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Centrosome Organization and Functions

Abstract

The centrosome, discovered near 1875, was named by Boveri when proposing the chromosomal theory of heredity. After a long eclipse, a considerable amount of molecular data has been accumulated on the centrosome and its biogenesis in the last 30 years, summarized regularly in excellent reviews. Major questions are still at stake in 2021 however, as we lack a comprehensive view of the centrosome functions. Cell autonomous polarity and its transmission through cell division, appears as a unifying theme for the numerous centrosome functions [1], but specific mechanisms are often unknown. I will first try to see how progress towards a unified view of the role of centrosomes during evolution is possible, and then review recent data on only some of the many important questions raised by this organelle.

Towards a unified view of the centrosome in Evolution?

The membrane-less centrosome is formed about the conserved plasma membrane-associated and conserved centriole/basal body of protozoans, which is a derived character of eukaryotes containing hundreds of conserved proteins [2-6]. In vertebrates, the beating flagellum/cilium is conserved only in the male germ line, and in some of their specialized epithelial cell lineages having numerous beating cilia at their apical side [7]. Instead, depending on the cell type or in the same cell at different moments, the centrosome associates to the plasma membrane by its mother-centriole distal end, and grow a non-motile (9+0) primary cilium acting as a sensory design [8-11]. The presence of ciliated centrosomes in organisms may depend on the topological environment of individual cells [12].

The centrosome plays a key role in the asymmetry of division as it contains two centrioles with one or several generations between them: the two centrosomes of a stem cell distribute according to a specific pattern in all differentiating systems [13,14]. As recently demonstrated for the yeast Spindle Pole Body (SPB) [15], this differential distribution may be critical for animal cell ageing [16]. It is present almost exclusively in two multicellular groups forming the super-clade of Amorphea [17, 18; see Azimzadeh contribution]. First in the Opisthokonta, as a primary cilium/centrosome organ in the animal lineage, and as an acentriolar centrosome, the SPB in the fungus lineage. Second, in the Amoebozoa, as a Nucleus Associated Body (NAB), in unicellular organisms like *D. discoideum*, that are able to make transient multicellular organisms [19]. A comprehensive account of the functional evolution of the primary cilium/centrosome organ will have to clarify the significance of having two centrioles, mother and daughter, and why it is present in most cells of multicellular organisms capable of locomotion, yet being absent in some other cells, like myotubes [20]. It will have also to build a mechanistic description on how centrosome and cell periphery are permanently communicating, making a sort of unique compartment ensuring the interface between the cell inside and the outside [21]. Finally, the functional significance of non-canonical centrioles in Ecdysozoa will have to be clarified. They have lost a great number of centriole proteins that are present in both unicellular protozoans and vertebrates [22]. As for the simpler acentriolar centrosome, why is it present as a SPB only in

multicellular fungi (the unicellular yeasts are the result of secondary transitions) that are unable of locomotion, and as a NAB in cells that are able to make transient multicellular organisms able of locomotion? The NAB shares with the centrosome the property of being cytoplasmic and linked to the nucleus in a flexible manner [31], contrasting with the SPB which is tightly associated with the nuclear surface or even inserted into the nuclear envelope. The mode of association to the nucleus, as well as the three dimensional core structure, must have functional correlates through the cytoskeleton organized by the centrosome: these are likely to bear on cell and tissue morphogenesis, but how? The morphogenetic power of the centrosome-based microtubule aster is shown during *Drosophila* early embryogenesis, which leads to about 6 000 nuclei within a common cytoplasm, each with an associated cytoplasmic body without plasma membrane. And yet, the secretory membrane system is organized in functionally compartmentalized units around individual nuclei, with the normal polarity before cell formation [23]. Uncoupling centrosome and nuclear divisions in the syncytium before nuclei migration to the embryo periphery in a *gnu* locus mutation [24], demonstrated that centrosomes were able to double at the correct pace and reorganize microtubules, actin and spectrin networks and plasma membrane in the syncytium. Thus the centrosome has a major role in organizing and polarizing the perinuclear cytoplasm in the absence of plasma membrane. It coordinates all the early embryo stages until cell formation, although it is largely dispensable for further development [25,26]. This suggests that major functions concentrated on the centrosome in vertebrate distal and subdistal appendages on the mother centriole in *Drosophila* development are either not necessary or associated with other structures in Ecdysozoa, allowing the effects of centrosome loss to be buffered. The absence of the distal part of centrioles and thus of the would support this view [27].

A burning question is the evolutionary origin of the centrosome, and first that of the centriole/basal body and the 9+2 axoneme. They are only speculations so far [28,29]. Microorganisms having the ancestral means for gliding motility, a very ancestral mode of locomotion [30], would also be candidates for showing organelles that predate centriole/basal body function or behavior. For example, mycoplasma such as *M. pneumonia*, so far known for their small size, minute genome, and total lack of a cell wall, are polarized, fusiformed bacteria which, instead of a polarized flagellum or a stalk like *Caulobacter crescentus* [31], have a cytoskeletal ‘attachment organelle’ involved in polarity, adherence, motility and cell division [32]. Moreover, its biogenesis seems to predate that of basal bodies: a new ‘attachment organelle’ forms in the vicinity of the old one through an apparent conservative mechanism and migrates to the other pole of the cell before its division together with the new nucleoid to which it is attached [32].

A physical view of the centrosome organization

The centrosome is a compact organelle with a toroidal organization of the pericentriolar material (PCM) with respect to the mother centriole, revealed by super-resolution optical microscopy [2,33-34]. The PCM increases considerably its size and capacity to nucleate microtubules during mitosis [35,36]. In 2014, mitotic centrosomes from *C. elegans* embryos were described as autocatalytic droplets of pericentriolar material organized by centrioles [37,38]. This view drew the attention of the field to the importance of phase transition mechanisms [39,40]. A growing interaction between cell biologists and polymer physicists has developed on the genesis

and stability of membrane-less organelles in time and space and on the regulation of phase transitions. (See Woodruff contribution).

How can the mature centriole organize PCM in mitosis? The inner layer of molecules is recruited by the centriole, whereas molecules in the outer layer are recruited through self-assembly or self-oligomerization. The recruitment of PCM proteins apparently correlates with the developing structure of the daughter centriole [41,42]. Thus, beyond its direct structural aspect, the PCM-centriole interface is an important question as it bears on how the daughter centriole become a mother centriole, i.e a centrosome. How can centrioles provide a unique and highly specific platform in cells that is recognized at physiological concentration by centriolar MT-binding proteins? Several proteins have been shown to participate in the process of daughter centriole acquiring the ability to reproduce, such as SAS7 in the worm *C. elegans*, which has a limited homology with Chibby in *Drosophila*, implicated in centriole-to-basal body conversion [42-44]. Thus, the maturation of daughter centrioles and the participation of centrioles in cilia formation may involve similar mechanism. The luminal centriole protein CEP44, an essential protein in human cells that binds to the A-microtubules and interacts with the inner protein POC1B, has been shown to affect centriole structure and centriole conversion in RPE1 h-TERT cells [41]. The loading of CEP44 and POC1B to the lumen of centrioles downstream of Cep295 and the action of δ - and ϵ -tubulin would result in the formation of the centriole blades, showing that the developing centriolar structure is necessary for recruitment of PCM proteins. Interestingly, there is no CEP44 homologue in *D. melanogaster* suggesting once more important differences between vertebrates and insects in the maturation of the daughter centriole [41].

During interphase, the so-called satellites are another type of membrane-less structures concentrated in the vicinity of the centrosome. Their functions have long been puzzling. Recently, several reports have significantly progressed in understanding their functions [45-47]. This question is fully addressed in F. Gergely contribution.

The distal and the subdistal appendages

Correlative super-resolution microscopy and EM has been used to determine where distal appendage proteins localize in relation to the centriole microtubules and appendage electron densities [48]. Distal appendages undergo a dramatic ultra-structural reorganization before mitosis, during which they temporarily lose outer components, while inner components maintain a nine-fold organization. Mammalian distal appendages associate with two adjacent centriole microtubule triplets via an elaborate filamentous base and appear as almost radial finger-like protrusions. Thus, these findings modify seriously the traditional view of mammalian distal appendages as a pinwheel-like structures that are maintained throughout mitosis. Instead of a space between each pinwheel blade, distal appendages reveal an unprecedented architectural and functional organization at the base of mammalian primary cilia [49]. Classical transmission EM had clearly indicated the proximity of distal and subdistal appendages, although they have very different functions. The super-resolved molecular architecture of subdistal appendages has suggested that they are indeed structurally or functionally related to distal appendages, implicating a regulatory mechanism of microtubule anchoring around the centrosome [50]. It has been convincingly shown that distal appendages are displaced from the mother centriole prior to mitosis

under the control of Nek2 kinase [51]. Overexpression of active Nek2A, but not kinase-dead Nek2A, prematurely displaced distal appendages from the interphase centrosomes in (RPE1) cells.

The centrosome as an actin-nucleating center

The way in which the actin and the tubulin networks interact and regulate each other is a critical question for a better understanding of cell dynamics and cell polarity. A ground-breaking result in the field was the demonstration in 2016 that the centrosome can also nucleate actin microfilaments [52,53]. The mechanism involves the regulation of the nucleation of microtubules by actin microfilaments, thus explaining the nucleation by the centrosome of either microfilaments or microtubules [54]. The presence of actin at the centrosome provides an additional spatial region where the two filaments systems can interact to regulate one another's behavior. By using both *in vitro* and *in vivo* assays to study centrosomal actin nucleation as cells pass through mitosis, it was shown that mitotic exit is accompanied by a burst in cytoplasmic actin filament formation, leading to the accumulation of actin around centrosomes as cells enter anaphase and to a corresponding reduction in the density of centrosomal microtubules [55]. Mitotic regulation of centrosomal WASH and the Arp2/3 complex seems to control local actin nucleation, to tune the levels of centrosomal microtubules during passage through mitosis. Another work showed that Arp2/3 complex inhibition decreased spindle actin [56]. As a consequence, mitotic spindle formation was impaired, which resulted in disorganized chromosomes congression and ultimately mitotic defects in non-transformed cells. Thus centrosomal Arp2/3 complex activity plays a role in the maintenance of genomic integrity during mitosis. It was also shown independently that prophase specific perinuclear actin in connection with polymerizing microtubules regulates the positioning of centrosome separation before nuclear envelope breakdown [57]. This depends apparently on the interaction between the LINC complex and actin: breaking this link results in centrosome mis-positioning and an increase in sister chromatid segregation errors. It is likely that the actin nucleating activity of centrosomes plays a role also in this mis-positioning. Revisiting the function of the centrosome in neuronal differentiation, a recent review has argued that centrosomal F-actin could be important to understand how neurons achieve distinct functional domains, one axon and several dendrites, which allow them to connect properly [58].

Basal bodies/centrioles from epithelial ciliated cells are known for long to be associated with acto-myosin [59]. However, only recently has the functional significance of this association been clarified in the brain ependymal cells [60]: a coordination between ciliary beating and actin organization exists that contributes to the protection of cilia and basal bodies/centrioles against the shear stress generated by ciliary beating and the associated fluid flow. Amazingly, disruption of the apical actin network causes basal bodies/centrioles to detach from the apical surface of ependymal cell. Thus, it is the cilia beating that controls the apical actin network around basal bodies/centrioles to protect them.

The centrosome positioning and cell polarity

Amongst all the organelles, the centrosome, as a single copy-organelle able to organize the cytoskeleton, and thus the distribution of the other organelles, at the cell scale, is bound to have a

dominant role in defining cell polarity [12, 61]. Its positioning has been looked at from different approaches [62,63, for a review 64], demonstrating, as expected, a pleiotropic regulation for this organelle positioning. The centrosome is a 'central body' mainly in eggs, and in free-living animal cells such as white blood cells. In cells within tissues, the centrosome is not at the cell center, but close to the cell periphery on the contrary. Indeed, it was demonstrated with kidney cells cultured on adhesive micro-patterns, that cell confinement could control centrosome positioning and cell polarity [65]. Actin play a specific role, not only for centrosome segregation during mitosis, but also in centrosome positioning during interphase [66]. It is the interaction of the MTs with the actin network rather than the cell contour itself which matters.

When the centrosome is ciliated, i-e in the majority of post-mitotic cells in the body, the mother centriole is physically associated with the plasma membrane, where it templates a primary cilium and controls the intra-ciliary traffic. Regulation of microtubule dynamics nucleated by the mother centriole is critical for its repositioning [67]. Centrosome repositioning was shown to be an early event of epithelial-to-mesenchymal transition in cultured conditions, before cells scattering proper, in elegant experiments using adhesive micro patterns. This demonstrated the critical role of this organelle in controlling cell polarity [68].

However, half of the MT nucleation in human RPE1 cells occurs at the Golgi Apparatus (GA) and relies on AKAP450 interaction with GM130 [69]. Is there a crosstalk between the GA and the centrosome? At the G2/M transition, when the centrosome MT nucleation activity increases, the activity at the GA is switched off and fully recovers after cell division. To examine the situation in interphase, gene ablation of four γ -TuRC canonical receptors and the Plk4 inhibitor centrinone to induce centrosome loss were used [70]. It showed that MT nucleation is a hierarchically regulated process: ablation of the centrosome strongly enhanced MT nucleation at the GA, while inhibition of GA-associated MT nucleation did not affect centrosome activity. Only silencing both MT nucleation activities laid to the formation of aggregates able to nucleate MTs in the cytoplasm.

The centrosome in neurogenesis

The critical involvement of the primary cilium/centrosome organ in microcephaly [20], suggested an important role of this organ in brain development. Two papers have significantly progressed in the mechanisms by which centrosomes influence brain development [71,72]. In neural progenitor cells that generate neurons and glia in the cerebral cortex, the centrosome is positioned away from the nucleus, anchored to the apical membrane of the ventricular zone of the cerebral cortex. This positioning apparently controls the mechanical properties of cortical cells in mice [81]. Disruption of the anchorage of the centrosome to the apical membrane results in the disorganization of microtubules and stretching and stiffening of the apical membrane as measured by AFM. As a consequence, their mitotic behavior and the size and formation of the cortex are modified. Disruption of the anchorage of the centrosome, done by the elimination of CEP83, also activates the YAP protein and promotes the over-proliferation of progenitor cells, followed by overproduction of intermediate progenitor cells, leading to the formation of an enlarged cortex with abnormal folding. Suppression of this effect by the simultaneous elimination of YAP suggests a new role of the centrosome in regulating the mechanical features of neural progenitor

cells and the size and configuration of the mammalian cerebral cortex. An important outcome of this work is to show a centrosome-dependent relationship between the mechanical properties of precursor cells and the size and formation of the cortex.

Basal progenitors then delaminate and settle in the sub-ventricular zone in enlarged brain regions. The length of time that cells stay in the sub-ventricular zone is essential for controlling further amplification and fate determination. In a search for regulators of sub-ventricular zone generation and expansion, AKNA [73], first annotated as an AT-hook transcription factor, was interesting as the level of its mRNA correlated with the time at which the sub-ventricular zone was generated [72]. This work shows that it is in fact a novel integral component of sub-distal appendages and that it is binding to microtubules, which reassembles at the centrosomes during late telophase and early G1 phase. AKNA loss of function impairs delamination, and leads to the retention of more basal progenitor cells in the ventricular zone, whereas AKNA overexpression induced a fast delamination. Moreover, AKNA-induced delamination occurs in interphase, during which AKNA localizes at centrosomes, and overexpression of the cytoplasmic form AKNA which lacks the centrosome-binding domain does not induce delamination. Importantly, AKNA efficiently recruited components of the γ -tubulin ring complex but no other centrosome- and microtubule-associated proteins. AKNA also co-immuno-precipitates with proteins having a role in microtubule organization (EB1, p150-glued, ODF2), thus appearing as capable of regulating microtubule nucleation at the centrosome, specifically in the brain. Apparently, AKNA regulates the delamination process by increasing centrosomal MTOC activity, weakening complexes at the cell junctions and promoting contraction of the apical side. The delamination from the ventricular zone resembles the epithelial–mesenchymal transition and indeed AKNA had some effect on EMT in other tissues. Live imaging in slices after AKNA overexpression or knockdown *in vivo* demonstrated that AKNA is key not only in bringing cells into the sub-ventricular zone but also in retaining them there. The switch in morphology and the radial migration of neurons apparently require a switch from a centrosomal to more non-centrosomal MTOC via endogenous downregulation of AKNA. Thus, microtubule organization differs profoundly for cell migration into the sub-ventricular zone, which requires AKNA and a centrosomal MTOC, versus migration out of the sub-ventricular zone, which requires the loss of AKNA.

Thus, AKNA orchestrates the delamination process by increasing centrosomal microtubule nucleation and recruiting nucleation factors and minus-end stabilizers, by destabilizing microtubules at the adherens junctions and by mediating constriction of the apical side. Regulating AKNA levels orchestrates delamination and retention in the sub-ventricular zone. Interestingly, this process is particularly relevant in species with highly proliferative cells in an enlarged sub-ventricular zone. Thus, the function of AKNA in ontogeny may have profound relevance in phylogeny.

Brain development may become the best experimental model to unravel centrosome functions.

The centrosome biogenesis during cell cycle progression

Long seen as the division organ only, most effort was first devoted to the coupling between centrosome biogenesis and cell cycle progression and its deregulation in disease [74]. The inhibition of centriole duplication either by an inhibitor of PLK4 [75] or by the auxin inducible degradation system [76] were very important to reveal the p53-dependent specific pathway for

monitoring centriole assembly [77]. The specificity of the drug was then questioned [78] and recently, PLK4 signaling outside centriolar networks was investigated by mass spectrometry of cellular protein phosphorylation in stable PLK4-expressing U2OS human cells exposed to centrinone. Surprisingly, sequence interrogation of ~300 significantly down-regulated phosphoproteins reveals an extensive network of centrinone sensitive [Ser/Thr]Pro phosphorylation sequence motifs, which might be either direct or indirect targets of PLK4 [79].

The initiation of centriole assembly by the transition from a uniform ring of PLK4 surrounding the mother centriole to a single PLK4 spot, corresponds to what physicists call a symmetry breaking. How this is achieved is the matter of different models, which involve several ways to regulate the activity of PLK4 [80,81; see Kitagawa contribution]. Important new ideas on how centrosome-specific oscillations in the association of a regulatory molecule like PLK4 could time its biogenesis have recently pointed to the ground-breaking possibility that perhaps many different biological processes have the ability to oscillate [82] : first, it was shown in fly early embryo that Plk4 functions as a clock, establishing both the rate and period of daughter centriole growth and thus the relationship between them to ensure that daughter centrioles grow to the correct size : using Sas-6-GFP or Ana2-GFP as a proxy to measure daughter centriole length in *D. melanogaster* embryos, since fly centrioles are short and since the cartwheel extends throughout the length of the daughter centriole, this work provided a quantitative description of the kinetics of daughter centriole growth and showed that the cartwheel grows from the proximal end [90]. Thus, Plk4 helps coordinate the inverse relationship between centriole growth and growth period. Then it was shown that PLK4 oscillation, which is normally entrained to the cell-cycle oscillator, can run autonomously [83]. This is indeed a very important result as it could illuminate the question of the physical and molecular principles that cells use to regulate the biogenesis of their organelles. In any case, it could potentially explain why centrioles can assemble independently of cell-cycle progression. The authors importantly discuss the possibility that the Plk4 centriole oscillation could be an example of a general mechanism describing the regulation of organelle biogenesis: oscillations in the levels/activity of key regulatory factors essential for organelle biogenesis could precisely time the initiation and duration of the growth process, ensuring that organelles grow at the right time and to the appropriate size. In such a model, cell cycle engine and circadian clocks could entrain the phase of a network of autonomous oscillators to ensure that biological processes occur in a coordinated manner.

Conclusion

Cellular functions such as microtubule-mediated nucleocytoplasmic transports, signaling pathways controlling the positioning of the centrosome, or centrosome in diseases, including non-cell-autonomous effects, could not be covered in this brief review. However, its contribution to so many cellular processes already, both as a signaling hub and a mutually exclusive organizing center for both tubulin- and actin-based polymers, together with the fact that centrosome biogenesis could be an example of a more general mechanism of organelle biogenesis, makes of the primary cilium/centrosome a critical organ for cell economy and polarity in Metazoa, including for the mechanical properties of the polarized cells during brain development. The current exploding research on the centrosome and primary cilium should lead to a better understanding of how time and space are controlled in animal cells.

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