Centrosome instability: when good centrosomes go bad

John M. Ryniawec1 · Gregory C. Rogers1

Received: 5 June 2021 / Revised: 10 August 2021 / Accepted: 26 August 2021 / Published online: 2 September 2021
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2021

Abstract
The centrosome is a tiny cytoplasmic organelle that organizes and constructs massive molecular machines to coordinate diverse cellular processes. Due to its many roles during both interphase and mitosis, maintaining centrosome homeostasis is essential to normal health and development. Centrosome instability, divergence from normal centrosome number and structure, is a common pathognomonic cellular state tightly associated with cancers and other genetic diseases. As novel connections are investigated linking the centrosome to disease, it is critical to understand the breadth of centrosome functions to inspire discovery. In this review, we provide an introduction to normal centrosome function and highlight recent discoveries that link centrosome instability to specific disease states.

Keywords Centrosome · Centriole · Microtubule-organizing center · Pericentriolar material · Mitotic spindle · Microtubule

A historical perspective

Since the advent of cell theory by Schleiden and Schwann nearly 200 years ago, the idea of self-replicating biological units and, thus, the basic requirement for cell division, have captivated scientists. In 1887, advances in cytology allowed for the discovery of karyokinetical division—equal segregation of genomic material into two daughter cells—in mitotic nematode embryos by Theodor Boveri and in meiotic worm eggs by Edouardo Van Beneden (called pseudo-karyokinesis due to its reductional nature) [1–3]. Independently, but concurrently, they discovered that condensed chromosomes are aligned between a bipolar filamentous array and, subsequently, divided into two daughter cells. In his original study, Boveri discussed the organization of this astral array, defining the centrosome as the center of each pole. His findings led him to believe that the centrosome is "the true division organ of the cell, it mediates the nuclear and cellular division" [1]. Over the next 30 years, Boveri made several seminal discoveries regarding the centrosome and became the father of an enduring field of study that would expand well beyond cell division [3].

Although the centrosome is involved in numerous biological processes, most historical research focused on the role of the centrosome during cell division. In 1890, David von Hansemann observed cancer cells undergoing multipolar mitosis, as opposed to a typical bipolar mitosis [4, 5]. This discovery led Boveri to hypothesize that cells containing supernumerary centrosomes (more than two) would generate a multipolar spindle during mitosis [3, 5]. While performing his classic dispermy experiments, Boveri noted that sea urchin eggs fertilized by two sperm also produced multipolar spindles. In many animals, including sea urchins, eggs normally lack centrosomes but acquire one from the sperm upon fertilization. When two sperm enter an egg, the resultant zygote contains not only double the number of chromosomes but double the number of centrosomes as well. Embryos with an abnormally elevated number of centrosomes can then undergo a multipolar mitosis accompanied by unequal chromosome segregation [3, 5–7]. Together with his observations that dispermic zygotes had "malfunctions", Boveri postulated in 1914 that a supernumerary centrosome-induced multipolar mitosis can directly generate aneuploid daughter cells and, potentially, cancer [3, 5, 8]. Since then, generations of scientists have cultivated centrosome biology into a field of its own and now explore a myriad of questions from how cells control centrosome biogenesis to understanding centrosome function during normal development and its dysregulation in disease.
Centrosome number is governed by the centriole, the duplicating element at the core of the organelle [9]. The centriole was first described in 1900 by none other than Boveri [3, 10]. In 1895, he reported a prominent, densely stained granule at the center of the centrosome, but it was not until five years later that he described its duplicating nature and named it the centriole [3, 10, 11]. While observing dividing sea urchin embryos, Boveri reported the separation of centrosomes during the 2 cell stage, prior to the second cleavage event. Since he knew that sperm contributed only one centrosome during fertilization, he concluded that the centrosome needed to duplicate prior to each round of mitosis [10]. Modern studies have corroborated his interpretation, centrioles in fact duplicate once per cell cycle ensuring that cells have only two centrosomes as they enter mitosis. Each centrosome then organizes a single pole of the mitotic spindle to ensure that a bipolar structure is produced [9]. The need for duplication was obvious to Boveri, but not to others of his time [3]. Without duplication of centrosomes (or the genome), developing organisms would run out of materials essential for the execution of cellular divisions before they fully matured. His conviction to this idea carved his place as the father of the centrosome field, instead of his contemporaries. And although Boveri first described the cyclical nature of centrosome duplication in 1900, it was not until the modern age of molecular biology and genetic manipulation that we truly began to understand the mechanisms that underlie this cycle [1, 3, 9, 10].

The centriole itself is an important cellular organelle; not only does it control centrosome copy number, but centriole structure is critical for centrosome function and the assembly of other microtubule-based protein machines, like cilia (Fig. 1) [12]. The first transmission electron micrograph of the centriole was published in 1954, when Fawcett and Porter observed the basal bodies of cilia in multiciliated cells (although they did not identify these structures as centrioles, but rather as “basal corpuscles”) [13]. Therefore, the first centriole micrographs are commonly attributed to de Harven and Bernhard in 1956, when the authors characterized centrioles in the cells of newts, chicken, mice, rats, and human cancer tissues [14]. This study described the evolutionarily conserved barrel-shape of the centriole and established that the centriole is composed of microtubule bundles arranged in ninefold radial symmetry [13–15]. As electron microscopy techniques improved, so did our appreciation of the diversity of centriole structure. While most mammalian centrioles are made of triplet microtubule bundles, animals such as Caenorhabditis elegans and Drosophila melanogaster can produce centrioles with singlet and doublet microtubules [16]. Furthermore, surveys of different Drosophila tissues revealed diverse centriole architecture, even within an individual. Some Drosophila tissues have long centrioles composed of microtubule triplets, while others have short centrioles made of a mixture of microtubule doublets and singlets [17]. It is this tissue-specific structural diversity within an individual that highlights the complex nature
of centriole assembly. Indeed, this diversity reveals that centrioles are not constructed from a singular blueprint. Instead, the molecular mechanisms underlying centriole architecture must be plastic, responding to contextual cues to build the correct centriole for the cell’s needs.

The centrosome: a tiny organelle with big responsibilities

Nearly 140 years since the term ‘centrosome’ was used, we continue to discover new functions and find new ways that centrosomes contribute to development and homeostasis. No matter how many functions we identify, one fact remains true: the central role of the centrosome is to construct specialized microtubule-based assemblies. Centrosomes are the major microtubule-organizing center (MTOC) in most animal cells and are composed of a pair of centrioles surrounded by an organized proteinaceous shell called the pericentriolar material (PCM) [18]. The PCM meshwork essentially acts as a platform for docking γ-tubulin ring complexes, which facilitate microtubule polymerization [19]. Thus, centrosomes act as a microtubule hub to facilitate mitotic spindle assembly, generate specialized microtubule networks, and establish polarity within cells. Additionally, centrosomes can convert to basal bodies, whereby a centriole docks at the plasma membrane and grows a microtubule projection, called the axoneme that acts as the central structure of cilia and flagella. These specialized organelles generate cellular motility, extracellular flow, and sense the external environment [20, 21]. Below, we present an overview of centrosome functions.

Functions of the interphase centrosome

Although the most enigmatic function of the centrosome is construction of the mitotic spindle, the centrosome’s roles in interphase cells have become exceedingly evident (Fig. 2). In a stereotypical mammalian cell, a single centrosome is anchored near the nuclear envelope. This orients microtubules so that their plus (+) ends grow away from the centrosome and towards the cell’s periphery. The inherent polarity is used by cells to generate and maintain cellular polarity, organize the cytoplasm by positioning organelles, and traffic membranous and protein cargo towards or away from the nucleus. Other cell types, such as neurons and epithelial cells, rely heavily on the centrosome for

![Fig. 2](image-url)
their cellular morphology and specialized functions [22]. In these cells, centrosomes can generate microtubules which are reorganized within neuronal processes or arranged as parallel arrays along lateral epithelial surfaces [10]. Not surprisingly, Boveri hypothesized in 1887 that the centrosome is an enduring and permanent cellular organelle, not just a transient structure during mitosis [1, 3]. The variety of centrosome functions certainly validates his theory.

Due to its polarized nature, the interphase microtubule array created by the centrosome provides a roadmap for the directional movement of microtubule-based motor proteins throughout the cell [18, 22, 23]. Kinesin motor proteins that transport organelles and vesicles are plus (+) end directed and processive, meaning they are able to make long excursions along microtubules and towards the cell periphery (anterograde transport) [23]. Kinesins power the movement of a variety of intracellular cargo (including endosomal vesicles and lysosomes) through their interactions with cargo receptors (Gadkin:AP-1 or SKIP:Arl8, respectively) [23–25]. Conversely, cytoplasmic dynein motors move toward the minus (−) ends of microtubules and drive the retrograde transport of subcellular cargoes [26]. Since microtubule minus-ends are anchored at the centrosome, which is typically tethered to the nucleus, cytoplasmic dynein moves cargo towards the nucleus and maintains the Golgi apparatus’ perinuclear position [27].

One of the most striking examples of this biology is the trafficking of melanosomes—specialized vesicles containing the pigment protein melanin [23, 28]. Studies in Xenopus and zebrafish revealed that upon stimulation with cAMP-producing hormones, perinuclear melanosomes move towards the periphery of a melanophore cell [29, 30]. Conversely, reducing cAMP levels results in retrograde movement of melanosomes towards the centrosome [30]. Subsequent in vivo and in vitro studies confirmed that changing the balance of motor activity regulates the directional transport along centrosome-derived microtubule arrays [31, 32]. These studies exemplify how cells can dynamically change their use of centrosome-derived microtubule arrays to respond to diverse stimuli. Importantly, the trafficking of melanosomes allows pigment producing cells to protect underlying skin stem cells from UV damage [28].

To establish this cellular roadmap, the centrosome is linked to the nuclear envelope which allows it to generate a polarized microtubule array that extends towards the cellular periphery. Disrupting this linkage can result in improper nuclear positioning, chromosome segregation defects, and abnormal cellular morphology [33–35]. Nuclear tethering is a microtubule-dependent process which, in turn, helps position the nucleus [36–38]. While there are multiple mechanisms in mammalian cells that link centrosomal microtubules to the nuclear periphery [39], conserved mechanisms of centrosome-nuclear tethering rely on cytoplasmic dynein anchored on the outer nuclear membrane [40].

First described in C. elegans, cytoplasmic dynein is tethered to the nucleus through an interaction with the LINC (Linker of Nucleoskeleton and Cytoskeleton) complex [34]. As its name implies, the LINC complex is a molecular bridge across the nuclear membrane that mechanically links the nuclear lamina, chromosomes, and chromatin-binding proteins in the nucleus with the cytoplasmic cytoskeleton (actin, microtubules, and intermediate filaments) [41–43]. In C. elegans, the cytoplasmic LINC protein ZYG-12, which is embedded in the outer nuclear membrane, interacts with the dynein light chain DLI-1 to tether cytoplasmic dynein to the nucleus [35, 44]. Nuclear-anchored dynein then pulls on centrosomal microtubules and positions the centrosome near the nucleus [43].

The polarity provided by the interphase microtubule array also assists in building the trans-Golgi network [27, 46–48]. During mitosis, the Golgi apparatus disassembles into vesicles and must reform at the start of the next cell cycle. Although the Golgi apparatus can independently form cisternae, centrosomal microtubules are required to stack the cisternae into the ribbons that are stereotypical of this large organelle. Fascinatingly, like the centrosome, the Golgi apparatus also acts as a MTOC capable of nucleating its own population of microtubules, mediated by CLASPs and AKAP350 [49, 50]. Cross-linking of Golgi-derived microtubules with centrosomal microtubules assists in the membrane fusion necessary to organize the Golgi ribbons into stacks [46, 51]. Moreover, these interactions establish a directional nucleus-centrosome-Golgi axis that creates a higher order polarity within the cell. Notably, the axis points toward the leading edge of migrating cells and, when disrupted, interferes with directional cell migration [27, 48, 51–54]. Furthermore, the nucleus-centrosome-Golgi axis points towards lumens in tissues and cultured organoids, allowing cells to make use of this established apico-basal polarity for trafficking events [47, 53]. Meaning, without the ability to establish a nucleus-centrosome-Golgi axis, cells have reduced secretion and exocytosis [51]. Surprisingly, recent evidence suggests that Golgi organization by centrosomal MTOCs appears to be restricted to G1-phase and early mitosis in cultured cells [54]. The cell cycle restriction of the nucleus-centrosome-Golgi axis may suggest a stronger role in trafficking within non-proliferating, differentiated cell types than in tissue culture cells.

Specialized cell-types further co-opt centrosome-associated polarity cues to direct polarized secretion [47]. For example, upon antigen stimulation, lymphocytes quickly repolarize their centrosome-Golgi axis toward the developing immunological synapse—the site where a lymphocyte and antigen-presenting cell makes contact [55]. This is accomplished by dynein anchored at the immunological
synapse which grabs centrosomal microtubules and generates a pulling force towards this site, thereby repositioning the centrosome [56, 57]. Upon arriving at the immunological synapse, the mother centriole transiently docks with the plasma membrane helping to reposition the microtubule cytoskeleton [58, 59]. The newly generated cytoskeletal hub helps to strengthen the synapse and ensures the directed effector functions of the lymphocyte. T-cells unable to polarize their centrosome to the immunological synapse cannot sustain downstream signaling and, as a result, are unable to continue cytokine production, cytolytic killing, or B cell co-stimulation [56, 60, 61].

Developing neurons, another specialized cell-type, use centrosome-derived microtubules to direct axon extension [47, 62]. Dissociated neurons cultured in vitro project multiple neurites before selecting one to elongate and become an axon [63]. Early studies showed that the centrosome and Golgi polarize towards the selected axon prior to its extension [64]. Additionally, centrosome-derived microtubules are essential for the elongation process [65, 66]. Although it cannot be ruled out that the centrosome is merely responding to polarity cues, some have suggested that the positioning of the centrosome selects the axon. Further, centrosome polarization is associated with neuronal migration in the developing cortex [62]. However, the necessity for the centrosome in this process has not been experimentally dissociated from its role in neuronal delamination during mitosis, which may be a prerequisite step for neuronal migration.

Finally, the centriole plays another role in interphase cells by acting as the basal body for cilia and flagella. Cilia and flagella are organelles that protrude from the main cell body and are composed of a long microtubule-based axoneme sheathed in plasma membrane [20, 21]. Flagella are commonly used to propel cells, such as sperm. Cilia, on the other hand, come in two varieties: motile and non-motile. In *Tetrahymena*, motile cilia line the outside of the cell and coordinate their beating to promote cell locomotion. In mammals, motile cilia are commonly seen on multi-ciliated cells and are known to generate fluid flow outside of the cell, such as oviduct epithelia and cell in the airways of the lung that move mucus [21].

Primary cilia, on the other hand, are non-motile cilia that act much like antennas for the cell. They receive signals from extracellular cues, both chemical and mechanical (such as extracellular flow) and stimulate many cellular responses [67]. The most well-known signaling axis coordinated by primary cilia is Hedgehog signaling, which interprets developmental cues to trigger differentiation or entry into the cell cycle [67–69]. In the absence of a Hedgehog signaling molecule, signaling receptors are excluded from the cilium. However, Hedgehog stimulation triggers translocation of receptors and downstream signaling molecules to promote Gli transcription factor activation [70–74]. Depending on the context, Hedgehog signaling can promote cell survival, differentiation, or proliferation. Proper regulation of this signaling axis is essential for organogenesis and neural patterning [47]. Mutations in cilia proteins, both those that localize to the basal body and along the axoneme, cause a variety of diseases known collectively as ciliopathies and include polycystic kidney disease, polydactyly, and left–right patterning defects [75].

Generally, primary cilia are features of G0/G1-phase cells in mammals and are assembled after cells exit mitosis [67]. In cells with a single cilium, the older centriole of the pair (the ‘mother’) docks at the plasma membrane to initiate ciliogenesis [20]. From there, specialized vesicles are recruited to a structure on the centriole, called the distal appendages (Fig. 1), which promote remodeling of the plasma membrane to accommodate the morphological changes necessary for cilium extension [76, 77]. Microtubules then begin to grow off of the distal end of the cilium, now referred to as the basal body, pushing the membrane outwards and filling the center of the cilium. Growth of the microtubule extension, called the axoneme, is facilitated by cilia-specific proteins allowing the cilium to preserve its identity and, when the cilium disassembles in S/G2-phase, the centriole is retained [78]. Since ciliary disassembly seems to be a prerequisite prior to mitosis, the centriole that was formerly a basal body is available to organize the centrosome during the next mitosis [67]. The centriole plays a similar role in terminally differentiated multiciliated cells as well, although these cells have specialized centriole assembly pathways that allow for the rapid generation of hundreds of new centrioles that are competent to form basal bodies [79]. Since centrioles spawn cilia, not surprisingly, the loss of centrioles can cause ciliopathies and associated phenotypes [75]. Since the focus of this review is on centrosome-specific pathologies, ciliopathies are not discussed in depth here (reviewed in 67, 80).

While the centrosome is best known for its mitotic role in spindle assembly, the interphase centrosome plays diverse roles, particularly in specialized cell-types [18]. The multitude of functions for centrosomes seem to rely on strict adherence to the proper structure of the centrosome and centrosome. As such, centrosome-associated mutations commonly alter interphase-specific centrosome functions and many of the cell-types affected by these mutations have adapted the centriole to perform specialized tasks. Therefore, identifying the etiology and pathogenesis of these diseases may reveal cell-type specific requirements for centriole structures [81].
Functions of the mitotic centrosome

During mitosis, centrosomes assist in the construction of the mitotic spindle, a microtubule-based protein machine designed to segregate chromosomes. The spindle is a bipolar array of microtubules that interact with a plethora of motor proteins, kinesins and cytoplasmic dynein, which help power the apparatus [82–84]. Coordination of mitotic spindle function is conducted by the centrosome, without which, shape, size, timing, and the fidelity of chromosome segregation all suffer [18].

Cells normally enter mitosis with only two centrosomes and each centrosome has the capacity to organize a distinct pole of the spindle. During the beginning of mitosis, the two centrosomes separate towards opposite sides of the cell and guide assembly of a bipolar, fusiform-shaped spindle with microtubule plus-ends that partially overlap at the spindle equator and astral microtubules that interact with the cell cortex (Fig. 3). Due to the back-to-back geometry of the joined sister chromatid pair, kinetochores face opposite centrosomes and, consequently, this orientation facilitates proper amphitelic kinetochore-microtubule attachment [85]. Bioriented sister chromatids that experience an appropriate amount tension across their centromeres eventually line-up on the spindle equator and form the metaphase plate in an elaborate tug-of-war (an event known as ‘congression’).

Ultimately, sister chromatids disjoin and segregate to opposite spindle poles and into newly formed daughter cells which also inherit a single centrosome. Given the ability to organize spindle poles, it is critical that cells contain precisely two centrosomes during mitosis [86]. If cells contain too many or too few centrosomes, the number of spindle poles can change, compromising the fidelity of cell division [87].

Prior to entering mitosis, the two recently duplicated centrosomes reside near one another, creating a single microtubule organizing center during interphase (Fig. 2). However, centrosomes must move away from each other and towards opposite ends of the cell to generate a bipolar spindle during mitosis [88]. This feat is primarily accomplished by the kinesin-5 motor Eg5, a bipolar, plus-end directed homotramer with two motor domains at either end of a central rod [89, 90]. Since each centrosome nucleates microtubules with their plus-ends pointing away, kinesin-5 tetramers are optimally designed to crosslink the overlapping microtubules between them. Eg5 motor activity is slow and non-processive but, working collectively, a population of these motors can slide antiparallel microtubules apart and push their attached centrosomes away from one another [91, 92]. The importance of Eg5 can be seen when cells are treated with the kinesin-5-specific chemical-inhibitor, monastrol, which effectively blocks centrosome separation causing formation of a monopolar spindle and mitotic arrest [93].

Fig. 3 The mitotic spindle is composed of different populations of microtubules. Many, but not all, of these microtubules are generated by centrosomes which are attached to the spindle poles. Spindle microtubule minus-ends are either embedded in the pericentriolar material (PCM) or bundled together and form tapered spindle poles. Spindle microtubules are also randomly nucleated in the vicinity of chromosomes as well as produced laterally along pre-existing microtubules by the augmin complex. As their name implies, kinetochore microtubule plus-ends bind kinetochores in an ‘end-on’ attachment, which promotes their stability by suppressing plus-end disassembly.

Less stable microtubule populations include interpolar microtubules with partially overlapping plus-ends that reside in the spindle midzone. These anti-parallel regions are crosslinked by plus-end directed kinesin-5 motors that effectively push spindle microtubules apart and contribute to spindle shape. Non-kinetochore microtubules also interact with chromosome arms. Astral microtubules grow away from chromosomes and towards the cell cortex where they are tethered by cytoplasmic dynein and other microtubule-binding proteins. Astral microtubules allow motors at the cell cortex to produce force and orient or rotate the spindle within the cell.
In preparation for mitosis, centrosomes also increase their microtubule nucleation capacity by expanding the size of their pericentriolar material (PCM), a process known as centrosome maturation [18]. The expanding PCM is built around an existing scaffold that coats the outside of the centriole barrel [19]. Activation of the mitotic kinase Polo (Polo-like kinase/Plk1 in humans) at the centrosome drives maturation [94, 95]. Polo targets the centrosome scaffold and its kinase activity drives a positive feedback loop that results in rapid PCM expansion [95–100]. Increased PCM generates more binding sites for the microtubule nucleation machinery, including XMAP215, TPX-2, and NEDD1, which directly stabilize microtubules and recruit γ-tubulin ring complexes [101–105]. Together, this dramatically increases the microtubule-nucleating capacity of the centrosome during mitosis.

The high microtubule density in the mitotic spindle, partially attributed to centrosome maturation, is used to generate the forces that power mitosis. Microtubules attach to chromosomal kinetochores to align chromosomes between the two centrosomes during metaphase. Cells rely on the inherent dynamic instability of microtubules, along with assistance from molecular motors, to push and pull the chromosomes into alignment [106–108]. Kinetochore microtubules also contribute to the force production necessary to generate isometric tension across centromeric DNA. Sufficient tension on sister kinetochores is necessary to satisfy the spindle assembly checkpoint and transit into anaphase [109]. Thus, both the increased microtubule nucleation capacity and the bipolarity provided by the centrosomes facilitate efficient chromosome segregation.

Additionally, the centrosome organizes the minus-ends of spindle microtubules, helping to focus the spindle poles [110]. Most microtubules in the mitotic spindle are not directly anchored to the centrosome but rather released from the centrosome or nucleated through different mechanisms (for example, the Augmin/HAUS branching microtubule nucleation pathway) [111–115]. Minus-end directed kinesin-14 (Ncd in Drosophila, HSET in humans) and cytoplasmic dynein motor complexes then crossbridge and move along parallel microtubules, thereby focusing spindle microtubules into a tapered pole near the centrosome [86, 111, 116–118]. Microtubule minus-end-associated proteins such as patronin (CAMSAP in humans), Mud (NuMA in humans), and Asp (ASPM in humans) concentrate at the poles and link them to centrosomes [119–121].

Although the centrosome is required for efficient mitotic progression, the fact that most kinetochore microtubules are not directly anchored at the mature centrosome seems contradictory to its necessity [113, 122]. However, electron micrographs of kinetochore microtubules suggest they are dynamically unstable at their minus ends, indicative of microtubules released from the centrosome [113, 115, 123–125]. Therefore, the increased microtubule nucleation capacity at the mature centrosome may contribute more microtubules to the mitotic spindle than is immediately apparent. Additionally, centrosome-derived microtubules act as anchor points for microtubule cross-linking, resulting in the vast majority of microtubules being physically connected to the spindle pole [125]. These interactions are suggested to provide physical stability that buffers the forces that microtubules experience [125]. Together, the diverse populations of microtubules within the spindle are used to generate pushing forces (primarily exerted by interpolar microtubules) and pulling forces (primarily provided by kinetochore microtubules) that facilitate spindle elongation and chromosome segregation during anaphase [118].

Finally, centrosomes disassemble at the end of mitosis to reestablish proper microtubule nucleation capacity and cellular organization [18]. As cells enter mitosis, kinases become activated to facilitate centrosome maturation (such as Plk1 and Aurora A) but little is known about the reverse process [99]. During mitotic exit, protein phosphatases are thought to dominate the cellular landscape and reestablish the interphase centrosome. In part, Protein Phosphatase 2A (PP2A) dephosphorylates an unknown target at the centrosome in telophase, likely PCM components Spd-2/Cep192 and/or Cnn/CDK5RAP2/Spd-5, to weaken the structural integrity of the PCM [126]. A combination of pulling forces on centrosome microtubules and endocytic trafficking machinery then remove excess PCM proteins and transport them away from the centrosome [127–130]. This leaves the centrosome with the smaller core scaffold of PCM that is maintained through interphase but act as the foundation for the next round of centrosome maturation prior to the next mitosis [18].

Just as centrosome maturation nucleates and captures microtubules at the beginning of mitosis to promote spindle assembly, centrosome disassembly promotes the reorganization of the interphase microtubule cytoskeleton [131, 132]. At the end of mitosis, microtubules are released from the centrosome at a rate that is sevenfold higher than metaphase release rates [132]. This release, along with centrosome fragmentation, contributes to both reduced microtubule density at and microtubule nucleation capacity of the interphase centrosome [115, 132, 133]. Although increased microtubule-nucleating activity is observed in cancer cells with an excess of centrosomes (known as ‘centrosome amplification’), it is yet unclear as to the effect of maintaining active, mature centrosomes during interphase [81].

Along with coordinating spindle assembly, centrosomes also orient the mitotic spindle within the cell, defining the cell division axis. To generate and maintain tissues, cells take cues from their microenvironment to inform when and where they must divide. As such, most cells do not divide
in random directions. Instead, the mitotic spindle is oriented along a specific axis to facilitate tissue growth and decide cell fate [129, 134]. For example, cells within a planar epithelium must divide symmetrically along that plane or they will be expelled from the tissue, resulting in smaller tissues and organs [134]. Centrosomes are required to reliably orient the mitotic spindle along the designated axis.

Centrosomes not only nucleate microtubules that comprise the spindle, but they also produce microtubules that grow towards the cell periphery called astral microtubules (Fig. 3). The minus-ends of astral microtubules are anchored at the centrosome while their plus-ends interact with the cell cortex [135]. Because of this, astral microtubules can be captured by microtubule-binding proteins and motors that concentrate at the cortex, such as cytoplasmic dynein and Mud [136]. Through these interactions, spindles can rotate and reorient along the division axis. For example, in symmetrically dividing planar epithelium, cytoplasmic dynein localizes to cell–cell junctions to accomplish this task [137].

Spindle orientation can also influence cell fate decisions by promoting the asymmetric distribution of cell fate determinants. Like symmetric divisions along epithelial planes, capture and/or pulling of astral microtubules by proteins embedded in the cell cortex reposition the mitotic spindle (and thus, the cleavage plane) to produce daughter cells of different sizes and/or containing different polarity proteins and cell fate determinants [138]. Asymmetric cell divisions are a common mechanism to generate stratified epithelia and specialized cell-types, including neurons. However, the signals used to concentrate dynein generally rely on polarization cues, such as apical-basal or anterior–posterior signals to divide along a polarized axis [134].

A classic example of asymmetric division occurs in the Drosophila neuroblast, a neural stem cell that delaminates from the neuroectoderm during larval brain development (Fig. 4). The neuroblast is a polarized cell-type whose apical surface sits adjacent to the neuroectoderm layer [139]. The apical surface of the cell is maintained by asymmetric localization of the Par complex: Bazooka (Baz, Par3 in humans), Par6, and atypical Protein Kinase C (aPKC) [140, 141]. Opposite that, the cell fate determinant factors Numb, Prospero, and Brat localize to the basal side of the cell [142]. If the neuroblast divides parallel to the neuroectoderm (symmetrically), these fate determinants will be equally segregated between them, giving rise to two new neuroblasts. However, if the neuroblast divides perpendicular to the neuroectoderm, it produces one neuroblast and one ganglion mother cell (GMC); the GMC eventually becomes a neuron because inherits cell fate determinants, resulting in its cellular differentiation while the apical surface of the neuroblast is maintained adjacent to the neuroectoderm [143]. Self-renewing neuroblasts divide asymmetrically multiple times, producing clusters of GMCs at the basal domain [139].

Centrosomes are essential for efficient neuroblast differentiation. Apically localized microtubule-binding proteins capture astral microtubules from one centrosome to orient the mitotic spindle [146, 147]. Baz, a member of the apical Par complex, binds the adaptor protein Insutechable which recruits the microtubule-binding Gai/Pins/Mud complex [150, 151]. Mud then captures astral microtubules and anchors one centrosome on the apical side of the neuroblast [152, 153].

Interestingly, in most interphase Drosophila cells, centrioles recruit low amounts of PCM and, thus, do not nucleate microtubules [154, 155]. The neuroblast, however, is a unique cell-type in the fruit fly because it retains a centrosome with microtubule-organizing activity during interphase [155]. As a neuroblast exits mitosis, the centriole pair disengages and separates. Remarkably, while the older ‘mother’ centriole sheds its PCM, the younger ‘daughter’ centriole retains its PCM and associated microtubules [146, 147]. Consequently, the younger centriole (which continues to function as a centrosome) is fastened to apical side of the neuroblast through microtubule interactions with the Gai/Pins/Mud complex, while the older centriole freely migrates to the basal cell side [108]. As the neuroblast enters the next mitosis, the basal-positioned mother centriole recruits PCM and begins to function as a centrosome again by producing microtubules and assisting in spindle formation. At the end of mitosis, the older mother centriole is deposited into the new GMC [148].

Unique mechanism in the neuroblast also contribute to inactivation of the older, mother centrosome. Instead of phosphatases, mother centrosome inactivation involves another kinase. Specifically, Polo-like Kinase 4 (Plk4) extensively phosphorylates the PCM protein Spd2, which releases Spd2 from centrioles and inactivates the older centrosome [156]. In neuroblasts expressing kinase-dead Plk4 or a phospho-null Spd-2 mutant, both centrioles retain PCM and remain active MTOCs during interphase. Consequently, neuroblasts cannot properly orient their spindle and fly brains do not develop properly [156]. Although we often simplify the centrosome’s mitotic role to spindle assembly, the centrosome orchestrates most aspects of mitosis. Because of this breadth of function, it is no surprise that the centrosome is essential for mitosis in most somatic cells. However, a major gap in our knowledge is understanding how centriole and centrosome structure contributes to each of these roles, as well.
Centrosome instability: when good centrosomes go bad

Centrosome instability causes chromosomal instability

Most genetic diseases caused by mutations in centrosome genes affect specialized functions in unique cell-types (e.g., neural stem cells). The centrosome is essential for efficient mitosis and development and, not surprisingly, mutations that interfere with general centrosome functions are lethal [81]. This is because genomic integrity is especially vulnerable during mitosis. Chromosomes must be equally divided into two daughter cells to avoid potentially lethal or, conversely, oncogenic errors. Dramatic centrosome dysfunction, particularly changes to centrosome number, place cells at risk of chromosome missegregation [86, 87]. As such,

![Illustration of dividing Drosophila neuroblast in third larval instar stage. Neuroblasts are asymmetrically dividing neural stem cells that display a non-canonical centrosome maturation cycle.](image)

**Fig. 4** Illustration of dividing *Drosophila* neuroblast in third larval instar stage. Neuroblasts are asymmetrically dividing neural stem cells that display a non-canonical centrosome maturation cycle. a After dividing, the neuroblast contains a single centrosome with a mother (M)-daughter (D) centriole pair. The centrosome is tethered to the apical region of the cell through a microtubule-dependent interaction with a protein complex consisting of dynein-dynein light chain 2 (LC2)-Mud-Ana2 [144]. At this point, the mother–daughter centriole pair have physically separated (an event known as ‘disengagement’ [145]). b Unlike the mother centriole, the daughter contains the centriole protein Centrobin/Cbn and, along with Polo kinase, functions to retain its PCM and ability to nucleate a microtubule aster [146–149]. While the daughter centriole remains fastened to the apical cortex, the mother centriole sheds its PCM and is unable to function as a centrosome. Instead, it migrates to the basal side of the side where the mother ganglion cell cluster reside. It is unknown how the mother centriole moves to this side of the cell. Possibly is it delivered along the cytoskeletal filaments or is simply diffusion-based. c Both the older mother centriole and younger daughter undergo duplication in S-phase. Just prior to the next mitosis, the older mother centriole acquires the ability to recruit PCM and function as a centrosome, producing its own microtubule aster. d The mitotic spindle rotates and is oriented along the apical-basal axis. During anaphase, the spindle moves slightly towards the basal side of the cell, producing a small ganglion mother cell and a larger self-renewing neuroblast that retains the younger daughter centriole [148]
cells have developed extensive mechanisms to detect and respond to the mitotic errors caused by centrosome dysfunction [157]. These mechanisms police the fidelity of mitosis to eliminate cells that have experienced, or may have experienced, genomic instability.

The Spindle Assembly Checkpoint (SAC) is the best-known mitotic surveillance mechanism. The SAC prevents cells from progressing to the metaphase-anaphase transition until all chromosomes are aligned at the metaphase plate and does so by inhibiting the anaphase-promoting complex/cyclosome (APC/C) [109, 158]. The APC/C is a large E3 ubiquitin-ligase that triggers mitotic progression by targeting cyclin B1 for proteolysis and, subsequently, enables sister chromatid separation by promoting the degradation of the key cyclin B1 protease, separase [159]. Active separase then cleaves Scc1, a subunit of the sister chromatid-tethering cohesion complex, resulting in chromosome disjunction and separation [160]. Unattached kinetochores trigger the SAC by activating Mad2 which binds and sequesters the APC/C activator, Cdc20 [161]. Once all chromosome pairs are attached to spindle microtubules and their kinetochores are under proper tension, Cdc20 is freed to activate the APC/C [162, 163]. Normally, the SAC protects genomic integrity by providing cells with sufficient time to correct improperly attached kinetochores before completing mitosis [109]. In the context of centrosome dysfunction however, the SAC can prevent mitotic progression when chromosomes are improperly attached to an abnormal spindle.

Centrosomes are paramount to efficiently generating a bipolar mitotic spindle but are not absolutely required [163]. Alternative microtubule nucleation mechanisms exist, both at chromosomes and through microtubule branching, which can generate a microtubule network capable of self-assembling into a mitotic spindle [111, 164, 165]. However, bipolar spindle formation is dramatically stalled in somatic vertebrate cells that lack centrosomes [163, 164]. Therefore, the SAC protects cells without centrosomes from inefficient spindle formation by slowing mitotic progression until all chromosomes experience sufficient tension. Without this vital sensor, chromosome missegregation would ensue, producing chromosomal instability (i.e., changes in chromosome number and/or structure) [165].

The SAC also protects cells from mitotic defects caused by having too many centrosomes, a phenomenon called ‘centrosome amplification’ and an emerging hallmark of cancer cells [167]. Each of these supernumerary centrosomes can nucleate microtubules and organize a spindle pole during mitosis. As cells with centrosome amplification enter mitosis, kinesin-5 motors push centrosomes apart, producing spindles with too many poles (called a multipolar spindle) [168]. Chromosomes can then be captured by any of these spindle poles, sometimes even more than two; such abnormally attached chromosomes are subject to improper forces and, thus, struggle to satisfy the SAC. In some cases, cells undergo a multipolar cell division resulting in three or more daughter cells, which are typically inviable [168]. In this way, the SAC is the first line of defense against defects in spindle shape caused by centrosome amplification (or loss) and the consequent chromosomal instability that is produced.

Even though the SAC is intended to hold cells in mitosis until problems in kinetochore attachment and centromeric tension are resolved, cells do not remain in mitosis indefinitely. Instead, cells that spend too long a time in mitosis experience different fates, including delayed mitotic-linked cell death or mitotic slippage (a scenario where cells exit mitosis without completing chromosome segregation) [169]. Mitotic slippage not only doubles cellular ploidy but the number of centrosomes as well [170]. Interestingly, cells that exit mitosis after a prolonged mitotic delay are not out of trouble, as they are susceptible to G1-phase arrest and apoptosis [169]. The mechanisms that trigger this arrest in daughter cells is poorly understood but it is linked to the amount of time spent in the previous mitosis, an effect mediated through p53 [171]. On average, cultured human cells that remain in mitosis for more than 84 min trigger this checkpoint, even if they successfully undergo cell division. For reference, normal cultured human cells spend closer to 30 min in mitosis [172].

While centrosome amplification can result in mitotic catastrophe or arrest, cellular mechanisms exist to circumvent the problems associated with a multipolar mitosis [173]. Multipolar spindles are transient intermediate structures as cells can cluster their supernumerary centrosomes into two distinct foci, resulting in a functional ‘pseudo’-bipolar spindle (Fig. 5) [168, 174]. Centrosome clustering is mediated by the minus-end directed motors, cytoplasmic dynein and the kinesin-14, HSET [175, 176]. Similar to kinesin-5-mediated centrosome separation, minus-end directed motors crosslink and slide antiparallel microtubules emanating from two centrosomes, but slide them in the opposite direction to pull centrosomes together and drive their coalescence [175, 176]. Not surprisingly, cancer cells with supernumerary centrosomes commonly have high levels of HSET and a robust ability to cluster excess centrosomes [177]. For example, 45% of MDA-MB-231 breast cancer cells display centrosome amplification (> 2 centrosomes), but only undergo a multipolar division approximately 5% of the time, due to their efficient clustering mechanism [168].

Although pseudo-bipolar spindles generate viable daughter cells, they are extraordinarily prone to chromosome segregation defects, resulting in whole chromosome aneuploidy [173]. As a multipolar spindle makes contacts with chromosomes, microtubules emanating from multiple centrosomes can connect with the same sister kinetochore. When centrosomes cluster, they can move to either side of the spindle,
Fig. 5 Illustration of mitotic centrosome clustering and the chromosomal instability it can cause. a Mitotic cells containing two or more centrosomes (amplification) form a transient intermediate structure known as a multipolar spindle. Each centrosome can form a distinct spindle pole and form end-on attachments at kinetochores (red lines). Minus-end directed microtubule-based motor proteins crosslink and slide antiparallel microtubules emanating from centrosomes and drive there clustering. In the example shown, the extra centrosome makes an attachment with a kinetochore facing the left spindle pole, but then moves to the right spindle pole. b Centrosome clustering allows spindles to assume a bipolar fusiform shape (known as a ‘pseudo-bipolar spindle’) that is capable of segregating chromosomes. Whereas most centrosomes form proper ‘amphitelic’ kinetochore attachments (kinetochores on a sister chromatid pair are attached to opposite spindle poles), kinetochores linked to clustered centrosome sometimes form merotelic attachments (one kinetochore is attached to opposite spindle poles). Such improper attachments are dangerous as they undergo sufficient tension to satisfy the Spindle Assembly Checkpoint (SAC) and progress to anaphase. c Whereas most sister chromatids disjoin and segregate to opposite sides of the side, merotelic attached chromatids are trapped in the central spindle forming a ‘lagging chromosome’. d Lagging chromosomes are randomly segregated into a daughter cell, often producing whole chromosome aneuploidy. Even if a chromosome segregates into the proper daughter cell, there is an additional problem because, instead of decondensing and mixing with the other chromosomes in the primary nucleus, these chromosomes form micronuclei. Micronuclear envelopes frequently rupture in the subsequent S-phase causing chromosome shattering (or chromothripsis).
resulting in a merotelic kinetochore attachment (one kinetochoore is attached to opposite spindle poles) (Fig. 5) [168, 174]. During anaphase when most sister chromatids disjoin and move towards opposite side poles, merotelically-attached chromatids become trapped in the central spindle in a ‘tug-of-war’ and these are referred to as lagging chromosomes [178]. During cytokinesis, lagging chromosomes are randomly segregated into a daughter cell, potentially resulting in the production of two aneuploid daughter cells [179, 180].

Even if a lagging chromosome is segregated into the proper daughter cell, cells face new dangers. Due to its late arrival, lagging chromosomes may end up decondensing at regions too distant to allow incorporation into the primary nucleus of the cell. Instead, the single chromosome will form its own nuclear envelope, known as a micronucleus, which are common in cancer cells [181]. Micronuclei contain some of the same protein components as the nucleus but are less likely to have the correct ratio of these components [182]. Consequently, micronuclear import/export, transcription, and DNA replication are often defective and, as a result, the chromosome can experience genotoxic stress [181–183].

This is further compounded by the fact that the micronuclear membrane is more likely to rupture due to a reduced integrity of the nuclear lamina [182]. As the cytoplasm rushes into the micronucleus, slowly replicating DNA can experience double-stranded breaks [181, 184, 185]. In fact, chromosome shattering and subsequent restitching, called chromothripsis, is also common in cancer [181, 186, 187]. Chromothripsis gives rise to a several different structural alterations, including random chromosomal rearrangements, duplications, and deletions [186]. These genomic rearrangements can give rise to oncogenic translocations, loss of heterozygosity at deleted loci, and breakage-fusion-bridge cycles due to improper restitching of telomeres [188].

**Mechanisms selecting against centrosome instability**

There is a growing body of evidence describing the prevalence of centrosome defects and their pathological consequences. Therefore, we find it prudent to establish the term ‘centrosome instability’ which describes the pathognomonic state of centrosome dysfunction, such as a divergence of centrosome structure and copy number from normal, healthy cells. As previously described, centrosome instability gives rise to many forms of chromosomal instability. Notably, cells have evolved p53-dependent mechanisms to indirectly identify centrosome instability due to the associated genomic damage this causes [189]. In response to most forms of DNA damage, protein levels of p53 increase either by inactivation from the E3 ubiquitin-ligase, Mdm2, or through direct phosphorylation [190]. Since p53 is a transcription factor, its stabilization also results in translocation to the nucleus. Depending on the type of damage, extent of damage, and the length of time it takes to repair this damage, p53 promotes the expression of genes that can either slow the cell cycle, promote cell cycle arrest and senescence, or induce apoptosis [191]. Because cells with centrosome defects have a propensity for chromosomal instability, p53 ensures centrosome homeostasis [189].

For example, centrosomes can be experimentally eliminated by treatment with a reversible chemical-inhibitor of Plk4 called centrinone [122]. Plk4 is the master-regulator of centrosome assembly and its inhibition prevents further centrosome duplication [192]. Over time, Plk4 inhibition generates a large population of cells without centrosomes by effectively diluting centrosome-containing cells from a dividing population [122]. Whether cells continue to divide however, depends on their p53 status. Without centrosomes, cells spend a long time in mitosis [163]. Whereas cells with intact p53 frequently display G1-phase arrest after a prolonged mitosis, p53-deficient cell lines continue to progress through the cell cycle, resulting in a proliferating acentrosomal cell line. Washout of centrinone triggers massive Plk4 activation and de novo centrosome assembly (a non-canonical assembly pathway that does not rely on centrosome formation from existing centrosomes), which can generate a subpopulation of cells with centrosome amplification [122]. This dramatic change in copy number is a prime example of the plasticity associated with centrosome instability. In cell lines that maintain a normal number of centrosomes, cells with centrosome amplification are quickly removed from the population. Fascinatingly, when certain cancer cells lines that stably maintain an abnormally high number of centrosomes are exposed to a centrinone treatment and washout regimen, the population does not correct to a normal centrosome number. Instead, the dividing population eventually returns to their abnormal basal level of amplification and appear the same as the untreated control cells [122, 193]. At present, it is a mystery how cells can establish and maintain memory of abnormal centrosome copy number [193].

Interestingly, prolonged mitosis is sufficient to induce a p53-mediated arrest, even if cells do not experience DNA damage [172]. However, other than requiring p53, the mechanisms that mediate this arrest are different depending on whether cells display centrosome loss or amplification [157]. Cells without centrosomes that undergo a prolonged mitosis may arrest in G1-phase of the next cell cycle, and the chance of arrest increases with each consecutive prolonged mitosis [172]. Genome-wide CRISPR screens revealed that cell cycle arrest requires the deubiquitinate USP28 and p53-Binding Protein 1 (53BP1) to, somehow, activate p53 and trigger p21-mediated cell cycle arrest [194–196]. This phenomenon has been named the ‘mitotic surveillance pathway’. Conversely, cells can also arrest in G1-phase after
Centrosome instability, however, this does not require either 53BP1 or USP28. Thus, although cells respond the same way (specifically, G1-phase arrest), the mechanisms responding to changes to centrosome number are different and not currently understood.

As previously discussed, centrosome instability promotes the formation of micronuclei that are prone to rupture and the chromosomes they contain can experience chromothripsis [181, 182, 186]. Not only does this cause genomic damage, but cytoplasmic DNA is an innate immune trigger commonly used to identify viral infection [197]. Double-stranded DNA viruses in the cytoplasm activate the cGAS-STING pathway, leading to cellular senescence and secretion of pro-inflammatory cytokines [198]. This pathway is also co-opted by the cell to sense micronuclear rupture [197]. Upon binding DNA, cGAS generates cyclic GMP-AMP (cGAMP) dinucleotides. cGAMP then binds STING, forcing it to dimerize and activate noncanonical NF-κB pathways, including expression of p16 which leads to senescence [197, 199]. Additionally, senescence-associated secretory protein (SASP) cytokines, such as IL-6 and IL-12, are produced, priming nearby cells to undergo senescence [198]. SASP production in vivo has been linked to many aging phenotypes and is generally thought of as deleterious to the health of tissues [200].

Notably, centrosome amplification itself has been linked to a novel secretome. When naïve cells are cultured in conditioned media from cells containing centrosome amplification, they become more invasive [201]. In the context of p53-deficient cancers, this secretome promotes an invasive behavior in cells that contain normal centrosome numbers if they are in the vicinity of a cell that has supernumerary centrosomes. Including SASP production, these studies indicate that cells with centrosome instability can use paracrine signaling to influence neighboring cells before their ultimate demise [197, 201].

When considering the importance of the centrosome, its presence is not enough. Proper regulation of centrosome number and architecture underlie all of its functions. Although we do not know the full consequences of centrosome structural aberrations, mutants that subtly alter its structure are implicated in disease and result in impaired viability [81]. Furthermore, the existence of diverse centrioles in different cell-types suggest that centriole plasticity is essential for proper development and cellular homeostasis [15]. Understanding the diversity of centriole assembly outside of commonly used model systems will be a significant challenge for the field.

**Centrosome instability in disease**

Since the first connection of centrosomes and cancer by Boveri in the early 1900’s, associations between centrosome instability and cancer have abounded [8]. Although these associations are common, models of centrosome instability over the past couple decades have given us mixed results regarding their link to cancer. Before discussing, it is important to understand the impact of the centrosome during development in metazoans.

Many studies in cell lines have shown the crucial role of the centrosome in mitosis, giving rise to the notion that centrosomes are required for life. However, a landmark study in *Drosophila* testing this question yielded surprising results: flies without centrosomes are viable and even advance to adulthood, although they died soon after hatching because they lack mechanosensory cilia [202]. Moreover, within certain tissues, the absence of centrosomes caused mitotic errors, DNA damage, and apoptosis [203]. Although cell division in these flies was slow, error prone, and asymmetric cell division was unreliable, flies were viable. The story, however, is complicated by the fact that *Drosophila* embryos contain a maternal load of proteins, capable of assembling enough centrosomes to support the animal through early development. Not until the larval stages do these mutant flies actually lack centrosomes [202]. Although unexpected, these findings challenged the dogma regarding the essentiality of centrosomes.

Additional work using the fruit fly model focused on examining the impact of centrosome amplification using transgenic animals overexpressing Plk4 [204]. Remarkably, flies tolerate centrosome amplification without acquiring large-scale aneuploidy, producing generations of such mutant flies. This study revealed that fly cells possess a robust centrosome clustering mechanism, and coupled with a strong SAC, ensures mitotic fidelity and viability [204]. This model, however, allowed the researchers to address a question originally proposed by Boveri: is centrosome amplification sufficient to cause tumor formation? Whereas flies without centrosomes appeared morphologically similar to wild type flies, centrosome amplification caused hyperplastic expansion of neuroblasts [204]. However, this increase was slight and did not result in the development of large brain tumors in the mutant flies. Instead, the researchers took larval brain tissue from centrosome amplified hosts and transplanted them into the abdomen of a naïve fly. Normal brain tissue can survive in the abdomen of flies without over-proliferating. In contrast, larval brains with centrosome amplification continued to proliferate, forming tumors in the fly’s abdomen [204, 205]. Additionally, the researchers observed a few cases of metastasis to distant tissues such as the eye [204].
This was the first direct evidence showing centrosome instability was sufficient to initiate tumor-like growth.

Not surprisingly, mouse models of centrosome amplification were more difficult to generate; similar to fly models, mouse models use transgenic Plk4 overexpression to achieve centrosome overproduction in cells. Unlike the fly, mouse models of centrosome amplification corroborated the original notion that centrosome homeostasis is required for proper development, as most mice die during development or shortly after birth. Surprisingly though, these initial studies found that centrosome amplification was not sufficient to form tumors [206]. Instead, the first models of centrosome amplification displayed high levels of cell death due to severe aneuploidy. For instance, centrosome amplification in the developing brain caused reduced brain size (microcephaly) and neonatal death of the mice. Even when Plk4 was overexpressed in the brain of p53-deficient mice, they did not develop brain tumors, but instead showed progressive neural degradation due to aneuploidy in progenitor cell populations [207].

Other mouse models of Plk4 overexpression showed of much the same. Plk4 overexpression in the developing epidermis was well tolerated. These cells continued to divide, albeit at a lower rate, and maintain the tissue [208]. However, a follow-up study using a similar epidermis model showed that most mice died soon after birth because skin could not develop properly to support barrier function [209]. In mice that did survive, epidermal stratification was delayed due to p53-dependent and -independent apoptosis in progenitor cells. In order to improve viability and access tumorigenicity, transgenic mice were crossed to conditional p53 knockout mice that lacked p53 expression in the epidermis. Notably, the authors discovered that transient centrosome amplification in the skin during development led to tumor formation in almost 100% of mice. As a caveat, p53-deficient mice already had a high rate of tumor formation (50% of mice), however centrosome amplification dramatically accelerated tumor onset [209]. Taken together, all signs pointed towards centrosome amplification not being sufficient to initiate tumorigenesis in mice. Possibly, centrosome amplification had exacerbated chromosomal instability in already genomically-vulnerable cells.

Other investigators were undeterred however by these results and continued to pursue the question of whether centrosome amplification promotes tumor formation. The definitive answer arrived in a model where centrosome amplification was induced in cells of adult mice. Using a doxycycline-inducible promoter, long-term Plk4 overexpression was driven within already developed tissues [210]. Remarkably, centrosome amplification caused spontaneous tumors to grow in mice with intact p53. Tumors appeared in approximately 80% of mice and cells within these tumors were highly aneuploid. So, why did these mice form tumors when other models of centrosome amplification caused cell death in tissues? The authors speculate that transgenic Plk4 was expressed at lower levels within their model, causing only a modest increase in centrosome numbers. Perhaps centrosome clustering in dividing cells could tolerate having one or two extra centrosomes during mitosis, but excessive centrosome amplification in other transgenic models was insurmountable and caused a strong p53 response which comprised cell survival.

In addition to chromosomal instability, supernumerary centrosomes promote invasive behavior and metastasis in cancer cells. When cells produce too many centrosomes, this apparently increases the microtubule nucleation capacity of each centrosome, which promotes Rac1 activation and metastasis [211]. Furthermore, chromosomal instability due to mitotic dysfunction is sufficient to promote metastasis by increasing the micronuclear burden. In turn, micronuclear envelopes rupture, exposing DNA to the cytoplasm and activating the cGAS/STING pathway to promote transcription of an inflammatory response and metastasis [212].

Centrosome amplification is not only sufficient to promote pathological phenotypes in the laboratory, examples of centrosome amplification can be seen in nearly all spontaneous solid tumors and blood cancers [166]. Additionally, many anti-mitotic treatments have the unwanted side-effect of generating polyploid cells that possess excess centrosomes [87]. Remarkably, centrosome amplification is not the only centrosome dysfunction associated with cancer. Recent work has discovered the opposite scenario of centrosome loss in localized prostate cancer [213]. In fact, centrosome loss can generate the identical forms of chromosomal instability caused by centrosome amplification, including whole chromosome aneuploidy, the formation of micronuclei, and chromosome shattering [122, 163, 213–215]. Moreover, centrosome loss can generate sufficient chromosomal instability to transform non-tumorigenic immortalized prostate epithelial cells, capable of forming xenograft tumors in mice [213]. However, models of centrosome loss in mammals have not explored tumorigenesis due to embryonic lethality and it remains to be determined whether centrosome loss is as widespread in cancers as centrosome amplification [216–218].

While changes to centrosome copy number are common in cancer, mutations that effect centrosome function have also been found in individuals with developmental disorders. Mutations in core centriole, cilia, and PCM genes are associated with microcephaly, lissencephaly, polydactyly, primordial dwarfism, and many others [67, 81]. Genetic mouse models that examined loss of patient-related centrosomal and cilia proteins have found that many of these mutations are directly causal. Most mechanisms of disease
arise because these mutant mice struggle to generate specific sets of neurons from neuronal progenitor cells. For instance, Cep63-deficient mice that show a reduced ability to duplicate centrosomes experience mitotic errors in neuronal progenitors, causing p53-dependent apoptosis and microcephaly [219]. Conversely, Cep83-deficient mice cannot properly anchor centrosomes to the apical cell surface in brain cortex progenitor cells and, consequently, these cells undergo excessive symmetric cell divisions. As a result, too many progenitor cells are produced but not enough cortical neurons, which manifests in smoothing of the brain cortex (aka, lissencephaly) [220].

It remains unclear why neural development is so sensitive to centrosome dysfunction, while other tissues remain unaffected. Possibly, neuronal cells and brain tissue require specialized centrosome functions. Conversely, there may be less selective pressure against these specific mutations. It follows that mutations affecting all cells, including the germ line, would be subject to more stringent evolutionarily pressure. This may also explain why there are no specific centrosome mutations that predispose an individual to cancer. Mutations that affect mitotic functions of the centrosome would obviously be lethal and, therefore, selected against. Mammalian models of centrosome amplification point to this idea, as the offspring are non-viable [209].

Perspective and pressing questions

While many seminal studies over the past 30 years have elucidated a myriad of centrosome functions in regulation of the microtubule cytoskeleton, recent discoveries highlight emerging functions of the centrosome as a hub of other biological processes. For instance, centrosome amplification can interrupt autophagosome trafficking, disrupting autophagy and preventing degradation of autophagic targets [221]. Conversely, disrupting selective autophagy of centrosome components—a process known as doryphagy—causes centrosome fragmentation and disruption [222]. Additionally, the centrosome has recently been implicated in organization of the actin cytoskeleton, including concentrating the actin regulator LIM Kinase 1 during mitosis [223, 224]. These novel functions only add to the list of pressing questions regarding centrosome instability.

Examples of centrosome instability are becoming more prevalent in a wide gamut of diseases; however, it is unclear how centrosome instability arises. While we see changes to centrosome number in nearly every major cancer type, the mechanisms that drive changes to centrosome number remain a mystery. Perhaps centrosome instability in normal tissue is more common than we appreciate, but these cells are simply removed from normal populations through the many levels of selective pressure previously discussed. Theoretically, however, centrosome instability should be detrimental to genome integrity even in cancer cells. So, are there mechanisms that exacerbate centrosome instability within tumors (i.e., microenvironmental, inflammatory, or other cell-extrinsic factors)?

Changes to centrosome copy number only affects a small subset of cells within a tumor [87]. So, how does centrosome number heterogeneity effect that tumor? While previous work identified a pro-migratory secretion phenotype associated with centrosome amplification, the consequence to patients is yet unclear [201]. However, tumors with high genomic heterogeneity are generally more aggressive [225]. Since centrosome instability promotes chromosomal instability, tumors with high centrosome copy number heterogeneity should have high genomic heterogeneity and, thus, should also be more aggressive. Therefore, can we identify those patients with high centrosome copy number heterogeneity as a proxy for genomic instability to aid prognosis? Or could centrosome instability provide a targetable vulnerability for treating genomically unstable cancers? One recent example of this has shown that centrosome amplification sensitizes cells to autophagy inhibitors [221]. Therefore, new combination drug targets may emerge as new centrosome functions or disease roles are discovered.

Acknowledgements G.C. Rogers is grateful for support from the National Cancer Institute P30 CA23074 and R01CA242226 as well as the National Institute of General Medical Sciences R35GM136265.

Author contributions JMR performed the literature search and wrote the manuscript. GCR revised the work and created the figures.

Funding G.C. Rogers is grateful for support from the National Cancer Institute P30 CA23074 and R01CA242226 as well as the National Institute of General Medical Sciences R35GM136265.

Declarations

Conflict of interest The authors declare that they have no conflict or competing interests.

Ethical approval The authors give their consent.

Consent for publication The authors give consent for publication.

References

1. Boveri T (1887) Ueber den Antheil des Spermatozoon an der Teilung des Eies Sitzungsber. Ges Morph Physiol Munchen. https://doi.org/10.1098/rsb.2013.0469
2. Van Beneden E, Neyt A (1887) Nouvelles recherches sur la fécondation et la division cellulaire karyokinetique chez l’Ascaris du cheval. Moniteur belge 14:2497–2498
3. Scheer U (2014) Historical roots of centrosome research: discovery of Boveri’s microscope slides in Würzburg. Philos Trans
81. Bettencourt-Dias M, Hildebrandt F, Pellman D et al (2011) Centrosomes and cilia in human disease. Trends Genet 27:307–315. https://doi.org/10.1016/j.tig.2011.05.004
82. Mountain V, Compton DA (2000) Dissecting the role of molecular motors in the mitotic spindle. Anat Rec 261:14–24. https://doi.org/10.1006/ancr.2000.1317
83. Sharp DJ, Rogers GC, Scholey JM (2000) Microtubule motors in mitosis. Nature 407:41–47. https://doi.org/10.1038/35024000
84. Cross RA, McAinsh A (2014) Prime movers: the mechanochemistry of mitotic kinesins. Nat Rev Mol Cell Biol 15:257–271. https://doi.org/10.1038/nrm3768
85. Kashina AS, Baskin RJ, Cole DG et al (1996) A bipolar kinesin. Nature 382:420–425. https://doi.org/10.1038/3824200
86. Renda F, Khodjakov A (2021) Role of spatial patterns and kinetochore architecture in spindle morphogenesis. Semin Cell Dev Biol. https://doi.org/10.1016/j.semcdb.2021.03.016
87. Prosser SL, Pelletier L (2017) Mitotic spindle assembly in animal cells; a fine balancing act. Nat Rev Mol Cell Biol 18:187–201. https://doi.org/10.1038/nrm3768
88. Prosser SL, Pelletier L (2017) Prime movers: the mechanochemistry of mitotic kinesins. Nat Rev Mol Cell Biol 15:257–271. https://doi.org/10.1038/nrm3768
89. Sharp DJ, Rogers GC, Scholey JM (2000) Microtubule motors in mitosis. Nature 407:41–47. https://doi.org/10.1038/35024000
90. Prosser SL, Pelletier L (2017) Mitotic spindle assembly in animal cells; a fine balancing act. Nat Rev Mol Cell Biol 18:187–201. https://doi.org/10.1038/nrm3768
91. Kapitein LC, Peterman EJG, Kwok BH et al (2005) The bipolar motor Kinesin-5 into bipolar tetramers. Elife 3:e02217. https://doi.org/10.7554/eLife.02217
92. Ferenz NP, Gable A, Wadsworth P (2010) Mitotic functions of kinesin-5. Semin Cell Dev Biol 21:255–259. https://doi.org/10.1016/j.semcdb.2010.01.019
93. Garcia-Saez I, Skoufias DA (2021) Eg5 targeting agents: From therapeutic issues. Chromosome Res 24:105–126. https://doi.org/10.1007/s10577-015-9505-5
94. Goshima G, Mayer M, Zhang N et al (2008) Augmin: a protein complex that regulates centrosome size by controlling the rate of Cnn incorporation into the PCM. Curr Biol 20:2178–2186. https://doi.org/10.1016/j.cub.2010.11.011
95. Conduit PT, Feng Z, Richens JH et al (2014) The centrosome-specific phosphorylation of Cnn by Polo/Plk1 drives Cnn scaffold assembly and centrosome maturation. Dev Cell 28:659–669. https://doi.org/10.1016/j.devcel.2014.02.013
96. Wang G, Chen Q, Zhang X et al (2013) PMI recruits Plk1 to the pericentriolar matrix to promote primary cilia disassembly before mitotic entry. J Cell Sci 126:1355–1365. https://doi.org/10.1242/jcs.114918
97. Soung NK, Kang YH, Kim N et al (2006) Requirement of hCenexin for proper mitotic functions of polo-like kinase 1 at the centrosomes. Mol Cell Biol 26:8316–8335. https://doi.org/10.1128/MCB.00671-06
98. Novak ZA, Wainman A, Gatenmann L, Raff JW (2016) Cdk1 phosphorylates Drosophila Sas-4 to recruit Polo to daughter centrioles and convert them to centrosomes. Dev Cell 37:545–557. https://doi.org/10.1016/j.devcel.2016.05.022
99. Feng Z, Caballe A, Wainman A et al (2017) Structural basis for mitotic centrosome assembly in flies. Cell 169:1078–1089. https://doi.org/10.1016/j.cell.2017.05.030
100. Alvarez-Rodrigo I, Steinacker TL, Saurya S et al (2019) Evidence that a positive feedback loop drives centrosome maturation in fly embryos. Elife. https://doi.org/10.7554/eLife.51030
101. Zhang J, Megraw TL (2007) Proper recruitment of γ-tubulin and D-TACC/Msp to embryonic Drosophila centrosomes requires Centrosomin Motif 1. Mol Biol Cell 18:4037–4049. https://doi.org/10.1091/mbc.e07-05-0474
102. Faráde, Emonine L, Haren L, Merdes A (2018) Assembly and regulation of γ-tubulin complexes. Open Biol. https://doi.org/10.1098/rsob.170266
103. Kollman JM, Merdes A, Mourey L, Agard DA (2011) Microtubule nucleation by γ-tubulin complexes. Nat Rev Mol Cell Biol 12:709–721. https://doi.org/10.1038/nrm3209
104. Heald R, Tournebize R, Blank T et al (1996) Self-organization of microtubules into bipolar spindles around artificial chromosomes in Xenopus egg extracts. Nature 382:420–425. https://doi.org/10.1038/382420a0
105. Lee KS, Park JE, Ahn JH, Zeng Y (2021) Constructing PCM with architecturally distinct higher-order assemblies. Curr Opin Struct Biol 66:66–73. https://doi.org/10.1016/j.sbi.2020.09.013
106. Farache D, Emorine L, Haren L, Merdes A (2018) Assembly and regulation of γ-tubulin complexes. Open Biol. https://doi.org/10.1098/rsob.170266
107. Rogers GC, Rogers SL, Sharp DJ (2005) Spindle microtubules in flux. J Cell Sci 118:1105–1116. https://doi.org/10.1242/jcs.02284
108. Pickett-Heaps JD, Forer A (2001) Pac-Man does not resolve the enduring problem of anaphase chromosome movement. Proto-plasma 215:16–20. https://doi.org/10.1007/BF01280300
109. Lana-Gonzalez P, Westhorpe FG, Taylor SS (2012) The Spindle Assembly Checkpoint. Curr Biol 22:R966–R980. https://doi.org/10.1016/j.cub.2012.10.006
110. Borgal L, Wakefield JG (2018) Context-dependent spindle pole focusing. Essays Biochem 62:803–813. https://doi.org/10.1042/EBC20180034
111. Goshima G, Wollman R, Goodwin SS et al (2007) Genes required for mitotic spindle assembly in Drosophila S2 cells. Science 316:417–421. https://doi.org/10.1126/science.1141314
112. Goshima G, Mayer M, Zhang N et al (2008) Augmin: a protein complex required for centrosome-independent microtubule generation within the spindle. J Cell Biol 181:421–429. https://doi.org/10.1083/jcb.200711053
113. Redemann S, Baumgart J, Lindow N et al (2017) C. elegans chromosomes connect to centrosomes by anchoring into the spindle network. Nature Commun. https://doi.org/10.1038/ncomms15288
114. Müller-Reichert T, Kiewisz R, Redemann S (2018) Mitotic spindles revisited—new insights from 3D electron microscopy. J Cell Sci. https://doi.org/10.1232/jcs.211383
115. Rusan NM, Fagerstrom CJ, Yvon AM et al (2001) Cell cycle-dependent changes in microtubule dynamics in living cells expressing green fluorescent protein-alpha tubulin. Mol Biol Cell 12:971–980. https://doi.org/10.1083/jcb.2001711053
116. Zhu C, Zhao J, Bibilova M et al (2005) Functional analysis of human microtubule-based motor proteins, the kinesins and dyneins, in mitosis/cytokinesis using RNA interference. Mol Biol Cell 16:3187–3199. https://doi.org/10.1091/mbc.e05-02-0167
117. Gaggioli T, Saredd U, Bingham JB et al (1996) Opposing motor activities are required for the organization of the mammalian mitotic spindle pole. J Cell Biol 135:399–414. https://doi.org/10.1083/jcb.135.2.399
118. Goshima G, Vale RD (2003) The roles of microtubule-based motor proteins in mitosis. J Cell Biol 162:1003–1016. https://doi.org/10.1083/jcb.200303022
Centrosome instability: when good centrosomes go bad

119. Ito A, Goshima G (2015) Microcephaly protein Asp focuses the minus ends of spindle microtubules at the pole and within the spindle. J Cell Biol 211:999–1009. https://doi.org/10.1083/jcb.201507001

120. Kiyomitsu T, Boerner S (2021) The nuclear appratus (NuMA) protein: a key player for nuclear formation, spindle assembly, and spindle positioning. Front Cell Dev Biol. https://doi.org/10.3389/fcell.2021.653801

121. Akhmanova A, Steinmetz MO (2019) Microtubule minus-end regulation at a glance. J Cell Sci. https://doi.org/10.1242/jcs.227850

122. Wong YL, Anzola JV, Davis RL et al (2015) Reversible centriole depletion with an inhibitor of Polo-like kinase 4. Science 348:1145–1160. https://doi.org/10.1126/science.aaa5111

123. O’Toole ET, McDonald KL, Müntler J et al (2003) Morphologically distinct centriole ends from five species. J Cell Biol 200:459–474. https://doi.org/10.1083/jcb.201209154

124. O’Toole E, Morphew M, McIntosh JR (2020) Electron tomography reveals aspects of spindle structure important for mechanical stability at metaphase. Mol Biol Cell 31:184–195. https://doi.org/10.1091/mbc.E19-07-0405

125. Schlaitz AL, Srayko M, Dammermann A et al (2007) The C. elegans RSA complex localizes protein phosphatase 2A to centrosomes and regulates mitotic spindle assembly. Cell 128:115–127. https://doi.org/10.1016/j.cell.2006.10.050

126. Hoffmann I (2021) Centrosomes in mitotic spindle assembly and spindle orientation. Nat Cell Biol 15:241–248. https://doi.org/10.1038/ncb2671

127. di Pietro F, Echard A, Morin X (2016) Regulation of mitotic spindle orientation: an integrated view. EMBO Rep 17:1106–1110. https://doi.org/10.15252/embr.201642292

128. Mittasch M, Tran VM, Rios MU et al (2020) Regulated changes in material properties underlie centrosome disassembly during mitotic exit. J Cell Biol 219:1–17. https://doi.org/10.1083/jcb.201912036

129. Schaefer M, Shevchenko A, Shevchenko A, Knoblich JA (2000) Centrobin controls mother-daughter centriole asymmetry in Drosophila neuroblasts. Nat Cell Biol 15:241–248. https://doi.org/10.1038/ncb2671

130. Januschke J, Reina J, Llamazaress (2013) Centrobin controls mother-daughter centriole asymmetry in Drosophila neuroblasts. Nat Cell Biol 15:241–248. https://doi.org/10.1038/ncb2671

131. Niehle JS, Dietrich H, Dietrich M, et al (2015) Cell adhesion molecule control of planar spindle orientation. Cell Mol Life Sci 73:1195–1207. https://doi.org/10.1007/s00018-015-2116-7

132. Siller KH, Doe CQ (2009) Spindle orientation during asymmetric cell division. Nat Cell Biol 11:365–374. https://doi.org/10.1038/ncb0409-365

133. Piehl M, Tulu US, Wadsworth P et al (2004) Centrosome protein Mud regulates spindle polarity and cell proliferation in neuroblasts and epithelia. J Cell Biol 163:1089–1098. https://doi.org/10.1083/jcb.200306079

134. Cai Y, Yu F, Lin S et al (2003) Apical complex genes control mitotic spindle geometry and relative size of daughter cells in Drosophila neuroblasts and pl asymmetric divisions. Cell 112:51–62. https://doi.org/10.1016/s0092-8674(02)01170-4

135. Shaher AA, Rojas-Carrasco PM, et al (2011) Annu2/cpt/mud complex regulates spindle orientation in Drosophila neuroblast. Dev Cell 21:520–533. https://doi.org/10.1016/j.devcel.2011.08.002

136. Wodarz A, Ramrath A, Kuchinque U, Knust E (1999) Bazooka provides an apical cue for Inscteatable localization in Drosophila neuroblasts. Nature 402:544–547. https://doi.org/10.1038/990128

137. Tuncay H, Elnet K (2016) Cell adhesion molecule control of planar spindle orientation. Cell Mol Life Sci 73:1195–1207. https://doi.org/10.1007/s00018-015-2116-7

138. O’Ttoole ET, McDonald KL, Mäntler J et al (2003) Morphologically distinct microtubule ends from five species. J Cell Biol 200:459–474. https://doi.org/10.1083/jcb.201209154

139. O’Toole E, Morphew M, McIntosh JR (2020) Electron tomography reveals aspects of spindle structure important for mechanical stability at metaphase. Mol Biol Cell 31:184–195. https://doi.org/10.1091/mbc.E19-07-0405

140. Xie S, Reinecke JB, Farmer T et al (2018) Vesicular trafficking plays a role in centriole disengagement and duplication. Mol Biol Cell 29:2622–2631. https://doi.org/10.1091/mbc.18-04-0241

141. Schaefer M, Shevchenko A, Shevchenko A, Knoblich JA (2000) Centrobin controls mother-daughter centriole asymmetry in Drosophila neuroblasts. Nat Cell Biol 15:241–248. https://doi.org/10.1038/ncb2671

142. Januschke J, Llamazaress (2013) Centrobin controls mother-daughter centriole asymmetry in Drosophila neuroblasts. Nat Cell Biol 15:241–248. https://doi.org/10.1038/ncb2671

143. Cai Y, Yu F, Lin S et al (2003) Apical complex genes control mitotic spindle geometry and relative size of daughter cells in Drosophila neuroblasts and pl asymmetric divisions. Cell 112:51–62. https://doi.org/10.1016/s0092-8674(02)01170-4

144. Wang C, Li S, Januschke J et al (2011) Annu2/cpt/mud complex regulates spindle orientation in Drosophila neuroblast. Dev Cell 21:520–533. https://doi.org/10.1016/j.devcel.2011.08.002

145. Tsou MF, Stearns T (2006) Mechanism limiting centrosome duplication to once per cell cycle. Nature 442:947–951. https://doi.org/10.1038/nature04985

146. Rusan NM, Feifer M (2007) A role for a novel centrosome cycle in asymmetric cell division. J Cell Biol 177:13–20. https://doi.org/10.1083/jcb.200612140

147. Schaefer M, Shevchenko A, Shevchenko A, Knoblich JA (2000) A protein complex containing Inscteatable and the Gz-binding protein Pins orients asymmetric cell divisions in Drosophila. Curr Biol 10:353–362. https://doi.org/10.1016/s0960-9822(00)00401-2

148. Siller KH, Cabernard C, Doe CQ (2006) The NuMa-related Mud protein binds Pins and regulates spindle orientation in Drosophila neuroblasts. Nat Cell Biol 8:594–600. https://doi.org/10.1038/ncb1412

149. Iizumi Y, Ohita N, Hisata K et al (2006) Drosophila Pins-binding protein Mud regulates spindle-polarity coupling and centrosome organization. Nat Cell Biol 8:594–600. https://doi.org/10.1038/ncb14109

150. Rogers GC, Rusan NM, Peifer M, Rogers SL (2008) A multi-component assembly pathway contributes to the formation of acentrosomal microtubule arrays in interphase Drosophila cells. Mol Biol Cell 19:3163–3178. https://doi.org/10.1091/mbc.e07-10-1069
155. Russan NM, Rogers GC (2009) Centrosome function: sometimes less is more. Traffic 10:472–281. https://doi.org/10.1111/j.1600-0854.2009.00880.x

156. Gambartodo D, Penettier RJM et al (2019) Plk4 regulates centriole asymmetry and spindle orientation in neural stem cells. Dev Cell 50:11-24.e10. https://doi.org/10.1016/j.devcel.2019.04.036

157. Lambrus BG, Holland AJ (2017) A new mode of mitotic surveillance. Trends Cell Biol 27:314–321. https://doi.org/10.1016/j.tcb.2017.01.004

158. Rieder CL, Cole RW, Khodjakov A, Sluder G (2017) The checkpoint delaying anaphase in response to chromosome monoorientation is mediated by an inhibitory signal produced by unattached kinetochores. J Cell Biol 130:941–948. https://doi.org/10.1083/jcb.130.4.941

159. Lischetti T, Nilsson J (2015) Regulation of mitotic progression by the spindle assembly checkpoint. Mol Cell Oncol 2:e970484. https://doi.org/10.4161/23723548.2014.970484

160. Yanagida M (2005) Basic mechanism of eukaryotic chromosome segregation. Philos Trans R Soc Lond B Biol Sci 360:609–621. https://doi.org/10.1098/rstb.2004.1615

161. Szczaniecka MM, Hardwick KG (2008) The spindle checkpoint: how do cells delay anaphase onset? SEB Exp Biol Ser 59:243–256

162. Li X, Nicklas RB (1995) Mitotic forces control a cell-cycle checkpoint. Nature 373:630–632. https://doi.org/10.1038/373630a0

163. Sir JW, Pütz M, Daly O et al (2013) Loss of centrioles causes chromosomal instability in vertebrate somatic cells. J Cell Biol 203:747–756. https://doi.org/10.1083/jcb.201309033

164. Meunier S, Vernos I (2016) Acentrosomal microtubule assembly in mitosis: the where, when and how. Trends Cell Biol 27:314–321. https://doi.org/10.1016/j.tcb.2017.01.004

165. Ovejero S, Bueno A, Sacristán MP (2020) Working on genomic stability: from the S-phase to mitosis. Genes 11:225. https://doi.org/10.3390/genes11020225

166. Chan JY (2011) A clinical overview of centrosome amplification in human cancers. Int J Biol Sci 7:1122–1144. https://doi.org/10.7150/ijbs.7.1122

167. Kwon M, Godinho NJ, Chandhok NS et al (2008) Mechanisms to suppress multipolar divisions in cancer cells with extra centrosomes. Genes Dev 22:2189–2203. https://doi.org/10.1101/gad.1700908

168. Ganem NJ, Godinho SA, Pellman D (2009) A mechanism linking extra centrosomes to chromosomal instability. Nature 460:278–282. https://doi.org/10.1038/nature08136

169. Sinha D, Duijf PHG, Khanna KK (2019) Mitotic slippage: an old tale with a new twist. Cell Cycle 18:7–15. https://doi.org/10.1080/15384101.2018.1559557

170. Storchova Z, Pellman D (2004) From polyploidy to aneuploidy, checkpoint: how do cells delay anaphase onset? SEB Exp Biol Ser 59:243–256. https://doi.org/10.1098/rstb.2004.1615

171. Thompson SL, Compton DA (2011) Chromosome missegregation in human cells arises through specific types of kinetochore-microtubule attachment errors. Proc Natl Acad Sci U S A 108:17974–17978. https://doi.org/10.1073/pnas.1109720108

172. Crasta K, Ganem NJ, Dagher R et al (2012) DNA breaks and chromosome pulverization from errors in mitosis. Nature 482:53–58. https://doi.org/10.1038/nature10802

173. Hatch EM, Fischer AH, Deerinck TJ, Hetzer MW (2013) Catastrophic nuclear envelope collapse in cancer cell micronuclei. Cell 154:47–60. https://doi.org/10.1016/j.cell.2013.06.007

174. Terradas M, Martín M, Tusell L, Genesac A (2009) DNA lesions sequenced in micronuclei induce a local defective damage response. DNA Repair 8:1225–1234. https://doi.org/10.1016/j.dnarep.2009.07.004

175. Kato H, Sandberg AA (1968) Chromosome pulverization in human cells with micronuclei. J Natl Cancer Inst 40:165–179

176. Xu B, Sun Z, Liu Z et al (2011) Replication stress induces micronuclei comprising of aggregated DNA double-strand breaks. PLoS ONE 6:e18618. https://doi.org/10.1371/journal.pone.0018618

177. Zhang CZ, Spektor A, Cornils H et al (2015) Chromothripsis from DNA damage in micronuclei. Nature 522:89–93. https://doi.org/10.1038/nature14493

178. ICGC/TCGA (2020) Pan-cancer analysis of whole genomes consortium. Nature 578:82–93. https://doi.org/10.1038/s41586-020-1969-6

179. Umbreit NT, Zhang CZ, Lynch LD et al (2020) Mechanisms generating cancer genome complexity from a single cell division error. Science. https://doi.org/10.1126/science.aba0712

180. Tarapore P, Fukasawa K (2002) Loss of p53 and centrosome hyperamplification. Oncogene 21:6234–6240. https://doi.org/10.1080/sj.onc.1205707

181. Meek DW (2015) Regulation of the p53 response and its relationship to cancer. Biochem J 469:325–346. https://doi.org/10.1042/BJ20150517

182. Hafner A, Bulyk ML, Jambhekar A, Lahav G (2019) The multiple mechanisms that regulate p53 activity and cell fate. Nat Rev Mol Cell Biol 20:199–210. https://doi.org/10.1038/s41580-019-0110-x

183. Arquint C, Nigg EA (2016) The PLK4-STIL-SAS-6 module at the core of centriole duplication. Biochem Soc Trans 44:1253–1263. https://doi.org/10.1042/BST20160116

184. Sala R, Farrell K, Stears T (2020) Growth disadvantage associated with centrosome amplification drives population-level centriole number homeostasis. Mol Biol Cell 31:2646–2656. https://doi.org/10.1091/mbc.E19-04-0195
Centrosome instability: when good centrosomes go bad

194. Fong CS, Mazo G, Das T et al (2016) 53BP1 and USP28 mediate p53-dependent cell cycle arrest in response to centrosome loss and prolonged mitosis. Elife. https://doi.org/10.7554/eLife.16270

195. Lambrus BG, Daggubati V, Uetake Y et al (2016) A USP28–53BP1–p53 signaling axis arrests growth after centrosome loss or prolonged mitosis. J Cell Biol 214:143–153. https://doi.org/10.1083/jcb.201604054

196. Mettiger F, Anzola JV, Kaulich, et al (2016) 53BP1 and USP28 mediate p53 activation and G1 arrest after centrosome loss or extended mitotic duration. J Cell Biol 214:155–166. https://doi.org/10.1083/jcb.201604081

197. Mackenzie KJ, Carroll P, Martin CA et al (2017) cGAS surveillance of micronuclei links genome instability to innate immunity. Nature 548:461–465. https://doi.org/10.1038/nature23449

198. Coppé JP, Patil CK, Rodier F et al (2008) Senescence-associated secretory phenotypes reveal cell-non-autonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6:e301. https://doi.org/10.1371/journal.pbio.0060301

199. Yang H, Wang H, Ren J et al (2017) cGAS is essential for cellular senescence. Proc Natl Acad Sci U S A 114:E4612–E4620. https://doi.org/10.1073/pnas.1705499114

200. Xu M, Pirtskhalava T, Farr JN et al (2018) Senolytics improve physical function and life span in old age. Nat Med 24:1246–1256. https://doi.org/10.1038/s41591-018-0092-9

201. Armandis T, Monteiro P, Adams SD et al (2018) Oxidative stress in cells with extra centrosomes drives non-cell-autonomous invasion. Dev Cell 47:409–424.e409. https://doi.org/10.1016/j.devcel.2018.10.026

202. Basto R, Lau J, Vinogradova T et al (2006) Flies without centrioles. Cell 125:1375–1386. https://doi.org/10.1016/j.cell.2006.05.025

203. Poulton JS, Cunningham JC, Peifer M (2014) Acentrosomal Drosophila epithelial cells exhibit abnormal cell division, leading to cell death and compensatory proliferation. Dev Cell 30:731–745. https://doi.org/10.1016/j.devcel.2014.08.007

204. Basto R, Brunk K, Vinadogrova T et al (2008) Centrosome amplification can initiate tumorigenesis in flies. Cell 133:1032–1042. https://doi.org/10.1016/j.cell.2008.05.039

205. Caussinus E, Gonzalez C (2005) Induction of tumor growth by altered stem-cell asymmetric division in Drosophila melanogaster. Nat Genet 37:1125–1129. https://doi.org/10.1038/ng1632

206. Vitre B, Holland AJ, Kulukian A et al (2015) Chronic centrosome amplification without tumorigenesis. Proc Natl Acad Sci U S A 112:E6321–E6330. https://doi.org/10.1073/pnas.1519388112

207. Marthiens V, Rujano MA, Pennetier C et al (2013) Centrosome amplification causes microcephaly. Nat Cell Biol 15:731–740. https://doi.org/10.1038/ncb2746

208. Kulukian A, Holland AJ, Vitre B et al (2015) Epidermal development, growth control, and homeostasis in the face of centrosome amplification. Proc Natl Acad Sci U S A 112:E6311–E6320. https://doi.org/10.1073/pnas.1518376112

209. Serçin O, Larsimont JC, Karambelas AE et al (2016) Transient PLK4 overexpression accelerates tumorigenesis in p53-deficient epithelium. Nat Cell Biol 18:100–110. https://doi.org/10.1038/ncb3270

210. Levine MS, Bakker B, Boeckx B et al (2017) Centrosome amplification is sufficient to promote spontaneous tumorigenesis in mammals. Dev Cell 40:313–322.e315. https://doi.org/10.1016/j.devcel.2016.12.022

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.