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Corresponding Author: Mijung Kwon

Authors: Mijung Kwon[1,2,*], Soohyun Song[1,2], Surim Jung[1,2]

Institution: [1]Department of Life Science and [2]Research Center for Cellular Homeostasis, Ewha Womans University, Seoul 03760, Korea,

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Expanding Roles of Centrosome Abnormalities in Cancers

Soohyun Song[1,2#], Surim Jung[1,2#] and Mijung Kwon [1, 2*]

1 Department of Life Science, Ewha Womans University, Seoul 03760, Korea

2 Research Center for Cellular Homeostasis, Ewha Womans University, Seoul 03760, Korea

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***Correspondence to:** Mijung Kwon (mjkwon@ewha.ac.kr), Tel: +82-2-3277-4909, Fax: +82-2-3277-2385

[#]These authors contributed equally to this work.

ABSTRACT

Centrosome abnormalities are hallmarks of human cancers. Structural and numerical centrosome abnormalities correlate with tumor aggressiveness and poor prognosis, implicating that centrosome abnormalities could be a cause of tumorigenesis. Since Boveri made his pioneering recognition of the potential causal link between centrosome abnormalities and cancer more than a century ago, there has been significant progress in the field. Here, we review recent advances in the understanding of the causes and consequences of centrosome abnormalities and their connection to cancers. Centrosome abnormalities can drive the initiation and progression of cancers in multiple ways. For example, they can generate chromosome instability through abnormal mitosis, accelerating cancer genome evolution. Remarkably, it is becoming clear that the mechanisms by which centrosome abnormalities promote several steps of tumorigenesis are far beyond what Boveri had initially envisioned. We highlight various cancer-promoting mechanisms exerted by cells with centrosome abnormalities and how these cells possessing oncogenic potential can be monitored.

INTRODUCTION

The centrosome, the major microtubule organizing center (MTOC) in animal cells, plays critical roles in controlling various cellular processes, including cell shape, cell polarity, and mitosis (1-3). It is composed of a pair of centrioles embedded in an electron-dense amorphous protein matrix called the pericentriolar material (PCM), which is required for microtubule nucleation. Centrioles duplicate once per cell cycle during the S phase in a manner similar to DNA replication. This tight control of centrosome numbers allows normal cells to enter mitosis with two centrosomes, ensuring bipolar spindle formation, which leads to two daughter cells, each inheriting one centrosome in the interphase.

Deviations in any of these events may lead to centrosome anomalies that are linked to several diseases. Notably, centrosome aberrations are hallmarks of human cancers and are commonly found in many solid and hematological cancers (4-8). The link between centrosome aberrations and cancer was first proposed in the late nineteenth century. Hansemann and Galeotti observed abnormal mitotic figures as a signature of pathological mitosis in cancers (9, 10). Boveri who studied the cell divisions in cells with extra centrosomes recognized that aneuploid progenies are generated from multipolar mitosis, leading to the proposal that abnormal mitosis from centrosome aberrations can promote tumorigenesis (11). However, for a long time, it was uncertain if centrosome aberrations could have a causal role in tumorigenesis. Over the recent decades, a growing body of evidence has revealed that centrosome abnormalities contribute to different steps of tumorigenesis. The tumor promoting roles of centrosome aberrations are more multifaceted than what Boveri had initially envisioned. In this review, we will summarize centrosome defects in cancers and highlight recent advances in the understanding of mechanisms by which they promote different steps of cancer progression.

CENTROSOME ABERRATIONS IN CANCERS

Centrosome aberrations are commonly found in various human cancers, including cultured cancer cells and clinical specimens (4-8). Centrosome defects are largely categorized into numerical and structural alterations (4, 12). Numerical aberrations of centrosomes refer to centrosome amplification, which is characterized by the presence of extra centrioles, and they are the most frequently reported centrosome defects in cancers. An increased number of centrosomes is frequently associated with extensive karyotypic aberrations and poor patient outcomes in human cancers (5, 13). Structural abnormalities are detected as altered centrosome size or shape due to changes in the amount or composition of the PCM (14). In cancer cells or specimens, an enlarged centrosome labeled by a PCM marker likely indicates an increased amount of PCM and thus can be interpreted as structural centrosome aberrations. However, enlarged PCM size observed in cancer specimens may also be attributed to true structural defects or numerical centrosome defects due to extra centrioles that had coalesced into one big mitotic spindle pole. Thus, full characterization of the extent of numerical and structural centrosome abnormalities in cancer specimens would require careful analyses of high-resolution three-dimensional (3D) images labeled with both centriole and PCM markers.

Systematic efforts have been made to assess centrosome defects in numerous cancer cell lines and clinical specimens (6, 15-17). A comparative microscopy-based analysis of centrosome defects that examines NCI-60 panel of human cancer cell lines confirmed a widespread increase of centriole number in these cell lines (6). Moreover, a method has been designed to indirectly estimate centrosome amplification using the gene expression signature associated with centrosome amplification called CA20 (15). It is composed of twenty genes including centrosome structural proteins, which have been experimentally demonstrated to induce centrosome amplification. The correlation among CA20 upregulation, high CIN and

poor clinical outcome was confirmed by analyzing the CA20 transcriptomic signature across breast cancers (15) and in 9721 tumors from 32 cancer types available in The Cancer Genome Atlas (TCGA) (16). Further studies on direct experimental validation of CA20 or any equivalent gene expression signatures as a surrogate marker for centrosome amplification will facilitate its utility for diagnostic and prognostic markers in human cancers.

THE ORIGINS OF CENTROSOME AMPLIFICATION

How do extra centrosomes arise in cancer? Several mechanisms can account for centrosome amplification, including dysregulated centrosome duplication, prolonged arrest in the G2 phase, cytokinesis failure, and increased centriole length (4, 8, 12, 18). Dysregulation of the centrosome duplication cycle can lead to centriole overduplication, consequently generating supernumerary centrioles. This can be achieved by altered expression of centrosomal proteins if their normal expression levels are critical for limiting centrosome duplication to once per cell cycle. In particular, polo-like kinase 4 (PLK4) is a master regulator of centriole duplication (19, 20) and it is frequently upregulated in some tumors (21). Elevated levels of PLK4, due to either PLK4 overexpression or failure to normally degrade PLK4, lead to centrosome overduplication (22-28). Defects in cell cycle progression, such as prolonged arrest in the G2 phase, induce centrosome reduplication (29, 30); consistently, DNA damage can induce centrosome amplification by increasing the duration of the G2 phase (31, 32). Centrosome amplification can arise from cytokinesis failure that generates tetraploid cells with twice the normal centrosome number and DNA content (4, 8, 12, 18). Elongated centrioles can trigger centriole amplification (6), suggesting that structural centrosome defects can be linked to numerical defects, consistent with the observation that they often coexist in tumors (5, 6).

MECHANISMS BY WHICH EXTRA CENTROSOMES PROMOTE TUMORIGENESIS

Manipulation of centrosome number by controlled expression of PLK4 has proven to be invaluable in investigating the roles of centrosome amplification in tumorigenesis *in vivo*. The first compelling evidence that extra centrosomes can drive tumorigenesis was demonstrated in a fly model with PLK4 overexpression (23). When neuroblasts or epithelial cells harboring extra centrosomes were transplanted into host flies, they generated tumors (23, 33). Although the mechanisms contributing to tumors may differ between these tissues, disruption of normal asymmetric cell division was the major mechanism that drove tumorigenesis in the flies (Fig 1A) (23). This conclusion was supported by the observation that neuroblasts containing extra centrosomes displayed a minimal level of aneuploidy but showed defects in asymmetric cell division (23), which was shown to induce uncontrolled proliferation of neural stem cell population and tumor formation (34).

Tumor initiating roles of centrosome amplification seem clear in the fly model, but it is more complex and highly context-dependent in mammals. For example, spontaneous tumorigenesis was not observed in the mouse brain and epidermis, which was genetically engineered to induce centrosome amplification by PLK4 overexpression (35-37). However, additional p53 loss facilitated spontaneous tumor formation or hyperplasia in other mouse models (38, 39), suggesting that p53 could be a hurdle for centrosome amplification in contributing to tumorigenesis. Later, a study utilizing a single copy of transgene to induce a modest increase in PLK4 expression level demonstrated that centrosome amplification is sufficient to drive spontaneous tumor formation in mice *in vivo* (40). Tumors arising from this mouse model exhibited complex karyotypes that are frequently found in human cancers

(40). Based on these reports, it is now evident that centrosome amplification can sufficiently initiate tumorigenesis in mammals.

How do cells tolerate the presence of extra centrosomes? Cells harboring extra centrosomes, if not organized, have the devastating potential of undergoing multipolar divisions that can produce inviable progenies due to gross chromosome missegregation (8, 18, 41). However, cells bearing supernumerary centrosomes escape this detrimental division and form pseudo-bipolar spindles by organizing extra centrosomes into two groups through the centrosome clustering process (Fig 1B) (23, 42-44). Centrosome clustering is essential for the viability of cells containing extra centrosomes because multipolar divisions are generally lethal (43, 45). Moreover, the clustering of extra centrosomes can drive chromosome instability (CIN) by promoting a high incidence of incorrect merotelic chromosome attachments because bipolar anaphase spindles are assembled through transient multipolar spindle intermediates (45, 46). This attachment error from multiple centrosomes results in an increased frequency of lagging chromosomes, leading to anaphase chromosome missegregation (Fig 1B) (45, 46). Thus, mitotic centrosome clustering in cells with extra centrosomes can enable the survival of cells with ongoing genetic instability, promoting tumorigenesis. In addition, lagging chromosomes are often missegregated and subsequently encapsulated into micronuclei with their own nuclear envelope which is distinct from the main nucleus (Fig 1B). Due to defective nuclear envelope assembly, micronuclei are prone to rupture (47-49). With defective DNA replication and fragile nuclear envelope, chromosomes in micronuclei acquire DNA damage and undergo extensive chromosome rearrangements through chromothripsis (50, 51). Thus, extra centrosomes can serve as a driver in promoting both numerical and structural chromosomes aberrations that can contribute to tumorigenesis (Fig 1B).

Based on the results from the studies described above, multiple factors may account for the context-dependent nature of the centrosome amplification consequences. For example, inefficient centrosome clustering and functional p53 can compromise the proliferation of cells with extra centrosomes by inducing lethal multipolar divisions or cell cycle arrest, thus preventing tumor growth (35, 38, 39). Moreover, in addition to generating aneuploidy progenies as Boveri initially envisioned, cells with extra centrosomes appear to employ various mechanisms to promote tumorigenesis.

MECHANISMS BY WHICH CENTROSOME ABERRATIONS PROMOTE INVASION

As an MTOC, centrosomes play critical roles in the proper control of chromosome segregation and the maintenance of tissue architecture (1, 2). In addition to driving CIN by disrupting mitotic fidelity (45, 46, 52), numerical and structural aberrations of centrosomes can disrupt tissue architectures and promote the initial step of the invasion-metastasis cascade. Metastasis, the spread of a tumor from its site of origin to different parts of the body, is a major cause of the lethality of human cancer, as about 90% of cancer-associated deaths are caused by metastatic disease rather than primary tumors (53). Therefore, understanding the roles of abnormal centrosomes in various steps of tumorigenesis, especially during the metastatic local invasion, would be beneficial for the development of improved cancer prevention and treatment strategies. The following discussion focuses on various mechanisms through which abnormal centrosomes promote cellular invasion (Fig 1C).

The first experimental evidence came from a study showing that centrosome amplification can induce invasive protrusions in 3D cultures of mammary epithelial cells (Fig 1C-1) (54). In this study, PLK4 overexpression-mediated centrosome amplification led to the

formation of invasive structures that can degrade the surrounding extracellular matrix (ECM). Interestingly, cellular invasion does not appear to be caused by aneuploidy, but it is mediated by increased microtubule nucleation resulting from centrosome amplification which leads to the activation of the small GTPase Rac1 (54). Increased Rac1 activity has been observed in many advanced human cancers and is known to promote invasion and metastasis through a variety of mechanisms, including activation of actin polymerization and disruption of cell-cell adhesion (55, 56). Consistently, cells with extra centrosomes showed disruption of E-cadherin-mediated cell junction due to increased Rac1 activity (54). Although the exact mechanisms underlying Rac1 activation by centrosome amplification remain unclear, these findings suggest that centrosome amplification can promote cellular invasion by altering the organization and dynamics of interphase microtubules.

In addition, cells with extra centrosomes can promote the invasion of adjacent cells by secretion of pro-invasive factors (Fig 1C-2) (57). This non-cell autonomous mechanism was discovered by experiments utilizing the conditioned media from cells harboring extra centrosomes. When it was added to the recipient cells containing normal centrosome numbers, the conditioned media promoted paracrine invasion in a 3D culture model. Multiple cytokines and chemokines were released by cells harboring extra centrosomes, including IL-8, ANGPTL4, and GDF-15, prominent factors implicated in cancer invasion. The altered secretion by centrosome amplification termed as the extra centrosomes-associated secretory phenotype (ECASP) did not depend on Rac1 activity but was partly regulated by increased reactive oxygen species (ROS) in cells with extra centrosomes (57). While the exact molecular mechanisms by which ROS triggers ECASP remain unclear, these results suggest that elevated levels of ROS can promote non-cell autonomous invasion through ECASP.

Furthermore, small extracellular vesicles (EVs) secreted by cells harboring centrosome amplification have recently been reported to promote the invasion of pancreatic

ductal adenocarcinoma (PDAC) by activating pancreatic stellate cells (PSCs) (Fig 1C-2) (58). EVs are important mediators responsible for communication between tumor cells and stromal cells, playing critical roles in both primary tumorigenesis and metastasis (59). Depending on their size and origin, EVs are broadly classified into microvesicles (large EVs) that are formed by the budding of the plasma membrane, and exosomes (small EVs) that are generated through the fusion of the multivesicular bodies with the plasma membrane (60). Interestingly, centrosome amplification led to increased secretion of exosomes (small EVs) but not microvesicles (large EVs) in PDAC, and this altered secretion was due to lysosomal dysfunction resulting from ROS in these cells (58). Moreover, small EVs secreted by cells with extra centrosomes promoted PDAC invasion by activating PSCs indirectly, suggesting that cancer cells with extra centrosomes can alter the microenvironment of tumors, consequently promoting cancer invasion (58).

In addition to centrosome amplification, structural centrosome defects have been shown to induce invasive phenotypes (Fig 1C-3, 4) (61, 62). To mimic structural centrosome aberrations observed in cancer, the PCM component ninein-like protein (NLP) has been experimentally manipulated for overexpression because NLP overexpression is commonly observed in human cancers (63, 64) and it induces spontaneous tumor in transgenic mice (65). Indeed, NLP overexpression in 3D culture models showed non-cell autonomous dissemination of mitotic cells, displaying budding phenotype from epithelia (Fig 1C-3) (61). This epithelial budding appears to occur selectively in mitotic cells containing normal centrosomes that coexist within the epithelia. This is because cells overexpressing NLP displayed weakened E-cadherin-mediated cell adherence junctions due to increased microtubule nucleation. In addition, these cells were generally stiffer than the neighboring cells with normal centrosome structures. Together, these conditions may set heterogeneously tensioned mosaic epithelia where a few soft mitotic cells containing normal centrosomes are

selectively disseminated from stiffer epithelia. Consequently, these disseminated dividing cells were mostly viable and thus may serve as potential metastatic cancer cells (61).

Structural centrosome abnormalities can also promote basal extrusion of damaged cells, thus contributing to invasion (Fig 1C-4) (62). To maintain epithelial homeostasis and architecture, it is important to properly discard damaged cells by extruding them into the apical luminal cavity (66). A reversal in cell extrusion directionality from apical to basal has been observed in cancers that are associated with several oncogenic mutations (67, 68). Interestingly, similar to oncogenic mutations found in K-Ras or APC, structural centrosome abnormalities induced by overexpression of either NLP or CEP131 promoted basal cell extrusion, leading to the dissemination of potentially metastatic cells (62).

Collectively, research in the past years revealed that numerical and structural centrosome aberrations promote the initial step of the invasion-metastasis cascade. Moreover, the non-cell autonomous effects of abnormal centrosomes highlight the fact that small populations of cells with centrosomes aberrations in tumor mass can alter their microenvironment and that of the surrounding tumor cells. However, further studies to uncover multifaceted mechanisms and their cooperation during the invasion-metastasis cascade are warranted.

LIMITING THE PROLIFERATION OF CELLS WITH TOO MANY OR NO CENTROSOMES

While numerical and structural centrosome defects have oncogenic potential, protective mechanisms may suppress the proliferation of cells with centrosome defects, especially in mammals. In cells with decreased or increased number of centrosomes, p53 can

play a common and critical role in preventing the continued proliferation of these cells through distinct upstream signaling pathways (Fig 2).

Halting cell proliferation in response to centrosome loss

Multiple studies have shown that centrosome loss can activate p53-dependent cell cycle arrest or apoptosis (69-71), suggesting that the p53 pathway acts as a barrier to the continued proliferation of cells with centrosome loss.

To identify signaling components that are responsible for blocking cell proliferation upon centrosome loss, three studies performed genome-wide CRISPR/Cas9 knockout screens using cells where centrosome loss was induced by PLK4 inhibition (72-74). These studies commonly identified a USP28-53BP1-p53 signaling axis also termed a mitotic surveillance pathway, that is essential for cell cycle arrest in response to centrosome loss (Fig 2, left) (72-75). In support of its role, knockouts of each component of a USP28-53BP1-p53 signaling axis allowed the continuous proliferation of cells that had lost centrosomes (72-74). Despite its well-known function in DNA damage response, the activation of the USP28-53BP1-p53 mitotic surveillance pathway triggered by centrosome loss does not seem to involve DNA damage (73-75), raising the question of how cells sense centrosome loss. Several observations are consistent with the idea that centrosome loss may be indirectly sensed as an increased duration of mitosis, triggering cell cycle arrest. First, centrosome loss has been shown to slow down spindle assembly and increase the mitotic duration (prolonged mitosis) (70-73). Second, prolonged prometaphase induced by microtubule depolymerization also led to a p53-dependent cell cycle arrest (76), suggesting that signaling that responds to centrosome loss and prolonged mitosis are shared. Third, this idea was further confirmed by

the observation that the same components of the USP28-53BP1-p53 signaling axis are also required for cell cycle arrest induced by prolonged mitosis (72-74).

While the indirect mechanism described above is a likely explanation of how cells sense centrosome loss as a perturbed and prolonged mitosis to suppress their growth, a recent study proposes an alternative mechanism where centrosomal p53 may act as a sensor for centrosome loss by monitoring centrosome integrity (77). This study proposes that centrosome loss disrupts the normal localization of p53 to mitotic centrosomes, resulting in the formation of ectopic fragmented foci that recruits 53BP1 to suppress cell growth in an ATM kinase-dependent manner (77). Thus, further work would be required to better define the detailed mechanisms that limit the growth of potentially dangerous cells with increased chances of making mitotic errors and the role of the mitotic surveillance pathway *in vivo*.

Halting cell proliferation in response to centrosome amplification

Likewise, centrosome amplification has also been shown to restrict cell proliferation through p53 stabilization (78). However, evidence suggests that different pathways, independent of USP28 or 53BP1, are involved (Fig 2, right) (73). The first evidence came from the finding that the kinase LATS2-mediated Hippo pathway activates p53-mediated cell cycle arrest in tetraploid cells with extra centrosomes and diploid cells with centrosome amplification (79). Depletion of LATS2 did not restore cell proliferation in cells that have lost centrosomes, suggesting that LATS2 is not required for centrosome loss surveillance (71, 73). Thus, it is unlikely that the upstream signaling components that respond to centrosome loss and centrosome amplification are shared (75).

Another pathway that is regulated by the PIDDosome was shown to induce p53 stabilization and cell cycle arrest in tetraploid cells with extra centrosomes and cells with

centrosome amplification (Fig 2, right) (80). Centrosome amplification was sufficient to trigger PIDDosome activation. Moreover, PIDDosome-dependent caspase-2 activation was induced upon the presence of extra mother centrioles, implicating a direct pathway that depends on the extra mature centrosomes (80). The mechanisms mediating the localization of the PIDDosome component PIDD1 to mother centrioles and concurrence of PIDDosome-dependent caspase-2 activation have been recently uncovered (81, 82). In cells with supernumerary centrosomes, PIDD1 is recruited to extra mother centrioles through the centriolar distal appendage protein ANKRD26, mediating PIDDosome activation (81, 82). In these cells, knockout of ANKRD26, a PIDD1 recruitment factor to distal appendages of mother centrioles, abrogated caspase-2 activation and p21 upregulation, leading to improvement of cell proliferation (81).

Molecular pathways by which decreased or increased number of centrosomes trigger p53-mediated cell cycle arrest have been uncovered. If cells have functional p53, activation of these pathways could be a hurdle to the continued growth of cells harboring numerical centrosome defects. In this context, cancer cells that continuously proliferate despite the presence of numerical centrosome defects might develop adaptation to have defective mitotic or extra centrosome-surveillance pathways described above. Thus, the loss of some pathway components described above may serve as useful biomarkers for defining cancers with specific centrosome defects for better diagnosis and treatments.

CONCLUSIONS AND PERSPECTIVES

It is becoming clear that centrosome abnormalities have a profound impact on tumor biology. For the past decades, tremendous progress has been made in uncovering the nature

of centrosome defects and the complex context-dependent consequences of centrosome abnormalities in cancers, revealing the multifaceted role that they play in the initiation and progression of cancers.

Many important questions remain to be elucidated with further research. Considering that the majority of the previous studies focused on the effects of centrosome amplification in cancers, a better understanding of the origins and consequences of structural centrosome defects would expand our mechanistic insight into tumorigenesis. While centrosome abnormalities can promote invasive phenotypes through various mechanisms, it will be interesting to explore their roles in the other steps of the invasion-metastasis cascade in appropriate animal models. In addition, the finding that cells that have lost centrosomes or have extra centrosomes can undergo cell cycle arrest has inspired intense efforts to identify pathways that could limit the proliferation of potentially dangerous cells with an increased propensity for genome instability. Interesting issues to be addressed in the future include whether the cells harboring numerical centrosome abnormalities require additional adaptation to promote tumorigenesis and what the long-term consequences of pathway activation are in an *in vivo* context. From a cancer therapeutic perspective, because centrosome amplification is a major driver of CIN, targeting cells with extra centrosomes might be an effective CIN-directed anti-cancer therapeutic strategy. Furthermore, development of better biomarkers and a gene signature that predicts centrosome amplification will be invaluable in identifying appropriate patients for improved cancer diagnosis and treatment.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

FIGURE LEGENDS

Figure 1. Mechanisms by which centrosome aberrations promote tumor progression

(A) Centrosome amplification impairs normal asymmetric division, leading to expansion of stem cell population and tissue outgrowth. (Left) Asymmetric division of neuroblasts in *Drosophila melanogaster* determines the pools of differentiated neurons and dividing stem cells, maintaining tissue homeostasis. This process depends on asymmetric maturation of two centrosomes (2C) and their interaction with the cell cortex, segregating different cell fate determinants into each of two daughter cells. (Right) In cells with centrosome amplification (>2C, over 2 centrosomes), asymmetric cell division is disrupted by centrosome clustering, resulting in symmetric cell division. Subsequently, symmetric division leads to uncontrolled proliferation of self-renewing neural stem cells and tissue overgrowth. **(B)** Centrosome amplification induces chromosomal instability (CIN), leading to numerical and structural aberrations of chromosomes frequently found in cancers. Mitotic centrosome clustering leads to an elevated rate of chromosome segregation errors due to incorrect merotelic attachment (not shown), generating lagging chromosomes. Unequal segregation of lagging chromosomes generates aneuploidy, producing progenies with chromosome gain (e.g. oncogenes) or loss

(e.g. tumor suppressor genes). In addition, lagging chromosome and subsequent formation of micronucleus can drive chromothripsis, localized and extensive chromosome rearrangements through chromosome shattering and rejoining. **(C)** Centrosome aberrations promote invasive properties. Mechanisms by which centrosome amplification (left) or structural defects (right) induce invasive behaviors are categorized, according to cell autonomous (top) or non-cell autonomous (down) mode of regulation. (1) Centrosome amplification induces cell autonomous invasion through increased microtubule (MT) nucleation followed by the activation of small GTPase Rac1. (2) Cells with extra centrosomes induce non-cell autonomous invasion through increased secretion that are mediated by extra centrosome-associated secretory phenotype (ECASP) or small extracellular vesicles (small EVs). Both secretions are mediated by increased reactive oxygen species (ROS) resulting from centrosome amplification. (3) NLP overexpression-mediated structural aberrations of centrosomes facilitate mitotic cell budding in non-cell autonomous manner. Within epithelia, cells expressing an elevated level of NLP is stiffer with weakened E-cadherin-mediated cell adherence junctions, squeezing out mitotic cells containing normal centrosomes to be disseminated. (4) Structural centrosome aberrations induced by overexpression of NLP or CEP131 lead to basal extrusion of damaged cells by mispositioning of contractile actomyosin ring.

Figure 2. Molecular pathways that limit the proliferation of cells with numerical centrosome aberrations

Distinct molecular pathways mediate cell cycle arrest or cell death in response to centrosome loss (left) or centrosome amplification (right). While stabilization of p53, a key mediator of cell cycle arrest and cell death, occurs in both conditions, upstream signaling pathways that regulate p53 differ in the condition of centrosome loss and amplification. (Left) Centrosome loss activates the USP28-53BP1-p53 mediated, mitotic surveillance pathway that is also activated by prolonged mitosis. [USP28, ubiquitin-specific protease 28 that interacts with 53BP1 (83); 53BP1, a p53 binding protein 1 (84)]. (Right) Centrosome amplification, on the other hand, activates the LATS2-mediated Hippo pathway or PIDDosome-mediated pathway. In the LATS2-mediated Hippo pathway, LATS2 binds and inhibits MDM2, an E3 ubiquitin ligase for degradation of p53, thus stabilizing p53 (85). In the PIDDosome-mediated pathway, PIDDosome is a protein complex composed of PIDD1 (protein with a death domain induced by p53), RAIDD (adaptor protein with a caspase-recruitment domain and death domain), and caspase-2 (86). The centriolar distal appendage protein ANKRD26 recruits PIDD1 to the distal appendage of mature centrioles, initiating the PIDDosome activation and the subsequent caspase-2 activation (enlarged box region). Consequently, activated caspase-2 or LATS2 suppresses the p53 inhibitor MDM2, leading to p53 stabilization (85, 87).

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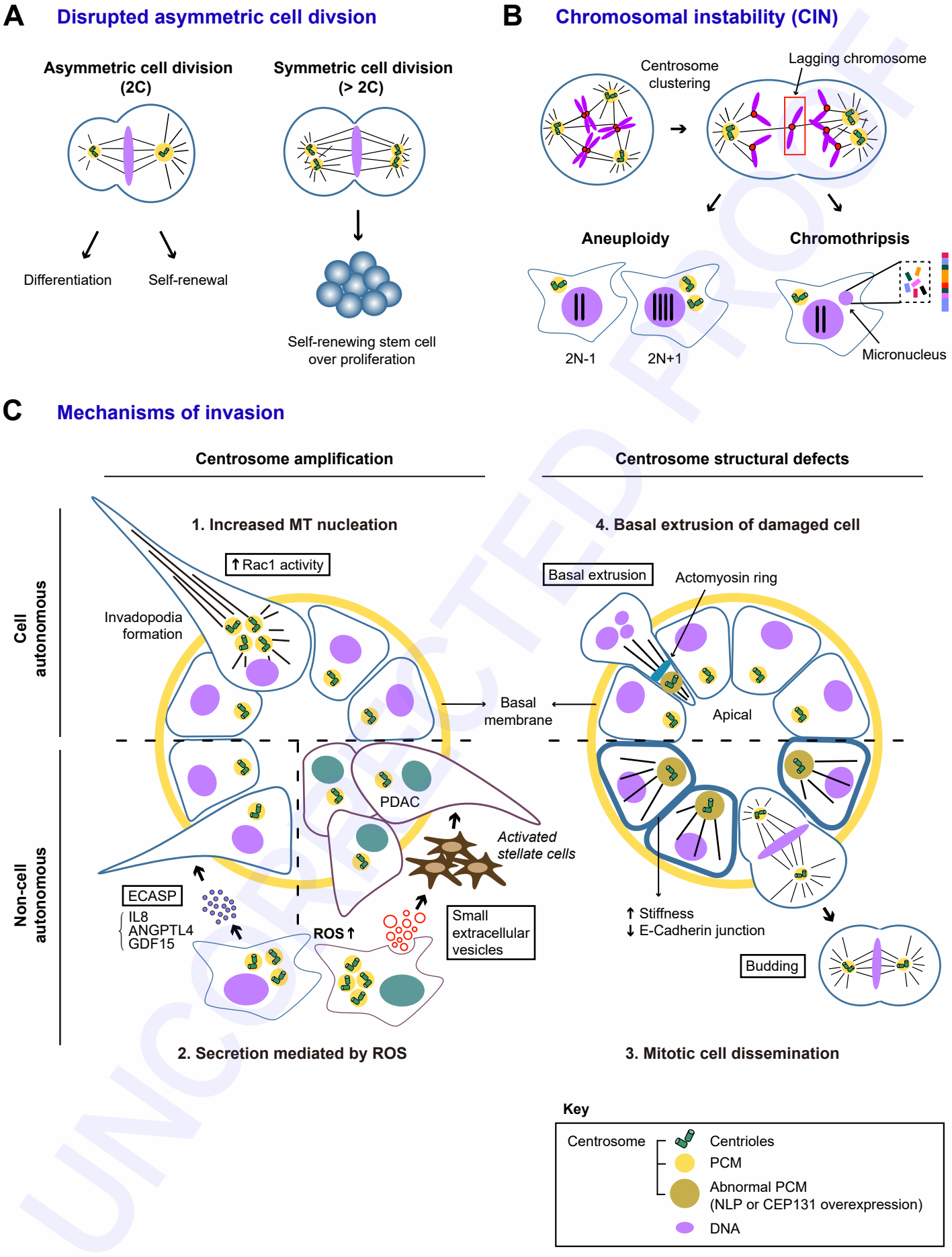

Figure 1

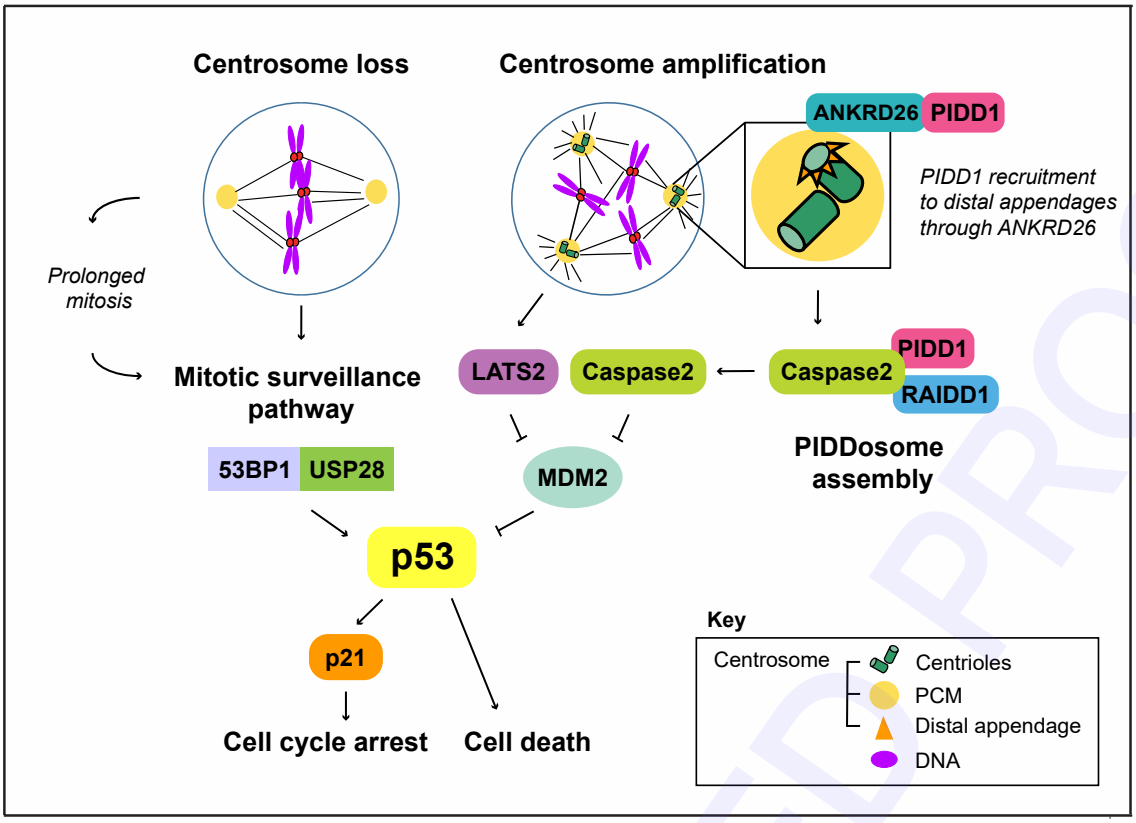

Figure 2