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Centriole Elimination: A Mechanism for Resetting Entropy in the Cell

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Abstract

Centrioles are highly conserved organelles within the eukaryotic domain of life, playing an indispensable role in microtubule organization, cellular differentiation, and the formation of cilia and flagella. However, in the processes of oogenesis and spermatogenesis in certain organisms, centrioles undergo elimination, thereby preventing the transmission of either young or aged centrioles to the zygote, depending on the specific system of asymmetric division. The removal of centrioles in gametes can be interpreted as a mechanism of resetting cellular entropy and restoring totipotency, which is crucial for embryonic development. In somatic cells, centriole elimination is also observed during terminal differentiation, suggesting a potential connection to replicative aging. Research indicates that the programmed removal of centrioles is linked to degradation mechanisms involving microtubule breakdown and the ubiquitin-proteasome system. Centrioles are unique in the cellular architecture as they lack self-repair mechanisms, leading to the continuous accumulation of entropy, thereby contributing to cellular and organismal aging. Consequently, eliminating centrioles where they are no longer needed can be seen as a countermeasure against aging. Furthermore, centriole elimination plays a pivotal role in preventing centrosome-related pathologies, abnormal cell division, and possibly even oncogenesis. Investigating the mechanisms of centriole elimination opens promising avenues in biomedicine, including strategies for tissue rejuvenation and aging control.

Keywords: centrioles, elimination, entropy, totipotency, differentiation, aging.

Introduction

Centrioles represent evolutionarily conserved organelles that perform a variety of fundamental cellular functions, including cell motility, intracellular signaling, and differentiation. Despite their structural stability and persistence, centrioles can be actively removed under specific

physiological conditions—a phenomenon first recognized in oocytes in pioneering studies by Theodor Boveri (Boveri, 1887). Since then, additional cases of centriole elimination have been identified, yet the overarching molecular and regulatory mechanisms remain largely elusive, preventing a comprehensive understanding of its functional significance across different cell types. In many terminally differentiated cells, centrioles become anchored beneath the plasma membrane, where they act as basal bodies, dictating the structural organization of the axoneme in primary cilia (Breslow, D. K., & Holland, A. J., 2019). Additionally, centrioles play an essential role in the formation of axonemes within motile cilia and flagella, which are crucial for cellular movement and environmental sensing. Given these diverse functional roles, centrioles are indispensable for proper signal transduction and cell motility.

Moreover, in the majority of cycling animal cells, centrioles are embedded within the pericentriolar material (PCM, also known as the pericentriolar matrix), forming the centrosome, which serves as the primary microtubule-organizing center (MTOC). This role is crucial both during interphase, for maintaining cellular architecture, and during mitosis, where centrosomes facilitate bipolar spindle assembly, ensuring precise chromosome segregation and asymmetric distribution of biomolecules and cellular structures (Pintard, L., & Bowerman, B., 2019). Given their essential role in cellular organization, structural alterations or numerical aberrations of centrioles have been implicated in a variety of pathologies, including ciliopathies and cancer (Braun, D. A., & Hildebrandt, F., 2017). The number of centrioles within a cell is tightly regulated. In cycling cells, the initial centriole pair consists of a mother centriole—characterized by distal and subdistal appendages—and a daughter centriole, which remains linked to the mother via a flexible connection. During the early S-phase, a new procentriole begins to form at a nearly orthogonal angle relative to each existing centriole. By the G2/early mitotic phase, the two pairs of centrioles, now surrounded by PCM and thus forming functional centrosomes, separate to direct the assembly of a bipolar spindle. The molecular pathways and regulatory proteins governing this tightly orchestrated centriole duplication cycle are well characterized (Gomes et al., 2021).

However, while centriole numbers increase from two to four in cycling cells, different mechanisms govern centriole control in other contexts. For instance, some cells initially lack centrioles but later assemble them de novo (Takumi, K., & Kitagawa, D., 2022). This process occurs in early rodent embryos, as well as in certain plant species such as mosses, ferns, and gymnosperms. Additionally, it has been observed in Naegleria gruberi, a unicellular protist undergoing transformation from an amoeboid to a flagellated state (Gomes et al., 2021). Interestingly, de novo centriole formation often involves bicentriolar structures coiling in opposite directions. Experimentally induced de novo centriole assembly has also been demonstrated in human cells depleted of centrioles (Khodjakov et al., 2002). Moreover, in multiciliated epithelial cells, multiple procentrioles cluster around existing centrioles and specialized organelles called deuterosomes, leading to the rapid expansion of centriole numbers into the hundreds (Dirksen, 1971). Finally, centriole numbers can also be reduced from four or

two down to zero through the process of centriole elimination.

Centriole Proteins Can Be Mistaken for Centrioles

Centrioles are ultrastructurally defined by their characteristic ninefold symmetrical arrangement of microtubules. However, they can also be functionally identified as structures capable of recruiting PCM and initiating axonemal organization. The elimination of centrioles is a process wherein both their ultrastructure and functional capacity are lost. Given their minute size and limited copy number within most cells, centriole presence or absence has often been assessed indirectly by tracking protein foci containing centriole-associated markers, rather than relying solely on high-resolution electron microscopy (EM). In some cases, such as human cells depleted of RBM14, Neurl4, or TRIM37, foci containing centriole-associated proteins, which act as MTOCs, were revealed by EM analysis to lack microtubules entirely (Balestra et al., 2021). These findings highlight that centriole-associated protein foci do not necessarily correspond to actual centrioles, despite maintaining the capacity to recruit PCM and function as MTOCs. More broadly, during centriole elimination, protein foci containing centriole-associated markers may persist and recruit PCM even in the absence of the signature microtubule-based centriole structure. Clearly, assessing multiple centriole markers minimizes the risk of misinterpretation in such cases. Furthermore, advancements in microscopy now provide resolutions sufficient to detect the distinctive ninefold radial symmetry of centriole microtubules (Chang et al., 2023), and these techniques will likely become the gold standard for verifying centriole presence in foci containing centriole-associated proteins.

It is highly probable that, similar to oogenesis in animals, centrioles undergo reduction during spermatogenesis in rodents. By the final stages of gametogenesis, both centrioles completely degenerate, despite the retention of foci containing the core centriole protein centrin (Courtois et al., 2012). The absence of centrioles in both oocytes and sperm results in acentriolar cell divisions in the early embryo for the first eight divisions (as observed in mice and potentially other species), followed by de novo centriole formation at the blastocyst stage (Gueth-Hallonet et al., 1993).

Elimination in the Female Germ Line

Centrioles are entirely absent in the oocytes of vertebrates (Hertig, A. T., & Adams, E. C., 1967), a phenomenon that was initially hypothesized based on early observations made by Boveri in sea urchin eggs. The elimination of centrioles during oogenesis is now widely recognized as a ubiquitous biological event, occurring universally across all multicellular animal organisms.

Despite its broad prevalence, the specific timing and mechanisms underlying centriole elimination during oogenesis exhibit remarkable variation across different biological systems. In the first mechanism, observed in species such as X. laevis, M. musculus, and H. sapiens, as well as in C. elegans and Drosophila, centrioles are eliminated during the prolonged prophase of meiosis I, leading to the formation of acentriolar meiotic spindles (Januschke et

al., 2006). Recent studies employing correlated light and electron microscopy (CLEM) in C. elegans have revealed that centrioles lose their characteristic central tube structure in late pachytene, followed by their complete disappearance in early diplotene (Pierron et al., 2023). In Drosophila, the maturing oocyte is initially endowed with a cluster of numerous centrioles supplied by 15 supporting nurse cells (Januschke et al., 2006). This centriole cluster plays a crucial role in facilitating the transport of mRNA and proteins from the nurse cells to the oocyte and persists until meiotic spindle assembly begins, although the overall number of centrioles within the cluster appears to decline beforehand (Becalska, A. N., & Gavis, E. R., 2009). Subsequently, centriole elimination involves the exit of Polo kinase from the pericentriolar material (PCM), followed by PCM loss and, ultimately, the degradation of the organelles themselves (Pimenta-Marques et al., 2016).

A second mechanism, observed in echinoderms, mollusks, and annelids, operates differently: centrioles are not removed during oogenesis but are instead expelled during and after female meiotic divisions. In these species, due to the strategic positioning of centrioles at spindle poles, three out of four centrioles are ejected into polar bodies during the two meiotic divisions, leaving behind a single centriole within the oocyte (Nakashima, S., & Kato, K. H., 2001). In the sea star P. miniata, this remaining centriole is invariably the daughter centriole, whereas both maternal centrioles and one additional daughter centriole are discarded into the polar bodies (Borrego-Pinto, 2016). Similar to Drosophila, the daughter centriole first sheds its surrounding PCM and subsequently disappears, following sperm centriole-mediated recruitment of PCM components.

These observations collectively underscore the existence of significant diversity in the mechanisms ensuring that no functional centriole remains within the oocyte. If irreversible differentiation inducers are linked to centrioles, then such a strict centriole elimination process likely signifies a cytogenetic reset, restoring totipotency. Furthermore, with the removal of the centriole—the only irreparable structure within the cell—its accumulated entropy is also effectively nullified.

Elimination in the Male Germ Line

Reduction in centriole numbers, and in some cases their complete removal, can also occur during spermatogenesis. While spermatozoa often introduce two fully functional centrioles into the zygote, as seen in C. elegans, sea urchins, and sea stars (Wolf et al., 1978), this is not universally the case. For instance, in human sperm, the distal centriole, which serves as the template for the flagellar axoneme, degenerates during spermatogenesis. This process involves the disassembly of microtubule triplets, while the centriole proximal to the nucleus remains largely intact (Avidor-Reiss et al., 2020). Some centriolar proteins, including POC1B, CETN1/2, POC5, and CPAP, persist at the site where the distal centriole once resided (Fishman et al., 2018). It has been proposed that both the proximal and residual distal structures derived from sperm continue to function in the zygote, as indicated by their ability to recruit

centrosomal components in Xenopus extracts.

An intriguing case is observed in Drosophila, where mature sperm contain a giant centriole (GC), which serves as the axoneme template, and a degenerate proximal centriole-like structure (PCL) (Blachon et al., 2014). While the GC maintains its microtubule wall, the PCL lacks this feature (Khire et al., 2016). Moreover, numerous centriolar proteins, such as Asl, Ana1, Bld10, Ana2, Sas6, and Sas4, are lost from both centrioles by the end of spermatogenesis. In contrast, Poc1B remains in the GC and becomes enriched in the PCL. Both the GC and PCL retain functionality in the zygote, as evidenced by their ability to recruit the PCM component Asl and centriolar proteins Sas6 and Sas4, mirroring findings in human sperm. Notably, the loss of Asl from mature sperm is essential for proper sperm aster formation following fertilization (Khire et al., 2015). Interestingly, Asl must be recruited from the maternal protein pool to assemble these sperm asters. Similarly, in bovine sperm, one canonical and one degenerate centriole are introduced into the zygote, both of which attract PCM components and SAS-6 (Kai et al., 2015). Ultrastructural analysis of early bovine embryos further reveals that atypical centrioles present in the early embryo can initiate procentriole formation (Uzbekov et al., 2023). Collectively, these findings demonstrate that sperm-derived centrioles, while sometimes degenerative, can retain essential functional roles.

Elimination of Centrioles in Somatic Cells

Centriole elimination is by no means restricted to germ cells. Numerous instances of organelle removal have been documented in somatic cells across diverse eukaryotic species. Notably, centriole removal is a hallmark of terminal differentiation in many cell types, as documented in C. elegans and Drosophila. This suggests that: (1) centrioles are necessary for irreversible differentiation during development but not for later maturation, and (2) since centrioles are inherently difficult to repair, they are eliminated once they become redundant in terminally differentiated cells. Generally, centrioles are preserved only in terminally differentiated cells that bear primary cilia, where centrioles function as basal bodies templating the axonemal structure of cilia. However, in sensory neurons of C. elegans, centrioles degenerate following axoneme assembly (Serwas et al., 2017), leaving only concentrated PCM components at the ciliary base (Magescas et al., 2021). This finding further highlights the potential hazards posed by centrioles due to entropy accumulation over time as a result of their irreparability.

How Pervasive is Centriole Elimination During Development?

This question was comprehensively addressed during C. elegans embryogenesis (Kalbfuss et al., 2023). Given that nematodes possess ciliated sensory neurons but lack motile cilia and flagella, centriole elimination could be studied without the confounding influence of cilia and flagellar template constraints. Systematic analysis in L1 larvae revealed that centrioles are eliminated in approximately 88% of cells during C. elegans embryogenesis (Kalbfuss, N., &

Gönczy, P., 2023). Detailed cell lineage tracing further demonstrated that centriole elimination occurs in a highly stereotypical manner, at defined developmental time points for each specific cell type.

Interestingly, centriole elimination frequently occurs in cell types that form syncytia or undergo polyploidization, such as Drosophila follicular cells, nurse cells, midgut enterocytes, secretory salivary gland cells, enterocytes, adipocytes, and intestinal cells of C. elegans. However, numerous examples demonstrate that neither polyploidization nor syncytium formation is a strictly necessary or sufficient condition for systematic centriole elimination. For instance, some polyploid cells retain centrioles or even amplify them, as observed in polyploid giant trophoblast cells of mammals (Buss et al., 2022). Additionally, centrioles persist in certain polyploidized cells that re-enter mitosis, such as the rectal papillary cells of Drosophila. Moreover, centriole elimination also occurs in cells that do not undergo either syncytium formation or polyploidization, including most cells during C. elegans embryogenesis, as well as ommatidial and interommatidial cells in the Drosophila eye. In terminally differentiated human erythrocytes, centrioles are actively extruded from the cell.

The fact that centrioles are eliminated in a stereotypical manner in certain cell types but not in others suggests that this process is not merely a consequence of inevitable centriole degradation over time due to their irreparability but rather an actively programmed event. Merely exiting the cell cycle is insufficient to trigger organelle removal, as evidenced by numerous terminally differentiated cells that retain cilia or flagella, along with their centrioles. Furthermore, in C. elegans, some terminally differentiated cells in the adult organism maintain foci enriched in centriolar proteins, whereas others, which exited the cell cycle later, do not. These observations collectively imply that centriole elimination should be regarded as a manifestation of cell fate, a hallmark of irreversible differentiation processes. Correspondingly, in C. elegans embryos, altering the fate of a progenitor cell that typically generates cells devoid of centrioles, such as pharyngeal cells, into that of a progenitor that usually gives rise to centriole-containing cells, such as intestinal cells, results in the retention of centrioles. Similarly, preventing the transdifferentiation of a cell that normally retains centrioles into one that typically eliminates them also alters the fate of centrioles, leading to their preservation.

Centriole elimination is by no means restricted to female germ cells but is widely observed in cells that lack cilia or flagella.

Possible Reasons for Centriole Elimination

In the context of oogenesis, the answer is straightforward: to ensure species continuity by resetting the cytogenetic status (restoring totipotency). Indeed, centriole elimination from the female gamete is essential in most metazoan organisms to ensure the correct number of centrioles in the zygote, thereby facilitating the assembly of a bipolar spindle (Manandhar et al., 2005). Failure to do so risks the formation of a tetrapolar spindle, leading to aberrant chromosome segregation and abortive development. This is corroborated by experiments on P. miniata, where experimentally induced retention of maternal centrioles in the

zygote results in the formation of a tetrapolar spindle (Uetake et al., 2002). Similarly, in Drosophila, the retention of maternal centrioles interferes with meiotic spindle assembly, causes mitotic defects, and leads to embryonic developmental failure. Furthermore, in pathological polyspermy, such as in sea urchins, excess centrioles give rise to multipolar spindles and improper chromosome segregation (Snook et al., 2011).

One plausible explanation is that the requirement for at least one centriole/centrosome during spermatogenesis to seed axonemal formation of the flagellum constrains the evolution of elimination mechanisms. Additionally, centriole elimination during oogenesis may function as a barrier against parthenogenesis, as demonstrated in Xenopus embryos, where injection of purified human centrosomes can lead to successful parthenogenetic development (Maller et al., 1976). The Centriolar Theory of Differentiation postulates that the primary biological rationale for centriole elimination in oocytes is the restoration of totipotency in the new organism.

Unlike in oogenesis, the biological significance of centriole elimination in terminally differentiated somatic cells remains largely unexplored, apart from the Centriolar Theory of Aging, which posits that the accumulation of old centrioles (and entropy) is a fundamental driver of organismal aging. The current lack of understanding regarding this proposed significance is largely due to an insufficient grasp of the underlying mechanisms and, consequently, the means to artificially preserve centrioles. Therefore, we can only speculate on potential reasons why centriole elimination may be advantageous in terminally differentiated somatic cells. First, beyond entropy accumulation in old centrioles, it is possible that aging centrioles must be removed to prevent the formation of uncontrolled microtubule-organizing centers (MTOCs). This could be particularly important in differentiated cell types where non-centrosomal MTOCs operate (Sanchez, A. D., & Feldman, J. L., 2017). Second, centriole elimination might help prevent inappropriate proliferation. Human cells lacking centrioles exhibit a p53-dependent G1/S arrest (Mikule et al., 2007). Thus, eliminating old centrioles could serve as an additional regulatory step to curtail unrestrained proliferation, thereby reinforcing tumor suppression. Third, centriole elimination (whether of old or young centrioles) may be required to erase information stored within the organelle, such as post-translational modifications (PTMs) of stable components. Since centrioles are conservatively inherited across cell generations, their components have the potential to transmit information over extended periods (Kochanski, R. S., & Borisy, G. G., 1990). This information potential is illustrated by the behavior of stem cells in Drosophila, which invariably retain either the centrosome containing the old or young mother centriole, depending on the tissue type (Conduit, P. T., & Raff, J. W., 2010). Consequently, temporal information may be encoded in centriole lineage and necessitate erasure under specific circumstances. Finally, centriole elimination may be crucial in terminally differentiating cells to prevent primary cilium formation, which could pose risks by aberrantly activating signaling pathways dependent on this structure, triggering apoptosis, and ultimately erasing cytogenetic potency information to restore totipotency.

In addition to its fundamental importance in oogenesis, future research into centriole elimination mechanisms is expected to shed light on the significance of this process in specific somatic cell types.

Regulation of Centriole Elimination

Similar to the variability in the time required for centriole assembly, ranging from mere minutes in early embryos of Spisula, Drosophila, or C. elegans (Pelletier et al., 2006) to several hours in cultured human cells, significant variability appears to apply to centriole elimination as well (Kong et al., 2020). Ultrastructural analysis of centriole elimination during C. elegans oogenesis revealed that the initial structural change involves the loss of the central tube in late pachytene, which resides inside the centriole microtubule wall. By early diplotene, approximately four hours later, only remnants of centriolar microtubules remain. In Drosophila oogenesis, centriolar protein foci diminish in intensity starting at stages 9–12 and become entirely undetectable by stage 14, corresponding to roughly one day of development (He, L., Wang, X., & Montell, D. J., 2011). The specific timeline of centriole elimination varies across species and cell types, underscoring its dynamic and regulated nature.

The elimination of centrioles frequently takes place in close proximity to the nucleus, but it can also occur in other regions of the cell. For instance, in C. elegans, centriole foci are positioned at a distance from the nuclear envelope during elimination because they migrate through the dendrite of the PQR cell in L1 larvae (Li et al., 2017). In this context, the centriole-associated SAS-6::GFP focus vanishes when it is approximately 5 µm away from the cell body. Furthermore, one of the two centrioles remains close to the nucleus and retains SAS-6 for a longer duration, increasing the likelihood that the elimination mechanism is more active at a distance from the nucleus or that the nucleus plays a protective role. Similarly, in the worm embryo, centriole elimination in ciliated neurons begins when these cells initiate retrograde migration, during which the nucleus moves away from the centrioles that remain at the tip of the dendrite. However, it remains possible that in the aforementioned cases, centriole elimination is also initiated when the centrioles are still near the nucleus, but the monitoring of only certain centriole proteins fails to reveal this event. In line with the idea that centrioles undergo restructuring prior to their migration, SAS-4 cannot be detected on the centrioles of the PQR neuron even when it is still located near the nucleus. Collectively, these observations indicate that the subcellular positioning of eliminated centrioles may vary depending on the physiological context. Nevertheless, a high-resolution ultrastructural analysis is required to more precisely determine the location within the cell where organelle elimination begins.

Selectivity

Female germ cells, such as those in C. elegans, contain two pairs of centrioles/procentrioles following the meiotic S-phase, all of which are subsequently eliminated (Mikeladze-Dvali et al., 2012). Interestingly, the oocyte in Drosophila inherits a significantly greater number of

centrioles than just four from the 15 interconnected nurse cells and somehow manages to eliminate all of them. Consequently, centriole elimination in worms and flies appears to target both centrioles and procentrioles and governs more than four organelles in flies. In contrast, the elimination mechanism in starfish is specifically selective for daughter centrioles. Indeed, experimental retention of maternal centrioles in the cytoplasm by preventing polar body extrusion leads to their persistence in P. miniata. Under these experimental conditions, the maternal centrioles maintain PCM and MTOC activity, whereas both daughter centrioles are eliminated. Therefore, in this case, centriole removal specifically targets daughter centrioles. Moreover, these findings suggest that the elimination mechanism can act on not just a single daughter centriole, as typically expected, but on at least two. A comparable selectivity is observed in another starfish species, A. forbesi, except that in this case, the experimentally retained maternal centrioles, while persisting, lose their MTOC activity. Overall, these observations suggest that, depending on the cellular context, centriole elimination can either affect all present centrioles or selectively target a subset of them.

Elimination in Polyspermy

In echinoderms and other species where centrioles are eliminated during and after meiotic divisions, sperm-derived centrioles exist in the same cytoplasmic environment as the daughter centriole derived from the oocyte, which is about to be eliminated. This raises the question of how sperm-derived centrioles evade elimination in the newly fertilized embryo. Conceptually, either the elimination mechanism acts locally, or paternal and maternal centrioles are somehow distinct, ensuring that the elimination process exclusively targets the organelle originating from the female gamete.

The selectivity of centriole elimination becomes even more evident during physiological polyspermy, where multiple sperm fertilizations are required for successful embryogenesis (Iwao et al., 2020). In the newt Cynops pyrrhogaster and the ctenophore Beroe ovata, multiple sperm enter the oocyte, yet only two large microtubule asters form, presumably around two sperm-derived centrioles. Consequently, the remaining centrioles must be either eliminated or inactivated (Carré, D., & Sardet, C., 1984). It is likely that mechanisms leading to the removal of supernumerary sperm nuclei, termed accessory nuclei, also contribute to the elimination of their accompanying centrioles. In B. ovata, the female pronucleus migrates toward multiple sperm-derived nuclei, probing them before fusing with only one, while the others subsequently degenerate (Rouvière et al., 1994). It has been proposed that failure to enter mitosis leads to the degeneration of accessory nuclei since the injection of metaphase-promoting factor (MPF) from unfertilized Xenopus eggs into fertilized Cynops eggs results in the persistence of accessory nuclei and multipolar divisions, also indicating the presence of centrioles (Iwao, Y., & Elinson, R. P., 1990). Typically, accessory nuclei are highly ubiquitinated and enriched with autophagosome markers (LC3) and autolysosome markers (LAMP1), in contrast to the zygotic nucleus, suggesting that autophagy plays a role in the elimination of accessory nuclei. More broadly, it is possible that autophagy also

participates in the removal of their accompanying centrioles. Additionally, ubiquitination prepares proteins for degradation via the proteasome (Nandi et al., 2006), which could also contribute to centriole elimination.

It has been suggested that the selection of which aster is preserved is mediated by differences in the availability of specific proteins, particularly α-/β-/γ-tubulins. By analogy, variations in the cytoplasmic pool of centriolar proteins may be decisive in balancing centriole retention and elimination. Another hypothesis proposes that the female pronucleus may be enriched with factors necessary for aster retention, which are transported to the nearest sperm pronucleus via microtubules. By analogy, it is conceivable that the female pronucleus is also enriched with factors favoring centriole retention, which are similarly delivered to the rescued centriole pair.
Thus, physiological polyspermy vividly illustrates that the fate of multiple centrioles can diverge within the same cytoplasmic environment.

Centriole Maintenance

The very fact that centrioles can be eliminated in the first place is particularly remarkable, given the overall exceptional stability of these organelles. Unlike cytoplasmic microtubules, which are highly dynamic and depolymerize upon nocodazole or cold treatment, centriolar microtubules do not undergo dynamic instability and remain intact under conditions that dismantle cytoplasmic microtubules (Inoué, S., & Sato, H., 1967). Furthermore, the axoneme of primary cilia, which is built by centrioles and also consists of ninefold microtubule structures, is dynamic and frequently disassembles during each cell cycle, whereas the centriole persists (Kasahara, K., & Inagaki, M., 2021). Similarly, after fertilization, the sperm axoneme is often incorporated into the zygote and subsequently disassembled, while the centrioles remain intact (Fechter et al., 1996). Moreover, while α/β-tubulin dimers exhibit high turnover in cytoplasmic microtubules (Saxton et al., 1984), they do not appear to be significantly turned over within a single cell cycle in human centrioles. Accordingly, pre-existing centrioles persist for days even after centriole formation has been blocked using the Plk4 inhibitor centrinone in p53-deficient human cells (Wong et al., 2015). These results emphasize that centrioles are essential for non-terminally differentiated cells, supporting the Centriole Differentiation Theory, which posits that centrioles are crucial for the transport and distribution of irreversible differentiation inducers until they are fully and sequentially released in the progeny.

The structural integrity of centrioles is primarily ensured by the presence of triplet and doublet microtubules, which distinguish them from the cytoplasmic microtubules that exist as single tubular polymers. Typically, cytoplasmic microtubules are composed of 13 protofilaments, forming a hollow cylindrical structure. However, in the majority of species, centriolar microtubules adopt a unique geometric arrangement by forming either triplet or doublet configurations. Each triplet consists of a single complete microtubule, known as the A-microtubule, which is composed of 13 protofilaments, along with two additional incomplete microtubules—B- and C-microtubules—each containing 10 protofilaments. In contrast, doublets consist

of only the A- and B-microtubules (Guichard et al., 2013). These structural distinctions are spatially organized within the centriole, where triplet microtubules are predominantly located in the proximal region, while doublet microtubules are found in the distal part. The assembly of these specialized microtubule structures requires the presence of δ-tubulin and ε-tubulin isoforms, which have been identified as essential factors in both the unicellular green alga Chlamydomonas reinhardtii and human cells (Dutcher et al., 2002). In human cells lacking both p53 and either δ-tubulin or ε-tubulin, centrioles fail to develop their characteristic triplet microtubule structure, instead forming unstable singlet microtubules. These aberrant centrioles are prone to disintegration during mitosis, resulting in daughter cells that are initially devoid of centrioles. Subsequently, these cells undergo de novo centriole formation. The proteins TEDC1 and TEDC2 are also thought to play a role in this process, as they interact with δ-tubulin and ε-tubulin, and their deletion results in phenotypic effects similar to those observed when δ-tubulin or ε-tubulin is absent (Breslow et al., 2018). Collectively, these findings suggest that centriole elimination may be initiated through the disruption or weakening of triplet and doublet microtubule structures. However, it is important to note that centrioles in Caenorhabditis elegans are composed of singlet microtubules yet remain remarkably stable, indicating that triplet and doublet microtubules may not be a universal prerequisite for centriole stability.

Another potential mechanism conferring exceptional stability to centrioles involves specific stabilizing proteins. In human cells, such proteins include HsPOC1A and HsPOC1B, both of which associate with microtubules, as well as the pericentriolar material (PCM) component CAP350. Despite their apparent stabilizing function, the precise molecular mechanisms by which these proteins reinforce centriole integrity remain unclear (Le Clech, 2008). Additionally, Centrobin, a protein specifically associated with daughter centrioles, has been implicated in centriole stabilization (Zou et al., 2005). Expression of a truncated version of the tubulin-binding domain of Centrobin (Centrobin-TuBD) results in centriole loss in approximately 25% of cells. Although Centrobin is generally regarded as a component exclusive to procentrioles and daughter centrioles, it has been proposed that Centrobin-TuBD may compete with maternal centriole proteins by binding to tubulin, thereby displacing proteins essential for centriole stability (Gudi et al., 2011). Moreover, Centrobin is known to protect CPAP from proteasomal degradation, as CPAP is absent from centrioles when Centrobin is depleted, and this deficiency can be rescued by proteasome inhibition (Gudi et al., 2015).

The protein Bld10p, which serves as a vertebrate ortholog of Cep135 (Matsuura et al., 2004), has also been identified as a crucial stabilizing factor for centrioles. In Chlamydomonas, centriole assembly is entirely dependent on the presence of Bld10p, as centrioles fail to form in its absence. Additionally, expression of an N-terminally truncated version of Bld10p results in premature loss of the cartwheel structure, suggesting that the connection between the cartwheel and triplet microtubules is unstable without full-length Bld10p. Furthermore, some triplets are entirely absent under these experimental

conditions. In Tetrahymena, cells that lack Bld10p and are arrested in the G1 phase—thus preventing the formation of new procentrioles—exhibit a progressive decline in centriole numbers over time (Bayless et al., 2012). Beyond this, Bld10p plays a role in stabilizing A- and C-microtubules while ensuring the correct positioning of triplet microtubules, likely enabling them to withstand the mechanical forces generated by ciliary beating.

It is hypothesized that altering the turnover rates of stabilizing proteins such as HsPOC1A, HsPOC1B, CAP350, or Cep135/Bld10p may prime centrioles for elimination. Proteomic analysis using pulse-SILAC in human cells has revealed a wide range of turnover rates among 145 centriolar and centrosomal proteins, with an average exchange of approximately 57% of the protein pool over a 20-hour period (Jakobsen et al., 2011). NEK2 exhibits the highest turnover rate, with approximately 96% of the centriolar protein pool being replaced within 20 hours, whereas TUBG1 has the lowest rate, exchanging only about 22% in the same time frame. HsPOC1A and HsPOC1B have turnover rates of approximately 35% and 47%, respectively, while Cep350 and Centrobin are more dynamic, with turnover rates of approximately 74% and 73%, respectively. Cep135 has an intermediate turnover rate of about 56%. The cessation of incorporation of high-turnover proteins into centrioles could serve as a rapid mechanism to initiate organelle removal. Conversely, proteins with lower turnover rates may be selectively degraded through post-translational modifications and proteasomal pathways. However, whether turnover rates actively change during centriole elimination and how these changes might be regulated remain unexplored questions.

An additional key centriole stabilizer in C. elegans is SAS-1, as evidenced by the observation that centrioles derived from sperm of sas-1 mutants lose structural integrity shortly after fertilization (Gönczy et al., 1999). Similarly, if maternal SAS-1 function is absent, centrioles initially form but disassemble during embryogenesis. Recently, SAS-1 has also been implicated in centriole elimination during oogenesis, where its disappearance precedes that of other centriolar components and coincides with the loss of the central tube, in which SAS-1 is localized. Moreover, in the sas-1(t1521ts) mutant worms, both centriolar microtubule signals and SAS-4 fade more rapidly than usual, accompanied by premature centriole disintegration. It has been suggested that SAS-1, when expressed in human cells, associates with and stabilizes microtubules (von Tobel et al., 2014). SAS-1 is homologous to human C2CD3, which is essential for centriole completion and primary cilia formation in mammals and mice (Balestra et al., 2013). However, the precise molecular mechanisms by which SAS-1 and possibly C2CD3 contribute to centriole stability remain unclear.

Finally, centriole integrity may depend on post-translational modifications (PTMs) of α- and β-tubulin. Centriolar microtubules undergo extensive PTMs, including acetylation, detyrosination, and polyglutamylation (Janke, C., & Magiera, M. M., 2020). Injection of antibodies targeting polyglutamylated tubulin into human cells results in centriole elimination, suggesting that such PTMs are crucial for centriole maintenance (Bobinnec et al., 1998).

However, further research is required to determine whether PTM modulation directly facilitates centriole elimination.

Factors Contributing to Destabilization

Given the widespread nature of centriole elimination across various species, it is quite striking that there remains a significant gap in our understanding of the fundamental mechanisms underlying this process. This lack of insight is particularly noteworthy considering the several genome-wide screens that have been conducted, which could have identified key components that contribute to centriole elimination (Neumann et al., 2010). Large-scale genetic and RNA interference-based screens conducted in C. elegans have played a pivotal role in identifying evolutionarily conserved centriole assembly proteins, achieved through the visualization of early embryos using time-lapse differential interference contrast (DIC) microscopy (Sönnichsen et al., 2005). However, intriguingly, these screens failed to generate the phenotype that would be expected following an unsuccessful centriole elimination during oogenesis—namely, the formation of a tetrapolar spindle at the first division. Several possible explanations could account for this shortcoming. First, despite the extensive nature of these screens, it is possible that some critical components required for centriole elimination during oogenesis were not targeted, either because these genes are small, not predicted, or are resistant to RNA interference-mediated depletion. Second, genes that act redundantly might have been missed, potentially compensating for the loss of other factors involved in the process. Third, it is possible that the prevention of centriole elimination during oogenesis could result in an earlier gonadal phenotype, thus leaving out genes that are crucial for centriole elimination in oogenesis from the embryo's analysis. Finally, there may be the possibility that centrioles introduced by the oocyte upon the inactivation of a factor responsible for centriole elimination in oogenesis may not function as microtubule-organizing centers (MTOCs), much like the last daughter centriole in a newly fertilized sea star zygote, and thus evade detection by DIC microscopy.

Regardless of the cause, candidate screening in C. elegans revealed that the heterochronic protein LIN-41 and the RNA helicase CGH-1 are somehow involved in determining the timing of centriole elimination during oogenesis, although disruption of these factors merely delays, rather than completely abolishes, the process (Matsuura et al., 2016). It has been suggested that CGH-1, which is involved in the localization and stabilization of mRNA (Boag et al., 2008), might target mRNA encoding a protein that facilitates centriole elimination. Furthermore, the XX karyotype appears to be important for centriole elimination during oogenesis in C. elegans, as some oocytes in late prophase I contain centrioles in mutant males possessing female somatic gonads and germline. However, the molecular nature of the factor(s) modulated by the XX karyotype remains unresolved.

One potential explanation could be that the priming of centriole elimination is simply a manifestation of the deactivation of mechanisms that are responsible for maintaining the centrioles, as previously described for the stabilization of certain

proteins. It has been proposed that the pericentriolar material (PCM) plays a critical role in the maintenance of centrioles, such that its removal could potentially prime the process of centriole elimination. For example, in Tetrahymena, centrioles become unstable when the PCM component γ-tubulin is depleted (Shang, Y., Li, B., & Gorovsky, M. A., 2002), although the additional localization of γ-tubulin at the centriole core may be more relevant in this case (Schweizer et al., 2021). Similarly, the depletion of several PCM components, including Asl, D-Plp, Spd2, Cnn, or Polo kinase, results in the loss of centrioles in cultured Drosophila cells arrested in the S-phase. Interestingly, during Drosophila oogenesis, Polo moves away from the PCM before its removal occurs, whereas the expression of a Polo fusion protein with a centriole-targeting PACT domain leads to the preservation of centriolar foci after fertilization. These foci act as microtubule-organizing centers (MTOC) and interact with the spindle, leading to abnormal meiotic divisions; most of the resulting embryos halt during the first mitotic division with scattered DNA and multiple MTOCs. However, due to the lack of electron microscopy data, it remains unclear whether these additional foci are true centrioles or simply centriolar protein aggregates serving as MTOCs. Notably, neither PCM nor the activity of the Polo-like kinase Plk1 appears to be sufficient for centriole protection in other systems. For instance, maternal centrioles in A. forbesi remain intact after being experimentally retained in the oocyte, although they do not nucleate microtubules. Moreover, pharmacological inhibition of Plk1 does not lead to premature centriole elimination in P. miniata. Similarly, in C. elegans, centrioles are eliminated from the ciliary base despite the presence of PCM components. Additionally, PLK-1 is absent from centriolar foci in L1 larvae and the germline, except in the mitotic zone, and depletion of PLK-1, PLK-2, and PLK-3 does not result in premature elimination during oogenesis (Harper et al., 2011). Nonetheless, it would be intriguing to determine what drives the removal of Polo from centrioles in Drosophila and to explore the consequences of such removal. Ana1, which localizes to the wall of the centriole, may be particularly important in this context, acting downstream of the Polo-mediated removal process (Pimenta-Marques et al., 2024). Indeed, the depletion of Ana1 in Drosophila cells in S-phase promotes centriole loss, while the expression of Polo-PACT in cells lacking Ana1 does not result in the formation of additional centriolar foci, suggesting that Ana1 must be continuously replenished in centrioles through exchange with the cytoplasmic pool of proteins.

While the removal of Polo and PCM is essential for centriole elimination in Drosophila, including during oogenesis, these mechanisms do not appear to be universally employed across other systems for the initiation and execution of centriole elimination.

Conclusion

In most cases, the fundamental mechanisms governing centriole elimination remain poorly understood; however, there is already a broad understanding of when and where centrioles are eliminated, and an increasing array of tools are available to further address this issue. To shed more light on the mechanisms controlling centriole elimination, screenings specifically

designed for this process will be valuable. Genome-wide mutant screenings, RNA interference, or CRISPR/Cas9-based approaches aimed at identifying conditions with delayed or accelerated centriole elimination, not only during oogenesis but also in somatic cells, will likely uncover new important candidates. Given that the architecture and assembly mechanisms of centrioles are widely conserved among species, and considering that their elimination is common across the eukaryotic branch of the tree of life, it is highly probable that insights into common mechanisms can be derived from advancements in various systems. In this regard, new model organisms may be especially useful. One such system that could prove particularly insightful is Naegleria gruberi, which can rapidly transform from an amoeboid form without centrioles to a flagellate form with two centrioles. While Naegleria has been used to study de novo centriole formation during this transformation (Fritz-Laylin, L. K., & Fulton, C., 2016), it could also serve as a model for studying centriole elimination during the transition from flagellates to amoeboid forms. Additionally, valuable insights could be gained from other biological systems, such as the neoblasts of planarians and their non-dividing centriolar cells.

There is compelling evidence suggesting that centriole elimination is widespread and is directed by differentiation and cell fate. A process of similar scope and regulation is programmed cell death, or apoptosis (Nössing, C., & Ryan, K. M., 2023). Just as apoptosis has been found to be critical in numerous physiological conditions, including development, self-repair, homeostasis, and immune function, centriole elimination may play a role in more processes than initially anticipated in the pioneering work of Boveri. Decades of research into the mechanisms governing apoptosis have revealed complex pathways that can be finely regulated in a manner appropriate for each physiological context.

Just as dysregulated apoptosis can contribute to a range of pathological conditions (Bedoui et al., 2020), improper centriole elimination may have significant implications for disease. For example, premature centriole elimination may result in the cessation of embryo development, or in the case of an adult organism, impair self-repair or contribute to progeria. It will also be of great interest to investigate whether defective mechanisms of centriole elimination contribute to tumorigenesis. Experimentally induced centriole amplification is sufficient to trigger aneuploidy and subsequent tumor formation (Levine et al., 2017). It seems reasonable to hypothesize that a reduction in centriole number could also influence tumorigenesis. Mitotic errors, including lagging chromatids, micronuclei, aneuploidy, and polyploidy, are common in proliferating cells that lack centrioles and p53 (Lambrus et al., 2015). Furthermore, it has been suggested that cells lacking centrioles may induce genomic instability during the early stages of prostate cancer (Wang et al., 2020).

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