopoietic malignancies	ND
Pericentriolar material 1 (PCM1)	Component of the centriolar satellites involved in centrosome assembly and the organization of microtubule networks (217)	CC. Deleted in breast carcinomas; it is fused to JAK2 or RET genes upon t(8;9) translocation in hematopoietic and thyroid tumors (218–224)	Lower protein expression in ovarian carcinomas, breast tumors (220,225)

Table I. *Continued*

Name (symbol)[a]	Molecular and cellular function	Cancer-associated mutation[b]	Altered expression in primary tumors[c]
Pituitary tumor-transforming 1, securin (PTTG1)	It blocks ESPL1 function, preventing proteolysis of the cohesin complex and subsequent chromosome segregation (16)	ND	CIN. Over-expressed in a wide range of human tumors (165,226–232). A marker of metastatic tumors (233)
Polo-like kinase 1 (PLK1)	Ser/Thr kinase with important roles in many different mitotic events (234)	Specific point mutations that alter protein stability in some cell lines (235)	Elevated mRNA levels have been detected in a variety of tumor types (105)
Polo-like kinase 4 (PLK4/SAK)	Ser/Thr kinase involved in the APC/C-dependent destruction of cyclin B and in centriole duplication (234)	Loss of heterozygosity in hepatoma (92)	Aberrantly expressed in colorectal cancer (236)
Protein (peptidylprolyl *cis*/*trans* isomerase) NIMA-interacting 1 (PIN1)	Isomerase of specific pSer/Thr-Pro motifs involved in the regulation of many cellular processes including centrosome duplication and chro mosome stability (65)	ND	PIN1 is prevalently over-expressed in human cancers (237)
Protein regulator of cytokinesis 1 (PRC1)	Microtubule-binding protein required for the formation of the central spindle mid-zone and mid-body (238)	ND	CIN
RAD21 homolog (RAD21)	Component of the cohesin complex also involved in DNA repair and apoptosis (239)	Amplified in hormone-refractory prostate tumors (240)	CIN. Over-expressed in prostate cancer (240)
Ras association (RalGDS/AF-6) domain family 1 (RASSF1)	Inhibits the APC/C activity and mitotic progression through its interaction with CDC20 (87)	*De novo* methylation of its promoter is one of the most frequent epigenetic inactivation events detected in human cancer (241)	Decreased expression because of promoter hypermethylation in a high variety of human tumors (241)
Stromal antigen 1 (STAG1)	Component of the cohesin complex (242)	Genetic amplification and rearrangement of its locus in breast and ovarian cancer (243)	Over-expressed in prostate, breast and ovarian cancer and renal cell carcinoma (243,244)
Synuclein-γ, breast cancer-specific protein 1 (SNCG, BCSG1)	Interacts with and induces BUBR1 degradation (245)	Hypomethylated in breast and many other tumor types (246–248)	Highly expressed in advanced tumors, correlating with poor prognosis and metastasis (248–250)
Targeting protein for Xklp2 (TPX2)	Aurora A regulator required for the RAN-GTP-dependent assembly of microtubules around chromosomes (251)	Amplified in lung and pancreas cancers and giant-cell tumor of bone (252,253)	CIN. Over-expressed in the tumors where it is amplified (252,253) and in squamous cell lung cancer (66)
Transforming, acidic coiled-coil containing protein 3 (TACC3)	Microtubule-interacting protein required for centrosome-dependent microtubule assembly in mitosis (254)	ND	Altered expression in multiple myelomas, non-small cell lung cancer, breast tumors and ovarian cancer (255–259)
Ubiquitin-conjugating enzyme E2C (UBE2C)	Ubiquitin-conjugating enzyme required for the destruction of mitotic cyclins (260)	Genetic amplification (20q13.1) in different carcinomas (261)	CIN. Over-expressed in colon cancer and other carcinomas (64,262)
Ubiquitin-conjugating enzyme E2I (UBE2I/UBC9)	It is the sole E2 enzyme known to be required for sumoylation; its loss leads to major chromosome condensation and segregation defects (263)	ND	Over-expressed in ovarian cancer and lung adenocarcinoma (264,265)
ZW10 interactor, (ZWINT)	Involved in kinetochore formation and spindle checkpoint activity by targeting ZW10 to the kinetochores (51)	ND	CIN
ZW10, kinetochore-associated homolog (ZW10)	Component of the complex that recruits MAD1–MAD2 heterodimers to unattached kinetochores (266)	Mutations have been reported in colon cancer cells (190)	ND
Zwilch, kinetochore-associated homolog (ZWILCH)	Component of the complex that recruits MAD1–MAD2 heterodimers to unattached kinetochores (51)	Mutations have been reported in colon cancer cells (190)	CIN

ND, not described.

[a]Representative genes of the major pathways directly involved in mitosis were considered in this list. Genes listed here are altered in primary human tumors either by genetic or epigenetic alterations or significant aberrant expression. This table is not meant to be exhaustive and other proteins that may modulate mitosis, such as GSK3β, DNA damage regulators, etc., are not included here since they have major roles in other cellular processes. National Center for Biotechnology Information symbols are provided for each entry.

[b]Different genetic (DNA amplification, translocation, deletion, inversion or point mutation) and epigenetic alterations are included in this column. Genes included in the cancer census (CC) list (267) are also indicated. Criteria and gene list for this database can be found at http://www.sanger.ac.uk/genetics/CGP/cosmic/.

[c]Genes included in the CIN signature are indicated. This CIN signature is constituted by 70 genes whose aberrant expression is associated with CIN and poor prognosis (53).

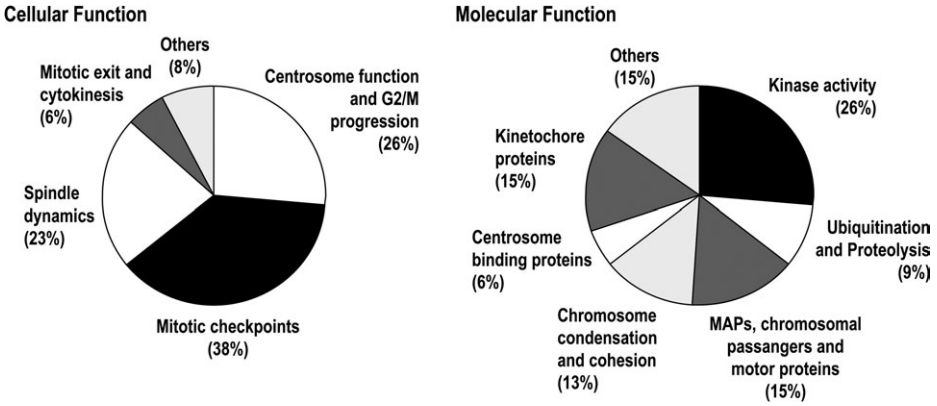

Fig. 3. Summary of mitotic alterations in cancer categorized by molecular or cellular function. Numbers reflect the percentage of molecules listed in Table I associated to specific cellular or molecular functions. Mitotic checkpoints, and specifically the SAC, are the major targets for tumor-associated alterations. Protein kinases (mostly centrosomal and checkpoint kinases) are significantly represented, suggesting diverse therapeutic uses in cancer.

However, these mice display a significantly higher susceptibility to carcinogen-induced tumors (80,84).

In contrast to SAC proteins, both CHFR and RASSF1 are not required for cell survival or proliferation (85,86). Both genes are inactivated in different human tumor types as a consequence of the hypermethylation of their promoter (Table I). In agreement with these data, mice deficient for any of these genes are predisposed to the development of spontaneous and carcinogen-induced tumors (85,86). *Chfr*-null cells display higher amounts of aurora A and Plk1, which might be involved in their CIN phenotype (85). Depletion of *Rassf1a*, on the other hand, provokes premature APC/C activation that results in accelerated degradation of mitotic cyclins, and causes a cell division defect characterized by centrosome abnormalities and multipolar spindles (87).

Ablation of some additional mitotic regulators also results in tumor susceptibility in the mouse. Mice lacking H2afx, a critical mitotic molecule involved in DNA repair, also show genetic instability (88). Furthermore, *H2AFX* heterozygosity enhances, as in the case of SAC genes, susceptibility to cancer (89). A similar situation has been reported for Plk4 and Npm1, two proteins involved in centrosome function (90,91). Plk4 and Npm1 are haplo-insufficient for tumor suppression since heterozygous mice display a significant increase in tumor susceptibility without losing the wild-type allele (91,92). Mice deficient in Lats1, a serine/threonine kinase involved in mitotic exit, develop soft tissue sarcomas and ovarian stromal cell tumors and are highly sensitive to carcinogenic treatments (93). Interestingly, these models parallel the reduced expression of this gene due to allelic loss and promoter hypermethylation in human soft tissue sarcomas and breast cancers (94,95).

Finally, genetic elimination of the transcription factor FoxM1 suggests putative therapeutic value for the inactivation of some mitotic proteins. Specific inhibition of FoxM1 in the mouse lung prior to the induction of tumors with urethane significantly diminished the size and number of lung adenomas (96). Since FOXM1 is involved in the transcriptional regulation of some mitotic proteins (61,97), these results suggest that inhibition of the proper targets might provide therapeutic advantages to arrest tumor cells.

CIN and cancer: conceptual and therapeutic implications

Cancer epidemiology studies show that abnormal expression of mitotic genes is quite frequent in different tumor types and correlates with CIN and poor prognosis (53). These data are in agreement with the phenotype of specific mouse models. Thus, complete inactivation of the spindle checkpoint regulator Mad2 induces mitotic defects incompatible with cell survival and proliferation, whereas the deletion of one allele results in cancer development without the loss of the second allele (81). Molecular studies suggest that both up- and down-regulation of some mitotic regulators induce similar aberrant mitotic cycles and lead to genomic instability. Similarly, not only MAD2 deficiency but also MAD2 over-expression is linked to tumor development in both humans and mouse models (54,98). These data suggest that subtle variations in mitotic protein levels may have oncogenic effects, whereas complete mutation or elimination of these proteins may not be compatible with cell survival. In other cases, mitotic regulators may be relevant in tumor development as 'modifier' genes, which serve to enhance or suppress oncogenic phenotypes induced by other mutations. At least three mitotic regulators, aurora A, NUMA1 and MAD1, have allelic variants that confer increased tumor susceptibility to their carriers (99–104).

The crucial role of several mitotic kinases in cell cycle progression has lead to an increased interest in the development of small-molecule inhibitors for aurora or polo family members in cancer treatment (9,105,106). In addition, many anti-tumor drugs currently used in the clinic, such as the taxanes and the vinca alkaloids, inhibit the cell cycle by altering the mitotic spindle (107). It is believed that these drugs, by reducing microtubule dynamics, keep the SAC in an active state, and that sustained SAC activation is often followed by cell death (108–110). Complete inhibition of the mitotic checkpoint is lethal to individual cells as it has been demonstrated by significantly reducing MAD2 or BUB1B levels in tumor cell lines (81,111). These results have led to the proposal of using SAC inhibitors for cancer therapy. In fact, abrogation of the DNA damage checkpoint (112) is being considered as a general strategy in cancer therapy and similar reasoning applies for the abrogation of the mitotic checkpoint. This hypothesis has been validated since some new-class TTK inhibitors have been identified that specifically override the mitotic arrest induced by spindle poisons (113,114). Mitotic regulators therefore offer a wide range of opportunities for drug design and the induction of tumor cell-specific death (9,110). Most current therapeutic studies have focused on cell cycle kinases since this biochemical activity has been traditionally taken as one of the best options in rational anti-tumoral drug design. Although alteration of kinases accounts for one-fourth of the mitotic proteins associated with cancer (Figure 3), further studies will undoubtedly extend current therapeutic strategies to other biochemical activities. As a relevant example, inhibition of the mitotic kinesin KSP (also known as Eg5) by small molecules has been reported to provide unique therapeutic advantages (115,116).

In summary, although unscheduled cell proliferation is usually promoted by alteration of G_1/S regulators, further dysregulation of mitotic proteins provides additional advantages to tumor cells. An integrated examination of biochemical studies, animal models and a multivariant analysis of molecular alterations in human cancer will significantly improve our knowledge on chromosome segregation and genomic stability. Understanding the molecular basis of these pathways will undoubtedly help in the development of new therapies against cancer progression and metastasis.

Table II. Tumor mouse models of mitotic regulators

Regulator	Model	Tumor-associated phenotype *in vivo*	Cellular phenotype
Aurora A	Cre-CAT-*Aurka*; Wap-Cre	Aurora-A over-expression induces mitotic abnormalities and hyperplasia in mammary glands (75)	Altered mitotic spindle morphology, chromosome mis-segregation, aneuploidy and cellular transformation
	MMTV-*Aurka*	Over-expression of aurora kinase A induces genetic instability preceding mammary tumor formation (74)	Same as above
Bub1B (BubR1)	*Bub1b*(+/−)	*Bub1b*(−/−) embryos failed to survive beyond day 8.5 *in utero* as a result of extensive apoptosis (79); *Bub1b*(+/−) mice rapidly develop lung as well as intestinal adenocarcinomas in response to carcinogens (84)	*Bub1b*(+/−) mouse embryonic fibroblasts are defective in spindle checkpoint activation, contain a significantly reduced amount of Pttg1 and Cdc20 and exhibit a greater level of micronuclei
	Bub1b(+/−); *Apc*Min(+/−)	Increased frequency and higher grades of colon tumors in the double mutant (268)	Increased proliferation and slippage through mitosis in the presence of nocodazole. Premature separation of sister chromatids and genomic instability (268)
Bub3	*Bub3*(+/−)	Whereas *Bub3*(−/−) are embryonic lethal, *Bub3*(+/−) mice show an increased CIN but not cancer predisposition (78)	*Bub3*(+/−) cells show mitotic checkpoint defects and chromosome mis-segregation (82)
	Bub3(+/−) *Rae1*(+/−)	Increased susceptibility to carcinogen-induced tumors (82)	Premature senescence and accumulate high levels of cell cycle inhibitors (82)
	Bub3(+/−); *p53*(+/−) or *Bub3*(+/−); *Rb1*(+/−)	No differences in either the number or the rate at which tumors appeared when compared with single mutants (83)	Not described
Chfr	*Chfr*(−/−)	Spontaneous tumors and increased skin tumor incidence after treatment with dimethylbenz(*a*) anthracene (85)	CIN and increased aurora A protein levels (85)
FoxM1	Mx-Cre *Foxm1*(−/−)	Diminished proliferation of lung tumor cells causing a significant reduction in number and size of lung adenomas (96)	Centrosome amplification, mitotic spindle defects, chromosome mis-segregation, delayed mitosis, failure in cytokinesis and mitotic catastrophe (61,269)
H2afx	*H2afx*(−/−)	*H2ax*-null mice are radiation sensitive, growth retarded and immune deficient (88)	CIN, repair defects and impaired recruitment of Nbs1, Tp53BP1 and Brca1 to irradiation-induced foci (88)
	H2afx(−/−); *p53*(−/−)	Compromised genomic integrity and enhanced susceptibility to cancer in mice lacking p53 (89)	Increased frequency of clonal non-reciprocal translocations and amplifications (89)
Lats1	*Lats1*(−/−)	Soft-tissue sarcomas and ovarian tumors (93)	Cycle arrest in G_2/M or apoptosis, through inhibition of Cdk1 kinase activity (270)
Mad2	*Mad2l1*(+/−)	*Mad2l1*(−/−) embryos die around day 7.5 of embryogenesis (76); 27% of the *Mad2l1*(+/−) mice develop lung adenocarcinomas after 18 month latencies (81)	Defective SAC, which results in chromosome mis-segregation and a p53-dependent apoptosis (76,77,81)
	CMV-TetO-*Mad2*	Inducible overexpression of Mad2 induce a wide variety of neoplasias and accelerates tumorigenesis induced by Myc [98]	Broken chromosomes, anaphase bridges and whole chromosome gains and losses [98]
Npm1	*Npm1*(+/−)	Although *Npm1*-null mice display embryonic lethality, *Npm1*(+/−) mice are viable and develop a hematological syndrome with features of human myelodysplastic syndrome (91)	Centrosome duplication and genomic instability (91)
Pin1	MMTV-*Pin1*	Transgenic over-expression of Pin1 in mouse mammary glands induces mammary hyperplasia and malignant mammary tumors with over-amplified centrosomes (65)	Centrosome duplication and accumulation resulting in chromosome mis-segregation, aneuploidy and increased cellular transformation (65,271)
Plk4	*Plk4*(+/−)	Increased incidence of spontaneous liver and lung cancers (92)	Slow proliferation and increased centrosomal amplification, multipolar spindle formation and aneuploidy (92)
Rassf1	*Rassf1*(−/−)	Increased spontaneous tumorigenesis at advanced age. Both *Rassf1*(−/−) and *Rassf1*(+/−) mice display increased carcinogen-induced tumor development (86)	Centrosome abnormalities and multipolar spindles. Premature APC/C activation and accelerated degradation of mitotic cyclins (87)

Note added in Proof: A recent screen for mutations in more than 200 human cancers (Greenman *et al.*, 2007 *Nature* 2007; **446,** 153-158) has identified additional mutations in mitotic kinases including Aurora and Polo kinases, several NEK proteins, LATS1-2, TLK1-2, and TTK, among others.

Acknowledgements

G. de C. and I.P. de C. are supported by Ramón y Cajal contracts from the Spanish Ministry of Education and Science. This work was funded by grants from the Fondo Investigaciones Sanitarias (PI051186) (G. de C.), the Fundación Ramón Areces, The human factor, mobility and Marie Curie activities of the European Commission (017448-IRG7) and Ministry of Education and Science (SAF2004-07459) (I. P. de C.) and from the Fundación Científica de la Asociación Española contra el Cáncer, Fundación Médica Mutua Madrileña and the Ministry of Science (SAF2006-05186) (M.M.). The Cell Division and Cancer Group is partially supported by the OncoCycle programme from the Comunidad de Madrid (S-BIO-0283-2006).

Conflict of Interest Statement: None declared.

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Received November 2, 2006; revised January 11, 2007; accepted January 11, 2007