



Review

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Centrosomes as signalling centres

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Centrosomes—as well as the related spindle pole bodies (SPBs) of yeast—have been extensively studied from the perspective of their microtubule-organizing roles. Moreover, the biogenesis and duplication of these organelles have been the subject of much attention, and the importance of centrosomes and the centriole–ciliary apparatus for human disease is well recognized. Much less developed is our understanding of another facet of centrosomes and SPBs, namely their possible role as signalling centres. Yet, many signalling components, including kinases and phosphatases, have been associated with centrosomes and spindle poles, giving rise to the hypothesis that these organelles might serve as hubs for the integration and coordination of signalling pathways. In this review, we discuss a number of selected studies that bear on this notion. We cover different processes (cell cycle control, development, DNA damage response) and organisms (yeast, invertebrates and vertebrates), but have made no attempt to be comprehensive. This field is still young and although the concept of centrosomes and SPBs as signalling centres is attractive, it remains primarily a concept—in need of further scrutiny. We hope that this review will stimulate thought and experimentation.

1. Introduction

Centrosomes function as the main microtubule-organizing centres (MTOCs) of animal cells [1]. Each centrosome consists of centrioles embedded in a pericentriolar matrix of proteins (PCM). The PCM comprises not only γ -tubulin ring complexes important for microtubule (MT) nucleation [2], but also a large number of proteins, many of which display coiled-coil domains [3,4]. Centrioles are cylindrical MT-based structures that display an evolutionarily conserved ninefold symmetry [5]. Of the two centrioles typically present in any one centrosome, the older one (the fully mature centriole) carries characteristic subdistal and distal appendages. Subdistal appendages are important for mature centrioles to function as MT-anchoring centres during interphase [6,7], whereas distal appendages enable mature centrioles to function as basal bodies for the formation of cilia and flagella [8]. Considerations of phylogeny suggest that evolutionary conservation of centrioles correlates with the need of an organism to form ciliary structures during its life cycle [9,10]. As yeast do not form cilia, they do not rely on centriole-based centrosomes for the organization of MTs. Instead, MTOC function in yeast is provided by spindle pole bodies (SPBs). SPBs are multilayered structures associated with the nuclear envelope and thus structurally distinct from centrosomes [11]. However, centrosomes and SPBs are functionally equivalent organelles in that both use a similar, γ -tubulin-based mechanism for MT nucleation. As a consequence, centrosomes and SPBs exert a strong influence on MT-based processes, notably intracellular transport and organelle distribution, cell shape and migration, as well as bipolar spindle formation and cell division.

Deregulation of centrosome structure and number has long been implicated in chromosomal instability and carcinogenesis [12–16]. Moreover, mutations in genes coding for centriolar and centrosomal proteins have been causally linked to human disease, notably ciliopathies and brain diseases [17,18]. As a result of these findings, recent years have seen a surge of interest in the structure and function of centrosomes, centrioles and SPBs. With the exception of multiciliated epithelial cells, where hundreds of centrioles are present, centrosomes and SPBs exist as only one or two copies per cell, depending on cell cycle stage. As these organelles play important roles in spindle formation and chromosome

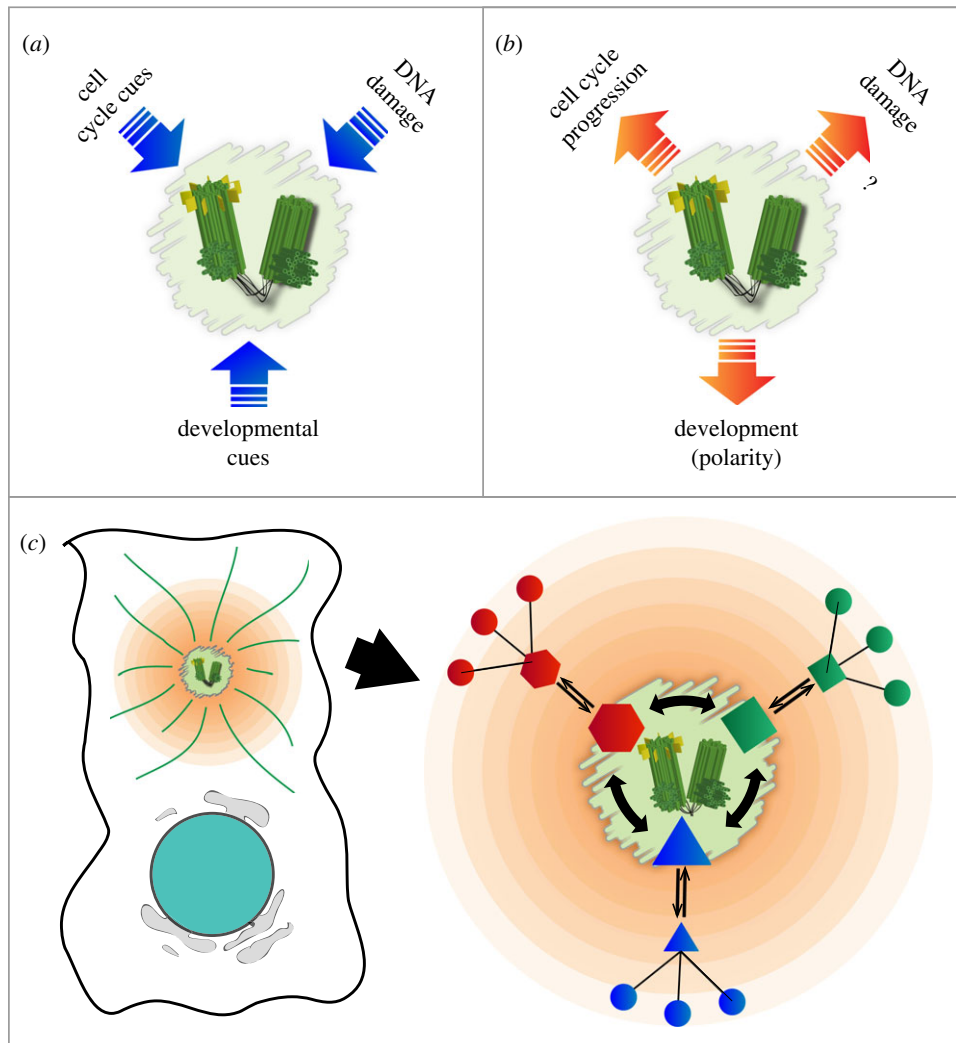


Figure 1. Centrosomes as signalling centres. It is well established that centrosomes (and SPBs) respond to multiple external signals (a). Increasing attention is being devoted to the alternative scenario, where centrosomes (and SPBs) function as signalling centres and solid-state platforms to influence cell physiology (b). The evolutionary advantages of using centrosomes (and SPBs) to locally concentrate signalling proteins could be manifold, as described in the main text. (c) Emphasizes the integration of multiple signalling pathways, the enhanced kinetics of biochemical reactions and the build-up of concentration gradients. (Online version in colour.)

segregation, their numbers as well as their MT-nucleating activities must be precisely controlled during the cell cycle. Additionally, centrosome separation prior to entry into mitosis [19–21], and the reversible formation of a primary cilium [22,23] also depend on cell cycle stage. Thus, it has long been recognized that centrosomes and SPBs are subjected to extensive regulation by cell cycle cues, developmental stimuli and DNA damage response pathways (figure 1a). Conversely, the centrosome has been proposed to serve as solid-state platform for the integration and coordination of various signalling pathways, and similar arguments have been made for yeast SPBs (figure 1b). In contrast to cytosolic signalling that merely depends on diffusion, the spatial concentration of signalling molecules at centrosomes and SPBs may enhance the kinetics of biochemical reactions and/or generate concentration gradients important for local responses (figure 1c). The anchoring of signalling proteins may also facilitate crosstalk between different signalling pathways and thereby contribute to the coordination of physiological responses (figure 1c). Moreover, asymmetries between individual centrosomes and SPBs provide opportunities for differential responses, potentially leading to differences in cell fate [22,24,25]. Finally, the mobility of centrosomes and their associated signalling molecules is expected to enhance the efficacy of signalling, as exemplified by events at the immune synapse [26].

An important corollary of the concept of centrosomes and SPBs as signalling centres is that structural and/or numerical aberrations in these organelles should affect cell physiology, cellular responses to stress and cell cycle progression [27–29]. Structural centrosome aberrations are typical of many cancers and believed to be important for cancer progression [16]. It may be rewarding to explore to what extent these structural alterations affect not only the MT-organizing capabilities of centrosomes, but also their signalling functions.

In this review, we assess a number of selected reports that bear on the notion of centrosomes and SPBs as signalling hubs. First, we summarize the evidence supporting such a role for yeast SPBs, with particular emphasis on the regulation of mitotic entry and exit. Then, we examine a few examples of centrosome-related signalling in the invertebrates *Caenorhabditis elegans* and *Drosophila melanogaster*. Finally, we extend our discussion to the centrosome of vertebrate cells. Reflecting the abundance of evidence relating to phosphorylation, this review focuses on the role of kinases and phosphatases at centrosomes and SPBs. Other post-translational modifications, including ubiquitylation, hydroxylation and acetylation, also occur at these organelles [30–34]; it seems safe to predict that the impact of these modifications will likely attract increasing interest in the future.

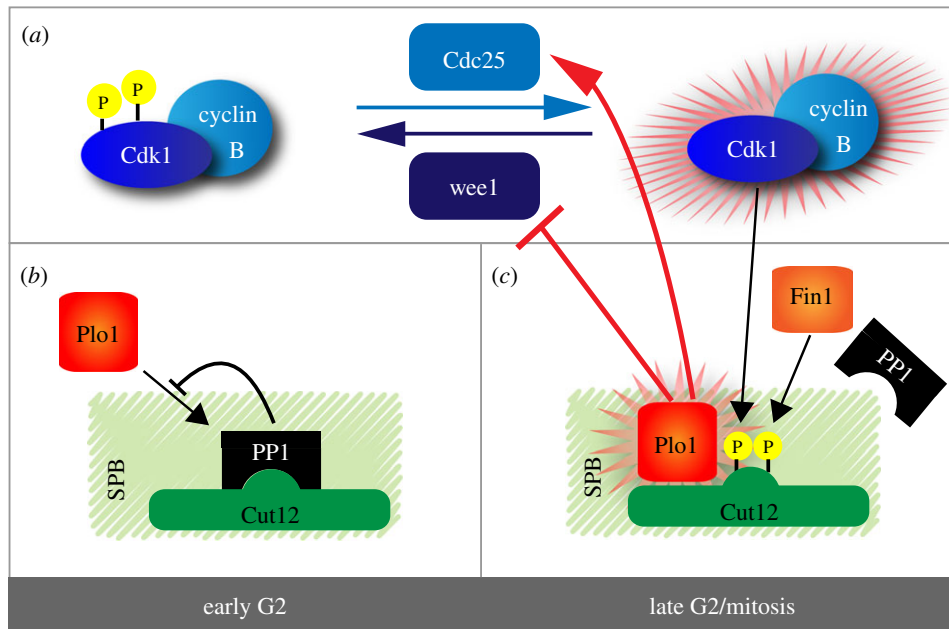


Figure 2. Activation of Cdk1/cyclin complexes at the fission yeast SPB. (a) General scheme of Cdk1/cyclin B activation at the G2/M transition. (b,c) Role of fission yeast SPB-component Cut12 in the assembly of components involved in the activation of Cdk1 at the G2/M transition. For details, see text and [36]. (Online version in colour.)

2. The importance of yeast spindle pole bodies for the regulation of mitosis

(a) Entry into mitosis

The cell cycle control machinery is centred on cyclin-dependent kinases (Cdks) and conserved from yeast to human. The traverse of M phase (mitosis and cytokinesis) depends on Cdk1 (also known as Cdc2 in fission yeast; CDC28 in budding yeast), which in mammals functions in association with A- and B-type cyclins. Activation of Cdk1 at the G2/M transition is controlled by antagonistic kinase and phosphatase activities. Core to this regulatory system is inhibitory phosphorylation imposed on Cdk1 by Wee1-related kinases, and relief of this inhibition by Cdc25 phosphatases [35]. Thus, entry into M phase requires both inhibition of Wee1-related kinases and activation of Cdc25 phosphatases (figure 2a). This is brought about by Polo-like kinase 1 (Plk1; Plo1 in fission yeast), which phosphorylates both Cdc25 and Wee1 [37–40], with the result that Cdc25 is activated whilst Wee1 is inhibited—in fact targeted for degradation [41] (figure 2a,c). Importantly, the recruitment of Plk1 to both Wee1 and Cdc25 depends on prior phosphorylation of these enzymes by an initial pool of activated Cdk1. This means that commitment to M phase depends on a positive feedback loop that displays all the features of a rapid and bistable switch.

Cdk1/cyclin B (also referred to as MPF in the early literature) has been observed at SPBs and centrosomes in many organisms [42–45]. These early observations already suggested that MTOCs might function as signalling platforms to promote mitotic entry, in addition to their roles in the organization of the MT network. The notion of MTOCs as signalling hubs has subsequently been strengthened, primarily through work on the yeast SPBs. This point is illustrated best by considering a series of studies on the SPB of the fission yeast *Schizosaccharomyces pombe*. Early work began with a screen that aimed at finding mutations that would allow cells to divide in the absence of Cdc25 phosphatase, which is essential for mitotic entry in wild-type cells. Surprisingly, this screen

resulted in the identification of a gain-of-function mutation in the SPB component Cut12 (also known as Stf1). This raised the question of how an alteration in a genuine SPB component could bypass the requirement for the Cdc25 phosphatase at the G2/M transition [46,47]. In the absence of Cut12, SPBs failed to activate MT nucleation and they did not integrate into the nuclear envelope, resulting in mitotic arrest [48]. Interestingly, this lack of Cut12 could be compensated for by enhancing Cdc25 levels, suggesting that SPB activation defects might reflect local impairment of Cdk1 activation [49]. These results suggested that signalling events on the SPB were somehow important for triggering entry into mitosis, but it remained unclear how Cut12 and/or the SPB contribute to this process.

Recently, it has been uncovered that Plo1, the fission yeast homologue of vertebrate Plk1, holds many of the answers. As in other species, fission yeast Plo1 is involved in a positive feedback loop that ensures robust Cdk1/cyclin B activation at the G2/M transition. In a normal cell cycle, active Plo1 is observed at SPBs shortly before cells enter mitosis. However, in cells harbouring mutant versions of Cut12 that suppress the requirement for functional Cdc25, Plo1 associated with SPBs prematurely and, moreover, displayed increased kinase activity. This suggested that lack of Cdc25 could be overcome by temporally advancing Plo1 activation at SPBs, which might then cause inhibition of Wee1-related kinases and result in activation of Cdk1/cyclin B [50,51]. This in turn led Hagan and co-workers to ask how gain-of-function mutations in Cut12 could impact on the spatio-temporal regulation of Plo1. The authors found that Cut12 mutations mapped to a conserved motif implicated in the recruitment of protein phosphatase 1 (PP1). Mutation of this PP1 docking site in Cut12 decreased not only the affinity of PP1 for Cut12, but also advanced the localization of active Plo1 to SPBs [52]. This implies that PP1 association with Cut12 normally delays Plo1 localization to SPBs, presumably by interfering with a direct association between Plo1 and Cut12 (figure 2b) [51]. In turn, PP1 association with Cut12 was shown to be regulated by two conserved phosphorylation sites within the PP1 binding motif. Phosphorylation of these

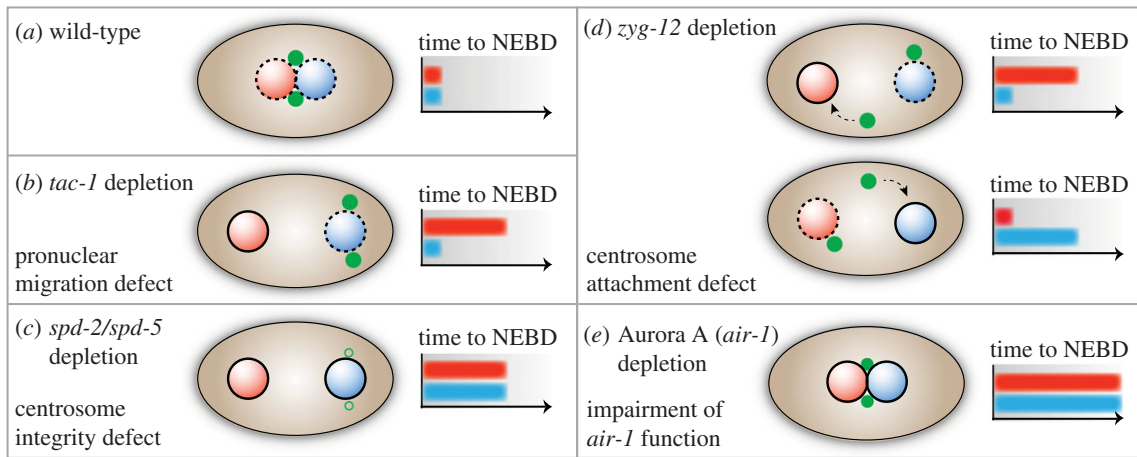


Figure 3. Centromeres promote the onset of NEBD in the *C. elegans* one-cell embryo. The scheme depicts the role of centromeres in facilitating NEBD in the *C. elegans* one-cell embryo (light grey/red, female pronucleus; dark grey/blue, male pronucleus; dashed black line, NEBD; filled black line, intact pronuclear membrane; black/green dots, centromeres), as described in [67,68]. Light/red and dark grey/blue bars refer to the timing of NEBD for the female and male pronucleus, respectively. (a) The situations are described for wild-type embryos, (b) embryos with a defect in pronuclear migration, (c) centromere integrity, (d) a centromere attachment defect and (e) embryos depleted of Aurora A. (Online version in colour.)

residues by Cdk1/cyclin B and Fin1, a kinase of the never in mitosis (NIMA) family, disrupted the association of PP1 with Cut12. As these phosphorylations occur late in G2 phase, this allows the recruitment of active Plo1 to SPBs and initial activation of SPB-associated Cdk1/cyclin B at the right time (figure 2c) [52]. This attractive model for the spatial control of Cdk1/cyclin B activation was confirmed by elegant re-targeting experiments demonstrating that activation of Cdk1/cyclin B or Plo1 at the SPB, but not at any other location, is sufficient to commit cells to mitotic entry [53].

(b) Exit from mitosis

The yeast SPB is also implicated in the control of mitotic exit. In particular, SPBs were recognized as important hubs for the assembly of signalling pathways known as the septum initiation network (SIN) in fission yeast and the mitotic exit network (MEN) in budding yeast, respectively. The SIN regulates key steps of cytokinesis, which in *S. pombe* comprises the formation and constriction of an actomyosin ring, septation and cell division, and asymmetry between the two SPBs has been implicated in the fine-tuning of these processes [54,55]. Central to the SIN are the GTPase Spg1, the three protein kinases Cdc7, Sid1, Sid2, as well as the inhibitory GAP complex Byr4–Cdc16. Importantly, the scaffolding protein complex Sid4–Cdc11 anchors the entire SIN cascade to SPBs [54]. This Sid4–Cdc11 scaffold is a stable integral part of SPBs and as such is thought to serve as a hub to assemble the various signalling components and regulators of the SIN [56]. In particular, Sid4 interacts with Plo1, a major activator of the SIN, whereas Cdc11 binds Spg1, thereby constitutively anchoring this GTPase to SPBs [56,57]. Spg1 drives the initiation of the SIN, and, when overexpressed, can trigger the onset of SIN signalling from any stage of the cell cycle [58]. In wild-type fission yeast, Spg1 is kept inactive during interphase by Byr4–Cdc16, and it is only activated upon entry into mitosis, when Byr4–Cdc16 dissociates from the SPBs [59,60]. Once activated, Spg1 is required for the activation of the three SIN kinases Cdc7, Sid1, Sid2. The terminal member of this cascade, Sid2, then translocates from the SPB to the site of division, where it drives cytokinesis [54]. As a rigorous test for the importance of the SPB in controlling SIN, fission yeast SPBs were subjected to laser ablation, a technically remarkable

undertaking [61]. Ablation of both SPBs, but not a single SPB, was found to impair cytokinesis, indicating that the spatial assembly of SIN components on at least one of the two SPBs is indeed required for successful cytokinesis.

Similar to the fission yeast SIN, the components of the budding yeast MEN are also tightly associated with SPBs [62,63]. Moreover, the MEN of *S. cerevisiae* also operates through a GTPase-driven protein kinase cascade, the organization of which is similar to the one described above for the SIN. The MEN counterpart of the SIN scaffold Cdc11 is the protein Nud1, which acts as an SPB-associated platform onto which the various MEN components assemble. Specifically, Nud1 is responsible for the SPB localization of the kinase Cdc15, and Cdc15 in turn is required for the recruitment and activation of the effector kinase complex Mob1–Dbf2 [64]. Importantly, the SPB scaffolding proteins Nud1 and Cdc11 serve not only as assembly platforms for signalling components in budding and fission yeast, respectively, but they actively modulate downstream signalling events, depending on their phosphorylation status [65,66].

Collectively, the above-discussed studies provide ample evidence to support the notion that yeast SPBs play important roles in the spatial and temporal integration of signalling by cell cycle regulatory proteins.

3. Centromere-related signalling in invertebrates

(a) Centromeres promote mitotic entry in early embryos of *Caenorhabditis elegans*

In the *C. elegans* one-cell embryo, the first mitotic division occurs according to a stereotypical temporal and spatial pattern. As in many other species, sperm contributes the first centromere to the *C. elegans* zygote. As a consequence, centromeres are initially positioned close to the posterior male pronucleus; they come into the vicinity of the female pronucleus only after pronuclear migration, when male and female pronuclei meet. In the wild-type embryo, the two pronuclei initiate the first mitotic division as soon as they meet, as reflected by synchronous nuclear envelope breakdown (NEBD; figure 3a). In striking contrast, when the two pronuclei are kept apart from each other through appropriate

experimental manipulation, they undergo NEBD in an asynchronous manner, with the female pronucleus showing a substantial delay (figure 3*b*). This setting provides a unique opportunity for studying the role of centrosomes in regulating mitosis, with observation of NEBD as a visual read-out [67,68]. The results of these studies indicate that centrosomes accelerate the onset of mitotic entry, probably through local concentration of a diffusible factor that promotes NEBD in a distance-dependent manner [67,68]. In support of this view, perturbation of centrosome integrity abrogated the asynchrony in the timing of NEBD of separated pronuclei (figure 3*c*), whereas the overall time until initiation of NEBD was increased. An even more striking observation was made upon RNAi-mediated depletion of the protein ZYG-12, which is essential for the attachment of centrosomes to the nuclear envelope of the male pronucleus; under these circumstances, the centrosomes moved freely in the cytoplasm and stimulated NEBD whenever they came close to a pronucleus: the closer a centrosome approached either the male or female pronucleus, the sooner this pronucleus underwent NEBD (figure 3*d*) [67,68]. This stimulation of NEBD was independent of MT-nucleation activity, as neither γ -tubulin depletion nor nocodazole treatment inhibited the process [67,68]. Instead, the centrosomal factor inducing mitotic entry was proposed to be Aurora A, a protein kinase known to associate with centrosomes in both invertebrates and vertebrates. In fact, depletion of Aurora A caused similar phenotypic consequences as perturbation of centrosome integrity, i.e. a general delay in NEBD initiation and abrogation of the asynchrony in NEBD between the two pronuclei (figure 3*e*).

How centrosome-associated Aurora A promotes NEBD is not fully understood. Aurora A has been implicated in the activation of Plk1 [69,70] and hence constitutes part of the positive feedback loop that drives activation of Cdk1/cyclin B. Thus, it is possible that Aurora A promotes NEBD through an indirect mechanism involving Cdk1/cyclin B [35]. Alternatively, or in addition, Aurora A might facilitate NEBD through direct phosphorylation of nuclear membrane components. In support of this latter possibility, a recent RNAi screen in *C. elegans* embryos defective for pronuclear migration points to an involvement of nucleoporins in Aurora A-mediated NEBD [71]. Depletion of several nucleoporins accelerated NEBD of separated female pronuclei, thereby decreasing the asynchrony in NEBD between the two pronuclei. Furthermore, at the onset of mitosis, some nucleoporins were locally removed from the nuclear envelope close to the site of centrosome association; this removal was dependent on intact centrosomes and active Aurora A, but not the presence of MTs [71]. Thus, it seems plausible that Aurora A can induce NEBD by directly or indirectly phosphorylating specific nucleoporins, leading to their dissociation from the nuclear envelope.

A next question to be addressed concerns the regulation of Aurora A abundance and activity at the *C. elegans* centrosome. According to one recent study, coordination between centrosome maturation timing and mitosis requires the UBXN-2 substrate adaptor for the AAA ATPase Cdc48/p97 [72]. RNAi-mediated depletion of UBXN-2 led to the accumulation of Aurora A at the centrosomes of one-cell embryos, indicating that UBXN-2/Cdc48/p97 negatively regulates centrosomal Aurora A levels. However, this ATP-dependent regulation of Aurora A association with centrosomes appears to be more relevant for the timing of centrosome separation and formation of astral MTs than for the timing of NEBD [72]. Instead, the timing of NEBD may depend primarily on

the regulation of Aurora A activity at the centrosome. In this context, it is interesting to note that studies performed with *Xenopus* egg extracts identified the centrosome as a primary site for Aurora A activation [73].

(b) Centrosomes help to establish polarity in *Caenorhabditis elegans* embryos

In addition to their function in promoting NEBD, centrosomes have also been implicated in the establishment of polarity in the *C. elegans* embryo. This symmetry-breaking event is required for the asymmetric division of the one-cell embryo into two blastomeres of distinct sizes, each having a distinct fate. During polarization, the anterior–posterior cell axis is defined by the formation of two distinct cortical domains that are characterized by different polarity protein compositions and contractile properties [74–76]. Importantly, the initial cue for polarization is provided by the centrosome that enters the egg with the sperm. Although the critical contribution of a centrosome-associated function to the induction of polarity is well established, the exact nature of this polarity cue has been the subject of some debate. One key issue has been whether the centrosome contributes a diffusible factor, or, alternatively, acts through an MT-dependent process [77–80]. *A priori*, the two mechanisms are not mutually exclusive. Recently, it has been reported that polarity could be induced by centrosomes even when these were positioned far from the cell cortex, although the distance from the cortex clearly affected the time required for symmetry breaking [81]. As cytoplasmic MTs constrain centrosome movement near the cortex, these MTs would thus be expected to favour the polarity-inducing action of centrosome-associated factors at the cortex [81].

(c) Roles of centrosomes in *Drosophila* development

In an early test for the role of centrosomes during *Drosophila* development, the fate of flies lacking the centriole duplication factor *DSAS-4* was examined [82]. Surprisingly, *DSAS-4* mutants proceeded normally through most of development and advanced to morphologically normal adult flies, even though centrioles and centrosomes were undetectable in adult cells. Adult *DSAS-4* mutant flies died shortly after birth, apparently because their sensory neurons lacked cilia [82]. This study clearly shows that flies are able to proceed through most of development by relying on a centrosome-independent pathway for bipolar spindle formation. However, when interpreting this finding, it is important to bear in mind that a maternally supplied pool of *DSAS-4* allowed centrosome formation during the earliest stages of embryogenesis [82]. In the complete absence of centrosomes, *Drosophila* early embryogenesis is severely disrupted [83]. Most likely this reflects a key role for centrosomes in bipolar spindle formation and spindle positioning during asymmetric divisions, including possible effects on the balance between stem cells and differentiating cells [25,76,84–86]. Taken together, these studies confirm that centrosomes are not essential for all cell divisions, but are critical for asymmetric divisions during early development as well as for ciliogenesis.

Drosophila also provides a prime example for the involvement of centrosomes in the response to DNA damage. When encountering damaged or incompletely replicated DNA, *Drosophila* cells will activate a checkpoint response that delays cell cycle progression. This response relies on pathways that have been evolutionarily conserved in other eukaryotic species.

In addition, however, *Drosophila* early embryos also manifest an intriguing DNA damage response that results in centrosome inactivation [87]. Early embryogenesis in *Drosophila* involves 13 extremely rapid nuclear divisions that proceed without cytokinesis, resulting in a syncytium. In these syncytial embryos, impaired DNA integrity was found to trigger intramitotic division failures that could be traced to the functional inactivation of spindle poles and centrosomes. This inactivation was characterized by loss of γ -tubulin from the centrosome, which led to anastral mitotic spindle assembly, mitotic delay and chromosome segregation failure. Most importantly, damaged nuclei associated with γ -tubulin-deficient centrosomes were detached from the cortex during cellularization and hence not incorporated into the developing embryo [87]. Subsequent studies revealed that this centrosome-related DNA damage response is mediated by Chk2, a key kinase implicated in 'classical' DNA damage response pathways [88]. Clearly, the pathway linking DNA damage to centrosome inactivation in *Drosophila* syncytial embryos represents a striking example for the importance of centrosomes in the safeguard of genome integrity.

In contrast to vertebrate mitoses, the nuclear envelope remains largely intact during nuclear division in syncytial *Drosophila* embryos. Instead, it is fenestrated selectively at the poles to allow spindle formation. This implies that centrosomes should remain 'attached' to nuclear envelopes throughout mitosis. Recent work revealed that this attachment requires the cooperation between *Drosophila* Polo (the founding member of the Plk1 family) and protein phosphatase 2A (PP2A) in association with a B-type regulatory subunit known as Twins [89]. Moreover, *Drosophila* genetics also revealed an antagonism between Polo/PP2A and the protein kinase Greatwall [89,90]; contributing to the emerging recognition that, in many species, this kinase-phosphatase balance plays a key role in the regulation of the G2/M transition (reviewed in [91–94]). Although precise mechanistic details of the interactions between these proteins remain to be clarified, the abovementioned studies again highlight the importance of centrosomes and spindle poles for the spatial assembly of regulators of mitotic progression, reminiscent of the situation described in §2 for the fission yeast SPB.

Finally, *Drosophila* is also one of the first species in which centrosomes were implicated in the spatial control of cyclin B degradation at the metaphase to anaphase transition. Live-cell imaging of cyclin B-GFP fusion proteins in *Drosophila* embryos revealed that cyclin B-GFP already begins to vanish from spindle poles in late metaphase, before it disappears from spindle MTs [95]. Furthermore, in *Drosophila centrosome fall off (cfo)* mutant embryos, where centrosomes are detached from the mitotic spindles, cyclin B-GFP destruction was inhibited at the spindles, but not at the centrosomes [96]. Together, these studies suggest that cyclin B destruction is first triggered at centrosomes/spindle poles, and that propagation of the destruction wave to the spindle requires an intact connection between the centrosome and spindle MTs [96].

4. Centrosomes as signalling platforms in vertebrates?

(a) Cell cycle progression

Some of the earliest evidence for the ability of centrosomes to trigger cell cycle events stems from the demonstration that

injection of purified centrosomes into eggs of both marine invertebrates and amphibians was sufficient to trigger parthenogenetic development [97,98]. These pioneering studies argue that centrosomes play a key role in the initiation of M phase in both vertebrates and invertebrates, similar to the conclusion drawn for yeast SPBs (see §2). Centrosomes have also been identified early on as an important hub for the localization of cAMP-dependent kinase [99,100]. Subsequently, this association was shown to be mediated by a specific targeting protein of the AKAP family [101–103], and the use of an elegant FRET biosensor demonstrates that locally confined regulation of cAMP signals at the centrosome impacts significantly on cell cycle progression [104]. Additionally, Cdk1/cyclin B, Cdc25B, Cdc25C, Plk1 and Aurora A have all been localized to centrosomes at the G2/M transition [43,105–110]. Thus, the entire signalling network implicated in the promotion of mitosis is present on vertebrate centrosomes. A phospho-specific antibody recognizing only the activated form of Cdk1/cyclin B was then used to demonstrate that initial activation of the complex occurs at the centrosome [111]. Recently, an elegant biosensor allowed careful analysis of the kinetics of Cdk1/cyclin B activation [112], and whereas the spatial resolution of this biosensor was limited, it would be interesting to explore the consequences of targeting a similar sensor to the centrosome. Interestingly, Cdc25B was also shown to act specifically on Cdk1/cyclin B at centrosomes [106,113]. Thus, centrosomes apparently facilitate the activation of Cdk1/cyclin B by bringing the necessary regulatory components into close spatial proximity, much like the situation discussed in §2 for yeast SPBs. However, while such a facilitating role appears plausible, the centrosome is not strictly essential for vertebrate somatic cells to enter mitosis: when centrosomes were removed by microsurgery or laser ablation, cells were still able to progress through mitosis with remarkably normal kinetics [114–116]. These results illustrate the efficiency of acentrosomal mechanisms for bipolar mitotic spindle formation, as noted already in the context of the phenotype associated with the *Drosophila* DSAS-4 mutant (see §3c). Tempering this conclusion, however, a recent study clearly demonstrates that genetic ablation of centrosomes from chicken DT40 B cells severely impaired cell cycle progression, indicating that centrosomes are critical for error-free segregation of large numbers of chromosomes [117].

Interestingly, the above mentioned studies on acentrosomal cells also revealed frequent defects in cytokinesis. Successful mitotic exit and cytokinesis rely on several key events. These include the timely onset of anaphase, triggered by cyclin degradation and consequent inactivation of Cdk1, as well as the formation of a central spindle, followed by assembly of an actomyosin ring beneath the cell cortex, ingression of the cleavage furrow and, finally, abscission [118]. The role of the mammalian centrosome in these late mitotic events is incompletely understood, but several intriguing observations have been reported. In particular, interest in a link between centrosomes and cytokinesis was kindled by the observation that, in some mammalian cells, the mother centriole moves towards the midbody (also known as the Flemming body) within the post-mitotic bridge [119]. Interestingly, this centriole movement appeared to correlate with abscission, the final step of cytokinesis, in that abscission occurred only after the centriole had moved back to the cell centre. These observations raised the possibility that centrioles provide a molecular cue to regulate abscission, reminiscent of the proposed role of the SPB in the MEN and SIN pathways in yeast [28]. Such a role would

explain the observation of frequent cytokinesis and abscission failures in cells from which centrosomes had been experimentally removed [115,119]. However, although centriole movement towards the midbody clearly occurs in some cultured cells, it does not appear to be a universal feature associated with cell division.

An alternative, perhaps related, role for the centrosome in cytokinesis is suggested by the observation that several centrosomal proteins localize to the midbody towards the end of mitosis, and the list of these proteins seems to be growing [4]. Of particular interest is Cep55, a centrosome- and midbody-associated protein required for mitotic exit [120,121]. Cep55 depletion results in cytokinesis failure, and Cep55 localization to the midbody is controlled by Plk1. This led to a model according to which Plk1 negatively regulates the association of Cep55 with the midbody until Plk1 is degraded late in mitosis. This would then allow Cep55 to be recruited to the midbody to promote abscission. Another interesting centrosome-associated protein implicated in cytokinesis is centriolin [122,123]. This protein also localizes to the maternal centriole in interphase and to the midbody prior to cytokinesis, and it is also required for mitotic exit. Of note, centriolin shares a small region of homology with the fission yeast SIN scaffolding component Cdc11 [122]. How centriolin, Cep55 and other centrosome- and midbody-associated proteins cooperate to regulate mitotic exit in human cells remains to be elucidated, but they are expected to impact on the regulation of vesicle transport and MT severing [124,125].

Another interesting question is whether mitotic exit and cytokinesis in human cells could be regulated, at least in part, by orthologues of the yeast SIN/MEN components. Counterparts for at least some of these genes could readily be identified in both invertebrate and vertebrate species (notably the kinases Mst1 and 2 as well as the kinases Lats1 and 2, along with associated regulatory proteins termed Mob, and the Cdc14 phosphatase), but the Mst and Lats kinases are implicated primarily in the proliferation-inhibitory Hippo signalling pathway [126–128]. Nevertheless, it is interesting that both Mst and Lats kinases have been functionally linked to the centrosome cycle [129]. Moreover, the human Hippo pathway component Mob1 has recently been localized to both the centrosome and the midbody and accordingly was proposed to control abscission through modulation of MT stability [130].

Centrosomes have also been implicated in the control of the G1/S transition, but the nature of this control has initially been controversial. Early studies showed that cell cycle progression from G1 to S was impaired when centrosomes were removed from certain cell types by microsurgery or laser ablation [114,115,131]. This then led to the hypothesis that a G1/S checkpoint might monitor centrosome status. Although this idea was initially intriguing, subsequent work has largely discounted it. In particular, it has been demonstrated that different types of untransformed human cells, including RPE1, can proceed through G1/S in the absence of centrioles, regardless of how the centrioles were removed [116]. Furthermore, centrosome removal or impairment of centrosome integrity was shown to trigger a cellular stress response that involves the activation of p38 kinase and p53. The latter then induces the Cdk inhibitor p21^{Cip1}, which readily explains the observed G1 arrests [28,29,116,132,133]. Thus, the idea of a specific centrosome-related G1 checkpoint has fallen out of favour, but centrosome integrity is likely to

be important for avoidance of stress responses and efficient traverse of the G1 phase of the cell cycle.

(b) The centrosome and the vertebrate DNA damage response

The role of the centrosome in DNA damage response has a chequered history. There are several intriguing hints for an important relationship [134], but definitive connections remain few and far between. One recurring theme is the finding that many proteins implicated in DNA damage response pathways, including Brca1, Brca2, Chk1, Chk2 and p53, seem to localize to centrosomes, usually in addition to cytoplasmic and/or nuclear localizations [28]. While some of these associations are undoubtedly real, it is important to bear in mind that artefactual stainings of centrosomes are not uncommon. These reflect either pre-existing anti-centrosome antibodies in rabbit sera or antibody cross-reactivity with centrosomal antigens [135]. Two contradictory studies on the purported centrosome association of the checkpoint kinase Chk1 may serve to illustrate this point: an initial, apparently convincing study reported that a specific, centrosome-associated population of Chk1 prevented premature activation of centrosomal Cdk1/cyclin B [136]. These data implicated Chk1 in the spatio-temporal regulation of cell division and, moreover, raised the possibility that the centrosome-associated pool of this enzyme might contribute to mediate the DNA-damage-induced inhibition of Cdk1/cyclin B. However, a subsequent study irrefutably showed that the reported centrosomal localization of Chk1 could be attributed to cross-reactivity of one particular antibody with a newly identified centrosomal protein, and that nuclear Chk1, not centrosomal Chk1, regulates Cdk1/cyclin B [137]. Likewise, the reported Cep63-dependent presence of Cdk1 at centrosomes [138] is almost certainly due to antibody cross-reactivity with Cep152 [139]. Thus, when interpreting immunocytochemical data reporting on unexpected centrosome-associations of particular proteins, it would seem wise to consider carefully the possibility of antibody-related artefacts [135,137,139,140].

Not only have proteins with well-established functions in DNA damage response pathways been reported to reside at centrosomes, but the opposite is also true: genuine centrosomal proteins have been implicated in DNA damage response. One early example is provided by a member of the centrin family of small, evolutionarily conserved calmodulin-related EF-hand proteins. Mammalian centrin-2 is considered the orthologue of the *S. cerevisiae* Cdc31 gene product, which is clearly required for SPB duplication [141]. Likewise, centrans are essential for the formation of basal bodies in ciliates [142,143]. Whether or not centrin-2 is required for centrosome duplication in human cells is controversial, but there is no question that this protein is a genuine component of vertebrate centrosomes [144–147]. Equally well established is the fact that centrin-2 interacts with xeroderma pigmentosum group C protein, a core component of nucleotide excision repair [148,149]. Much remains to be learned about the functions of centrin-2, but it is remarkable that genetic deletion of all centrin isoforms from chicken DT40 cells resulted in significant delays in nucleotide excision repair, but no obvious phenotypes associated with centrosome duplication or function [144].

In addition to centrans, other bona fide centrosome-associated components have also recently been implicated in DNA damage response pathways. These include pericentrin, a

core component of the centrosomal PCM [150], and Cep164, a protein associated with distal appendages of centrioles [151]. Mutations in pericentrin were found to cause Seckel syndrome, a disorder characterized by reduced brain and body size, and cells from these patients showed an impairment of ATR (ATM and Rad3-related)-dependent checkpoint signalling [152]. Similarly, mutations in Cep164 were shown to cause nephronophthisis-related ciliopathies [153]. Upon DNA damage, Cep164 was reported to accumulate within nuclear foci that are implicated in the activation of ataxia telangiectasia mutated (ATM), and knockdown of Cep164 in zebrafish resulted in impaired DNA-damage response. These findings echo earlier reports on links between centrosome-associated proteins and DNA damage response pathways, as exemplified by Cdk5rap2/Cep215 [154] or the microcephaly-related protein MCPH1/Brit1 [155]. These emerging connections are most intriguing, but in order to understand their (patho)physiological significance, it will be indispensable to decipher the wiring of the underlying molecular mechanisms and pathways.

At this point, the DNA damage-induced and Chk2-mediated loss of γ -tubulin from *Drosophila* centrosomes probably remains the best understood link between the DNA damage response field and the centrosome field (see §3c). Accordingly, attempts have been made to extend these findings from *Drosophila* to vertebrates. Considering that vertebrate embryos do not go through syncytial stages followed by cellularization, strict conservation of the *Drosophila* mechanism in vertebrates was not to be expected and, indeed, loss of γ -tubulin was not generally observed in response to DNA damage. Nevertheless, DNA damage was found to affect vertebrate centrosomes in multiple ways. When Chinese hamster ovary cells were forced to enter mitosis in the presence of damaged or incompletely replicated DNA, centrosomes often underwent splitting or fragmentation, leading to multipolar divisions and severe mitotic abnormalities [156]. Similarly, centrosome splitting was observed in immortalized RPE1 cells in response to ionizing radiation and other DNA damaging treatments, leading to the proposal that centrosome splitting may represent a general response to potentiate centrosome amplification [157]. Indeed, centrosome amplification has been frequently observed in response to DNA damage, for example in ATM- or ATR-deficient human cells [158], or in G2 arrested, Rad51-deficient chicken DT40 cells [159]. The molecular mechanisms underlying centrosome amplification in response to DNA damage remain to be elucidated, but both Chk1 and centriolar satellites have been implicated [158,160]. Moreover, APC/C activity was shown to oscillate, leading to successive rounds of Cdk2 and separase activation in the arrested cells [161]. Although

centrosome amplification does not necessarily require passage through mitosis [159], we emphasize that supernumerary centrosomes are expected to arise whenever cells with damaged DNA fail to arrest at the G2/M checkpoint and then advance to abortive divisions [16,140]. The physiological significance of centrosomal responses to DNA damage remains to be fully understood, but the possibility has been raised that centrosome fragmentation or amplification may constitute a safeguard mechanism to kill cells with DNA damage via induction of division failures [156,159].

5. Conclusion and perspectives

In this review, we have discussed a selection of reports that tend to support the view that centrosomes and SPBs may function as hubs or solid-state platforms for the integration of signalling pathways. We emphasize that we have made no attempt to be comprehensive. In particular, we have not addressed the evidence that attributes important roles to centrosomes in the replication of viruses and other intracellular pathogens, or in trafficking and turnover of cellular components. In addition, we are of the opinion that definitive evidence for an essential role of vertebrate centrosomes in any one signalling process is scarce. Considering that some cells go through the cell cycle without centrosomes just fine, this is probably not surprising. However, there is now strong evidence to indicate that SPBs contribute in major ways to the temporal and spatial organization of cell cycle regulatory components, and the same can be said for the centrosomes that act during early embryogenesis in invertebrates. Although it is tempting to extrapolate from these findings to vertebrates, it is to be expected that only truly advantageous functions have been conserved during evolution. At this time, several highly intriguing connections between centrosomes and DNA damage response pathways have been reported. Most of the dots still need to be filled in before we can possibly understand these connections, but this area certainly deserves further scrutiny. As the saying goes: ‘there is no smoke without fire’—or is there?

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