Unraveling the mysteries of centriolar satellites: time to rewrite the textbooks about the centrosome/cilium complex

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ABSTRACT **Centriolar satellites are membraneless granules that localize and move around centrosomes and cilia. Once referred to as structures with no obvious function, research in the past decade has identified satellites as key regulators of a wide range of cellular and organismal processes. Importantly, these studies have revealed a substantial overlap between functions, proteomes, and disease links of satellites with centrosomes and cilia. Therefore, satellites are now accepted as the "third component" of the vertebrate centrosome/cilium complex, which profoundly changes the way we think about the assembly, maintenance, and remodeling of the complex at the cellular and organismal levels. In this perspective, we first provide an overview of the cellular and structural complexities of centriolar satellites. We then describe the progress in the identification of the satellite interactome, which have paved the way to a molecular understanding of their mechanism of action and assembly mechanisms. After exploring current insights into their functions as recently described by loss-of-function studies and comparative evolutionary approaches, we discuss major unanswered questions regarding their functional and compositional diversity and their functions outside centrosomes and cilia.**

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STRUCTURAL AND CELLULAR COMPLEXITIES OF CENTRIOLAR SATELLITES

We will first highlight the complexity of centriolar satellites (hereafter satellites) by showcasing their structural and cellular properties as the third component of the vertebrate centrosome/cilium complex and as a member of the emerging class of membraneless organelles. Satellites were first described by electron microscopy as an array of 70–100-nm electron dense membraneless spherical granules that localize around the centrosome (Figure 1, A–C; Bernhard and de Harven, 1960; de Thé, 1964; Kubo *et al.*,1999). In different cell types and tissues, their cellular distribution ranges from clustering at the centrosomes, nucleus, or basal bodies, to scattering throughout cytoplasm (Figure 1, D–H; Kubo and Tsukita, 2003; Vladar and Stearns, 2007; Srsen *et al.*, 2009). Notably, the location of the major microtubule organizing center (MTOC) dictates satellite positioning in most cells, which is nicely exemplified in specialized cell types with noncentrosomal MTOCs (Kubo and Tsukita, 2003; Srsen *et al.*, 2006; Vladar and Stearns, 2007; Sanchez and Feldman, 2017). While satellites cluster around the nuclear envelope in myotubes, they are concentrated at the apical side in polarized epithelial cells of the intestine and kidney (Figure 1, E, G, and H). The variation in their cellular distribution suggests cell type and tissue-specific functions for satellites, which remains mostly unexplored.

The number, distribution, and composition of satellites are dynamically altered in response to different stimuli and during differentiation. For example, their composition is remodeled during cilium assembly induced by serum starvation or environmental stress by releasing key ciliogenesis factors from satellites to centrosomes and cilia (Hori and Toda, 2017). Activation of p38 MAPK pathway by cellular stresses such as UV radiation, heat shock, and transcription blocks displaces AZI1/CEP131 and CEP290 from satellites and promotes ciliogenesis (Villumsen *et al.*, 2013; Tollenaere *et al.*, 2015). Analogously, degradation of the satellite pool of OFD1 by autophagy promotes ciliogenesis (Tang *et al.*, 2013). Regulated satellite

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Abbreviations used: DYRK3, dual specificity tyrosine-phosphorylation-regulated kinase 3; MTOC, microtubule organizing center; PCM1, pericentriolar material 1.

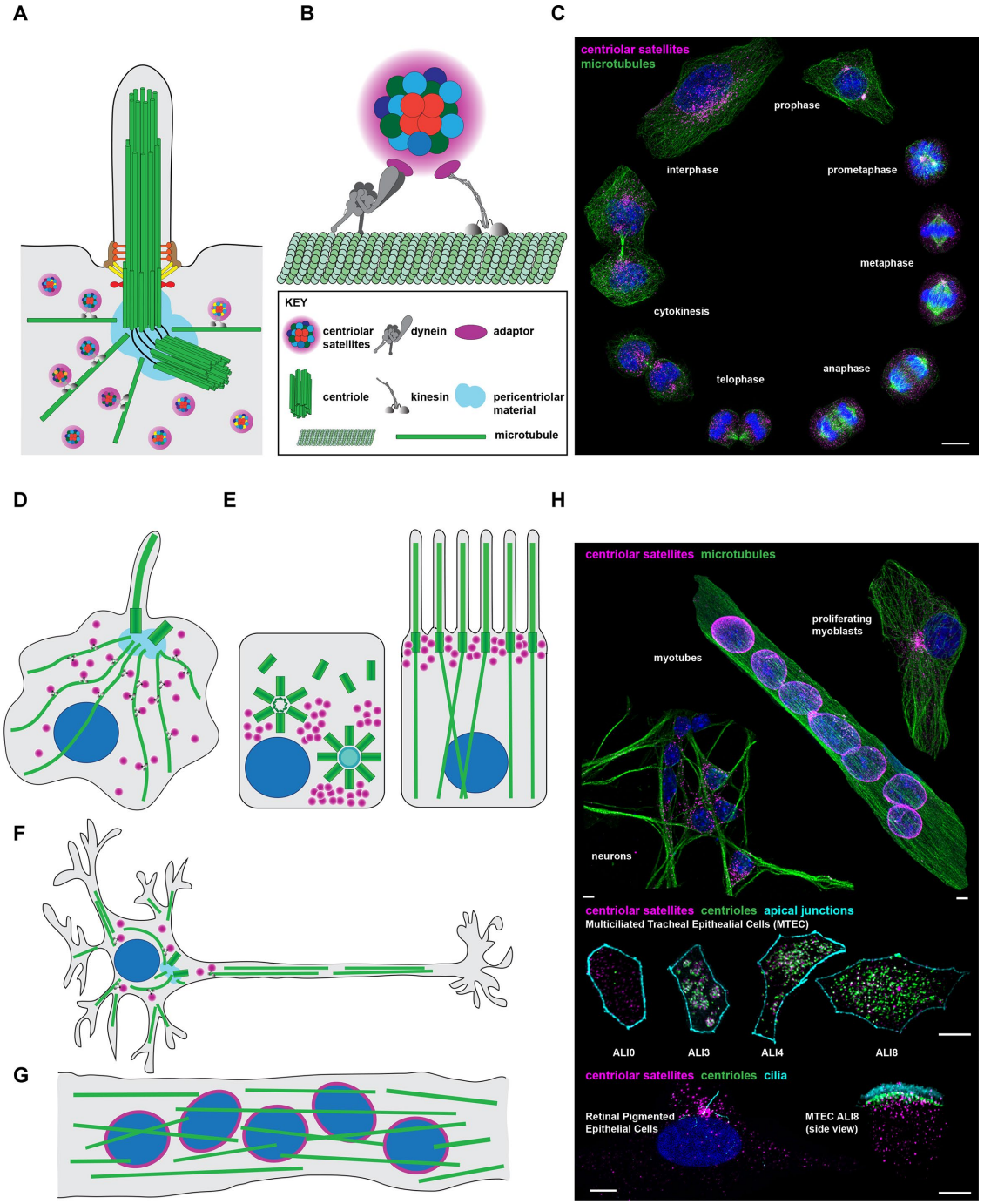

FIGURE 1: Centriolar satellite structure and distribution during cell cycle and in a variety of different cell types. (A) The vertebrate centrosome/cilium complex is composed of centrosomes, cilia, and centriolar satellites. At the core of centrosomes are two centrioles, which recruit pericentriolar material and nucleate formation of the primary cilium. Satellites are an array of membraneless structures that localize and move around centrosomes and cilia in a microtubule and molecular motor–dependent manner. There is compositional heterogeneity among different satellite granules. (B) Satellites are membraneless macromolecular protein complexes. They have extensive interactions with centrosome proteins, microtubule-associated proteins, and enzymes such as kinases and ubiquitin ligases. They interact with the dynein/dynactin complex and multiple kinesin motors, which engage in a "tug-of-war." Adaptor proteins mediate the interaction between motors and satellites. The residents of satellites are represented as circles within each satellite granule. (C) Satellites are dynamically regulated in mitosis. Human HeLa cells were fixed at different stages of mitosis and stained for satellites (anti-PCM1 antibody, magenta), microtubules (anti–α-tubulin antibody, green), and DNA (DAPI, blue). Satellites localize to duplicated centrosomes in prometaphase and spindle poles during early metaphase, dissolve as cells progress further in mitosis, and recondense back upon mitotic exit. Mitotic satellite dissolution is reflected as an increase in their cytoplasmic pool and decrease in the number of granules. Scale bar: 10 μm. (D–G) Cellular distribution of satellites in different cell types. Drawings are not to scale. (D) Majority of satellites concentrate around the basal body in epithelial cells that form primary cilia. (E) Satellites are remodeled during differentiation of in vitro mouse tracheal

remodeling is also nicely illustrated during the differentiation of multiciliated epithelial cells, which assemble hundreds of centrioles and cilia (Sorokin, 1968; Kubo *et al.*, 1999; Vladar and Stearns, 2007). At the centriole amplification stage, satellites form fibrous granules in close proximity to nascent centrioles duplicated from preexisting centrioles and deuterosomes. As cells differentiate further to form motile cilia, size and abundance of satellite granules decrease to a level that there is only a small pool scattered around the basal bodies at the apical surface in mature ciliated cells. While the events associated with satellite remodeling have so far been described in multiple different contexts, their functional significance and mechanistic underpinnings remain as significant, unresolved questions that will keep cell biologists busy for many years to come.

One of the initial observations made about satellites was their molecular motor-dependent retrograde and anterograde motility along microtubules in vitro and in cells (Kubo *et al.*, 1999). Recent systematic quantitation of the dynamic behavior of satellites by live imaging of their molecular marker PCM1 and one of their residents CCDC66 showed that a small fraction of satellites exhibits long-range bimodal motility, while the majority displays diffusive motility (Conkar *et al.*, 2019). Intriguingly, a subset of satellites also undergoes fission and fusion events, which is reminiscent of liquid-like behavior (Banani *et al.*, 2017; Conkar *et al.*, 2019). Another line of evidence in support of this behavior is the regulation of satellite integrity during mitosis by the dual specificity kinase DYRK3, the recently identified mitotic dissolvase for multiple membraneless organelles such as stress granules (Rai *et al.*, 2018). Satellites tightly cluster around duplicated centrosomes in prophase and spindle poles in early metaphase, dissolve as cells progress in mitosis when relative DYRK3 levels and activity increase, and recondense back upon mitotic exit when DYRK3 is degraded by the anaphase promoting complex (Figure 1C; Rai *et al.*, 2018). The discovery of DYRK3 during mitotic remodeling of satellites paves the way to addressing the longstanding questions that relate to how and why satellites dissolve during mitosis and how liquid–liquid phase transitions contribute to satellite assembly and maintenance.

COMPOSITION AND ASSEMBLY MECHANISMS OF CENTRIOLAR SATELLITES

Analogous to centrosomes, satellites are macromolecular protein complex assemblies. The first satellite protein identified was PCM1 (pericentriolar material 1), which functions as the scaffold for their assembly and maintenance (Kubo *et al.*, 1999; Wang *et al.*, 2016; Odabasi *et al.*, 2019). Although its terminology misleadingly suggests localization to the pericentriolar material, PCM1 exclusively localizes to satellites. Over the past two decades, identification of satellite components has been done in a piecemeal way by defining new proteins that interact or colocalize with PCM1, and thus there has not been a coherent picture of how satellites assemble and function. More recently, by taking advantage of mass spectrometry–based high-throughput proteomics and proximity labeling techniques, several studies profiled the larger proteome of satellites in different mammalian cell types (Firat-Karalar *et al.*, 2014; Gupta *et al.*, 2015; Gheiratmand *et al.*, 2019; Quarantotti *et al.*, 2019). Affinity purification of satellites using PCM1 as the bait identified 223 proteins, which reflects the relatively stable interactions of satellite proteome (Quarantotti *et al.*, 2019). Additionally, application of the proximity-dependent biotin identification (BioID) approach to 22 satellite proteins also identified weak, transient and insoluble interactions of satellites and generated an interactome composed of 660 proteins (Gheiratmand *et al.*, 2019). We note that these two approaches generated largely different satellite interactomes that only had 9% overlap (Figure 2A). While proteins implicated in centrosome organization, cilium assembly, and cell division were shared, several distinct biological processes such as transcriptional regulation and centrosome duplication were highly enriched in only one proteomic dataset. In agreement with a previous study that directly compared chromatin-associated protein complexes by BioID and affinity purification, these two approaches complement each other in mapping the satellite interactome and their resulting maps must be considered together to study the full extent of satellite functions and mechanisms (Lambert *et al.*, 2014).

A striking feature of the satellite interactome is its substantial overlap with the published centrosome proteome (Figure 2B; Jakobsen *et al.*, 2011; Gheiratmand *et al.*, 2019; Quarantotti *et al.*, 2019). The satellite-associated centrosome proteins function in a wide range of processes such as cilium assembly, microtubule nucleation and dynamics, mitosis, centriole duplication, and pericentriolar material organization, and a subset of them is mutated in ciliopathies, primary microcephaly, and amyotrophic lateral sclerosis. Although 50% of centrosome proteins are found at the satellites, their presence does not assign satellites competence in microtubule nucleation, de novo centriole duplication, and other centrosome-associated functions. While lack of centriole duplication proteins such as PLK4, SASS6, CEP152, and STIL might explain why they do not initiate centriole duplication, why satellite-associated γ-tubulin and HAUS complex do not nucleate microtubules is not known. One possibility is that the folding, modifications, or complex partners of these proteins are different than the ones at the centrosomes and that this inhibits their ectopic functions. In contrast to the striking enrichment of centrosome proteins, only about 14% of the ciliary proteome mapped by proximity labeling approaches was found in the satellite interactome (Figure 2C; Mick *et al.*, 2015; Kohli *et al.*, 2017). There are two likely explanations for the low coverage of cilium proteins. First, these proteins might not transit through satellites. Second, given that the proximity interaction landscape of the centrosome changes in ciliated cells, the satellite interactome generated from asynchronous cells might not reflect that of ciliated cells (Gupta *et al.*, 2015). Future proteomic profiling studies aimed at characterizing the satellite interactome in response to different stimuli and across different cell types and tissues is required to determine whether satellites adapt by dynamically changing their composition and to catalogue a more comprehensive inventory for satellites.

epithelial cells (MTEC) after induction with air–liquid interface (ALI). At the centriole amplification stage, satellites form fibrous granules in close proximity to nascent centrioles generated by parental centriole and deuterosome-mediated duplication pathways. In mature ciliated cells, a small pool of satellites is scattered below the basal bodies at the apical surface. (F) In neuronal cells, satellites are scattered throughout the cell body. (G) In muscle cells, satellites are concentrated around the nuclear envelope, the noncentrosomal MTOC. (H) Proliferating and differentiated mouse C2C12 cells, primary embryonic cortical neurons, in vitro MTEC cultures at different stages of differentiation, and retinal pigmental epithelial cells were fixed and stained for satellites (anti-PCM1 antibody, magenta), microtubules (anti–α-tubulin antibody) or centrioles (anti-Centrin antibody, green), apical junction markers (anti-ZO1 antibody) or cilia (anti–acetylated-tubulin antibody, cyan), and DNA (DAPI, blue). Scale bar: 5 μm.

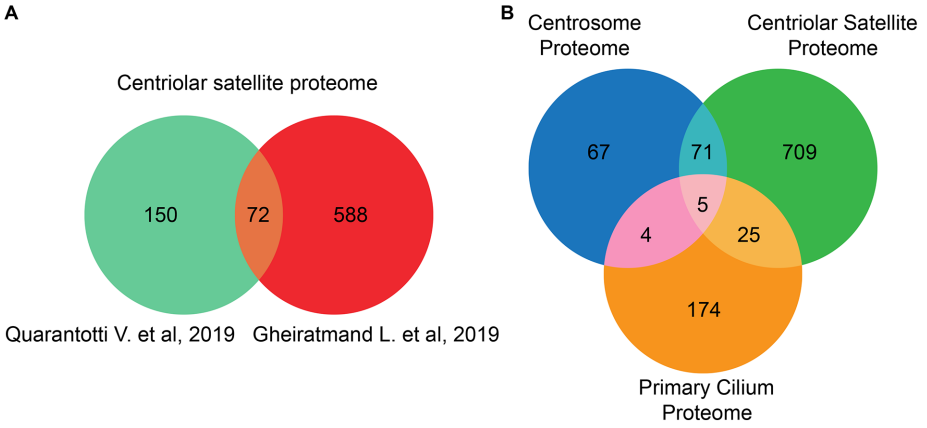

FIGURE 2: Comparative analysis of the centrosome, primary cilium, and centriolar satellite proteomes. (A) Comparison of shared and distinct protein numbers between satellite proteomes generated by different approaches. Venn diagram of the satellite proteome identified by affinity purification of PCM1 from sucrose gradient fractions enriched for satellites (Quarantotti *et al.*, 2019) and by BioID proximity mapping of 22 satellite proteins (Gheiratmand *et al.*, 2019). (B) Comparison of shared and distinct protein numbers between satellite, centrosome, and primary cilium proteomes. Venn diagram of the satellite proteome identified by affinity purifications (Quarantotti *et al.*, 2019) and BioID-based proximity mapping (Gheiratmand *et al.*, 2019), centrosome proteome identified by enrichment of centrosomes using sucrose gradients followed by protein correlation profiling (Jakobsen *et al.*, 2011), and primary cilium proteome identified by APEX-based proximity mapping of the ciliary targeting domains of NPHP3 (Mick *et al.*, 2015) and HTR6 (Kohli *et al.*, 2017).

In addition to corroborating the intimate molecular and functional relationship between centrosomes and satellites, there are two important findings revealed by the satellite interactome that open up new avenues about their biology as membraneless organelles. First, prey–prey clustering analysis of satellites identified core and peripheral interaction models, suggesting that satellite granules might be spatially organized like the pericentriolar material or stress granules (Luders, 2012; Jain *et al.*, 2016; Gheiratmand *et al.*, 2019). Second, comparative analysis of the proteomic profiles of satellite residents with that of PCM1 revealed compositional heterogeneity among satellite granules (Gheiratmand *et al.*, 2019). Proteomic profiling of different satellite subpopulations together with probing satellite assembly and disassembly mechanisms with biochemical and imaging assays will be essential in gaining insight into these emerging satellite properties.

FUNCTIONAL COMPLEXITIES OF CENTRIOLAR SATELLITES

The functions of satellites have so far been ascribed to the cellular processes associated with their residents, or more specifically, by phenotypic changes that occur upon their acute or chronic cellular loss (Hori and Toda, 2017). These studies collectively identified satellites as multifunctional organelles with regulatory functions during centriole duplication, cilium assembly, microtubule nucleation and organization, mitotic progression, autophagy, stress response, neurogenesis, and nuclear alignment (Hori and Toda, 2017; Prosser and Pelletier, 2020). A major limitation of studying satellite functions through their residents arises from the fact that these proteins not only localize to satellites, but also to other cellular structures such as centrosomes, cilia, and/or microtubules. For this reason, loss-of-function experiments cannot distinguish between functions associated with different cellular pools of these proteins, which also explains the discrepancy between phenotypes described upon depletion of PCM1 or its associated satellite interactors. Currently, identification of functions specific to satellites as discrete protein complexes can only be derived from characterization of satelliteless cells generated by cellular depletion or deletion of PCM1. Future experiments that make use of localized degradation of satellite pools of proteins or phenotypic rescue experiments with their satellite- or centrosome-localization mutants in null backgrounds will be essential in identifying the full repertoire of satellite-specific functions.

There are discrepancies between phenotypes associated with acute and chronic depletion of satellites from cells, which might be due to functional compensation mechanisms as previously described by a loss-of-function study of another satellite resident CEP131 (Hall *et al.*, 2013). Although CEP131 depletion in mouse fibroblasts by siRNA caused defective ciliogenesis, the fibroblasts from CEP131 null mutant mouse did not exhibit ciligonesis defects (Hall *et al.*, 2013). Shared phenotypes between acute and chronic depletion of satellites in epithelial cells are the ones associated with the primary cilium, which include defective cilium assembly, ciliary recruitment of signaling receptors, and epithelial cell organization (Wang *et al.*, 2016; Hori and Toda, 2017; Odabasi *et al.*, 2019). Of note, loss of satellites in zebrafish caused pronephric kidney cysts, hydrocephaly, and inverted heart looping reported, which corroborates key regulatory functions of satellites at the cilia (Stowe *et al.*, 2012). In addition to epithelial cells, satellite functions have also been described in various specialized cell types and tissues. In myotubes, satellites assemble into an insoluble matrix around the nuclear envelope and regulate nuclear positioning during their differentiation through recruitment of molecular motor–associated proteins to the nuclear envelope (Srsen *et al.*, 2006; Espigat-Georger *et al.*, 2016; Gimpel *et al.*, 2017). Despite the unique localization of PCM1 to fibrous granules around nascent centrioles in differentiating in vitro multiciliated tracheal cultures, PCM1 loss did not compromise centriole and cilia assembly in these cells (Vladar and Stearns, 2007). Finally, loss of satellites during embryonic neurogenesis revealed satellite functions in the maintenance of the neuronal progenitor pool and interkinetic nuclear migration of neuronal progenitors (Ge *et al.*, 2010; Zhang *et al.*, 2016). Despite the significant progress in unraveling the functional complexities of satellites in recent years, we note that the complete spectrum of satellite functions at the cellular, tissue, and organismal levels remains to be established.

Research on satellites has so far been undertaken with a biased view from a centrosome/cilium-centered perspective. However, there are several lines of data that suggest functions for satellites outside centrioles and cilia. First, satellites are present in cell types with noncentrosomal MTOCs where centrosomes are inactivated or centrioles are lost, and their composition remains mostly unaltered in mammalian cell lines ablated for centrioles (Kubo *et al.*, 1999; Gheiratmand *et al.*, 2019; Quarantotti *et al.*, 2019). Moreover, systems level characterization of the global proteome of satelliteless cells and the satellite interactome suggested links to actin-mediated processes, neurogenesis, and RNA granules (Gheiratmand *et al.*, 2019; Odabasi *et al.*, 2019; Quarantotti *et al.*, 2019). The centriole and cilia-independent functions of satellites should be investigated

through defining interactions and dynamic behavior of satellites in different contexts and utilizing unbiased approaches like functional screens.

MECHANISTIC UNDERPINNINGS OF CENTRIOLAR SATELLITE FUNCTIONS

The prevalent model for satellite mechanisms defines them as regulators of dynamic protein localization at the centrosome (Prosser and Pelletier, 2020). However, the mechanistic underpinnings of their targeting function remain enigmatic. Is it as simple as a classical trafficking model where satellites deliver or remove proteins from or to centrosomes by active transport along microtubules? Alternatively, do satellites function as sequestration sites to limit incorporation of proteins to the centrosome and to enhance biochemical reactions such as the ones that mediate posttranslational modifications? Here, we discuss the recent data that supports and challenges these models.

The idea that satellites act as trafficking machines was proposed based on their directed long-range motility to and away from centrosomes and defective centrosomal targeting of multiple proteins in satelliteless cells (Kubo *et al.*, 1999; Dammermann and Merdes, 2002; Conkar *et al.*, 2019). These lines of data are not sufficient as direct evidence for such function, and future studies utilizing photoactivation and pulse labeling–based time-lapse imaging of satellite residents are required to test it. This model also falls short in explaining how organisms that lack satellites maintain proper centrosome biogenesis and function. Taking into account the function of satellites as sites for regulated sequestration and release of proteins during ciliogenesis and autophagy, an alternative and/or complementary "proximity-dependent sequestration" model is proposed for satellites (Stowe *et al.*, 2012; Wang *et al.*, 2016; Joachim and Tooze, 2018). This model suggests that microtubule-mediated motility of satellites is required for maintaining their proximity to the centrosome and this proximity mediates timely and efficient exchange of the satellite proteins with the centrosome. While the exchange can be mediated simply by diffusion, a compelling mechanism can also be the fusion and splitting events between centrosomes and satellites (Banani *et al.*, 2017; Conkar *et al.*, 2019).

Finally, it is noteworthy to emphasize that various enzymes such as kinases, ubiquitin ligases, and deacetylases were also identified as part of the satellite interactome (Gheiratmand *et al.*, 2019; Quarantotti *et al.*, 2019). Functional characterization of the satellite pool of the E3 ubiquitin ligase MIB1 showed that satellites sequester MIB1 and prevent untimely centrosomal ubiquitination and degradation of KIAA0586/Talpid3 during initiation of ciliogenesis and GABARAP during autophagosome formation (Wang *et al.*, 2016; Joachim and Tooze, 2018). Corroborating the link between satellites and proteostatic regulation, PCM1 binds to ATG8 family members such as GABARAP and LC3 by an LC3-interacting region domain at its carboxy terminus and regulates degradation of satellite residents such as OFD1 by targeting them to the autophagosome–lysosome pathway (Tang *et al.*, 2013; Joachim *et al.*, 2017; Holdgaard *et al.*, 2019).

In addition to sequestering their resident enzymes to inhibit their activity at other cellular locations, satellites might also regulate their centrosomal and ciliary residents at the posttranslational level by concentrating them with relevant enzymes or by mediating their protein–protein interactions. The latter possibility was addressed by comparing the proximity interaction profile of five centrosome proteins in wild-type and satellite-less cells (Gheiratmand *et al.*, 2019). Although several functional modules were altered in satelliteless cells, most interaction modules were maintained suggesting that their assembly is independent of satellites. Analogous to these studies, future studies that compare the posttranslational modification profiles of satellite residents such as phosphorylation and ubiquitination in wild-type and satelliteless cells are required to test satellite functions as transit sites where proteins are modified and/or degraded.

ORIGIN AND EVOLUTION OF THE CENTRIOLAR SATELLITES

Research on satellites so far has focused on elucidating their function and regulation in the context of vertebrate centrosomes and cilia, which led to the misconception that satellites are specific to vertebrates. Now that we have a reasonably comprehensive inventory for satellite components, reevaluation of the previous comparative genomics studies as well as reconstruction of the evolutionary history of these proteins is required to gain unbiased insight into the cellular origins and functions of satellites. We would like to highlight the study by Hodges *et al.*, which reported phylogenetic analysis of PCM1 and 52 other centrosome proteins in 45 diverse eukaryotic organisms. In addition to confirming the presence of PCM1 orthologues in vertebrates, this analysis identified predicted orthologues for PCM1 in the annelid *Capitella*, the mollusk *Lottia gigantea*, the cnidarian *Nematostella vectensis*, the placozoan *Tricoplax adhaerens*, and the choanoflagellate *Monosiga brevicollis* (Hodges *et al.*, 2010). The presence of PCM1 outside vertebrates raises several questions that deserve further investigation: To what extent are the structure, functions, and mechanisms of satellites conserved among different organisms? Expression of PCM1 might not necessarily result in the formation of satellite granules in all cell types and organisms. A recent study that identified PCM1 as part of a liquid-like meiotic spindle domain associated with the spindles of oocytes lends support for this possibility (So *et al.*, 2019). How satellites contribute to the biogenesis and functions of centrosomes and cilia in organisms that have them and why they are dispensable in other ciliated organisms also remain as open questions. An important lead to the ancestral functions of satellites comes from the phylogenetic conservation profile of PCM1, which is similar to the profiles of proteins with sensory functions such as the chaperonin-like BBSome components and ninein (Hodges *et al.*, 2010). Uncovering the sensory functions of satellites requires future functional dissection using PCM1 mutant mouse models and organoid cultures such brain, kidney, and retina organoids as these organs are most commonly affected in diseases associated with satellite residents.

FUTURE PERSPECTIVES

The functions and mechanisms of satellites are proving to be more complex than once thought. Our knowledge on the biology of satellites has advanced significantly in the last decade and we described the progress in understanding their molecular composition, mechanism of action, and numerous functions along with the new emerging questions that remain open. These recent discoveries have put the field in a position where there is a clear need to adopt a more appropriate and consistent terminology about satellites and their resident proteins and to study satellite functions outside centrosomes and cilia, which we will discuss here as two major questions.

1) What criteria should we use to define proteins as "centriolar satellite" components?

Recent studies showed that about 50% of the centrosome proteome overlaps with the satellite proteome, which challenges the

current classification of proteins into "centrosome" or "satellite" categories. Once the proteomes of satellites in different contexts are identified in the future, we might even realize that all centrosome proteins at some point during their lifetime reside at satellites. If satellites are ubiquitous paths for centrosome proteins, it will be even more essential to develop methodologies that will distinguish between functions of centrosome- and satellite-associated pools of these proteins.

2) Does "centriolar satellite" terminology need reevaluation?

"Centiolar satellite" and "Pericentrosomal satellite" terminologies were based on the scattered localization of satellite granules around the centrosome in most cell types. With the realization that satellites are present in cells that lack centrioles and concentrate around noncentrosomal MTOCs in specialized cell types, the term "centriolar satellites" is clearly not inclusive enough to reflect changes in their distribution in a context-dependent way. Another terminology problem relates to the way their core scaffolding protein PCM1 was named. Even though PCM1 does not localize to the pericentriolar material and is exclusive to satellites, "pericentriolar material 1" nomenclature is misleading in terms of its cellular localization, especially for the newcomers into the field. Whether these issues are addressed by adopting new terminology or not, it is essential to identify and tease apart centriolar and noncentriolar functions and mechanisms of satellites.

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