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Review

Cytokinesis and cancer

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ABSTRACT

Cytokinesis is the final stage of cell division during which the two daughter cells separate completely. Although less well understood than some of the earlier phases of the cell cycle, recent discoveries have shed light on the mechanisms that orchestrate this process, including cleavage furrow formation, midbody maturation and abscission. One of the reasons why research on cytokinesis has been attracting increasing attention is the concept that failure of this process in mammals is associated with carcinogenesis. In this minireview, we will discuss the possible links between cytokinesis and cancer, and highlight key mechanisms that connect these processes.

1. Introduction

Cytokinesis is the physical separation of two daughter cells during cell division and is the final stage of the cell cycle [1]. After anaphase and chromosomal segregation, cells form a contractile ring which is a network of actin and myosin filaments, to drive the constriction of the plasma membrane, so that two daughter cells connected by a cytoplasmic bridge are generated. This intracellular bridge contains the midbody, which is resolved during the final stage of abscission [2]. Failure to complete cytokinesis has been proposed to promote tumourigenesis [3–5] by leading to tetraploidy [3,4,6] and ensuing chromosomal instability. Theodor Boveri was the first to introduce the idea that there might be a connection between abnormal mitosis and malignant tumours. He characterized the centrosome in 1888 and suggested that a cell with multiple centrosomes would lead to genomic instability and cancer. He proposed that this could happen either because of abnormal division of the centrosomes or by suppression of cell division, which would then lead to tetraploidy [7]. Since these early observations, many studies have provided support for Boveri's hypothesis, and here we review some of the key recent findings.

Normal mammalian somatic cells do not have any specific mechanism that arrests binucleate cells in G1 phase so as to prevent their propagation in case of cleavage failure. As a result, cleavage failure is a factor that can lead to tetraploidy and aneuploidy, and potentially to tumourigenesis [8]. However, it still remains controversial whether tetraploidy and genomic instability are the cause or result of cancer. Recent observations indicate that APC (adenomatous polyposis coli) mutations found in human colorectal cancer may inhibit cytokinesis by preventing mitotic spindle anchoring at the anaphase cortex and thus blocking initiation of cytokinesis. This supports the idea that tetraploidy may represent a first step in genomic instability and eventually cancer [6]. Moreover, it was recently found that abscission mediated via inactivation of the regulatory kinase Aurora B promotes completion of chromosome segregation and thus protects against tetraploidization and cancer [5]. In this review, we will discuss the mechanisms of cytokinesis and provide possible links between this process and carcinogenesis.

2. Mechanisms of cytokinesis in animal cells

2.1. Cytokinesis, the final stage of mitosis

The cell cycle consists of the distinct phases G1, S (DNA synthesis) and G2, collectively known as interphase, and M (mitosis). It is well established that a family of kinases, the cyclin-dependent kinases (CDKs) are responsible for driving cells from G2 phase into M phase that leads finally in chromosomal segregation. In order to achieve this, they recruit downstream transducers, which will be discussed below, that act directly on various components of

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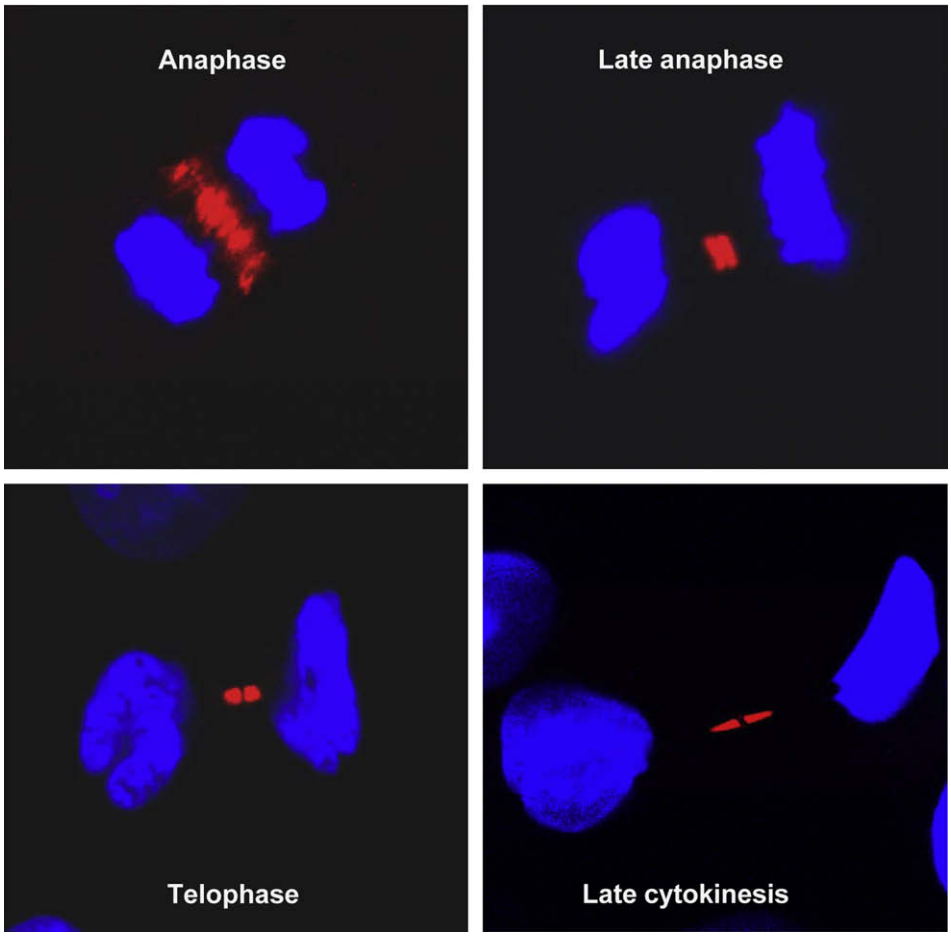

Fig. 1. Immunofluorescence images showing HeLa cells in late phases of the cell cycle. Aurora B is shown in red and DNA in blue. By anaphase, the spindle is elongated. By late anaphase the cleavage furrow starts to ingress and by early telophase the furrow is fully ingressed and the spindle is compacted into the midbody. By late telophase-cytokinesis, the midbody is narrowed and the cell is prepared for abscission.

mitotic chromosomes, the spindle apparatus and the cytoskeleton [9]. Mitosis can be subdivided into prophase, prometaphase, metaphase, anaphase, telophase and cytokinesis (Fig. 1). Cytokinesis was described more than 100 years ago, and the role of actin and myosin in cleavage as well as the role of the mitotic spindle were described more than 30 years ago [10]. Ever since, there has been an increasing rate of research in the cytokinesis field, and many recent findings have provided more detailed information concerning the molecular mechanisms of cytokinesis, including an extensive list of proteins that are involved (Table 1).

2.2. Early cytokinesis

In animal cells, cytokinesis begins with the assembly of a central spindle during anaphase [11]. Multiple proteins control the dynamics of the central spindle [12]. The most important are the microtubule associated protein (MAP) PRC1, the centralspindlin complex MKLP1 (mitotic kinesin-like protein 1) and the chromosome passenger complex (CPC). PRC1, a mitotic spindle associated CDK substrate, is a microtubule binding and bundling protein required to maintain the spindle midzone [13]. PRC1 is phosphorylated by CDK1 (Cdc2/Cyclin B) in early mitosis and turns into an inactive and monomeric state. During the metaphase-anaphase transition PRC1 is dephosphorylated and as a result interacts with KIF4, a kinesin motor that translocates PRC1 along mitotic spindles towards the plus end of antiparallel interdigitating microtubules. Through its dephosphorylation, PRC1 is oligomerized, and this promotes its microtubule bundling activity. More specifically, the plus end–associated, dephosphorylated PRC1 proteins bundle the antiparallel interdigitating microtubules to form the midzone which serves as a platform for the localization of the other critical proteins of the spindle, such as centraspindlin and chromosome passenger complex [14]. Centraspindlin is a heterotetramer that consists of MKLP-1 and CYK-4, which contains a GTPase-activating protein (GAP) domain for Rho GTPases. As a whole heterotetramer, containing two molecules of MKLP-1 and two molecules of CYK-4 RhoGAP, it promotes microtubule bundling in vitro [15] and RhoA regulation and recruits regulators of abscission [2].

The chromosome passenger complex is important for chromosome segregation and cytokinesis and consists of survinin, borealin and INCENP (inner centromere protein). These components regulate the activity and localization of the protein kinase Aurora B, the enzymatic component of CPC. The N-terminal domains of borealin and INCENP together with survinin form the core of CPC, which is required for targeting to the central spindle and the midbody. For the centromere targeting, also the C-terminal domain of borealin is required. Aurora B interacts with the core by binding to the IN-box (the conserved C-terminal region) of INCENP, and INCENP regulates the localization of Aurora B by interacting with borealin and survinin via its N-terminal domain [16].

The translocation of CPC from centromeres to the spindle midzone during anaphase is important for completing cytokinesis.

Table 1
Examples of proteins that mediate or regulate cytokinesis.

Microtubule-associated proteins
PRC1 [13,14]
Centralspindlin complex
CYK-4 [2,15]
MKLP1 [2,15]
Chromosome passenger complex
INCENP [16,17]
Survinin [16,17]
Borealin [16,17]
Aurora B [16,17]
ESRCTs and associated proteins
CEP55 [30–32]
TSG101 [31,32]
ALIX [31,32]
CHMP1B [33]
Spastin [33]
CHMP4B [31,32,34]
FYVE-CENT [34]
TTC19 [34]
Kinesins
KIF4A [14]
MKLP2 [17]
MPP1 [22]
KIF14 [23]
KIF13A [34]
Additional proteins
NuSAP [18]
Orbit [19]
ASP [20]
TBCD [21]
ECT2 [24]
FIP3 [25]
PLK1 [26,27]
Septins [28]
Anillin [29]

CDK1 phosphorylation of INCENP and Aurora B prevents the transfer of CPC in the central spindle, thus resulting in cytokinesis defects [17].

Apart from the proteins described above, which are the components of the central machinery of the spindle, there are many other proteins that concentrate on the central spindle during anaphase and telophase, including NuSAP, Orbit and ASP. NuSAP (nucleolar spindle-associated protein) is a microtubule associated protein (MAP) whose overexpression or depletion results in defects in cell proliferation, suggesting that it is involved in the mitotic spindle organization [18]. Orbit is also a MAP, first characterized in *Drosophila melanogaster*. It is required for the functional kinetochore attachment of microtubules and in order to maintain spindle polarity [19]. Another MAP, ASP (abnormal spindle), was also first identified in *D. melanogaster*. Mutations in ASP result in abnormal spindle poles [20]. Another protein found at the central spindle is tubulin cofactor D (TBCD). This protein localizes to the centrosome and to the midbody and contains a microtubule-binding region and two centriolar targeting regions. TBCD participates in spindle organization, cell abscission and in centriologenesis. Depletion of TBCD results in mitotic defects and incomplete microtubule retraction at the midbody during cytokinesis [21].

The importance of microtubule-driven processes during cell division is illustrated by the abundance of kinesin motors in the central spindle. KIF4A interacts with PRC1 and translocates it towards the plus end of microtubules [14]. MKLP2 is also a mitotic kinesin, essential for recruitment of CPC to the spindle zone. INCENP is required for the localization of MKLP2 and vice versa, and these proteins are both negatively regulated by CDK1 [17]. MPP1 (M phase phosphoprotein 1) is a plus-end-directed kinesin related protein with microtubule binding and bundling properties. Its knockdown results in failure of cytokinesis, indicating that it has an important role in cytokinesis [22]. Another kinesin, KIF14 has also an important role in cell division. The level of KIF14 has been correlated with mitotic progression in the cell cycle and this protein, together with its interactors PRC1 and citron kinase plays an important role in cytokinesis during midbody formation and in the completion of cytokinesis [23].

Many proteins important for cytokinesis act as subunits of larger complexes. One example is ECT2, a guanine nucleotide exchange factor for Rho GTPases that localizes to the central spindle by binding to centralspindlin. ECT2 interacts with CYK-4 in cell cycle regulated manner, meaning that the interaction is weak during metaphase when ECT2 is phosphorylated and increases during anaphase when ECT2 is dephosphorylated. CYK-4 and ECT2 are essential for RhoA localization, and CYK-4 can act as an activator of ECT2 [24]. Close to this complex of proteins comes FIP3, which is important for late cytokinesis and is a class II Rab11 family interactive protein. FIP3 binds to CYK-4 at late telophase, and for its recruitment in the midbody centralspindlin complex is required. The FIP3-binding region on CYK-4 overlaps with the ECT2-binding domain. FIP3 and ECT2 form exclusive complexes with CYK-4 and removal of ECT2 from the centraspindlin complex at late telophase is required for the recruitment of FIP3-containing endosomes to the cleavage furrow [25]. Another important protein of this complex is PLK1 (polo-like kinase 1) which binds to microtubules and interacts with MKLP2. Phosphorylation of MKLP2 by PLK1 is required for the localization of PLK1 to the central spindle during anaphase and telophase and the complex of these two proteins is necessary for the completion of cytokinesis [26]. It is also shown that PLK1 is important for the binding of ECT2 to CYK-4 and its recruitment to the midzone, thus promoting the initiation and completion of cytokinesis. It functions after CDK1 inactivation and independently from Aurora B [27].

Septins were first identified in a screen for genes essential for yeast cell division. These GTP-binding proteins form a ring of 10-nm filaments adjacent to the plasma membrane at the mother-bud neck junction at the time of bud emergence and disassemble prior to cytokinesis. In yeast, septins are important for the orientation of the spindle polar body, and they act as cell-cycle checkpoints. Mutations in yeast septin genes result in the inability to complete cytokinesis. The role of septins in mammalian cytokinesis is less clear, but depletion of SEPT2 or SEPT9 results in impaired cytokinesis and in an accumulation of binucleated cells as well as cells arrested at the midbody stage [28]. This suggests that septins play a conserved role in cytokinesis. The septin-interacting protein anillin localizes to the cleavage furrow and interacts with several other furrow components, such as F-actin and myosin II. Depletion of anillin causes furrow instability, suggesting that anillin serves as an organizer of the cytokinesis machinery [29].

2.3. The abscission step of cytokinesis

The mechanisms of physical cell separation during cytokinesis, known as abscission, are still incompletely understood, but at least three main processes are required. Firstly, membrane vesicles derived from the biosynthetic and endocytic recycling pathways are delivered to the plasma membrane of the constricting midbody in order to facilitate further narrowing. Secondly, interdigitating microtubules in the midbody need to be severed. Thirdly, the final abscission of a (presumably) thin membrane stalk that connects the two daughter cells is required. It is striking that several centrosomal proteins translocate to the midbody during cytokinesis, perhaps reflecting the need for microtubule organization in the midbody. One such protein is CEP55 (centrosomal protein 55 kDa) which localizes to the mitotic spindle during prometaphase and metaphase and to the spindle midzone and midbody

during anaphase and cytokinesis and is important for the last step of abscission. CEP55 binds directly MKLP1 and is controlled by centralspindlin, since knockdown of centralspindlin abolishes CEP55 from the midbody [30]. Interestingly, CEP55 also interacts with Tsg101, an endosomal sorting complex required for transport (ESCRT)-I subunit, and Alix, an ESCRT-associated protein and recruits these to the midbody. These proteins have an important role in the final step of abscission, presumably by recruiting subunits of ESCRT-III, which are thought to promote membrane severing through formation of constricting helical oligomers [31]. Depletion of CEP55, Tsg101 and Alix results in an increased number of multinucleated cells and cells arrested at the midbody stage. The mechanisms by which Tsg101 and Alix recruit and activate ESCRT-III are not entirely clarified. Alix might engage ESCRT-III to mediate final abscission, or ESCRT-I could recruit ESCRT-III through a direct interaction between ESCRT-I and –III subunits, as shown in vacuolar protein sorting in yeast [32].

The mechanisms of microtubule severing during midbody abscission have been elusive, but the ATPase spastin has recently emerged as a mediator of this process. Spastin is found in the central spindle and in the midbody during cytokinesis and displays microtubule severing activity. It interacts via its microtubule interacting and transport (MIT) domain with the ESCRT-III component CHMP1B, which recruits spastin on the midbody. Overexpression of a spastin mutant construct with an inactivated CHMP1B binding site results in cytokinesis defect, whereas the wild type construct has no such effect. This suggests that microtubule severing and membrane abscission could be coordinated via the spastin-ESCRT-III interaction and reveals a plausible function of spastin in abscission [33].

ESCRT proteins are best described for their functions in the biogenesis of multivesicular endosomes, and the sorting of ubiquitinated membrane proteins into these. It is conceivable that the midbody contains specific ESCRT-III regulators that tune these proteins to mediate cell-cell abscission instead of endosome-vesicle abscission. A candidate for such a regulator is the centrosomal protein TTC19, which translocates to the midbody during cytokinesis and interacts directly with the ESCRT-III subunit CHMP4B [34].The functional consequence of this interaction is not known, but because CHMP4B is thought to be an oligomerizing subunit of ESCRT-III, one possibility is that TTC19 might serve to control the length or shape of the CHMP4B oligomers.

Even though little is known about the lipid composition of the midbody, it is interesting to note that a specific membrane lipid, phosphatidylinositol 3-phosphate (PtdIns3*P*), has emerged as a regulator of cytokinesis. PtdIns3*P* is formed at the midbody through the activity of class III phosphoinositide 3-kinase (PI3K-III) and recruits a large protein, FYVE-CENT to the midbody. It is unclear whether FYVE-CENT as such regulates cytokinesis, but it appears to function as a scaffold for TTC19, thereby bringing this ESCRT interactor to the midbody. The translocation of FYVE-CENT to the midbody is driven by the kinesin-3 KIF13A, and the importance of these proteins in cytokinesis is illustrated by the finding that depletion of PI3K-III, TTC19, FYVE-CENT or KIF13A is sufficient to cause an increased number of cells undergoing cytokinesis, and increase in the proportion of bi- and multinucleated cells [34].

2.4. From tetraploidy to cancer

One possible consequence of abortive cytokinesis may be cleavage furrow regression and formation of binucleate cells. The state in which cells contain more than two sets of chromosomes is known as polyploidy. Polyploidy frequently occurs in nature and is thought to be a normal situation. However, under certain circumstances polyploidy may give rise to cancer. Polyploidy can be triggered mostly by three mechanisms: cell fusion, endoreplication or via a series of defects that result in an abortive cell cycle [35].Cell fusion is a process that occurs in various instances, such as in the formation of some tissues (syncytiotrophoblasts) and in the repair of others (liver, skeletal muscle, heart). It can also occur during disease, usually as a result of viral infection. It is not known whether cell fusion can happen spontaneously between cell types that are not programmed to go through cell fusion, but it is known that tetraploid cells can be created via cell fusion, with mixed genetic material and uncertain phenotype [35,36]. Endoreplication is another way of generating polyploid cells. In this process, cells increase their genomic DNA content without dividing. Endoreplication occurs in mammals, insects, plants and protists and constitutes an effective strategy of cell growth, often found in differentiated cells with high metabolic activity [37]. Finally, the abortive cell cycle is one more mechanism by which polyploid cells can be formed. This mechanism is triggered by a variety of events, such as DNA replication, defects in mitotic spindle function and cytokinesis as well as dissolving sister chromatin cohesion. As a result, the cell cycle is blocked or apoptosis is triggered. In some cases though, abortive cell cycle can result in only on delays in cell cycle progression, which in turns leads to tetraploidy. The main difference between abortive cell cycle and endoreplication is that endoreplication is a normal process whereas abortive cell cycle takes place under pathological situations [35].

Apart from these mechanisms, polyploidy can occur in cases of cell ageing, stress and as a protection against DNA damage. In the liver, the amount of polyploid cells increases with the age as well as upon oxidative damage, for example after hepatectomy. An explanation for this response could be that under limited resources, such as during stress, the energetic demands for proliferation compete with the energetic requirements for differentiation and as a result, cells that endoreplicate use the energy that would otherwise have gone into cell division processes, for the biosynthesis of extra proteins or cellular components needed in a polyploid cell. Finally, polyploidy is thought to protect cells from genotoxic damage by increasing their gene copy number. This idea seems controversial though; because of the fact that it is proven in yeast that increased DNA content in the cell is not necessarily an advantage for survival in the presence of DNA-damaging conditions [35].

Centrosomes organize the microtubules in animal cells and in general coordinate all the microtubule-related functions, such as cell shape, adhesion and motility, polarity and intracellular transport. Centrosomes are also important for chromosome segregation and cytokinesis and they determine the position of the cleavage plane during cytokinesis, which is important for the asymmetric divisions and morphogenesis. The number of centrosomes that are present in a cell determines the number of spindle poles. So, in the case of extra centrosomes, the cell will have multipolar spindles and in the case of failure in centrosome separation, the cells will have monopolar asters. Because of the great importance of centrosomes in cell division, they have a crucial role in cell cycle regulation and in checkpoints [38]. Taking this in consideration, it is expected that polyploid animal cells with many centrosomes can have various fates. First of all, they can undergo cell cycle arrest triggered by the tetraploidy checkpoint, which can mediate apoptosis. The cells that escape from this checkpoint often continue into a multipolar mitosis, which will end in aneuploidy and/or cell death. Rarely, a multipolar mitosis can result to a diploid cell, through a process known as reduction mitosis, which can occur either when a diploid genome is segregated to one pole during a multipolar mitosis or by loss of chromosomes over several cell divisions. Finally, some cancer cells with multiple centrosomes can even go through bipolar mitosis [35].

Aneuploid cells can arise from unstable tetraploid intermediates. Apart from the alterations in the total chromosomal number, such cells usually contain many chromosomal rearrangements,

such as amplifications, translocations and deletions. As a result, the caretaker genes can be lost, which may lead to chromosomal instability and eventually to cancer [4,35]. In order for the cells to avoid aneuploidy, they have evolved various protective mechanisms that prevent proliferation and survival of genetically unstable cells. One such mechanism is the Aurora B-controlled checkpoint that prevents furrow regression in cells with perturbed chromosomal segregation [5]. Also the DNA damage effector Checkpoint kinase 1 (CHK1) is important for DNA replication, intra-S phase and G2/M phase checkpoints as well as the mitotic checkpoint. Through its interaction with Aurora B, it serves also as a checkpoint for cytokinesis and since it is a DNA damage effector works as a link between DNA damage response and cell cycle [39]. Apart from this, a central mechanism is the mitotic checkpoint (spindle assembly checkpoint), which controls cell cycle during mitosis by preventing chromosome missegregation and thus aneuploidy. The signaling pathway of this checkpoint is well characterized. A central role in this pathway is played by CDC20, an E3 ubiquitin ligase which is the substrate specificity of the anaphase-promoting complex (APC). Kinetochores on unattached chromosomes generate an inhibitor that binds to CDC20. CDC20 in turn activates recognition by APC of substrates such as cyclin B and securin whose ubiquitination is required for chromosome segregation during anaphase. CDC20 binds to the mitotic checkpoint proteins MAD2, BubR1 and a complex containing both and in this way it inhibits APC-mediated ubiquitination of cyclin B and securin and blocks anaphase inhibition [40].

A more general checkpoint is the tetraploidy checkpoint that operates in G1 phase and recognizes tetraploid cells, formed either by failure of mitotic spindle or by failure of cytokinesis. This induces their arrest in a p53 dependent manner and thereby prevents the propagation of errors of late mitosis and the generation of aneuploidy. These findings came out after applying dihydrocytochalasin B (DCB) in primary rat fibroblasts [41]. Similar experiments were repeated by other studies with lower doses of DCB, and it has been concluded that tetraploid cells do not necessarily arrest in G1 [8]. This was also confirmed by a study showing that tetraploidy, aberrant centrosome number, increased cell size and failure of cytokinesis do not lead to G1 arrest [42]. It therefore seems that there is no specific p53-dependent mechanism that arrests binucleate cells in G1 phase so as to prevent them from becoming tetraploid in case of cytokinesis failure. The combination of these studies can be explained with the idea that cell stress and drug treatment activates p53 protein [43]. Finally, DNA damage triggers cell death and cell cycle arrest and it is another way that the cell uses to maintain genome integrity when the other checkpoint controls have failed [44].

3. Cell cycle and cytokinesis defects in human cancer

We have now discussed some of the proteins that are components of the cytokinetic machinery, the factors that regulate the cell division and the process through which tetra- and aneuploidy may cause cancer. In this section we will provide various examples that link cell cycle and cytokinesis defects with cancer.

Table 2
Examples of cancers associated with centrosomal abnormalities.

Abnormalities in centrosomes in various cancers
Breast and prostate cancer [45–47]
Bladder cancer and Malignant biliary tract disease [48,49]
Pancreatic cancer [50]
Head and neck sguamous cell carcinoma
Oral squamous carcinomas [51–53]
Neuroectodermals tumours [54]

3.1. Centrosome abnormalities and cancer

Cancer cells often have multiple centrosomes and present centrosomal abnormalities in general. This is obvious in various types of cancers (Table 2).

3.1.1. Breast and prostate cancer

Human breast tumours frequently contain alterations such as supernumerary centrioles, excess pericentriolar material, increased number of centrosomes and microtubule nucleating capacity and inappropriate phosphorylation of centrosomal proteins [45]. From a study in which breast tumours were analyzed for aneuploidy and chromosomal instability, it was revealed that centrosome size and number correlate with aneuploidy and chromosomal instability, whereas microtubule nucleation capacity does not, even though it correlated significantly with loss of tissue differentiation. Also, centrosome amplification and chromosomal instability occurred independently of p53 mutation. However, p53 mutation was responsible for significant increase in centrosome microtubule nucleation capacity. These data suggest that independent aspects of centrosome amplification correlate with chromosomal instability and loss of tissue differentiation and could be involved in tumour development and progression [46].Centrosome defects are also observed in prostate cancer samples. In this report, 109 tissue sections from radical prostatectomies with invasive carcinoma and 31 cases from metastatic prostate carcinoma were analyzed. Using pericentrin as a marker, it was revealed that centrosomes were structurally and numerically abnormal in the majority of the samples and the abnormality increased with the increasing genomic instability and in the most severe prostate cancer samples. Thus, pericentrin could be possibly used as prognostic marker for prostate cancer progression [47].

3.1.2. Bladder cancer

Bladder cancer samples frequently contain a number of centrosomes that is significantly increased compared to normal tissue, presumably as a result of cytokinesis failure. Interestingly this is correlated with an increase in chromosome numbers [48]. Centrosome abnormalities have been detected also in malignant biliary tract diseases. Forty malignant biliary diseases including gallbladder cancers (GC), intrahepatic cholangiocellular carcinoma (CCC) and extrahepatic bile duct cancers (BDC) were examined. It was found that 70% of the GC, 58% of the CCC and 50% of the BDC samples presented centrosome abnormalities and significantly higher compared to the benign controls. It was also noticed that in the advanced stage of malignancy the centrosomal abnormalities were much higher compared to the early stage, indicating that centrosome abnormality could be associated with the transition from early to advanced stage of malignancy in biliary tract malignant diseases [49].

3.1.3. Pancreatic cancer

From analyses of ductal carcinomas, adenomas, endocrine tumours, chronic pancreatitis as well as normal pancreatic tissues it has been revealed that 85% of the carcinomas and some adenomas displayed abnormal centrosomal profiles, characterized by an increase in size and number of centrosomes as well as irregular distribution. On the contrary, none of the normal ductal and stromal tissues showed these abnormalities, suggesting that centrosomal abnormalities occur in the early stage of pancreatic ductal carcinogenesis [50].

3.1.4. Squamous cell carcinomas

Centrosome abnormalities are also found in head and neck squamous cell carcinoma (HNSCC). In a recent study, tumour samples from 18 patients with HNSCC were analyzed, and in 17 of

these were found centrosome hyperamplification. Since the percentage is so high, it is implied that this could be used as a marker for HNSCC [51]. This observation is also interesting because of the fact that the p53 suppressor gene, the most frequently mutated in gene human cancers, is correlated with centrosome hyperamplification in HNSCC. Centrosome hyperamplification is either observed in p53 mutant tumours or in tumours that retain wild type p53 but contain overexpressed Mdm2, an oncogene that inhibits p53 transactivation function [52]. Centrosomal abnormalities have also been found increased in oral squamous cell carcinomas in cells in which the spindle checkpoint protein CDC20 is overexpressed [53]. This is explained because in cancer cells very often genes that encode for proteins involved either in mitotic checkpoints or in other important mitotic regulations are found mutated or overexpressed.

3.1.5. Neuroectodermal tumours

Centrosome amplification followed by numerical chromosome aberrations has been observed in primitive neuroectodermal tumours that lack the wild type p53 gene. Since p53 is important for centrosome duplication, the conclusion of this observation is that centrosome amplification can occur in tumours lacking wild type p53 and could be a mechanism for the generation of numerical chromosomal aberrations [54].

3.2. Cell cycle regulators and cancer

Multiple cell cycle regulators are found mutated in various cancers. In this section, we will highlight some of these regulators and their link to cancer (Table 3 and Fig. 2).

3.2.1. p53 and associated proteins

p53 is a tumour suppressor protein that is encoded by the *TP53* gene. It is found mutated or deleted in a wide range of cancers, including colon cancer, lung, esophagus, breast, liver, brain reticuloendothelial tissues and hemopoietic tissues cancer. The p53 protein is important for regulation of the cell cycle and serves a special role in responding to DNA aberrations [55]. A p53-responsive gene product, 14-3-3 isoform σ, is also linked to prostate and breast cancer. It was already known that 14-3-3 family of proteins are involved in cell cycle progression, DNA damage checkpoints and apoptosis, and it was shown recently that the 14-3-3 isoform σ functions as a regulator of mitotic translation through its direct mitosis specific binding to a variety of translation/initiation factors. Cells that lack 14-3-3 isoform σ show impaired cytokinesis, loss of Polo-like-kinase-1 at the midbody and accumulation of binucleate cells [56]. Additionally, $p21^{WAF1/CIP1}$ is transcriptionally regulated by the p53 tumour suppressor. In a recent study, it was found that inactivation of $p21^{WAF1/CIP1}$ occurs in low and high grade dysplastic nodules and together with other factors is responsible for malignant transformation during hepatitis B virus associated multistep hepatocarcinogenesis [57].

3.2.2. Mitotic checkpoint proteins

Aneuploidy in cancers is thought to be caused by chromosomal instability. Chromosomal instability in turn has been shown to be caused by loss of function mutations in mitotic checkpoint proteins.

hsMAD2, the human homologue of yeast MAD2 gene is a necessary component of the mitotic checkpoint, found to be low expressed in a human breast cancer cell line [58]. The mitotic checkpoint *hBUB1* is a human homologue of yeast *BUB1* gene, which controls mitotic checkpoints and chromosome segregation in yeast. Mutations in *hBUB1* were found in colorectal cancer cell lines with chromosomal instability, suggesting that a defect in a mitotic checkpoint is possible responsible for the formation of aneuploidy and cancer [59]. Also, *hRad9*, a structural homologue of yeast *rad9*, is involved in cell cycle checkpoints and apoptosis and is a gene of 11q13 chromosomal region, which is frequently amplified in breast cancer. *hRad9* was found upregulated in breast tumours in more than 50% of the cases and this upregulation in some but not all tumours was due to an increase in the gene number. Overexpression correlated with a larger tumour size, suggesting that the cell cycle checkpoint protein may promote breast cancer proliferation. Correspondingly, silencing of this protein could inhibit the proliferation of breast cancer cells in vitro. Taken these data together, *hRad9* may have a role in breast cancer progression [60].

Ataxia telangiectasia (AT) is a rare autosomal recessive disease, characterized by cerebella ataxia, immunodeficiency, increased sensitivity to ionizing radiation and predisposition to malignancies, especially leukemia and lymphoid malignancies. The gene mutated in AT is designated as ATM. The protein encoded by ATM gene is required for cell cycle checkpoint control at the G1/S border, S phase and G2/M checkpoints after DNA strand breakpoint damage [61].

The *CHK1* gene encodes for a serine/ threonine kinase involved in the regulation of cell cycle progression and DNA damage check-

Table 3
Examples of cell cycle and cytokinesis regulators that are mutated or aberrantly expressed in various cancers.

Gene/protein mutated in cancer	Type of cancer
p53 and associated proteins	
p53	Colon, lung, esophagus, breast, liver, brain reticuloendothelial tissues, hemopoietic tissues cancer etc. [55]
14-3-3 isoform σ	Prostate and breast cancer [56]
p21WAF1/CIP1	Hepatitis B virus multistep hepatocarcinogenesis [57]
Mitotic checkpoint proteins	
MAD2	Breast cancer [58]
BUB1	Colorectal cancer [59]
Rad9	Breast cancer [60]
ATM	Leukemia and lymphoid malignacies [61]
CHK1	Lymphoid neoplasms [62,39]
CHK2	Li-Fraumeni syndrome, Hodgkin's lymphoma, urinary bladder cancer [63–65]
chfr	Lung cancer [66]
BRIT1	Breast cancer cell lines, human epithelial tumours of ovary and prostate [67]
Septins	Various types of cancer, acute leukemia [68]
Anillin	Various types of cancer, lung cancer [69]
Mitotic regulators	
BRCA1	Breast and ovarian cancer [70]
Inositide-specific phospholipase c β1	Myelodysplastic syndrome [71]
FEZ1/LZTS1	Primary gastric cancer, primary transitional cell carcinoma of bladder, Bellini duct carcinoma, lung cancer, primary esophageal and prostate cancer [72]
centrobin	Lung cancer [73]
Protein kinases	
Aurora A	Various cancers, hepatocellular carcinoma etc. [74]
Aurora B	Various cancers [5,75]
Brd4	Various cancers [75]
Aurora 2	Breast, ovarian, colon, prostate, neuroblastoma andcervical cancer [76]
PLK1	Acute myelogenous and acute lymphoblastic leukemia [77]
Other proteins	
Rab21	Ovarian and prostate cancer [79]
KLHDC8B	Classical Hodgkin lymphoma [80]
GATA6	Ovarian cancer [81]
FYVE-CENT	Breast cancer [34,82]

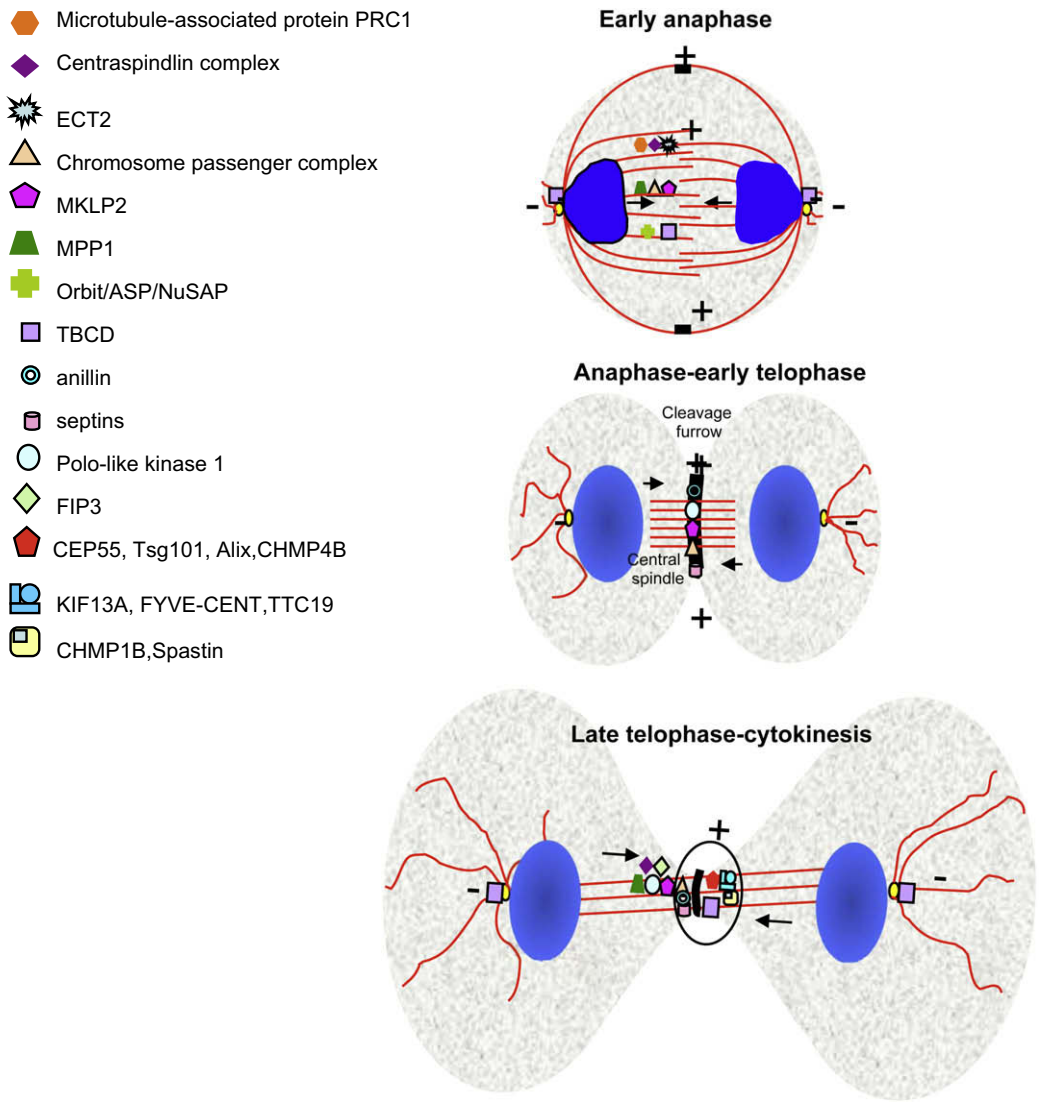

Fig. 2. Diagram illustrating the roles of spindle proteins that function during the various stages of cell division. DNA is indicated in blue, centrosomes in yellow and microtubules in red.

points. The protein and mRNA levels have been found to be very low in aggressive variants of human lymphoid neoplasms, where ATM, p53 and *CHK2* genes were wild type, suggesting that this protein is also important for the cell cycle regulation [62].That fits with the observation that *CHK1* abrogation during mitosis causes increased chromosome lagging and abnormal localization of Aurora B. Cells lacking *CHK1* present cytokinesis failure and multinucleation [39]. The *hCHK2* gene encodes the human homolog of the yeast Cds1 and Rad53G2 checkpoint kinases, which are activated in response to DNA damage thereby preventing cellular entry into mitosis, and they also regulate DNA repair and apoptosis. After DNA damage, *hCHK2* is phosphorylated and activated by ATM dependent and independent mechanisms and phosphorylates downstream effector molecules, including p53, CDC25, BRCA1, PML and E2F-1. Mutations in *hCHK2* occur in Li-Fraumeni syndrome, a rare familial multicancer syndrome characterized by the occurrence of sarcomas, breast cancer, brain tumours, leukemia and adrenal cortical tumours and its expression is downregulated in Hodgkin's lymphoma cell lines as well as in urinary bladder cancer[63–65]. The *chfr* gene is also a checkpoint gene for mitosis that also functions in a very early stage before chromosome condensation. This checkpoint is found mutated in human lung cancer, supporting the above data [66].

Another protein implicated in cell cycle checkpoints and cancer is BRCT-repeat inhibitor of hTERT expression, BRIT1, which functions as a factor in the DNA damage checkpoints that control multiple damage sensors and early mediators and regulates important molecules in the cell cycle checkpoint, thus affecting the timing of mitosis. BRIT1 is found in very low expression in breast cancer cell lines and in human epithelial tumours of the ovary and prostate compared to normal tissues. In addition, the loss of gene copy number of BRIT1 correlated with genomic instability and in loss of function defect in response to DNA damage. Also, BRIT1 has been shown to correlate with the occurrence of metastasis, suggesting that it might contribute to tumour aggressiveness. All these data indicate the importance of BRIT1 defects in cancer progression [67].

Finally, septins are important in regulating the cell cycle checkpoint and it was recently found that SEPT2, SEPT8, SEPT9 and SEPT11 were upregulated in various tumours, whereas SEPT4 and SEPT10 were down regulated in most cancer types. The abnormal expressions were in accordance with the tumour malignances or

prognosis of corresponding cancer patients, implicating that septins may play an important role in carcinogenesis. It is also known that SEPT5, SEPT6, SEPT9 and SEPT11 were found mutated in infant acute leukemia patients [68]. Anillin, which interacts with septins, is also implicated in carcinogenesis. Expression levels of anillin correlate with metastatic potential of human tumours of various kinds and inhibition of anillin expression is shown to suppress the growth of lung cancer cells in culture [69].

3.2.3. Mitotic regulators

BRCA1 has been implicated as an important factor involved in DNA repair and in regulation of cell cycle checkpoints in case of DNA damage. *BRCA1* is well known that is found mutated in 50% of inherited breast cancer cases and the acquisition of a single defective allele leads to elevated predisposition to both breast and ovarian cancer. Cells with *BRCA1* mutations present increased genomic instability and elevated levels of chromosome aberrations; therefore it is obvious that *BRCA1* has a very important function in DNA damage response [70]. Inositide-specific phospholipase c β1 is another regulator of cell cycle. This enzyme is involved in the progression of myelodysplastic syndrome, a hematological disease that evolves into acute myeloid leukemia in about 30% of the cases [71].

FEZ1/LZTS1 is a recently identified mitotic regulator implicated in cancer development. It has been found that *LZTS1* absence decreases CDK1 activity by affecting CDC25. CDC25 is a key activator of the CDKs. It has been proposed that in G2/M arrested cells, CDC25 may be efficiently ubiquitinated. *LZTS1* was found to be involved in CDC25 ubiquitination by protecting it from proteasome degradation during M phase, thereby regulating CDK1 activity. The expression of *LZTS1* has been found reduced in various types of cancers: primary gastric cancer, primary transitional cell carcinoma of bladder, Bellini duct carcinoma, lung cancer, in primary esophageal cancer, prostate cancer and other types of cancer. All these data indicate that indeed *LZTS1* can be regarded as a cell cycle regulator and is involved in carcinogenesis [72].

Depletion of a novel centrosomal protein, centrobin, inhibits centriole duplication and leads to impaired cytokinesis. It is also found to inhibit the proliferation of a lung cancer cell line and prevented the G1 to S transition of the cells, via the upregulation of p53, which is associated with the activation of cellular stress induced by the p38 pathway. Interestingly, inhibition of p38 activity could overcome the cell cycle arrest caused by centrobin depletion. These data indicate the importance of centrobin for cell cycle regulation [73].

3.2.4. Kinases

Protein kinases play a very central role in cell cycle regulation and also orchestrate molecular events in cytokinesis. Aurora A, a serine-threonine kinase has a variety of functions, including centrosome maturation and separation, bipolar spindle assembly, chromosome alignment and the transition from prophase to metaphase as well as cytokinesis. Aurora A is frequently overexpressed in human cancers, including hepatocellular carcinoma. Recent studies in transgenic mice overexpressing human Aurora A in the liver revealed a p53 dependent premitotic arrest during liver regeneration, clarifying the role of Aurora A in tumourigenesis [74]. The related kinase Aurora B is also very important for cell cycle and cancer progression [5]. Recent data show that the bromodomain protein Brd4 controls the transcription of Aurora B. Depletion of Brd4 results in cytokinesis failure in cancer cells, which is also observed after Aurora B depletion [75]. Also, Aurora 2 kinase (*STK15*) is found overexpressed in various types of cancer lines, such as breast, ovarian, colon, prostate, neuroblastoma and cervical cancers. Its overexpression leads to centrosome amplification, chromosomal instability and transformation [76]. Polo-like kinase 1 (PLK1) also belongs to the family of serine/threonine kinases and plays an important role in centrome maturation, bipolar spindle formation and cytokinesis during mitosis. PLK1 was found to be overexpressed in human leukemia cell lines as well as in cell samples from individuals with acute myelogenous leukemia and acute lymphoblastic leukemia, again suggesting its role in cancer progression [77]. Another serine/threonine protein kinase, citron, is also important for cytokinesis. Its localization to the central spindle depends on the kinesin-3 motor KIF14, and vice versa [23]. The overexpression of KIF14 in retinoblastoma suggests a possible involvement of the citron-KIF14 axis in carcinogenesis [78].

3.2.5. Other cytokinesis regulator proteins in cancer

Apart from proteins involved in mitosis checkpoints and in the cell cycle regulation, there are also additional proteins involved in cytokinesis that are found mutated in various cancers. Rab21 is a small GTPase that associates with several integrin α subunits. Recent data indicate that Rab21 activity, integrin-Rab21 association and integrin endocytosis are necessary for normal cytokinesis. Importantly, the *RAB21* gene was found mutated in ovarian carcinoma cell lines and in a prostate cancer tumour sample. Cells containing these mutations accumulate multinucleated profiles, in line with the notion that Rab21 controls cytokinesis [79]. *KLHDC8B* gene was recently characterized and it was found to be disrupted by translocations found in a family in which multiple individuals developed Classical Hodgkin lymphoma. This gene encodes a protein that contains seven kelch repeat domains and localizes to the midbody. Depletion of the protein results in binucleated cells indicating that it is necessary for cytokinesis [80]. GATA6 is a transcription factor that functions in early embryonic stem cell differentiation. This factor is usually lost in ovarian cancer. Depletion of GATA6 leads in cytokinesis failure, deformation of nuclear envelope and formation of polyploid and aneuploid cells. Thus GATA6 is also linked to tumourigenesis [81]. Finally, the cytokinesis regulator FYVE-CENT is found mutated in breast cancer samples [82]. Depletion of this protein results in an increased number of binuclear and multinuclear profiles, as well as cells arrested in cytokinesis, indicating its important role in cytokinesis [34].

4. Conclusions and perspectives

There is now a substantial body of evidence suggesting that aberrant cytokinesis may lead to aneuploidy, which may in turn develop into cancer. Multiple components of the machineries that mediate and regulate cytokinesis have been identified and functionally characterized, and some of these have clear associations to cancer. Nevertheless, there is still no conclusive evidence that cytokinesis failure may cause carcinogenesis and further research is warranted in order to prove or disprove this hypothesis. If the hypothesis is indeed correct, a question that arises is whether cytokinesis and its components can be targeted for the prevention or treatment of cancer. One central idea is the abrogation of G2 as anticancer strategy. For this purpose, possible targets could be the ATM, WEE1, and *CHK1*. ATM and WEE1 inhibitors are currently in development and CHK1 inhibitors are now in phase I/II of clinical trials [83]. PLK1 and Aurora kinases are also attractive drug targets, which are already in clinical trials [1,77]. Because cytokinesis failure is thought to be a relatively early event in carcinogenesis, it is also possible that detection of such aberrations might be exploited for early detection of cancers, which in turn would improve the therapeutic endpoints. In conclusion, future research on cytokinesis has the potential to yield novel insight that could satisfy the curiosity of cell biologists, and at the same time be beneficial to cancer patients.

References

[1] Eggert, U.S., Mitchison, T.J. and Field, C.M. (2006) Animal cytokinesis: from parts list to mechanisms. Annu. Rev. Biochem. 75, 543–566.
[2] Glotzer, M. (2005) The molecular requirements for cytokinesis. Science 307, 1735–1739.
[3] Fujiwara, T., Bandi, M., Nitta, M., Ivanova, E.V., Bronson, R.T. and Pellman, D. (2005) Cytokinesis failure generating tetraploids promotes tumorigenesis in p53-null cells. Nature 437, 1043–1047.
[4] Ganem, N.J., Storchova, Z. and Pellman, D. (2007) Tetraploidy, aneuploidy and cancer. Curr. Opin. Genet. Dev. 17, 157–162.
[5] Steigemann, P., Wurzenberger, C., Schmitz, M.H., Held, M., Guizetti, J., Maar, S. and Gerlich, D.W. (2009) Aurora B-mediated abscission checkpoint protects against tetraploidization. Cell 136, 473–484.
[6] Caldwell, C.M., Green, R.A. and Kaplan, K.B. (2007) APC mutations lead to cytokinetic failures in vitro and tetraploid genotypes in Min mice. J. Cell Biol. 178, 1109–1120.
[7] Boveri, T. (2008) Concerning the origin of malignant tumours by Theodor Boveri. Translated and annotated by Henry Harris. J. Cell Sci. 121 (Suppl. 1), 1–84.
[8] Uetake, Y. and Sluder, G. (2004) Cell cycle progression after cleavage failure: mammalian somatic cells do not possess a "tetraploidy checkpoint". J. Cell Biol. 165, 609–615.
[9] Jallepalli, P.V. and Lengauer, C. (2001) Chromosome segregation and cancer: cutting through the mystery. Nat. Rev. Cancer 1, 109–117.
[10] Rappaport, R. (1971) Cytokinesis in animal cells. Int. Rev. Cytol. 31, 169–213.
[11] Steigemann, P. and Gerlich, D.W. (2009) Cytokinetic abscission: cellular dynamics at the midbody. Trends Cell Biol. 19, 606–616.
[12] Glotzer, M. (2009) The 3Ms of central spindle assembly: microtubules, motors and MAPs. Nat. Rev. Mol. Cell Biol. 10, 9–20.
[13] Mollinari, C., Kleman, J.P., Jiang, W., Schoehn, G., Hunter, T. and Margolis, R.L. (2002) PRC1 is a microtubule binding and bundling protein essential to maintain the mitotic spindle midzone. J. Cell Biol. 157, 1175–1186.
[14] Zhu, C., Lau, E., Schwarzenbacher, R., Bossy-Wetzel, E. and Jiang, W. (2006) Spatiotemporal control of spindle midzone formation by PRC1 in human cells. Proc. Natl. Acad. Sci. USA 103, 6196–6201.
[15] Mishima, M., Kaitna, S. and Glotzer, M. (2002) Central spindle assembly and cytokinesis require a kinesin-like protein/RhoGAP complex with microtubule bundling activity. Dev. Cell 2, 41–54.
[16] Jeyaprakash, A.A., Klein, U.R., Lindner, D., Ebert, J., Nigg, E.A. and Conti, E. (2007) Structure of a Survivin–Borealin–INCENP core complex reveals how chromosomal passengers travel together. Cell 131, 271–285.
[17] Hummer, S. and Mayer, T.U. (2009) Cdk1 negatively regulates midzone localization of the mitotic kinesin Mklp2 and the chromosomal passenger complex. Curr. Biol. 19, 607–612.
[18] Raemaekers, T., Ribbeck, K., Beaudouin, J., Annaert, W., Van, C.M., Stockmans, I., Smets, N., Bouillon, R., Ellenberg, J. and Carmeliet, G. (2003) NuSAP, a novel microtubule-associated protein involved in mitotic spindle organization. J. Cell Biol. 162, 1017–1029.
[19] Maiato, H., Sampaio, P., Lemos, C.L., Findlay, J., Carmena, M., Earnshaw, W.C. and Sunkel, C.E. (2002) MAST/orbit has a role in microtubule-kinetochore attachment and is essential for chromosome alignment and maintenance of spindle bipolarity. J. Cell Biol. 157, 749–760.
[20] Gonzalez, C., Saunders, R.D., Casal, J., Molina, I., Carmena, M., Ripoll, P. and Glover, D.M. (1990) Mutations at the asp locus of Drosophila lead to multiple free centrosomes in syncytial embryos, but restrict centrosome duplication in larval neuroblasts. J. Cell Sci. 96 (Pt 4), 605–616.
[21] Fanarraga, M.L., Bellido, J., Jaen, C., Villegas, J.C. and Zabala, J.C. (2010) TBCD links centriologenesis, spindle microtubule dynamics, and midbody abscission in human cells. PLoS One 5, e8846.
[22] Abaza, A., Soleilhac, J.M., Westendorf, J., Piel, M., Crevel, I., Roux, A. and Pirollet, F. (2003) M phase phosphoprotein 1 is a human plus-end-directed kinesin-related protein required for cytokinesis. J. Biol. Chem. 278, 27844–27852.
[23] Gruneberg, U., Neef, R., Li, X., Chan, E.H., Chalamalasetty, R.B., Nigg, E.A. and Barr, F.A. (2006) KIF14 and citron kinase act together to promote efficient cytokinesis. J. Cell Biol. 172, 363–372.
[24] Yuce, O., Piekny, A. and Glotzer, M. (2005) An ECT2-centralspindlin complex regulates the localization and function of RhoA. J. Cell Biol. 170, 571–582.
[25] Simon, G.C., Schonteich, E., Wu, C.C., Piekny, A., Ekiert, D., Yu, X., Gould, G.W., Glotzer, M. and Prekeris, R. (2008) Sequential Cyk-4 binding to ECT2 and FIP3 regulates cleavage furrow ingression and abscission during cytokinesis. EMBO J. 27, 1791–1803.
[26] Neef, R., Preisinger, C., Sutcliffe, J., Kopajtich, R., Nigg, E.A., Mayer, T.U. and Barr, F.A. (2003) Phosphorylation of mitotic kinesin-like protein 2 by polo-like kinase 1 is required for cytokinesis. J. Cell Biol. 162, 863–875.
[27] Petronczki, M., Glotzer, M., Kraut, N. and Peters, J.M. (2007) Polo-like kinase 1 triggers the initiation of cytokinesis in human cells by promoting recruitment of the RhoGEF Ect2 to the central spindle. Dev. Cell 12, 713–725.
[28] Joo, E., Tsang, C.W. and Trimble, W.S. (2005) Septins: traffic control at the cytokinesis intersection. Traffic 6, 626–634.
[29] Hickson, G.R. and O'Farrell, P.H. (2008) Anillin: a pivotal organizer of the cytokinetic machinery. Biochem. Soc. Trans. 36, 439–441.
[30] Zhao, W.M., Seki, A. and Fang, G. (2006) Cep55, a microtubule-bundling protein, associates with centralspindlin to control the midbody integrity and cell abscission during cytokinesis. Mol. Biol. Cell 17, 3881–3896.
[31] Carlton, J.G. and Martin-Serrano, J. (2007) Parallels between cytokinesis and retroviral budding: a role for the ESCRT machinery. Science 316, 1908–1912.
[32] Raiborg, C. and Stenmark, H. (2009) The ESCRT machinery in endosomal sorting of ubiquitylated membrane proteins. Nature 458, 445–452.
[33] Yang, D., Rismanchi, N., Renvoise, B., Lippincott-Schwartz, J., Blackstone, C. and Hurley, J.H. (2008) Structural basis for midbody targeting of spastin by the ESCRT-III protein CHMP1B. Nat. Struct. Mol. Biol. 15, 1278–1286.
[34] Sagona, A.P., Nezis, I.P., Pedersen, N.M., Liestol, K., Poulton, J., Rusten, T.E., Skotheim, R.I., Raiborg, C. and Stenmark, H. (2010) PtdIns(3)P controls cytokinesis through KIF13A-mediated recruitment of FYVE-CENT to the midbody. Nat. Cell Biol. 12, 362–371.
[35] Storchova, Z. and Pellman, D. (2004) From polyploidy to aneuploidy, genome instability and cancer. Nat. Rev. Mol. Cell Biol. 5, 45–54.
[36] Ogle, B.M., Cascalho, M. and Platt, J.L. (2005) Biological implications of cell fusion. Nat. Rev. Mol. Cell Biol. 6, 567–575.
[37] Edgar, B.A. and Orr-Weaver, T.L. (2001) Endoreplication cell cycles: more for less. Cell 105, 297–306.
[38] Nigg, E.A. (2002) Centrosome aberrations: cause or consequence of cancer progression? Nat. Rev. Cancer 2, 815–825.
[39] Peddibhotla, S., Lam, M.H., Gonzalez-Rimbau, M. and Rosen, J.M. (2009) The DNA-damage effector checkpoint kinase 1 is essential for chromosome segregation and cytokinesis. Proc. Natl. Acad. Sci. USA 106, 5159–5164.
[40] Weaver, B.A. and Cleveland, D.W. (2009) The role of aneuploidy in promoting and suppressing tumors. J. Cell Biol. 185, 935–937.
[41] Andreassen, P.R., Lohez, O.D., Lacroix, F.B. and Margolis, R.L. (2001) Tetraploid state induces p53-dependent arrest of nontransformed mammalian cells in G1. Mol. Biol. Cell 12, 1315–1328.
[42] Wong, C. and Stearns, T. (2005) Mammalian cells lack checkpoints for tetraploidy, aberrant centrosome number, and cytokinesis failure. BMC Cell Biol. 6, 6.
[43] Stukenberg, P.T. (2004) Triggering p53 after cytokinesis failure. J. Cell Biol. 165, 607–608.
[44] Varmark, H., Sparks, C.A., Nordberg, J.J., Koppetsch, B.S. and Theurkauf, W.E. (2009) DNA damage-induced cell death is enhanced by progression through mitosis. Cell Cycle 8, 2951–2963.
[45] Lingle, W.L., Lutz, W.H., Ingle, J.N., Maihle, N.J. and Salisbury, J.L. (1998) Centrosome hypertrophy in human breast tumors: implications for genomic stability and cell polarity. Proc. Natl. Acad. Sci. USA 95, 2950–2955.
[46] Lingle, W.L., Barrett, S.L., Negron, V.C., D'Assoro, A.B., Boeneman, K., Liu, W., Whitehead, C.M., Reynolds, C. and Salisbury, J.L. (2002) Centrosome amplification drives chromosomal instability in breast tumor development. Proc. Natl. Acad. Sci. USA 99, 1978–1983.
[47] Pihan, G.A., Purohit, A., Wallace, J., Malhotra, R., Liotta, L. and Doxsey, S.J. (2001) Centrosome defects can account for cellular and genetic changes that characterize prostate cancer progression. Cancer Res. 61, 2212–2219.
[48] Yamamoto, Y., Eguchi, S., Junpei, A., Nagao, K., Sakano, S., Furuya, T., Oga, A., Kawauchi, S., Sasaki, K. and Matsuyama, H. (2009) Intercellular centrosome number is correlated with the copy number of chromosomes in bladder cancer. Cancer Genet. Cytogenet. 191, 38–42.
[49] Kuo, K.K., Sato, N., Mizumoto, K., Maehara, N., Yonemasu, H., Ker, C.G., Sheen, P.C. and Tanaka, M. (2000) Centrosome abnormalities in human carcinomas of the gallbladder and intrahepatic and extrahepatic bile ducts. Hepatology 31, 59–64.
[50] Sato, N., Mizumoto, K., Nakamura, M., Nakamura, K., Kusumoto, M., Niiyama, H., Ogawa, T. and Tanaka, M. (1999) Centrosome abnormalities in pancreatic ductal carcinoma. Clin. Cancer Res. 5, 963–970.
[51] Gustafson, L.M., Gleich, L.L., Fukasawa, K., Chadwell, J., Miller, M.A., Stambrook, P.J. and Gluckman, J.L. (2000) Centrosome hyperamplification in head and neck squamous cell carcinoma: a potential phenotypic marker of tumor aggressiveness. Laryngoscope 110, 1798–1801.
[52] Carroll, P.E., Okuda, M., Horn, H.F., Biddinger, P., Stambrook, P.J., Gleich, L.L., Li, Y.Q., Tarapore, P. and Fukasawa, K. (1999) Centrosome hyperamplification in human cancer: chromosome instability induced by p53 mutation and/or Mdm2 overexpression. Oncogene 18, 1935–1944.
[53] Thirthagiri, E., Robinson, C.M., Huntley, S., Davies, M., Yap, L.F., Prime, S.S. and Paterson, I.C. (2007) Spindle assembly checkpoint and centrosome abnormalities in oral cancer. Cancer Lett. 258, 276–285.
[54] Weber, R.G., Bridger, J.M., Benner, A., Weisenberger, D., Ehemann, V., Reifenberger, G. and Lichter, P. (1998) Centrosome amplification as a possible mechanism for numerical chromosome aberrations in cerebral primitive neuroectodermal tumors with TP53 mutations. Cytogenet. Cell Genet. 83, 266–269.
[55] Hollstein, M., Sidransky, D., Vogelstein, B. and Harris, C.C. (1991) P53 mutations in human cancers. Science 253, 49–53.
[56] Wilker, E.W., van Vugt, M.A., Artim, S.A., Huang, P.H., Petersen, C.P., Reinhardt, H.C., Feng, Y., Sharp, P.A., Sonenberg, N., White, F.M. and Yaffe, M.B. (2007) 14-3-3sigma controls mitotic translation to facilitate cytokinesis. Nature 446, 329–332.
[57] Lee, Y.H., Oh, B.K., Yoo, J.E., Yoon, S.M., Choi, J., Kim, K.S. and Park, Y.N. (2009) Chromosomal instability, telomere shortening, and inactivation of p21(WAF1/CIP1) in dysplastic nodules of hepatitis B virus-associated multistep hepatocarcinogenesis. Mod. Pathol. 22, 1121–1131.
[58] Li, Y. and Benezra, R. (1996) Identification of a human mitotic checkpoint gene: hsMAD2. Science 274, 246–248.

[59] Cahill, D.P., Lengauer, C., Yu, J., Riggins, G.J., Willson, J.K., Markowitz, S.D., Kinzler, K.W. and Vogelstein, B. (1998) Mutations of mitotic checkpoint genes in human cancers. Nature 392, 300–303.
[60] Cheng, C.K., Chow, L.W., Loo, W.T., Chan, T.K. and Chan, V. (2005) The cell cycle checkpoint gene Rad9 is a novel oncogene activated by 11q13 amplification and DNA methylation in breast cancer. Cancer Res. 65, 8646–8654.
[61] Boultwood, J. (2001) Ataxia telangiectasia gene mutations in leukaemia and lymphoma. J. Clin. Pathol. 54, 512–516.
[62] Tort, F., Hernandez, S., Bea, S., Camacho, E., Fernandez, V., Esteller, M., Fraga, M.F., Burek, C., Rosenwald, A., Hernandez, L. and Campo, E. (2005) Checkpoint kinase 1 (CHK1) protein and mRNA expression is downregulated in aggressive variants of human lymphoid neoplasms. Leukemia 19, 112–117.
[63] Kato, N., Fujimoto, H., Yoda, A., Oishi, I., Matsumura, N., Kondo, T., Tsukada, J., Tanaka, Y., Imamura, M. and Minami, Y. (2004) Regulation of Chk2 gene expression in lymphoid malignancies: involvement of epigenetic mechanisms in Hodgkin's lymphoma cell lines. Cell Death Differ. 11 (Suppl. 2), S153–S161.
[64] Bell, D.W., Varley, J.M., Szydlo, T.E., Kang, D.H., Wahrer, D.C., Shannon, K.E., Lubratovich, M., Verselis, S.J., Isselbacher, K.J., Fraumeni, J.F., Birch, J.M., Li, F.P., Garber, J.E. and Haber, D.A. (1999) Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. Science 286, 2528–2531.
[65] Bartkova, J., Guldberg, P., Gronbaek, K., Koed, K., Primdahl, H., Moller, K., Lukas, J., Orntoft, T.F. and Bartek, J. (2004) Aberrations of the Chk2 tumour suppressor in advanced urinary bladder cancer. Oncogene 23, 8545–8551.
[66] Mariatos, G., Bothos, J., Zacharatos, P., Summers, M.K., Scolnick, D.M., Kittas, C., Halazonetis, T.D. and Gorgoulis, V.G. (2003) Inactivating mutations targeting the chfr mitotic checkpoint gene in human lung cancer. Cancer Res. 63, 7185–7189.
[67] Chaplet, M., Rai, R., Jackson-Bernitsas, D., Li, K. and Lin, S.Y. (2006) BRIT1/MCPH1: a guardian of genome and an enemy of tumors. Cell Cycle 5, 2579–2583.
[68] Liu, M., Shen, S., Chen, F., Yu, W. and Yu, L. (2010) Linking the septin expression with carcinogenesis, Mol, Biol Rep.
[69] Zhang, L. and Maddox, A.S. (2010) Anillin. Curr. Biol. 20, R135–R136.
[70] Yun, M.H. and Hiom, K. (2009) Understanding the functions of BRCA1 in the DNA-damage response. Biochem. Soc. Trans. 37, 597–604.
[71] Lo, V.V., Calabrese, G., Manzoli, L., Palka, G., Spadano, A., Morizio, E., Guanciali-Franchi, P., Fantasia, D. and Cocco, L. (2004) Inositide-specific phospholipase c β1 gene deletion in the progression of myelodysplastic syndrome to acute myeloid leukemia. Leukemia 18, 1122–1126.
[72] Vecchione, A., Croce, C.M. and Baldassarre, G. (2007) Fez1/Lzts1 a new mitotic regulator implicated in cancer development. Cell Div. 2, 24.
[73] Song, L., Dai, T., Xiong, H., Lin, C., Lin, H., Shi, T. and Li, J. (2010) Inhibition of centriole duplication by centrobin depletion leads to p38–p53 mediated cell-cycle arrest. Cell Signal..
[74] Li, C.C., Chu, H.Y., Yang, C.W., Chou, C.K. and Tsai, T.F. (2009) Aurora-A overexpression in mouse liver causes p53-dependent premitotic arrest during liver regeneration. Mol. Cancer Res. 7, 678–688.
[75] You, J., Li, Q., Wu, C., Kim, J., Ottinger, M. and Howley, P.M. (2009) Regulation of aurora B expression by the bromodomain protein Brd4. Mol. Cell Biol. 29, 5094–5103.
[76] Zhou, H., Kuang, J., Zhong, L., Kuo, W.L., Gray, J.W., Sahin, A., Brinkley, B.R. and Sen, S. (1998) Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat. Genet. 20, 189–193.
[77] Ikezoe, T., Yang, J., Nishioka, C., Takezaki, Y., Tasaka, T., Togitani, K., Koeffler, H.P. and Yokoyama, A. (2009) A novel treatment strategy targeting polo-like kinase 1 in hematological malignancies. Leukemia 23, 1564–1576.
[78] Madhavan, J., Mitra, M., Mallikarjuna, K., Pranav, O., Srinivasan, R., Nagpal, A., Venkatesan, P. and Kumaramanickavel, G. (2009) KIF14 and E2F3 mRNA expression in human retinoblastoma and its phenotype association. Mol. Vis. 15, 235–240.
[79] Pellinen, T., Tuomi, S., Arjonen, A., Wolf, M., Edgren, H., Meyer, H., Grosse, R., Kitzing, T., Rantala, J.K., Kallioniemi, O., Fassler, R., Kallio, M. and Ivaska, J. (2008) Integrin trafficking regulated by Rab21 is necessary for cytokinesis. Dev. Cell 15, 371–385.
[80] Salipante, S.J., Mealiffe, M.E., Wechsler, J., Krem, M.M., Liu, Y., Namkoong, S., Bhagat, G., Kirchhoff, T., Offit, K., Lynch, H., Wiernik, P.H., Roshal, M., McMaster, M.L., Tucker, M., Fromm, J.R., Goldin, L.R. and Horwitz, M.S. (2009) Mutations in a gene encoding a midbody kelch protein in familial and sporadic classical Hodgkin lymphoma lead to binucleated cells. Proc. Natl. Acad. Sci. USA 106, 14920–14925.
[81] Cai, K.Q., Caslini, C., Capo-chichi, C.D., Slater, C., Smith, E.R., Wu, H., Klein-Szanto, A.J., Godwin, A.K. and Xu, X.X. (2009) Loss of GATA4 and GATA6 expression specifies ovarian cancer histological subtypes and precedes neoplastic transformation of ovarian surface epithelia. PLoS One 4, e6454.
[82] Sjoblom, T., Jones, S., Wood, L.D., Parsons, D.W., Lin, J., Barber, T.D., Mandelker, D., Leary, R.J., Ptak, J., Silliman, N., Szabo, S., Buckhaults, P., Farrell, C., Meeh, P., Markowitz, S.D., Willis, J., Dawson, D., Willson, J.K., Gazdar, A.F., Hartigan, J., Wu, L., Liu, C., Parmigiani, G., Park, B.H., Bachman, K.E., Papadopoulos, N., Vogelstein, B., Kinzler, K.W. and Velculescu, V.E. (2006) The consensus coding sequences of human breast and colorectal cancers. Science 314, 268–274.
[83] Bucher, N. and Britten, C.D. (2008) G2 checkpoint abrogation and checkpoint kinase-1 targeting in the treatment of cancer. Br. J. Cancer 98, 523–528.