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CELL SCIENCE AT A GLANCE

SPECIAL ISSUE: RECONSTITUTING CELL BIOLOGY

Centriole assembly at a glance

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ABSTRACT

The centriole organelle consists of microtubules (MTs) that exhibit a striking 9-fold radial symmetry. Centrioles play fundamental roles across eukaryotes, notably in cell signaling, motility and division. In this Cell Science at a Glance article and accompanying poster, we cover the cellular life cycle of this organelle – from assembly to disappearance – focusing on human centrioles. The journey begins at the end of mitosis when centriole pairs disengage and the newly formed centrioles mature to begin a new duplication cycle. Selection of a single site of procentriole emergence through focusing of polo-like kinase 4 (PLK4) and the resulting assembly of spindle assembly abnormal protein 6 (SAS-6) into a cartwheel element are evoked next. Subsequently, we cover the recruitment of peripheral components that include the pinhead structure, MTs and the MT-connecting A-C linker. The function of centrioles in recruiting pericentriolar material (PCM) and in forming the template of the axoneme are then introduced, followed by a mention of circumstances in which centrioles form *de novo* or are eliminated.

KEY WORDS: Centriole, Centrosome, Microtubules, PLK4, STIL, SAS-6

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Journal of Cell Science

 Journal of Cell Science (2019) 132, jcs228833. doi:10.1242/jcs.228833

Introduction

Over a century ago, Theodor Boveri spotted centrioles as beacons residing within centrosomes at spindle poles (Boveri, 1900). It later became apparent that centrioles play fundamental cellular functions also outside of mitosis. Not surprisingly, alterations in centriolar components or in processes that rely on them cause a variety of disease conditions (reviewed in Nigg and Holland, 2018; Nigg and Raff, 2009). Centriole architecture has been largely conserved over two billion years of evolution: the organelle is a cylinder that is typically ~500 nm long and ~250 nm wide with a striking 9-fold radial symmetry of microtubules (MTs). Moreover, the centriole is polarized: MT triplets are present proximally and MT doublets distally, whereas characteristic sub-distal and distal appendages are present on the mature organelle (see central panel in accompanying poster).

In this Cell Science at a Glance article and the accompanying poster, we cover the birth, life and death of the human centriole, with a mention of other systems when necessary. First, we highlight the licensing step needed to jumpstart the centriole assembly process. We then discuss how symmetry is broken to enable the emergence of a unique cartwheel, an element thought to scaffold centriole assembly. How peripheral elements are added to the emerging procentriole as well as post-translational modifications (PTMs) of MTs are evoked next, followed by the function of centrioles in recruiting pericentriolar material (PCM) and in providing a template of the ciliary axoneme. Circumstances in which centrioles form *de novo* or are eliminated are then discussed.

With well over one hundred annual publications that mention centrioles, this overview does not have the ambition to be comprehensive. Many structures of interest, including centriolar satellites and rootlets that connect resident centrioles, are not discussed hereafter. Likewise, many important proteins are not mentioned explicitly. Readers are invited to consult recent extensive reviews to that end (for example Banterle and Gönczy, 2017; Bornens, 2012; Firat-Karalar and Stearns, 2014; Loncarek and Bettencourt-Dias, 2018; Nigg and Holland, 2018). Being part of the Special Issue on ‘Reconstituting Cell Biology’ is particularly fitting – both centriole and PCM research have left the strictly cellular environment in recent years, with cell-free assays developed to reconstitute aspects of the biology of this fascinating organelle.

Preparing the terrain – centriole disengagement and torus formation

Centriole disengagement and formation of a platform in the shape of a torus around each resident centriole together prepare the terrain for the onset of procentriole assembly (see poster). Most proliferating cells are born with two centrioles that are referred to as the mother and daughter centriole. Usually towards the G1-S transition, a procentriole assembles near-orthogonal to the proximal end of each resident centriole, a configuration maintained until mitosis. At that time, the two units disengage from each other in a process that requires polo-like kinase 1 (PLK1) and possibly the cysteine protease separase (Hatano and Sluder, 2012; Loncarek et al., 2010; Tsou et al., 2009; Wang et al., 2011; discussed in Sluder, 2013). This disengagement step licenses both centriolar cylinders to each seed the assembly of one procentriole at the next cell cycle. Another crucial preparatory step for assembly is maturation of the newly formed centriole, notably through recruitment of centrosomal protein of 192 kDa (CEP192), to a sleeve around the outer centriolar wall (Gomez-Ferreria et al., 2007; Joukov et al., 2010; Tsuchiya et al., 2016; Zhu et al., 2008). A CEP152–CEP63–CEP57 complex is then recruited to form a torus surrounding the proximal part of the CEP192 sleeve (Cizmecioglu et al., 2010; Hatch et al., 2010; Lukinavicius et al., 2013; Sir et al., 2011; Sonnen et al., 2012). Whereas one procentriole emerges from this torus in most proliferating cells endowed with resident centrioles, as discussed below, procentrioles can also form *de novo* in some settings (see Box 1).

In summary, centriole disengagement and torus formation render each resident centriole competent to serve as an assembly site for one procentriole.

Defining an assembly site – symmetry breaking and PLK4 focusing

How does a single procentriole emerge from a seemingly isotropic torus containing CEP152–CEP63–CEP57? Two proteins are key for this process: polo-like kinase 4 (PLK4) and SCL-interrupting locus protein (STIL) (see poster). PLK4 trans-autophosphorylates its kinase domain, thus promoting activity, but also its degron motif, which results in targeting for degradation by the E3 ubiquitin ligase $SCF^{\beta\text{-TrCP}}$ (also known as F-box/WD repeat-containing protein 1A) (Brownlee et al., 2011; Cunha-Ferreira et al., 2009; Guderian et al., 2010; Holland et al., 2010; Rogers et al., 2009; Sillibourne et al., 2010). Moreover, PLK4-mediated phosphorylation of STIL promotes association of the two proteins and protects the kinase from degradation (Kratz et al., 2015; Moyer et al., 2015; Ohta et al., 2014; Zitouni et al., 2016). Together, this dual phosphorylation breaks symmetry and, starting from an initially uniform distribution on the torus, PLK4 – and perhaps phosphorylated STIL (pSTIL) – now transition to a single focal point, referred to as ‘focusing’.

Recent findings raise the possibility that PLK4 can do more than merely phosphorylate itself and STIL. In *Xenopus* egg extracts, Plk4 self-assembles into condensates that recruit STIL, as well as α-,

Box 1. Appearing from seemingly nowhere – *de novo* centriole formation

New centrioles assemble in the vicinity of resident centrioles in most proliferating cells, but there are interesting exceptions (see poster). Early cleavages of mouse embryos happen without centrioles, which appear *de novo* at the blastocyst stage (Courtois et al., 2012). Moreover, centrioles appear anew in the protist *Naegleria gruberii* when food sources are scarce, a prelude to the transition from amoeboid movement to flagellar motility (Fulton and Dingle, 1971). An orchestrated transcriptional program is deployed during this transition, which includes expression of mRNAs translated to yield SAS-6, SAS-4, as well as POC1, δ- and ε-tubulins (Fritz-Laylin and Cande, 2010). Likewise, centrioles appear *de novo* during spermiogenesis in the water fern *Marsilea vestita*, emanating in this case from an electron-dense region known as the blepharoplast (Hepler, 1976). Numerous centrioles also form from an electron-dense entity termed the deuterosome in multiciliated epithelial cells, although, in this case, resident centrioles are present to start with (Klos Dehring et al., 2013; Zhao et al., 2013). In human cells, bona fide *de novo* centriole formation occurs following removal of resident centrioles, for instance by laser microsurgery or chronic treatment with Centrinone (La Terra et al., 2005; Wong et al., 2015). Therefore, *de novo* assembly is somehow silenced by resident centrioles in human cells. In addition, the number and architecture of centrioles generated is aberrant, indicating that the underlying mechanism is error prone.

Although the dissection of *de novo* centriole assembly is lagging compared to that of the canonical centriole duplication pathway operating in most proliferating cells, the two share many requirements, whilst differing in some ways – as exemplified in human cells. Whereas PLK4 and hsSAS-6 are essential in both cases, the higher order oligomerization of hsSAS-6 dimers necessary for centriole assembly in the canonical pathway is dispensable during *de novo* formation (Wang et al., 2015), perhaps because peripheral elements, such as the A-C linker or MT, are particularly crucial in this case.

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β- and γ-tubulins, thereby generating microtubule organizing centers (MTOCs) (Montenegro Gouveia et al., 2018). Although analysis by electron microscopy (EM) indicates that these condensates are not centrioles, this observation can lead one to imagine that PLK4 concentrates other components than just STIL during organelle biogenesis. Mathematical modeling indicates that a crucial step in PLK4 focusing entails competition between transient maxima of kinase activity on the torus, which resolve into one focus stabilized by association with pSTIL (Leda et al., 2018). In conclusion, focusing of PLK4 and of its target STIL presumably impart the location from which the procentriole will emerge, around an element dubbed the cartwheel.

Building a scaffold – SAS-6 proteins and cartwheel assembly

Pioneering EM work identified a cartwheel in the first ∼100 nm of the emerging procentriole (reviewed in Hirono, 2014). Viewed in cross section, the cartwheel harbors a hub that is ∼22 nm in diameter, with nine spokes extending towards peripheral MT triplets (see poster). The spindle assembly abnormal protein 6 (SAS-6; in human also known as HsSAS-6 or, to some, as SASS6) is crucial for cartwheel assembly across systems. SAS-6 proteins harbor an N-terminal globular domain followed by a coiled-coil domain plus a C-terminal moiety, and undergo two types of self-association (Kitagawa et al., 2011; van Breugel et al., 2011). First, two SAS-6 molecules form a dimer through an association driven by the coiled-coil domains. Second, SAS-6 dimers undergo higher-order oligomerization through interactions of their N-terminal domains. The angle between adjacent dimers is ∼40°, such that nine homodimers could form a 9-fold symmetrical ring. The *Chlamydomonas* protein SAS-6 (CrSAS-6) can, indeed, form 9-fold symmetrical rings *in vitro*, although 8- and 10-fold symmetrical structures are generated as well (Hilbert et al., 2016; Kitagawa et al., 2011). This suggests that SAS-6 self-assembly is necessary, but not sufficient, to generate the 9-fold radial symmetry of the centriole organelle. Furthermore, high-speed photothermal off-resonance atomic force microscopy indicates that CrSAS-6 rings can self-assemble in <2 min (Nievergelt et al., 2018). A key step at the onset of cartwheel assembly is the interaction of SAS-6 with the focus on the torus harboring PLK4 and STIL (Ohta et al., 2014). However, whether HsSAS-6 can focus on the torus independently of PLK4 and STIL is not clear. Regardless, it is tempting to speculate that assembly of SAS-6 proteins on the torus surface dictates the signature near-orthogonal emergence of the procentriole (see Box 2).

How are SAS-6 rings that are only ∼4.5 nm in height assembled to form the entire cartwheel? Cryo-electron tomography (cryo-ET) of the exceptionally long cartwheel from *Trichonympha spp*. revealed that SAS-6 rings stack onto each other and that spokes emanating from rings merge towards the periphery (Guichard et al., 2012). Furthermore, CrSAS-6 cartwheel-like structures can stack autonomously into structures of an average height of ∼110 nm, akin to cartwheel sizes *in vivo*, raising the possibility that SAS-6 proteins contribute to setting the cartwheel length (Guichard et al., 2017). Interestingly, live analysis of GFP-tagged *Drosophila* Sas-6 via 3D-structured illumination microscopy (SIM) indicates that the protein incorporates from the proximal end of the cartwheel, suggesting that rings stack from that location (Aydogan et al., 2018).

In summary, self-assembly of SAS-6-bearing rings and their stacking is fundamental for building the cartwheel element that scaffolds the emerging procentriole, preparing for the addition of peripheral components.

Box 2. A simple hypothesis – the root of the orthogonal arrangement

A striking feature of the emerging procentriole is its near-orthogonal arrangement with the resident centriole. Although other scenarios can be envisaged, a simple mechanism by which such a stereotyped geometry could be attained derives from the arrangement of SAS-6 proteins on the surface of the torus. Coarse-grained Brownian dynamics simulations revealed that SAS-6 ring assembly is dramatically enhanced on a surface compared to being in solution (Klein et al., 2016). Transposed to the *in vivo* situation, these considerations raise the possibility that efficient ring formation occurs most readily following diffusion of SAS-6 proteins along the surface of the torus. Thereby, SAS-6 rings formed on this surface would be positioned necessarily near-orthogonal to the resident centriole and, thus, impart this topological relationship to the emerging organelle.

Going peripheral – pinhead, MTs and A-C linker

The SAS-6-based cartwheel is connected through the pinhead structure to peripheral MTs (see poster). The pinhead is polarized along the proximal–distal centriole axis and, therefore, may impart polarity to the entire organelle (Guichard et al., 2013). A prominent candidate pinhead protein is CEP135 and its *Chlamydomonas* homologue, basal body protein Bld10p (BLD10) (Matsuura et al., 2004; Ohta et al., 2002). Immuno-EM analysis positions Bld10p at the cartwheel spokes and the pinhead in *Chlamydomonas* (Hiraki et al., 2007). Moreover, the N-terminus of CEP135 interacts with MTs, as might be expected for a pinhead protein (Carvalho-Santos et al., 2012; Kraatz et al., 2016). Furthermore, *Chlamydomonas bld10* null mutants lack cartwheel and centriole (Matsuura et al., 2004). However, the situation is more nuanced in other systems. For example, deletion of CEP135 from chicken DT40 cells does not prevent procentriole assembly, even though it reduces its efficiency (Inan et al., 2013). Likewise, RNAi-mediated depletion of CEP135 in human cells leads to partial impairment of the process (Lin et al., 2013), although the interpretation of these depletion experiments is complicated by the existence of two *CEP135* transcripts with opposing roles (Dahl et al., 2015). Overall, it appears that either the pinhead is dispensable for procentriole assembly in some systems or else proteins other than CEP135 operate in a partially redundant manner in some cases.

With cartwheel and pinhead in place, centriolar MT triplets are added and elongate (see poster). MTs in each triplet are designated A-, B- and C-, starting from the inside. Only the A-MT is complete and contains 13 protofilaments, whereas the B- and C-MTs share protofilaments with A- and B-MTs, respectively (Greenan et al., 2018; Guichard et al., 2013). The mechanisms leading to the generation of such unusual MTs are not entirely clear, but divergent tubulin isotypes are one contributing factor: depletion of δ- and ε-tubulin from human cells results in centrioles that lack B- and C-MTs, and fall apart during mitosis (Wang et al., 2017), echoing findings with δ- and ε-tubulin mutants in *Chlamydomonas* and *Tetrahymena* (Dutcher and Trabuco, 1998; Dutcher et al., 2002; Ross et al., 2013). Moreover, so-called microtubule inner proteins (MIPS), whose molecular nature remains to be characterized, are visible in the cryo-EM map of centriolar MTs (Greenan et al., 2018; Guichard et al., 2013; Li et al., 2012). Another characteristic of centriolar MTs is their extremely slow net growth rate. Whereas cytoplasmic MTs can grow at velocities of several µm per minute, the net growth of centriolar MTs is several orders of magnitude lower than this, judging from EM analysis (Kuriyama and Borisy, 1981). However, probing the underlying dynamics could change this view. Perhaps centriolar MTs grow as fast as cytoplasmic ones

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but undergo very frequent catastrophes, resulting in a slow effective growth rate. Moreover, centrioles must be able to elongate much faster during the rapid early embryonic cycles in many species; how elongation rates of centriole MTs are modulated in such settings is not known.

Potentially, such modulation relies on proteins that regulate MT elongation during canonical centriole duplication, including the spindle assembly abnormal 4 (SAS-4) relative CPAP (also known as CENPJ), which caps MT plus ends (Sharma et al., 2016; Zheng et al., 2016). CPAP overexpression causes overly long centrioles (Kohlmaier et al., 2009; Schmidt et al., 2009; Tang et al., 2009), raising the possibility that CPAP somehow contributes to setting centriolar MT length. Longer centrioles are also observed upon overexpression of the CPAP-interacting protein CEP120 (Comartin et al., 2013) or the WD40-containing protein POC1 (Keller et al., 2009), as well as upon depletion of centriolar coiled-coil protein of 110 kDa (CP110), which resides at the very distal end of centrioles (Kohlmaier et al., 2009; Schmidt et al., 2009; Spektor et al., 2007; Tang et al., 2009). How these proteins modulate centriolar MT behavior remains to be fully elucidated.

One further characteristic of centriolar MTs are the numerous PTMs of α/β-tubulins, including acetylation, detyrosination, glycylation and polyglutamylation (Janke, 2014). Ultrastructure expansion microscopy (UltraExM), whereby samples are placed in a polymer and expanded isotropically before applying stimulated emission depletion (STED) super-resolution microscopy, revealed that polyglutamylation occurs strictly on C-MTs (Gambarotto et al., 2018 preprint). Moreover, polyglutamylation is restricted to a central part of *Chlamydomonas* centrioles (Hamel et al., 2017). Polyglutamylation appears to be important for centriole integrity since microinjection of antibodies against this modification results in PCM loss and, subsequently, in centriole disappearance (Bobinnec et al., 1998).

Another peripheral element that is likely to be important for centriole assembly is the A-C linker, a polarized structure connecting the A-MT from one triplet to the C-MT of the adjacent one (see poster). The A-C linker exhibits a characteristic ∼110º angle between neighboring triplets (Greenan et al., 2018; Guichard et al., 2013), which could contribute to establishing the 9-fold symmetry of the organelle, especially during *de novo* biogenesis. A prominent A-C linker candidate is the aforementioned POC1, which can bind MTs (Keller et al., 2009). Interestingly, *Tetrahymena* cells that lack POC1 exhibit aberrant positioning of MT triplets (Meehl et al., 2016), and centrioles are unstable in human cells co-depleted of POC1A and POC1B (Venoux et al., 2013).

Centriole assembly is completed by the formation of sub-distal and distal appendages during the cell cycle after the birth of the procentriole, transforming it into a mother centriole (reviewed in Bornens, 2002).

In conclusion, addition of the pinhead structure, MTs – which then acquire PTMs, the A-C linker and appendages turns the procentriole into a mature organelle.

The organelle at work – centrosome assembly and axonemal templating

Having discussed the mechanisms of centriole biogenesis, in the following we will consider two of the important functions exerted by this organelle: PCM recruitment and, thereby, centrosome assembly, as well as templating of the axoneme.

Recruitment of PCM relies notably on self-organizing properties of the functionally related proteins CDK5RAP2 in humans, Centrosomin (Cnn) in *Drosophila* and spindle-defective protein 5 (SPD-5) in *C. elegans*. In addition, pericentrin plays an important role in PCM formation in vertebrate cells (Loncarek et al., 2008). Interestingly, SPD-5 can phase-separate *in vitro* into gel-like condensates that recruit MT-nucleating proteins, as well as α- and/or β-tubulin, thus generating functional MTOCs (Woodruff et al., 2017). SPD-5 interacts with SPD-2 (CEP192 in human), which is present both at centrioles and at the PCM (Kemp et al., 2004; Pelletier et al., 2004), making it an ideal bridge between the two entities. Similarly, Cnn can form large-scale assemblies, albeit in a structured solid phase, and is also recruited by *Drosophila* Spd-2 (Feng et al., 2017). Both SPD-5 and Cnn assemblies are catalyzed by Plk1/POLO-mediated phosphorylation (Feng et al., 2017; Woodruff et al., 2015), indicating a shared regulatory mechanism. Overall, through the recruitment of dedicated proteins, such as CDK5RAP2, Cnn or SPD-5, centrioles direct centrosome assembly in most proliferating animal cells.

Centrosome position in animal cells is critical for many aspects of physiology, including location of the Golgi and, consequently, of the secretory apparatus. One particularly salient example occurs at the immunological synapse: when a killer T-cell encounters an antigen-presenting cell, the centrosome is repositioned to face the target cell, thus, directing secretion of lytic enzymes towards it (reviewed in Stinchcombe and Griffiths, 2014). Moreover, the position of the two centrosomes during mitosis dictates placement of the cleavage furrow and is, thus, particularly critical during development and in stem cell lineages (reviewed in Kiyomitsu, 2015).

When cells exit the cell cycle, the two centrioles often migrate to the plasma membrane, where the mother centriole – now also referred to as the basal body – docks below the plasma membrane through the fusion of vesicles that cap the distal appendages (reviewed in Wang and Dynlacht, 2018). Thereafter, the nine MT doublets of the mother centriole elongate to form the nine corresponding doublets of the axoneme. Primary cilia generated in this manner are crucial for many signaling pathways, including Hedgehog signaling. Centrioles also seed the formation of motile cilia and flagella (reviewed in Ishikawa, 2017). Here, in addition to elongation of the nine MT doublets, two centrally located MTs form in the transition zone between the centriole proper and the axoneme. The requirement of centrioles for motile cilia and flagella is likely to have imparted strong evolutionary constraint on centriole architecture (reviewed in Bornens and Azimzadeh, 2007).

Box 3. Life span of the centriole organelle

For how long are centrioles maintained once they have been assembled? Wear and tear of centriolar proteins undoubtedly occurs and, thus, one might have expected that they are readily replaced in the mature organelle. However, pioneering experiments in tissue culture cells indicated that centriolar α/β-tubulin undergoes little, if any, exchange during one cell cycle (Kochanski and Borisy, 1990). These findings are mirrored by observations in *Tetrahymena* using fluorescence recovery after photobleaching (FRAP) of fluorescently labeled α-tubulin (Pearson et al., 2009). Moreover, proteomic analysis using stable isotope labeling by amino acids in cell culture (SILAC) pulse-chase labeling in human cells identified candidate components that undergo little exchange (Jakobsen et al., 2011). Furthermore, marked mating experiments in *C. elegans* established that the pool of β-tubulin, SAS-6 and SAS-4 present in the two centrioles contributed by the sperm to the zygote, persist for several cell cycles with no detectable exchange with the cytoplasmic pool (Balestra et al., 2015). Therefore, at least some centriolar proteins exhibit remarkable persistence, raising the possibility that they carry information from one cell generation to the next and, perhaps, also from the sperm to the zygote.

In conclusion, centrioles serve many cellular functions, including that of assembling the PCM to generate centrosomes and of templating the axonemal MTs, thus being crucial for signaling and motility.

Lights out – centriole elimination

Whereas most animal cells contain centrioles – which can be extremely stable (Box 3) – there are situations where they are eliminated. The mechanisms by which this is achieved are only beginning to be uncovered, and it will be interesting to address whether they simply follow the assembly program in reverse or a different route. One particularly compelling case is encountered during fertilization: each gamete were to contribute a pair of centrioles, the zygote would have four centrioles to start with instead of the usual two. In most metazoan species, this is solved in that the zygote inherits two centrioles only from the sperm. Although centriole elimination from the female germ line can happen after fertilization in some species, it usually occurs during oogenesis, including in *C. elegans*, *Drosophila* and mammals (reviewed in Delattre and Gönczy, 2004; Manandhar et al., 2005). The mechanisms of centriole elimination during oogenesis are best understood in *Drosophila*, where they entail protection of the PCM by Plk1/POLO (Pimenta-Marques et al., 2016). In the wild-type, Plk1/POLO departs from the PCM, which then disappears, before the centrioles themselves are lost. This dissociation of Plk1/POLO from the PCM regulates centriole elimination, as shown by ectopically targeting Plk1/POLO to centrioles, which prevents PCM removal and centriole elimination, leading to failed embryogenesis.

There are other instances where centrioles vanish, including during spermatogenesis in mice, when both centrioles have degenerated by the time of fertilization (Manandhar et al., 1998). Since centrioles are also eliminated during oogenesis, early mice embryos undergo spindle assembly by using the non-centrosomal pathway (reviewed in Bennabi et al., 2016). Centriole elimination from sperm appears to be restricted to rodents as it does not occur in other mammals. In primates, the centriole that is used as the template for the flagellar axoneme remains reasonably intact; the other one degenerates to a large extent, yet retains sufficient integrity in order to initiate the formation of a procentriole in its vicinity in the zygote (Fishman et al., 2018). A case of centriole disappearance might also occur during muscle formation, when PCM components, such as pericentrin and γ-tubulin redistribute to the nuclear periphery upon fusion of myoblasts into myotubes (Fant et al., 2009; Tassin et al., 1985). It will be interesting to analyze the fate of centrioles during this process and address whether it matters to the differentiation program. More generally, untransformed human cells undergo p53-dependent arrest when centrioles are absent; for instance, following treatment with the PLK4 inhibitor Centrinone (Wong et al., 2015). When the p53 pathway is inactivated, as is frequently the case in human cancer cells, the absence of centrioles appears to be relatively well tolerated as cells still proliferate, although with chromosome segregation errors and cases of apoptosis (Wong et al., 2015).

In summary, there are situations in which centrioles are eliminated or inactivated, and such disappearance can be key for correct cellular behavior.

Conclusions and perspectives

In the following, we delineate some lines of work that are likely to be pursued in centriole research in the future. Given the minute size of centrioles, it will be important to localize proteins with even greater precision. Although SIM, STED and stochastic optical reconstruction microscopy (STORM) super-resolution approaches have proven transformative, further resolution improvements are needed. One promising avenue is UltraExM (Gambarotto et al., 2018 preprint), as mentioned above, but also novel super-resolution modalities, such as MINimal emission FLUXes (MINFLUX) microscopy (Balzarotti et al., 2017), which has the potential to achieve nanometer-scale precision. The impressive strides in cryo-EM should also prove fruitful here. And the Holy Grail may lie in conducting super-resolution time-lapse microscopy of centriole assembly in a cellular context.

This Cell Science at a Glance article focused primarily on centriole assembly, but the question of centriole number control is of central importance, especially given its implication for disease. In this context, it will be interesting to decipher mechanisms that enable different human cancer cell lines to each regain a set centriole number following washout of Centrinone (Wong et al., 2015). Moreover, centriole number control is an area in which fundamental discoveries might translate to the clinic. Although it is not yet clear whether PLK4 inhibitors will prove useful therapeutics (discussed in Holland and Cleveland, 2014), at least they pave the way for a related drug arsenal that targets centrioles.

As Theodosius Dobzhansky aptly stated “Nothing in biology makes sense except in the light of evolution”. This statement also applies to centriole biology. Despite obvious commonalities among all centriolar forms, there are also variations, including in fold symmetry and centriole length (reviewed in Gönczy, 2012). It will be exciting to uncover the underlying mechanisms, now that investigations in non-model organisms can be envisaged. Given the complexity of the centriole organelle, cell-free reconstitution of the assembly reaction might prove illuminating. Some steps have already been reconstituted, including self-assembly of SAS-6 proteins or phase-separation of PCM-like condensates (Kitagawa et al., 2011; Woodruff et al., 2015). Reconstituting other aspects of centriole biogenesis will bring the field closer to something that might have seemed like a dream to Theodor Boveri, i.e. building the centriole organelle from scratch.

Acknowledgements
We are grateful to Alexandra Bezler for comments on the manuscript. We apologize to those authors whose work we could not cover due to space constraints and to those whose contributions we were not aware of.

Competing interests
The authors declare no competing or financial interests.

Funding
Work on centriole biology in the laboratory of PG is supported by the European Research Council (AdG 340227).

Cell science at a glance
A high-resolution version of the poster and individual poster panels are available for downloading at http://jcs.biologists.org/lookup/doi/10.1242/jcs.228833.supplemental

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