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Centrosome Abnormality and Human Lung Cancer

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1. Introduction

The centrosome, which functions as a major microtubule-organizing center (MTOC), is composed of a pair of centrioles and surrounding protein aggregates called pericentriolar material (PCM); at any given time during the cell cycle, each cell contains one or two centrosomes (Fukasawa, 2007). Centrosomes play a crucial role in the formation of bipolar mitotic spindles, which are essential for accurate chromosome segregation (Zyss & Gergely, 2009). Numerical and functional abnormalities of centrosomes result in an increase in aberrant mitotic spindle formation, merotelic kinetochore-microtubule attachment errors, lagging chromosome formation, and chromosome segregation errors, all of which are thought to be possible causes of chromosome instability (Ganem et al., 2009; Nigg & Raff, 2009). Centrosome abnormalities and chromosome instability are characteristics of human lung cancer (Masuda and Takahashi, 2002; Koutsami et al., 2006; Jung et al., 2007; Shinmura et al., 2008), and abnormalities in genes responsible for centrosome regulation have been reported in lung cancer (Fukasawa, 2007; Lee et al., 2010). In this Review, the status of centrosome abnormalities in lung cancer, the mechanisms responsible for inducing centrosome abnormalities, and the relationship between centrosome abnormalities and chromosome instability are summarized.

2. Centrosome abnormalities in human lung cancer: Mechanisms causing centrosome abnormalities and chromosome instability

The presence of two centrosomes at mitosis is an important factor in the formation of bipolar mitotic spindles. Therefore, the numerical integrity of centrosomes is carefully controlled in human cells, and abrogation of this control results in centrosome amplification. First, we describe the normal centrosome duplication cycle, followed by three reports on centrosome abnormalities in lung cancer. Next, we describe investigations of the mechanism responsible for inducing centrosome amplification. Finally, we summarize the possible reasons why centrosome abnormalities cause chromosome instability.

2.1 Centrosome duplication cycle in human cells

Centrioles are cylindrical structures ($\sim 0.2 \mu\text{m}$ in diameter and $0.2\text{--}0.5 \mu\text{m}$ in length) and are composed of nine triplet microtubule arrays organized around a central cartwheel. Centrioles contain several tubulin isoforms and non-tubulin proteins such as CETN2, CP110,

SAS-6, and SAS-4 (Bettencourt-Dias & Glover, 2009). In animal cells, a pair of centrioles is embedded in a cloud of electron dense material known as PCM, and both structures constitute a larger structure named the centrosome, which serves as the main MTOC during both interphase and mitotic phase (Vorobjev & Nadezhkina, 1987). Centrosome duplication occurs once per cell cycle and is subject to strict control within cells. To organize a bipolar mitotic spindle, a centrosome is duplicated in S phase, additional PCM proteins are recruited during centrosome maturation in G₂, and the two centrosomes separate at mitotic entry (Figure 1). The primary function of PCM is microtubule nucleation. The assembly of microtubules is initiated on a γ -tubulin ring complex (γ TuRC), composed by γ -tubulin and additional subunits known as γ -tubulin complex proteins (Teixidó-Travesa et al., 2010).

Fig. 1. Centrosome duplication cycle.

The centrioles duplicate once per cell cycle. The formation of the daughter centriole on each mother centriole occurs during the late G₁ and S phases of the cell cycle. The daughter and mother centrioles are tightly associated in an orthogonal manner until the end of mitosis, and centriole disengagement occurs during mitotic exit. The initiation of centriole duplication requires the activity of several proteins, such as Cdk2-cyclin E and PLK4 kinases. The procentriole starts to assemble, and elongation depends on several proteins including centrin, CEP135, and γ -tubulin. During G₂ phase, additional PCM proteins are recruited, and centrosome maturation requires the activity of Aurora A and PLK1 kinases. During late G₂, the daughter centriole of the parental pair acquires subdistal appendages. Then, the two duplicated centrosomes separate and move to opposite end of the cell (centrosome separation). Finally, the two centrosomes form the poles of the bipolar mitotic spindle.

2.2 Centrosome abnormalities in lung cancer

Centrosome amplification has been reported in a variety of human primary cancers (e.g., breast cancer, lung cancer, bladder cancer, pancreatic cancer, and prostatic cancer) (Pihan et al., 1998; Sato et al., 1999; Pihan et al., 2001; Kawamura et al., 2004; Zyss & Gergely, 2009). With regard to primary lung cancer, Koutsami et al. (2006) examined 68 primary non-small cell lung carcinomas (NSCLCs) for the presence or absence of centrosome amplification using an immunofluorescence analysis with a monoclonal antibody for γ -tubulin, a centrosome marker; they showed that 36 (53%) of the 68 NSCLCs exhibited centrosome amplification. Centrosome amplification was not associated with clinicopathological markers such as stage, tumor grade, and histological subtype, but was associated with aneuploidy. Jung et al. (2007) examined 175 NSCLCs for centrosome abnormalities using an immunofluorescence analysis with an anti- γ -tubulin antibody; they showed that 50 (29%) of the 175 NSCLCs exhibited a centrosome abnormality. Aneuploidy, p16 expression, and the loss of pRB expression were significantly associated with centrosome abnormalities. Shinmura et al. (2008) examined 182 primary lung carcinomas for the presence or absence of centrosome amplification using an immunohistochemical analysis with an anti- γ -tubulin antibody and showed that 67 (37%) of the 182 cancers exhibited centrosome amplification. Thus, centrosome amplification is a common abnormality seen in human primary lung cancers.

2.3 Mechanisms inducing centrosome abnormalities

An immunofluorescence analysis using an antibody for centrosome or centriole markers in cultured cell lines can be used to determine the status of the centrosome number in the cells. The involvement of many kinds of agents and genes in centrosome regulation has been examined using such analyses. Here, these analyses are divided into those using lung cells and those using cells derived from other organs.

2.3.1 Mechanisms identified by using the lung cells

Holmes et al. (2006) showed that chronic exposure to lead chromate causes centrosome abnormalities and aneuploidy using WTHBF-6 cells, a cell line derived from normal human bronchial fibroblasts. Hexavalent chromium compounds [Cr(VI)] are human lung carcinogens (Le´onard & Lauwerys, 1980), and “particulate” Cr(VI) compounds are one of the most potent forms. They reported centrosome amplification in interphase and mitotic cells in response to treatment with lead chromate as a model particulate Cr(VI) compound. They suggested that one possible mechanism for lead chromate-induced carcinogenesis is through centrosome dysfunction, leading to the induction of aneuploidy. The same group (Holmes et al., 2010) also showed that chronic exposure to zinc chromate, another particulate Cr(VI) compound, induces centrosome amplification and spindle checkpoint bypass using human lung fibroblasts.

Arsenic is another environmental toxicant, and the biological effects of arsenic have been studied. Liao et al. (2007) showed that arsenic promotes centrosome abnormalities and cell colony formation in p53 compromised human lung cells. They used H1355 (a lung adenocarcinoma cell line with a p53 mutation), BEAS-2B (immortalized lung epithelial cells with functional p53) and pifithrin- α -treated BEAS-2B (p53-inhibited cells) and reported an increase in centrosome abnormalities in both arsenite-treated p53 compromised cell lines, compared with that in arsenite-treated BEAS-2B cells. Their findings provided evidence of

the carcinogenic promotional role of arsenic, especially in the presence of p53 abnormalities. The group also showed that arsenite promoted centrosome abnormalities in the presence of a p53-compromised status induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (nicotine-derived nitrosamine ketone, NNK) using BEAS-2B cells (Liao et al., 2010). Their findings provided evidence of an interaction between arsenite and cigarette smoking. Benzo[a]pyrene diol epoxide (B[a]PDE), the ultimate carcinogenic metabolite of benzo[a]pyrene, has been implicated in the mutagenesis of the *p53* gene, which is involved in smoking-associated lung cancer. Shinmura et al. (2008) showed that the exposure of *p53*-deficient H1299 lung cancer cells to B[a]PDE resulted in S-phase arrest, leading to abnormal centrosome amplification. They also revealed that the centrosome amplification could be primarily attributed to excessive centrosome duplication, rather than to centriole splitting, and the forced expression of POLK DNA polymerase, which has the ability to bypass B[a]PDE-guanine lesions in an error-free manner, suppressing B[a]PDE-induced centrosome amplification. The B[a]PDE exposure also led to chromosome instability, which was likely to have resulted from centrosome amplification. Thus, they concluded that B[a]PDE contributes to neoplasia by inducing centrosome amplification and consequent chromosome destabilization in addition to its mutagenic activity.

Fig. 2. Induction of centrosome amplification in *p53*-deficient H1299 lung cancer cells by exposure to benzo[a]pyrene diol epoxide (B[a]PDE).

H1299 cells were exposed to 0.6 μ M B[a]PDE for 72 hr and then immunostained with mouse anti- γ -tubulin monoclonal antibody (GTU-88; Sigma-Aldrich, St. Louis, MO, USA). Alexa Fluor 546 (red)-conjugated anti-IgG antibody (Molecular Probes, Eugene, OR, USA) was used to detect the antibody-antigen complexes. The nuclei were stained with 4',6-diamidino-2-phenylindol (DAPI, blue). An increase in the number of centrosomes, i.e., centrosome amplification, was observed in both interphase cells and mitotic phase cells. The arrows indicate the positions of centrosomes.

The lung is easily subjected to many kinds of environmental agents, some of which may be derived from cigarette smoking or occupational exposure. As described in the above three paragraphs, some environmental carcinogens induce centrosome amplification. Other environmental carcinogens attacking DNA may also induce centrosome amplification, since cell cycle arrest has been shown to occur during centrosome amplification. Further precise analyses of environmental agent-related centrosome amplification are needed to understand the relationship between environmental carcinogens and lung cancer more clearly.

The S-phase kinase-interacting protein-2 (SKP2) plays a key role in the progression of cells from a quiescent to proliferative state, and the SKP2 protein is overexpressed in lung cancer. Jiang et al. (2005) showed that the RNA silencing of SKP2 inhibits proliferation and centrosome amplification using the lung cancer cell lines A549 and H1792. Their results suggest that SKP2 plays an oncogenic role in lung cancer and has a centrosome regulating function.

NORE1 (RASSF5) is a member of the *RASSF* gene family, and NORE1A is the longest and major splice isoform of the *NORE1* gene (Nakamura et al., 2005). Its product, NORE1A, is a nucleocytoplasmic shuttling protein and has a growth-suppressive function (Moshnikova et al., 2006). Shinmura et al. (2011) showed that NORE1A suppresses the centrosome amplification induced by hydroxyurea using a *p53*-deficient H1299 lung cancer cell line, and NORE1A expression was down-regulated in NSCLC. Both of these findings imply that NORE1A has a key preventative role against the carcinogenesis of NSCLC.

2.3.2 Mechanisms identified using cells derived from other organs

CDK2-cyclin E, a known inducer of S-phase entry (Heichman, 1994), has an important role in the regulation of centrosome duplication (Hinchcliffe et al., 1999; Matsumoto et al., 1999). The activation of CDK2-cyclin E during late-G1 phase coordinates the initiation of centrosome and DNA duplication. Several CDK2-cyclin E targets, including nucleophosmin (NPM) (Okuda et al., 2000), have been identified. NPM binds and modulates the activities of multiple proteins including tumor suppressor proteins (e.g., *p53*) and some oncogenic proteins (e.g., ROCK2) (Colombo et al., 2002; Ma et al., 2006b). The reduced as well as increased expression of NPM can lead to the oncogenic transformation of cells. Actually, NPM is frequently mutated, lost or overexpressed in cancers (Grisendi et al., 2006), and both the overexpression and the depletion of NPM in cultured cells can lead to neoplastic transformation (Kondo et al., 1997; Grisendi et al., 2005). NPM localizes between the paired centrioles of the unduplicated centrosome, probably functioning in centriole pairing (Shinmura et al., 2005). When NPM is phosphorylated by CDK2-cyclin E, most of the NPM dissociates from the centrosomes, leading to the centrosome duplication. In this context, NPM negatively controls centrosome duplication; indeed, the depletion of NPM leads to centrosome amplification (Grisendi et al., 2005; Wang et al., 2005). NPM was reported to have the ability to control centrosome duplication in association with ROCK2 (Ma et al., 2006b), a member of the Rho-associated, coiled-coil containing protein kinase family that is frequently overexpressed in cancer (Nishimura et al., 2003). After NPM phosphorylation by CDK2-cyclin E, the binding between NPM and ROCK2 increases and ROCK2 is activated at centrosomes, leading to centrosome duplication (Ma et al., 2006b). In ROCK2 activation, the binding of Rho small GTPase to the auto-inhibitory region is also required (Kanai et al., 2010). Among three isoforms of Rho, both RhoA and RhoC, but not RhoB, promoted centrosome duplication and centrosome amplification.

Another target of CDK2–cyclin E in centrosome regulation is MPS1, a spindle checkpoint kinase that is localized at the centrosome (Fisk et al., 2003). MPS1 is stabilized and activated by CDK2–cyclin E phosphorylation and involved in centrosome duplication. Mortalin, a member of the heat-shock protein 70 molecular chaperone family, is localized at the centrosome and physically interacts with and is phosphorylated by MPS1. The phosphorylation of mortalin activates MPS1 in a positive-feedback manner, and this phenomenon is important for MPS1-related centrosome duplication (Kanai et al., 2007). Mortalin is frequently upregulated in cancers (Wadhwa et al., 2006).

CDK2 forms a complex with cyclin A in addition to cyclin E, and CDK2–cyclin A has been implicated in the regulation of centrosome duplication (Meraldi et al., 1999). CDK2–cyclin A and CDK2–cyclin E share some substrates (Tokuyama et al., 2001). The CDK2–cyclin A complex is active in S and G2 phases during the cell cycle, and CDK2–cyclin A may have a crucial role in centrosome over-duplication and/or amplification (Hanashiro et al., 2008). As another type of CDK–cyclin complex, the overactivation of CDK4/6–cyclin D has been shown to induce centrosome amplification (Nelsen et al., 2005). The major target of CDK4/6–cyclin D is the RB tumor-suppressor protein (Duensing et al., 2000). The conditional loss of *Rb* in mice results in centrosome amplification (Balsitis et al., 2003; Iovino et al., 2006).

CDK2 activity is also negatively controlled by the CDK inhibitor p21, one of the major transactivation targets of the p53 tumor-suppressor protein (Bálint & Vousden, 2001). p53 is involved in the regulation of centrosome duplication, which was first demonstrated in cells and tissues from *p53*-deficient mice (Fukasawa et al., 1996; Fukasawa et al., 1997). When cells are exposed to DNA-synthesis inhibitors such as hydroxyurea, centrosomes undergo reduplication without DNA synthesis, resulting in centrosome amplification (Balczon et al., 1995). Centrosome reduplication occurs efficiently when *p53* is mutated or lost (Tarapore et al., 2001a). In normal cells, p53 is stabilized under cellular stresses by the inhibition of MDM2, leading to the upregulation of p21, which blocks the initiation of centrosome reduplication through the inhibition of cyclin–CDK2 complexes (Bálint & Vousden, 2001). On the other hand, p21 is not upregulated in cells lacking *p53*, allowing the activation of CDK2, which in turn triggers centrosome reduplication.

Besides the *p53*–p21 pathway, *p53* has the ability to control centrosome duplication. *p53* is localized at centrosomes (Blair Zajdel & Blair, 1988; Brown et al., 1994; Tarapore et al., 2001b; Tritarelli et al., 2004; Ma et al., 2006a; Shinmura et al., 2007) and appears to control centrosome duplication independently of its transactivation function. Even if *p53* is a mutant without transactivation function, *p53* retains the ability to localize to centrosomes and partially suppresses centrosome duplication (Shinmura et al., 2007). However, the mechanism underlying this role of *p53* is currently unknown.

The proteins that control *p53* stability are also involved in the regulation of centrosome duplication. The ectopic expression of human papilloma virus (HPV) E6 protein, which promotes the degradation of *p53*, induces centrosome amplification (Duensing et al., 2000). MDM2 is an E3 ubiquitin ligase that promotes the degradation of *p53* and is often overexpressed in cancers (Manfredi, 2010). The forced expression of MDM2 in cells containing wild-type *p53* efficiently leads to centrosome amplification (Carroll et al., 1999). Aurora A kinase (AURKA) phosphorylates *p53* at Ser315, resulting in MDM2-mediated *p53* destabilization (Katayama et al., 2004), and the forced expression of Aurora A induces centrosome amplification (Zhou et al., 1998).

Polo-like kinase 1 (PLK1) is a key regulator of centrosome maturation (Barr et al., 2004; Bettencourt-Dias and Glover, 2007). Its deregulation is linked to centrosome abnormalities and oncogenesis (Zyss and Gergely, 2009). PLK1 belongs to the mammalian PLK family, which is comprised of five members (PLK1 - PLK4 and PLK5P) (Lens et al., 2010). PLK1 is involved in a variety of mitotic events, including centrosome maturation and separation, G2/M transition, mitotic spindle formation, chromosome segregation, and cytokinesis, and several kinds of PLK1 substrates are known (Barr et al., 2004; Petronczki et al., 2008). PLK1 targets multiple centrosomal proteins (e.g., γ -tubulin) to fulfill the mitotic function of centrosomes. Ninein-like protein (NLP) interacts with γ TuRC during interphase, and participates in the establishment of the cytoplasmic microtubule network (Casenghi et al., 2003; Rapley et al., 2005). At the onset of mitosis, the cooperation of PLK1 and NLP promotes the centrosomal localization of γ -tubulin and other mitosis specific PCM components, resulting in a higher microtubule nucleation capacity of the mitotic centrosome (Casenghi et al., 2003; Rapley et al., 2005). The phosphorylation of NEDD1 by PLK1 is required for the targeting of γ TuRC to the centrosome (Zhang et al., 2009). In mitosis, centrosomes must withstand the pulling forces exerted by chromosome-attached microtubules. To withstand such forces, PLK1 also plays a role in maintaining the structural integrity of the centrosome during mitosis (Oshimori et al., 2006). Kizuna is localized at the centrosomes and is phosphorylated by PLK1 during mitosis. The reduced expression of kizuna results in centrosome fragmentation and the dispersion of PCM, leading to the formation of aberrant mitotic spindles and chromosome segregation errors.

Another PLK, PLK4, is involved in recruiting the structural components required for the formation of procentrioles at the proximal side of the older centriole, in cooperation with CDK2-cyclin E (Habadanck et al., 2004). The upregulation of PLK4 expression is a strong stimulus for centriole multiplication (Kleylein-Sohn et al., 2007). The timely degradation of PLK4 by the SCF slimb ubiquitin ligase is important for the restriction of procentriole formation (Cunha-Ferreira et al., 2009). The SCF component CUL1 also functions as a centrosomal suppressor of centriole multiplication by regulating the PLK4 protein level (Korzeniewski et al., 2009). PLK4 kinase activity also regulates its own stability (Holland et al., 2010; Guderian et al., 2010). CEP152 interacts with PLK4 and CPAP and controls centrosome duplication in human cells (Dzhindzhev et al., 2010). PLK4 is transcriptionally regulated by p53 (Li et al., 2005). Clinically, the expression of PLK4 is upregulated in colon cancer (Macmillan et al., 2001), while the expression of PLK4 is downregulated in hepatocellular carcinoma because of promoter hypermethylation and the loss of heterozygosity (LOH) (Pellegrino et al., 2010; Rosario et al., 2010).

The role of the *morgana*/chp-1 in centrosome regulation has been reported by Ferretti et al. (2010). Mutations in *morgana* result in centrosome amplification. Morgana forms a complex with Hsp90, ROCK1 and ROCK2, and directly binds to ROCK2. Morgana downregulation promotes the interaction between ROCK2 and NPM, leading to an increase in ROCK2 activity, which in turn results in centrosome amplification. Morgana is downregulated in a large fraction of lung and breast cancers. They suggested that *morgana* plays a role in preventing centrosome amplification and tumorigenesis.

NLP, a previously described substrate of PLK1 (Casenghi et al., 2003), is a BRCA1-associated centrosomal protein that is involved in microtubule nucleation and spindle formation (Jin et al., 2009). NLP is overexpressed as a result of *NLP* gene amplification in lung cancer, and NLP overexpression causes centrosome amplification (Shao et al., 2010).

The *BRCA1* gene is responsible for susceptibility to familial breast/ovarian cancer and participates in diverse cellular functions (Venkitaraman, 2002). The *BRCA1* is localized at the centrosomes (Hsu & White, 1998; Okada & Ouchi, 2003) and is involved in the regulation of centrosome duplication (Xu et al., 1999). *BRCA1* is associated with *BARD1*, and this association mediates the ubiquitylation of γ -tubulin, which is important for maintaining the numeral integrity of centrosomes. The *BRCA2* gene is another causative gene of familial breast/ovarian cancer and its protein product functions in homologous recombination (HR) repair (Venkitaraman, 2002). The loss of *BRCA2* results in centrosome amplification (Tutt et al., 1999), implying a relationship between a defect in DNA repair and the abnormal amplification of the centrosomes. HR repair is mediated by several proteins including *RAD51*, and the downregulation of *RAD51* leads to centrosome amplification (Bertrand et al., 2003). The reduced expression or loss of *XRCC2*, *XRCC3*, and *RAD51B-D*, which are other HR components, induces centrosome amplification and chromosome instability (Griffin et al., 2000; Smiraldo et al., 2005; Date et al., 2006; Renglin Lindh et al., 2007; Cappelli et al., 2011).

Centrosome amplification induced by DNA damage occurs during a prolonged G2 phase (Dodson et al., 2004). A centrosome-autonomous signal that involves centriole disengagement causes centrosome amplification in G2 phase after DNA damage (Inanç et al., 2010), suggesting that genotoxic stress can decouple the centrosome cycle and chromosome cycle.

The active nucleocytoplasmic transport of proteins is mediated by the nuclear localization signal (NLS) and nuclear export signal (NES) (Turner & Sullivan, 2008). NLS-containing proteins are transported from the cytoplasm to the nucleus, whereas NES-containing proteins are exported from the nucleus to the cytoplasm by *XPO1*, the human homolog of yeast *Crm1*. The inhibition of *XPO1* causes centrosome amplification via the disruption of the nucleocytoplasmic transport of *NPM* (Forgues et al., 2003; Shinmura et al., 2005; Wang et al., 2005). *XPO1* is involved in the centrosomal localization of various proteins (Han et al., 2008). Importin β and *RANBP1* are other proteins involved in nucleocytoplasmic transport, and these proteins also have the ability to regulate centrosomes (Di Fiore et al., 2003; Ciciarello et al., 2004).

SGOL1 interacts with protein phosphatase 2A, is localized in the centromere, and prevents the cohesin complex from precocious cleavage at the centromere via the dephosphorylation of *SA2*, one of the cohesin subunits (Kitajima et al., 2006; Riedel et al., 2006). Clinically, *SGOL1* expression is downregulated in colorectal cancer, and *SGOL1*-knockdown leads to centrosome amplification and chromosome instability in a colon cancer cell line (Iwaizumi et al., 2009; Dai et al., 2009). A *SGOL1*-P1 transcript containing an exon-skip of exon 3, resulting in the formation of a premature stop codon, is expressed in colorectal cancer, and the overexpression of *SGOL1*-P1 in a colon cancer cell line resulted in an increased number of cells with aberrant chromosome alignment, precociously separated chromatids, delayed mitotic progression, and centrosome amplification (Kahyo et al., 2011). Furthermore, the overexpression of *SGOL1*-P1 inhibited the localization of endogenous *SGOL1* and cohesin subunit *RAD21/SCC1* to the centromere, suggesting that *SGOL1*-P1 may function as a negative factor to native *SGOL1* (Kahyo et al., 2011).

2.4 Relationship between centrosome abnormalities and chromosome instability

Chromosome instability is defined as a persistently high rate of the gain and loss of whole chromosomes (Thompson et al., 2010). Chromosome instability is a major source of

aneuploidy (Lengauer et al., 1997; Rajagopalan and Lengauer, 2004), and chromosome instability is thought to be involved not only in cancer initiation, where aneuploidy may have a causal role, but also in cancer development, where increased rates of chromosome missegregation may enable the clonal expansion of cells with a greater malignant potential (Rajagopalan & Lengauer, 2004; Weaver et al., 2007; Gao et al., 2007; Ganem et al., 2009). Defects in chromosome cohesion, weakened spindle assembly checkpoint (SAC) signalling, impaired microtubule-kinetochore attachment, defects in cell cycle regulation, and centrosome abnormalities can cause chromosome instability (Lingle et al., 1998; Draviam et al., 2004; Thompson & Compton, 2008; Weaver & Cleveland, 2008; Thompson et al., 2010). Regarding centrosome abnormalities, two mechanisms underlying chromosome instability have been proposed. The first mechanism is that centrosome amplification generates chromosome instability by promoting multipolar anaphase, which is an abnormal division that produces more than three aneuploid daughter cells (Nigg, 2002). The other mechanism is that centrosome amplification generates chromosome instability by promoting merotelic kinetochore-microtubule attachments (Ganem et al., 2009; Silkworth et al., 2009). Merotely is a type of error in which single kinetochores attach to microtubules emanating from different poles (Salmon et al., 2005; Cimini, 2008) and is common in cells showing chromosome instability (Thompson & Compton, 2008). Cells with centrosome amplification often coalesce the extra centrosomes during mitosis to ensure that anaphase occurs with a bipolar spindle (Quintyne et al., 2005). The extra centrosomes induce transient multipolar spindle intermediates prior to the coalescence of the centrosomes into bipolar spindles; this event increases the incidence of merotelic kinetochore-microtubule attachments and elevates the chromosome missegregation rates (Ganem et al., 2009; Silkworth et al., 2009). Ganem et al. (2009) showed that the presence of extra centrosomes is correlated with an increase in lagging chromosomes (Figure 3), promoting chromosome missegregation through excessive merotely induced by transient multipolar spindle intermediates. Since merotelic attachments are poorly sensed by the SAC (Salmon et al., 2005; Cimini, 2008), the merotelic attachments arising from centrosome amplification are not fully repaired and give rise to lagging chromosomes during anaphase, possibly leading to missegregation events.

Fig. 3. Lagging chromosomes in human cancer cells.

(A, B) Lagging chromosome formation detected in a B[a]PDE-treated H1299 lung cancer cell line. (A) Normal segregation; (B) an anaphase cell showing lagging chromosome formation. The nuclei were stained with DAPI (blue). (C) Lagging chromosomes are shown in a hematoxylin-and-eosin-stained section of a squamous cell carcinoma of the lung. In (B) and (C), the arrows indicate lagging chromosomes.

3. Conclusion

The progress in our understanding of the relationship between centrosome abnormalities and cancer during the past 15 years has been enormous. We have learned that centrosome abnormalities are common among diverse human cancers including lung cancer. Many molecules are involved in the control of the numeral and/or functional integrity of centrosomes, and the abrogation of these mechanisms results in centrosome abnormalities, which promote chromosome instability. From a therapeutic standpoint, anti-cancer drugs targeting the centrosome have now been developed (Mazzorana et al., 2011). Future studies using a genome-wide approach and new scientific technologies will further increase our knowledge of the role of the centrosome in human cells, and such knowledge will likely help to establish effective cancer therapies.

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5. References

- Balczon, R., Bao, L., Zimmer, W.E., Brown, K., Zinkowski, R.P., & Brinkley, B.R. (1995). Dissociation of centrosome replication events from cycles of DNA synthesis and mitotic division in hydroxyurea-arrested Chinese hamster ovary cells. *Journal of Cell Biology*, Vol.130, No.1, (July), pp. 105-115, ISSN 0021-9525
- Bálint, E.E. & Vousden, K.H. (2001). Activation and activities of the p53 tumour suppressor protein. *British Journal of Cancer*, Vol.85, No.12, (December 14), pp. 1813-1823, ISSN 0007-0920
- Balsitis, S.J., Sage, J., Duensing, S., Münger, K., Jacks, T., & Lambert, P.F. (2003). Recapitulation of the effects of the human papillomavirus type 16 E7 oncogene on mouse epithelium by somatic Rb deletion and detection of pRb-independent effects of E7 in vivo. *Molecular and Cellular Biology*, Vol.23, No.24, (December), pp. 9094-9103, ISSN 0270-7306
- Barr, F.A., Silljé, H.H., & Nigg, E.A. (2004). Polo-like kinases and the orchestration of cell division. *Nature Reviews Molecular Cell Biology*, Vol.5, No.6, (June), pp. 429-440, ISSN 1471-0072
- Bertrand, P., Lambert, S., Joubert, C., & Lopez, B.S. (2003). Overexpression of mammalian Rad51 does not stimulate tumorigenesis while a dominant-negative Rad51 affects centrosome fragmentation, ploidy and stimulates tumorigenesis, in p53-defective CHO cells. *Oncogene*, Vol.22, No.48, (October 23), pp. 7587-7592, ISSN 0950-9232
- Bettencourt-Dias, M. & Glover, D.M. (2007). Centrosome biogenesis and function: centrosomics brings new understanding. *Nature Reviews Molecular Cell Biology*, Vol.8, No.6, (June), pp. 451-463, ISSN 1471-0072
- Bettencourt-Dias, M. & Glover, D.M. (2009). SnapShot: centriole biogenesis. *Cell*, Vol.136, No.1, (January 9), pp. 188-188.e1, ISSN 0092-8674
- Blair Zajdel, M.E. & Blair, G.E. (1988). The intracellular distribution of the transformation-associated protein p53 in adenovirus-transformed rodent cells. *Oncogene*, Vol.2, No.6, (June), pp. 579-584, ISSN 0950-9232

- Brown, C.R., Doxsey, S.J., White, E., & Welch, W.J. (1994). Both viral (adenovirus E1B) and cellular (hsp 70, p53) components interact with centrosomes. *Journal of Cellular Physiology*, Vol.160, No.1, (July), pp. 47-60, ISSN 0021-9541
- Cappelli, E., Townsend, S., Griffin, C., & Thacker, J. (2011). Homologous recombination proteins are associated with centrosomes and are required for mitotic stability. *Experimental Cell Research*, Vol.317, No.8, (May 1), pp. 1203-1213, ISSN 0014-4827
- Carroll, P.E., Okuda, M., Horn, H.F., et al. (1999). Centrosome hyperamplification in human cancer: chromosome instability induced by p53 mutation and/or Mdm2 overexpression. *Oncogene*, Vol.18, No.11, (March 18), pp. 1935-1944, ISSN 0950-9232
- Casenghi, M., Meraldi, P., Weinhart, U., Duncan, P.I., Körner, R., & Nigg, E.A. (2003). Polo-like kinase 1 regulates Nlp, a centrosome protein involved in microtubule nucleation. *Developmental Cell*, Vol.5, No.1, (July), pp. 113-125, ISSN 1534-5807
- Ciciarello, M., Mangiacasale, R., Thibier, C., et al. (2004). Importin beta is transported to spindle poles during mitosis and regulates Ran-dependent spindle assembly factors in mammalian cells. *Journal of Cell Science*, Vol.117, No.26, (December 15), pp. 6511-6522, ISSN 0021-9533
- Cimini, D. (2008). Merotelic kinetochore orientation, aneuploidy, and cancer. *Biochimica et Biophysica Acta-Reviews on Cancer*, Vol.1786, No.1, (September), pp. 32-40, ISSN 0304-419X
- Colombo, E., Marine, J.C., Danovi, D., Falini, B., & Pelicci, P.G. (2002). Nucleophosmin regulates the stability and transcriptional activity of p53. *Nature Cell Biology*, Vol.4, No.7, (July), pp. 529-533, ISSN 1465-7392
- Cunha-Ferreira, I., Rodrigues-Martins, A., Bento, I., et al. (2009). The SCF/Slimb ubiquitin ligase limits centrosome amplification through degradation of SAK/PLK4. *Current Biology*, Vol.19, No.1, (January 13), pp. 43-49, ISSN 0960-9822
- Dai, J., Kateneva, A.V., & Higgins, J.M. (2009). Studies of haspin-depleted cells reveal that spindle-pole integrity in mitosis requires chromosome cohesion. *Journal of Cell Science*, Vol.122, No.22, (November 15), pp. 4168-4176, ISSN 0021-9533
- Date, O., Katsura, M., Ishida, M., et al. (2006). Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. *Cancer Research*, Vol.66, No.12, (June 15), pp. 6018-6024, ISSN 0008-5472
- Di Fiore, B., Ciciarello, M., Mangiacasale, R., et al. (2003). Mammalian RanBP1 regulates centrosome cohesion during mitosis. *Journal of Cell Science*, Vol.116, No.16, (August 15), pp. 3399-3411, ISSN 0021-9533
- Dodson, H., Bourke, E., Jeffers, L.J., et al. (2004). Centrosome amplification induced by DNA damage occurs during a prolonged G2 phase and involves ATM. *EMBO Journal*, Vol.23, No.19, (October 1), pp. 3864-3873, ISSN 0261-4189
- Draviam, V.M., Xie, S., & Sorger, P.K. (2004). Chromosome segregation and genomic stability. *Current Opinion in Genetics & Development*, Vol.14, No.2, (April), pp. 120-125, ISSN 0959-437X
- Duensing, S., Lee, L.Y., Duensing, A., et al. (2000). The human papillomavirus type 16 E6 and E7 oncoproteins cooperate to induce mitotic defects and genomic instability by uncoupling centrosome duplication from the cell division cycle. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.97, No.18, (August 29), pp. 10002-10007, ISSN 0027-8424

- Dzhindzhev, N.S., Yu, Q.D., Weiskopf, K., et al. (2010). Asterless is a scaffold for the onset of centriole assembly. *Nature*, Vol.467, No.7316, (October 7), pp. 714-718, ISSN 0028-0836
- Ferretti, R., Palumbo, V., Di Savino, A., et al. (2010). Morgana/chp-1, a ROCK inhibitor involved in centrosome duplication and tumorigenesis. *Developmental Cell*, Vol.18, No.3, (March 16), pp. 486-495, ISSN 1534-5807
- Fisk, H.A., Mattison, C.P., & Winey, M. (2003). Human Mps1 protein kinase is required for centrosome duplication and normal mitotic progression. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.100, No.25, (December 9), pp. 14875-14880, ISSN 0027-8424
- Forgues, M., Difilippantonio, M.J., Linke, S.P., et al. (2003). Involvement of Crm1 in hepatitis B virus X protein-induced aberrant centriole replication and abnormal mitotic spindles. *Molecular and Cellular Biology*, Vol.23, No.15, (August), pp. 5282-5292, ISSN 0270-7306
- Fukasawa, K., Choi, T., Kuriyama, R., Rulong, S., & Vande Woude, G.F. (1996). Abnormal centrosome amplification in the absence of p53. *Science*, Vol.271, No.5256, (March 22), pp. 1744-1747, ISSN 0036-8075
- Fukasawa, K., Wiener, F., Vande Woude, G.F., & Mai, S. (1997). Genomic instability and apoptosis are frequent in p53 deficient young mice. *Oncogene*, Vol.15, No.11, (September), pp. 1295-1302, ISSN 0950-9232
- Fukasawa, K. (2007). Oncogenes and tumour suppressors take on centrosomes. *Nature Reviews Cancer*, Vol.7, No.12, (December), pp. 911-924, ISSN 1474-175X
- Ganem, N.J., Godinho, S.A., & Pellman, D. (2009). A mechanism linking extra centrosomes to chromosomal instability. *Nature*, Vol.460, No.7252, (July 9), pp. 278-282, ISSN 0028-0836
- Gao, C., Furge, K., Koeman, J., et al. (2007). Chromosome instability, chromosome transcriptome, and clonal evolution of tumor cell populations. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.104, No.21, (May 22), pp. 8995-9000, ISSN 0027-8424
- Griffin, C.S., Simpson, P.J., Wilson, C.R., & Thacker, J. (2000). Mammalian recombination-repair genes XRCC2 and XRCC3 promote correct chromosome segregation. *Nature Cell Biology*, Vol.2, No.10, (October), pp. 757-761, ISSN 1465-7392
- Grisendi, S., Bernardi, R., Rossi, M., et al. (2005). Role of nucleophosmin in embryonic development and tumorigenesis. *Nature*, Vol. 437, No. 7055, (September 1), pp. 147-153, ISSN 0028-0836
- Grisendi, S., Mecucci, C., Falini, B., & Pandolfi, P.P. (2006). Nucleophosmin and cancer. *Nature Reviews Cancer*, Vol.6, No.7, (July), pp. 493-505, ISSN 1474-175X
- Guderian, G., Westendorf, J., Uldschmid, A., & Nigg, E.A. (2010). Plk4 trans-autophosphorylation regulates centriole number by controlling betaTrCP-mediated degradation. *Journal of Cell Science*, Vol.123, No.13, (July 1), pp. 2163-2169, ISSN 0021-9533
- Habedanck, R., Stierhof, Y.D., Wilkinson, C.J., & Nigg, E.A. (2005). The Polo kinase Plk4 functions in centriole duplication. *Nature Cell Biology*, Vol.7, No.11, (November), pp. 1140-1146, ISSN 1465-7392
- Han, X., Saito, H., Miki, Y., & Nakanishi, A. (2008). A CRM1-mediated nuclear export signal governs cytoplasmic localization of BRCA2 and is essential for centrosomal localization of BRCA2. *Oncogene*, Vol.27, No.21, (May 8), pp. 2969-2977, ISSN 0950-9232

- Hanashiro, K., Kanai, M., Geng, Y., Sicinski, P., & Fukasawa, K. (2008). Roles of cyclins A and E in induction of centrosome amplification in p53-compromised cells. *Oncogene*, Vol.27, No.40, (September 11), pp. 5288-5302, ISSN 0950-9232
- Heichman, K.A. & Roberts, J.M. (1994). Rules to replicate by. *Cell*, Vol.79, No.4, (November 18), pp. 557-562, ISSN 0092-8674
- Hinchcliffe, E.H., Li, C., Thompson, E.A., Maller, J.L., & Sluder, G. (1999). Requirement of Cdk2-cyclin E activity for repeated centrosome reproduction in *Xenopus* egg extracts. *Science*, Vol.283, No.5403, (February 5), pp. 851-854, ISSN 0036-8075
- Holland, A.J., Lan, W., Niessen, S., Hoover, H., & Cleveland, D.W. (2010). Polo-like kinase 4 kinase activity limits centrosome overduplication by autoregulating its own stability. *Journal of Cell Biology*, Vol.188, No.2, (January 25), pp. 191-198, ISSN 0021-9525
- Holmes, A.L., Wise, S.S., Sandwick, S.J., et al. (2006). Chronic exposure to lead chromate causes centrosome abnormalities and aneuploidy in human lung cells. *Cancer Research*, Vol.66, No.8, (April 15), pp. 4041-4048, ISSN 0008-5472
- Holmes, A.L., Wise, S.S., Pelsue, S.C., et al. (2010). Chronic exposure to zinc chromate induces centrosome amplification and spindle assembly checkpoint bypass in human lung fibroblasts. *Chemical Research in Toxicology*, Vol.23, No.2, (February 15), pp. 386-395, ISSN 0893-228X
- Hsu, L.C. & White, R.L. (1998). BRCA1 is associated with the centrosome during mitosis. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.95, No.22, (October 27), pp. 12983-12988, ISSN 0027-8424
- Inanç, B., Dodson, H., & Morrison, C.G. (2010). A centrosome-autonomous signal that involves centriole disengagement permits centrosome duplication in G2 phase after DNA damage. *Molecular Biology of the Cell*, Vol.21, No.22, (November 15), pp. 3866-3877, ISSN 1059-1524
- Iovino, F., Lentini, L., Amato, A., & Di Leonardo, A. (2006). RB acute loss induces centrosome amplification and aneuploidy in murine primary fibroblasts. *Molecular Cancer*, Vol.5, (September 20), pp. 38, ISSN 1476-4598
- Iwaizumi, M., Shinmura, K., Mori, H., et al. (2009). Human Sgo1 downregulation leads to chromosomal instability in colorectal cancer. *Gut*, Vol.58, No.2, (February), pp. 249-260, ISSN 0017-5749
- Jiang, F., Caraway, N.P., Li, R., & Katz, R.L. (2005). RNA silencing of S-phase kinase-interacting protein 2 inhibits proliferation and centrosome amplification in lung cancer cells. *Oncogene*, Vol.24, No.21, (May 12), pp. 3409-3418, ISSN 0950-9232
- Jin, S., Gao, H., Mazzacurati, L., et al. (2009). BRCA1 interaction of centrosomal protein Nlp is required for successful mitotic progression. *Journal of Biological Chemistry*, Vol.284, No.34, (August 21), pp. 22970-22977, ISSN 0021-9258
- Jung, C.K., Jung, J.H., Lee, K.Y., et al. (2007). Centrosome abnormalities in non-small cell lung cancer: correlations with DNA aneuploidy and expression of cell cycle regulatory proteins. *Pathology Research and Practice*, Vol.203, No.12, pp. 839-847, ISSN 0344-0338
- Kahyo, T., Iwaizumi, M., Shinmura, K., et al. (2011). A novel tumor-derived SGOL1 variant causes abnormal mitosis and unstable chromatid cohesion. *Oncogene*, Vol.30, No.44, (November 3), pp.4453-4463, ISSN 0950-9232
- Kanai, M., Ma, Z., Izumi, H., et al. (2007). Physical and functional interaction between mortalin and Mps1 kinase. *Genes to Cells*, Vol.12, No.6, (June), pp. 797-810, ISSN 1356-9597

- Kanai, M., Crowe, M.S., Zheng, Y., Vande Woude, G.F., & Fukasawa, K. (2010). RhoA and RhoC are both required for the ROCK II-dependent promotion of centrosome duplication. *Oncogene*, Vol.29, No.45, (November 11), pp. 6040-6050, ISSN 0950-9232
- Katayama, H., Sasai, K., Kawai, H., et al. (2004). Phosphorylation by aurora kinase A induces Mdm2-mediated destabilization and inhibition of p53. *Nature Genetics*, Vol.36, No.1, (January), pp. 55-62, ISSN 1061-4036
- Kawamura, K., Izumi, H., Ma, Z., et al. (2004). Induction of centrosome amplification and chromosome instability in human bladder cancer cells by p53 mutation and cyclin E overexpression. *Cancer Research*, Vol.64, No.14, (July 15), pp. 4800-4809, ISSN 0008-5472
- Kitajima, T.S., Sakuno, T., Ishiguro, K., et al. (2006). Shugoshin collaborates with protein phosphatase 2A to protect cohesin. *Nature*, Vol.441, No.7089, (May 4), pp. 46-52, ISSN 0028-0836
- Kleylein-Sohn, J., Westendorf, J., Le Clech, M., Habedanck, R., Stierhof, Y.D., & Nigg, E.A. (2007). Plk4-induced centriole biogenesis in human cells. *Developmental Cell*, Vol.13, No.2, (August), pp. 190-202, ISSN 1534-5807
- Kondo, T., Minamino, N., Nagamura-Inoue, T., Matsumoto, M., Taniguchi, T., & Tanaka, N. (1997). Identification and characterization of nucleophosmin/B23/numatrin which binds the anti-oncogenic transcription factor IRF-1 and manifests oncogenic activity. *Oncogene*, Vol.15, No.11, (September), pp. 1275-1281, ISSN 0950-9232
- Korzeniewski, N., Zheng, L., Cuevas, R., et al. (2009). Cullin 1 functions as a centrosomal suppressor of centriole multiplication by regulating polo-like kinase 4 protein levels. *Cancer Research*, Vol.69, No.16, (August 15), pp. 6668-6675, ISSN 0008-5472
- Koutsami, M.K., Tsantoulis, P.K., Kouloukoussa, M., et al. (2006). Centrosome abnormalities are frequently observed in non-small-cell lung cancer and are associated with aneuploidy and cyclin E overexpression. *Journal of Pathology*, Vol.209, No.4, (August), pp. 512-521, ISSN 0022-3417
- Lee, W., Jiang, Z., Liu, J., et al. (2010). The mutation spectrum revealed by paired genome sequences from a lung cancer patient. *Nature*, Vol.465, No.7297, (May 27), pp. 473-477, ISSN 0028-0836
- Lengauer, C., Kinzler, K.W., & Vogelstein, B. (1997). Genetic instability in colorectal cancers. *Nature*, Vol.386, No.6625, (April 10), pp. 623-627, ISSN 0028-0836
- Lens, S.M., Voest, E.E., & Medema, R.H. (2010). Shared and separate functions of polo-like kinases and aurora kinases in cancer. *Nature Reviews Cancer*, Vol.10, No.12, (December), pp. 825-841, ISSN 1474-175X
- Le'onard, A. & Lauwerys, R.R. (1980). Carcinogenicity and mutagenicity of chromium. *Mutation Research-Reviews in Mutation Research*, Vol.76, pp. 227-239. ISSN 1383-5742
- Li, J., Tan, M., Li, L., Pamarthy, D., Lawrence, T.S., & Sun, Y. (2005). SAK, a new polo-like kinase, is transcriptionally repressed by p53 and induces apoptosis upon RNAi silencing. *Neoplasia*, Vol.7, No.4, (April), pp. 312-323, ISSN 1522-8002
- Liao, W.T., Lin, P., Cheng, T.S., Yu, H.S., & Chang, L.W. (2007). Arsenic promotes centrosome abnormalities and cell colony formation in p53 compromised human lung cells. *Toxicology and Applied Pharmacology*, Vol.225, No.2, (December 1), pp. 162-170, ISSN 0041-008X

- Liao, W.T., Yu, H.S., Lin, P., & Chang, L.W. (2010). Arsenite promotes centrosome abnormalities under a p53 compromised status induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). *Toxicology and Applied Pharmacology*, Vol.243, No.1, (February 15), pp. 55-62, ISSN 0041-008X
- Lingle, W.L., Barrett, S.L., Negron, V.C., et al. (2002). Centrosome amplification drives chromosomal instability in breast tumor development. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.99, No.4, (February 19), pp. 1978-1983, ISSN 0027-8424
- Ma, Z., Izumi, H., Kanai, M., Kabuyama, Y., Ahn, N.G., & Fukasawa, K. (2006a). Mortalin controls centrosome duplication via modulating centrosomal localization of p53. *Oncogene*, Vol.25, No.39, (August 31), pp. 5377-5390, ISSN 0950-9232
- Ma, Z., Kanai, M., Kawamura, K., Kaibuchi, K., Ye, K., & Fukasawa, K. (2006b). Interaction between ROCK II and nucleophosmin/B23 in the regulation of centrosome duplication. *Molecular and Cellular Biology*, Vol.26, No.23, (December), pp. 9016-9034, ISSN 0270-7306
- Macmillan, J.C., Hudson, J.W., Bull, S., Dennis, J.W., & Swallow, C.J. (2001). Comparative expression of the mitotic regulators SAK and PLK in colorectal cancer. *Annals of Surgical Oncology*, Vol.8, No.9, (October), pp. 729-740, ISSN 1068-9265
- Manfredi, J.J. (2010). The Mdm2-p53 relationship evolves: Mdm2 swings both ways as an oncogene and a tumor suppressor. *Genes & Development*, Vol.24, No.15, (August 1), pp. 1580-1589, ISSN 0890-9369
- Masuda, A. & Takahashi, T. (2002). Chromosome instability in human lung cancers: possible underlying mechanisms and potential consequences in the pathogenesis. *Oncogene*, Vol.21, No.45, (October 7), pp. 6884-6897, ISSN 0950-9232
- Matsumoto, Y., Hayashi, K., & Nishida, E. (1999). Cyclin-dependent kinase 2 (Cdk2) is required for centrosome duplication in mammalian cells. *Current Biology*, Vol.9, No.8, (April 22), pp. 429-432, ISSN 0960-9822
- Mazzorana, M., Montoya, G., & Mortuza, G.B. (2011). The centrosome: a target for cancer therapy. *Current Cancer Drug Targets*, Vol.11, No.5, (June 1), pp. 600-612, ISSN 1568-0096
- Meraldi, P., Lukas, J., Fry, A.M., Bartek, J., & Nigg, E.A. (1999). Centrosome duplication in mammalian somatic cells requires E2F and Cdk2-cyclin A. *Nature Cell Biology*, Vol.1, No.2, (June), pp. 88-93, ISSN 1465-7392
- Moshnikova, A., Frye, J., Shay, J.W., Minna, J.D., & Khokhlatchev, A.V. (2006). The growth and tumor suppressor NORE1A is a cytoskeletal protein that suppresses growth by inhibition of the ERK pathway. *Journal of Biological Chemistry*, Vol.281, No.12, (March 24), pp. 8143-8152, ISSN 1059-1524
- Nakamura, N., Carney, J.A., Jin, L., et al. (2005). RASSF1A and NORE1A methylation and BRAFV600E mutations in thyroid tumors. *Laboratory Investigation*, Vol.85, No.9, (September), pp. 1065-1075, ISSN 0023-6837
- Nelsen, C.J., Kuriyama, R., Hirsch, B., et al. (2005). Short term cyclin D1 overexpression induces centrosome amplification, mitotic spindle abnormalities, and aneuploidy. *Journal of Biological Chemistry*, Vol.280, No.1, (January 7), pp. 768-776, ISSN 0021-9258
- Nigg, E.A. (2002). Centrosome aberrations: cause or consequence of cancer progression? *Nature Reviews Cancer*, Vol.2, No.11, (November), pp. 815-825, ISSN 1474-175X

- Nigg, E.A. & Raff, J.W. (2009). Centrioles, centrosomes, and cilia in health and disease. *Cell*, Vol.139, No.4, (November 13), pp. 663-678, ISSN 0092-8674
- Nishimura, Y., Itoh, K., Yoshioka, K., Tokuda, K., & Himeno, M. (2003). Overexpression of ROCK in human breast cancer cells: evidence that ROCK activity mediates intracellular membrane traffic of lysosomes. *Pathology & Oncology Research*, Vol.9, No.2, pp. 83-95, ISSN 1219-4956
- Okada, S. & Ouchi, T. (2003). Cell cycle differences in DNA damage-induced BRCA1 phosphorylation affect its subcellular localization. *Journal of Biological Chemistry*, Vol.278, No.3, (January 17), pp. 2015-2020, ISSN 0021-9258
- Okuda, M., Horn, H.F., Tarapore, P., et al. (2000). Nucleophosmin/B23 is a target of CDK2/cyclin E in centrosome duplication. *Cell*, Vol.103, No.1, (September 29), pp. 127-140, ISSN 0092-8674
- Oshimori, N., Ohsugi, M., & Yamamoto, T. (2006). The Plk1 target Kizuna stabilizes mitotic centrosomes to ensure spindle bipolarity. *Nature Cell Biology*, Vol.8, No.10, (October), pp. 1095-1101, ISSN 1465-7392
- Pellegrino, R., Calvisi, D.F., Ladu, S., et al. (2010). Oncogenic and tumor suppressive roles of polo-like kinases in human hepatocellular carcinoma. *Hepatology*, Vol.51, No.3, (March), pp. 857-868, ISSN 0270-9139
- Petronczki, M., Lénárt, P., & Peters, J.M. (2008). Polo on the Rise-from Mitotic Entry to Cytokinesis with Plk1. *Developmental Cell*, Vol.14, No.5, (May), pp. 646-659, ISSN 1534-5807
- Pihan, G.A., Purohit, A., Wallace, J., et al. (1998). Centrosome defects and genetic instability in malignant tumors. *Cancer Research*, Vol.58, No.17, (September 1), pp. 3974-3985, ISSN 0008-5472
- Pihan, G.A., Purohit, A., Wallace, J., Malhotra, R., Liotta, L., & Doxsey, S.J. (2001). Centrosome defects can account for cellular and genetic changes that characterize prostate cancer progression. *Cancer Research*, Vol.61, No.5, (March 1), pp. 2212-2219, ISSN 0008-5472
- Quintyne, N.J., Reing, J.E., Hoffelder, D.R., Gollin, S.M., & Saunders, W.S. (2005). Spindle multipolarity is prevented by centrosomal clustering. *Science*, Vol.307, No.5706, (January 7), pp. 127-129, ISSN 0036-8075
- Rajagopalan, H. & Lengauer, C. (2004). Aneuploidy and cancer. *Nature*, Vol.432, No. 7015, (November 18), pp. 338-341, ISSN 0028-0836
- Rapley, J., Baxter, J.E., Blot, J., et al. (2005). Coordinate regulation of the mother centriole component nlp by nek2 and plk1 protein kinases. *Molecular and Cellular Biology*, Vol.25, No.4, (February), pp. 1309-1324, ISSN 0270-7306
- Renglin Lindh, A., Schultz, N., Saleh-Gohari, N., & Helleday, T. (2007). RAD51C (RAD51L2) is involved in maintaining centrosome number in mitosis. *Cytogenetic and Genome Research*, Vol.116, No.1-2, pp. 38-45, ISSN 1424-8581
- Riedel, C.G., Katis, V.L., Katou, Y., et al. (2006). Protein phosphatase 2A protects centromeric sister chromatid cohesion during meiosis I. *Nature*, Vol.441, No. 7089, (May 4), pp. 53-61, ISSN 0028-0836
- Rosario, C.O., Ko, M.A., Haffani, Y.Z., et al. (2010). Plk4 is required for cytokinesis and maintenance of chromosomal stability. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.107, No.15, (April 13), pp. 6888-6893, ISSN 0027-8424

- Salmon, E.D., Cimini, D., Cameron, L.A., & DeLuca, J.G. (2005). Merotelic kinetochores in mammalian tissue cells. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, Vol.360, No.1455, (March 29), pp. 553-568, ISSN 0080-4622
- Sato, N., Mizumoto, K., Nakamura, M., et al. (1999). Centrosome abnormalities in pancreatic ductal carcinoma. *Clinical Cancer Research*, Vol.5, No.5, (May), pp. 963-970, ISSN 1078-0432
- Shao, S., Liu, R., Wang, Y., et al. (2010). Centrosomal Nlp is an oncogenic protein that is gene-amplified in human tumors and causes spontaneous tumorigenesis in transgenic mice. *Journal of Clinical Investigation*, Vol.120, No.2, (February 1), pp. 498-507, ISSN 0021-9738
- Shinmura, K., Tarapore, P., Tokuyama, Y., George, K.R., & Fukasawa, K. (2005). Characterization of centrosomal association of nucleophosmin/B23 linked to Crm1 activity. *FEBS Letters*, Vol.579, No.29, (December 5), pp. 6621-6634, ISSN 0014-5793
- Shinmura, K., Bennett, R.A., Tarapore, P., & Fukasawa, K. (2007). Direct evidence for the role of centrosomally localized p53 in the regulation of centrosome duplication. *Oncogene*, Vol.26, No.20, (May 3), pp. 2939-2944, ISSN 0950-9232
- Shinmura, K., Iwaizumi, M., Igarashi, H., et al. (2008). Induction of centrosome amplification and chromosome instability in p53-deficient lung cancer cells exposed to benzo[a]pyrene diol epoxide (B[a]PDE). *Journal of Pathology*, Vol.216, No.3, (November), pp. 365-374, ISSN 0022-3417
- Shinmura, K., Tao, H., Nagura, K., et al. (2011). Suppression of hydroxyurea-induced centrosome amplification by NORE1A and down-regulation of NORE1A mRNA expression in non-small cell lung carcinoma. *Lung Cancer*, Vol.71, No.1, (January), pp. 19-27, ISSN 0169-5002
- Silkworth, W.T., Nardi, I.K., Scholl, L.M., & Cimini, D. (2009). Multipolar spindle pole coalescence is a major source of kinetochore mis-attachment and chromosome mis-segregation in cancer cells. *PLoS One*, Vol.4, No.8, (August 10), pp. e6564, ISSN 1932-6203
- Smiraldo, P.G., Gruver, A.M., Osborn, J.C., & Pittman, D.L. (2005). Extensive chromosomal instability in Rad51d-deficient mouse cells. *Cancer Research*, Vol.65, No.6, (March 15), pp. 2089-2096, ISSN 0008-5472
- Tarapore, P., Horn, H.F., Tokuyama, Y., & Fukasawa, K. (2001a). Direct regulation of the centrosome duplication cycle by the p53-p21Waf1/Cip1 pathway. *Oncogene*, Vol.20, No.25, (May 31), pp. 3173-3184, ISSN 0950-9232
- Tarapore, P., Tokuyama, Y., Horn, H.F., & Fukasawa, K. (2001b). Difference in the centrosome duplication regulatory activity among p53 'hot spot' mutants: potential role of Ser 315 phosphorylation-dependent centrosome binding of p53. *Oncogene*, Vol.20, No.47, (October 18), pp. 6851-6863, ISSN 0950-9232
- Teixidó-Travesa, N., Villén, J., Lacasa, C., et al. (2010). The gammaTuRC revisited: a comparative analysis of interphase and mitotic human gammaTuRC redefines the set of core components and identifies the novel subunit GCP8. *Molecular Biology of the Cell*, Vol.21, No.22, (November 15), pp. 3963-3972, ISSN 1059-1524
- Thompson, S.L. & Compton, D.A. (2008). Examining the link between chromosomal instability and aneuploidy in human cells. *Journal of Cell Biology*, Vol.180, No.4, (February 25), pp. 665-672, ISSN 0021-9525

- Thompson, S.L., Bakhoun, S.F., & Compton, D.A. (2010). Mechanisms of chromosomal instability. *Current Biology*, Vol.20, No.6, (March 23), pp. R285-R295, ISSN 0960-9822
- Tokuyama, Y., Horn, H.F., Kawamura, K., Tarapore, P., & Fukasawa, K. (2001). Specific phosphorylation of nucleophosmin on Thr(199) by cyclin-dependent kinase 2-cyclin E and its role in centrosome duplication. *Journal of Biological Chemistry*, Vol.276, No.24, (June 15), pp. 21529-21537, ISSN 0021-9258
- Tritarelli, A., Oricchio, E., Ciciarello, M., et al. (2004). p53 localization at centrosomes during mitosis and postmitotic checkpoint are ATM-dependent and require serine 15 phosphorylation. *Molecular Biology of the Cell*, Vol.15, No.8, (August), pp. 3751-3757, ISSN 1059-1524
- Turner, J.G. & Sullivan, D.M. (2008). CRM1-mediated nuclear export of proteins and drug resistance in cancer. *Current Medicinal Chemistry*, Vol.15, No.26, pp. 2648-2655, ISSN 0929-8673
- Tutt, A., Gabriel, A., Bertwistle, D., et al. (1999). Absence of Brca2 causes genome instability by chromosome breakage and loss associated with centrosome amplification. *Current Biology*, Vol.9, No.19, (October 7), pp. 1107-1110, ISSN 0960-9822
- Venkitaraman, A.R. (2002). Cancer susceptibility and the functions of BRCA1 and BRCA2. *Cell*, Vol.108, No.2, (January 25), pp. 171-182, ISSN 0092-8674
- Vorobjev, I.A. & Nadezhkina, E.S. (1987). The centrosome and its role in the organization of microtubules. *International Review of Cytology-A Survey of Cell Biology*, Vol.106, pp. 227-293, ISSN 0074-7696
- Wadhwa, R., Takano, S., Kaur, K., et al. (2006). Upregulation of mortalin/mthsp70/Grp75 contributes to human carcinogenesis. *International Journal of Cancer*, Vol.118, No.12, (June 15), pp. 2973-2980, ISSN 0020-7136
- Wang, W., Budhu, A., Forgues, M., & Wang, X.W. (2005). Temporal and spatial control of nucleophosmin by the Ran-Crm1 complex in centrosome duplication. *Nature Cell Biology*, Vol.7, No.8, (August), pp. 823-830, ISSN 1465-7392
- Weaver, B.A., Silk, A.D., Montagna, C., Verdier-Pinard, P., & Cleveland, D.W. (2007). Aneuploidy acts both oncogenically and as a tumor suppressor. *Cancer Cell*, Vol.11, No.1, (January), pp. 25-36, ISSN 1535-6108
- Weaver, B.A. & Cleveland, D.W. (2008). The aneuploidy paradox in cell growth and tumorigenesis. *Cancer Cell*, Vol.14, No.6, (December 9), pp. 431-433, ISSN 1535-6108
- Xu, X., Weaver, Z., Linke, S.P., et al. (1999). Centrosome amplification and a defective G2-M cell cycle checkpoint induce genetic instability in BRCA1 exon 11 isoform-deficient cells. *Molecular Cell*, Vol.3, No.3, (March), pp. 389-395, ISSN 1097-2765
- Zhang, X., Chen, Q., Feng, J., et al. (2009). Sequential phosphorylation of Nedd1 by Cdk1 and Plk1 is required for targeting of the gammaTuRC to the centrosome. *Journal of Cell Science*, Vol.122, No.13, (July 1), pp. 2240-2251, ISSN 0021-9533
- Zhou, H., Kuang, J., Zhong, L., et al. (1998). Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. *Nature Genetics*, Vol.20, No.2, (October), pp. 189-193, ISSN 1061-4036
- Zyss, D. & Gergely, F. (2009). Centrosome function in cancer: guilty or innocent? *Trends in Cell Biology*, Vol.19, No.7, (July), pp. 334-346, ISSN 0962-8924

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