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REVIEW ARTICLE

Centrosome: A Microtubule Nucleating Cellular Machinery

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Abstract | Centrosome serves as the primary site of microtubule organization in a majority of animal cells. These microtubules carry out several significant functions in the cell such as cell division, chromosome segregation, mechanical support and cellular transport. Proteins localized at the centrosome play extensive role in orchestrating the process of microtubule organization, growth and stabilization in space and time. Anomalies in centrosome number, structure and functioning disturb microtubule organization and lead to several human diseases. Advancements in proteomics and microscopy methods have been instrumental in identifying molecular mechanisms pertaining to the microtubule organizing function of centrosomes. This review focuses on the involvement of centrosome as a microtubule nucleating center of the cell. We present the major molecular mechanisms at the centrosome which affect microtubule nucleation and activation. Finally, we discuss human diseases associated with defective microtubule organization resulting from centrosome abnormalities.

Keywords: *Centrosome, Pericentriolar material (PCM), Microtubules (MT), γ-tubulin, Microtubule-associated proteins (MAPs)*

1 Introduction

The term microtubule organizing centers (MTOCs) was coined by Pickett-Heaps to define microtubule nucleation sites in the cell [78]. Several decades ago, Edouard Van Beneden and Theodor Boveri identified centrosome which primarily functions as a MTOC in many animal cells [4, 102]. Electron microscopy revealed that the centrosome contains a pair of microtubule-based cylindrical structures called centrioles surrounded by an electron-dense proteinaceous matrix termed as the pericentriolar material (PCM). The PCM was subsequently identified to play essential role in microtubule nucleation [68, 86, 104, 110].

Microtubules (MTs) are dynamic cytoskeletal structures formed by the polymerization of α/β-tubulin heterodimers via a process requiring assistance of several nucleating factors [85]. Centrosome is involved in spatio-temporal organization of MT arrays with defined geometry [66]. Several centrosome localized proteins serve as adaptor proteins to facilitate this process. One such protein component of PCM, γ-tubulin[72, 92] forms a lock-washer shaped protein complex termed the γ-Tubulin Ring Complex (γ-TuRC) which is the major MT nucleating molecular machinery present at the centrosome [67]. The γ-TuRC core structure is formed by the lateral association of γ-Tubulin Small Complex (γ-TuSC) with multiple γ-tubulin Complex Proteins (GCPs)[73]. Additionally, several associated factors aid in γ-TuRC targeting and activation at MTOCs.

Recent proteomic analyses of purified centrosomes and biotin proximity labelling technique have led to the discovery of hundreds of centrosome proteins and their interactors[3, 29, 39]. Several of these proteins have been functionally characterized and super-resolution microscopy has enabled viewing their spatial organization at the centrosome[25, 54, 91]. The overwhelming

γ-tubulin: It belongs to the family of tubulin proteins. It is a part of multi-subunit protein complex called γ-TuRC which is involved in microtubule nucleation.

Microtubule Organizing Center (MTOC): Cellular structure involved in organizing microtubules by regulating their nucleation, stabilization and anchoring.

Centrosome: A major microtubule organizing center involved in regulating organization of mitotic spindles during cell division in animal cells. It is also involved in various other cellular functions such as cell motility, polarity and signalling. It is made up of a pair of microtubule-based structures called centrioles at the core which are embedded in a proteinaceous matrix referred as the pericentriolar material.

Microtubules: Part of cytoskeleton formed by lateral association of polarized tubular filaments resulting from the head-to-tail polymerization of α- and ß-tubulin heterodimers. They are involved in maintaining cell shape, cell movements, intracellular transport of organelles and cell division.

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γ-tubulin complex proteins (GCPs): γ-tubulin-associated proteins involved in the assembly of multi-subunit protein complexes at minus-ends of microtubules.

Gamma-Tubulin Small Complex (γ-TuSC): It is a 300 kDa tetrameric sub-complex comprised of two molecules of γ-tubulin and one molecule of GCP 2 and 3.

Gamma-Tubulin Ring Complex (γ-TuRC): It is a major microtubule nucleating molecular machinery of the cell. The core structure is formed by the lateral association of multiple γ-TuSCs with additional associated GCPs.

inter-play of increasing number of centrosome proteins enhances the molecular understanding of MT organization at centrosomes. Hence, this review showcases the central role of centrosome in MT nucleation. It also presents the link between defective centrosome-mediated MT organization and fatal human diseases.

2 Microtubule Cytoskeleton Assembly

The tubulin superfamily members, namely α-, β- and γ-tubulins play major role in MT formation. The α- and β-tubulin heterodimers assemble in a head-to-tail manner of laterally associated linear polymers termed as protofilaments (PFs), which serve as basic building blocks of the MTs[59]. Majority of organisms have MTs made up of 13 PFs while specialized MTs with 11, 12 or 15 PFs have also been reported in some cases[6, 15, 32]. All PFs in a MT have same orientation which results in polarity of the structure. One end of a MT has α-tubulin ring (referred as minus-end) while the opposite end is constituted by β-tubulin ring (referred as plus end). The end of polymerizing MTs is often stabilized by GTP-cap[87]. However, the GTP bound to the β-tubulin at the plus-end has a tendency to hydrolyze to GDP after assembling in MT which leads to plus-end disassembly and shrinkage[79]. Similar to the plus-end, minus-end also undergoes periods of growth and shrinkage but at a slower rate in comparison to the plus-end and hence it is more stable[13].

2.1 γ-TuRC: Composition and Geometry

The third tubulin super-family member, γ-tubulin is a major player involved in MT nucleation. γ-tubulin together with specific sets of γ-tubulin complex proteins (GCPs), is involved in formation of multi-subunit protein complexes referred as the γ-tubulin ring complex (γ-TuRC) and/or γ-tubulin small complex (γ-TuSC), which differ in their protein composition and capacity to nucleate MTs[50]. MTs can be nucleated either by γ-TuRCs or γ-TuSCs but the γ-TuRC pathway is prevalent in vertebrates. These multi-subunit protein complexes are present at minus-ends of MTs and provide binding sites for MTs emanating from MTOCs. In most eukaryotes, γ-TuSC is made-up of a dimer of GCP2 and GCP3, each bound to one molecule of γ-tubulin. In contrast, γ-TuRC contains five distantly related proteins i.e. GCP2, GCP3, GCP4, GCP5 and GCP6[70]. Depleting these GCPs cause reduced recruitment of γ-tubulin complexes to the MTOCs and induce errors in centriole duplication and bipolar spindle formation[12, 21, 99]. Recently, cryo-electron microscopy has revealed the asymmetric cone-shaped structure of γ-TuRC, where GCP4/GCP5 and GCP4/GCP6 form unique Y-shaped assemblies similar to GCP2/GCP3 in γ-TuSC (Peng[61, 101]). Two distinct domains of GCPs i.e. N-terminus Grip1 and C-terminus Grip2, are involved in their lateral interactions and γ-tubulin association, respectively[21]. Structural work has identified interesting details about the functioning of γ-TuRC. For instance, the γ-tubulin assembled in γ-TuSC is subjected to conformational activation in order to achieve microtubule geometry which is potentially provided by the flexibility of GCP3 hinge region[48, 51]. GCP phosphorylation also regulates conformational changes needed for the activation of γ-TuRC[49]. γ-TuRCs can assemble in cytosol and/or MTOCs depending on the organism and cell type. The activation of γ-TuRCs coincides with its recruitment to the MTOCs which could be centrosome, golgi, mitochondria, nuclear envelope, cell membrane and/or spindles[20]. This review focuses on the role of centrosome as the major MT organizing center.

3 Centrosome: A Microtubule Organizing Center (MTOC)

Centrosome is a cytoplasmic non-membranous cell organelle of approximately 0.4–1 μm in size. It acts as a major MTOC in various animal cells and performs diverse functions including regulation of cell motility and polarity during the interphase stage of the cell cycle[98, 100, 107]. Interestingly, centrosome has been suggested to act as a signalling center by providing platform for the interaction of several cell cycle kinases and phosphatases[2]. Structurally, it is comprised of a core structure made up by two orthogonally arranged MT-based hollow cylinders referred as centrioles, which are embedded in an electron-dense proteinaceous matrix known as pericentriolar material (PCM). These centrioles are composed of nine triplet MTs symmetrically arranged around a central cartwheel-like structure. There is an intrinsic age-related asymmetry among the centriole pair. The mature centriole is referred as the mother centriole and the less mature one is called the daughter centriole. The mother centriole also exhibits ultra-structural differences as compared to the daughter centriole, for instance distal and sub-distal appendages are observed only on the mother centriole at certain stage in the cell cycle of vertebrates[103]. In ciliated or flagellated cells, the distal appendages assist in the mother centriole anchoring to the plasma membrane. The anchored mother centriole generates MT-based

axoneme of cilia or flagella, thereby functions as basal body of these cellular structures (Fig. 1)[47, 88]. The PCM was long thought to be an unorganized proteinaceous cloud until recently when sub-diffraction light microscopy techniques successfully identified the concentric toroids of discrete diameter around the centrioles in the PCM of cells at the interphase stage of cell cycle[54, 65, 91]. However during mitosis, PCM is known to expand and loose the organized concentric arrangement of proteins.

Centrosome duplicates during the cell division in a regulated fashion which result in arrangement of a new centriole adjacent to the proximal wall of each parent centriole and accompanied with accumulation of robust PCM around them. At the late G1 phase of the cell cycle, the centriole pair present in a centrosome disengages by a process of centriole disengagement. They move apart but are still tethered loosely by several proteinaceous tethering factors. This signals the centriole for duplication in the S-phase of the cell cycle. Each pre-existing centriole serves as a template for the organization of a new centriole (procentriole) which involves cartwheel-like assembly of core centriole proteins. The centrosome specific kinase, Polo-Like Kinase 4 (PLK4) (SAK, *Drosophila* orthologue) is a key centrosome duplication factor. Accordingly, PLK4/SAK misregulated expression result in abnormal centrosome number[5]. Work in *Caenorhabditis elegans* has identified sequential recruitment of the core cartwheel proteins[16]. In *C. elegans,* ZYG-1 (functional orthologue of PLK4/SAK) requires the PCM protein SPD-2 (CEP192, human orthologue) for centriole recruitment[77]. ZYG-1 is involved in the recruitment of the centriole cartwheel hub and spoke protein SAS-6. SAS-6 requires another core protein, SAS-5 (ANA2, *Drosophila* orthologue; STIL, human orthologue) for central cartwheel tube formation[76]. The length of radial spokes and their association with centriole microtubules is regulated by CEP135 (Bld10, *Drosophila* orthologue)[33, 42] and CPAP (SAS-4, *Drosophila* and *C. elegans* orthologue) centriole proteins[57, 60], respectively. Depending on the cell type, the procentrioles elongate by MT growth to achieve proper organelle length. In the G2 phase of the cell cycle, centrosomes accumulate robust PCM which prepare them for spindle organization. These mature centrosomes also start separating from each other by breaking their tethering proteins and move towards opposite poles of a cell in order to organize bipolar spindle by the M phase of the cell cycle[22].

Centrosome forms MTs both during interphase (radial astral MT organization) and mitosis (spindle MT apparatus)[44] by orchestrating events involved in MT nucleation, anchoring and/or stabilization and release. The sub-distal appendages are suggested to engage in the process of MT nucleation by housing the γ-tubulin protein in their head region[17]. However, the outer region of centrosome *i.e.* PCM serves as a major platform for several protein complexes involved in MT nucleation. Immuno-electron microscopic tomography of isolated centrosomes revealed ring structures in the PCM containing multiple copies of γ-tubulin which are involved in MT nucleation[68]. Further studies later identified these structures as γ-TuRCs[67]. Several proteins localized at PCM are known be required for MT nucleation (Fig. 2). Table 1 provides a list of some of the well-studied centrosome localized proteins and their role in microtubule organization (indicated in the Fig. 2). The following section provides an insight into the molecular mechanisms governing MT nucleation at the centrosome.

3.1 Mechanisms Regulating Centrosome-Dependent MT Nucleation

During the G2 phase of the cell cycle, γTuRCs are accumulated at the PCM. There is growth in the size of PCM which is subsequently getting ready for the spindle organization. The process is referred as centrosome maturation. Hundreds of proteins involved in centrosome duplication and maturation have been identified by the mass spectrometry[1] and RNAi approaches[18]. The cell-cycle kinases are involved in dynamic localization of PCM matrix proteins, namely PCNT (pericentrin), CDK5RAP2/CEP215 and CEP192 which recruit γ-TuRCs. In *C. elegans*, PLK-1 mediated phosphorylation of PCM localized SPD-5 (functional orthologue of human CEP215 and *Drosophila* Cnn) and SPD-2 (CEP-192 human orthologue) were shown to result into supramolecular scaffolds which could explain PCM expansion during mitosis[53, 106]. These PCM proteins and kinases exist in positive feedback loop for their efficient timely recruitment and activation as observed during the PCM expansion. In humans, CEP192[28] is involved in PCNT-dependent recruitment of Aurora A and PLK1[43]. During interphase, Aurora A binds to CEP192 and gets activated by trans-autophosphorylation of its catalytic domain. The PLK1 phosphorylates threonine-44 residue of CEP192 via a self-priming mechanism and this recruits PLK1 to

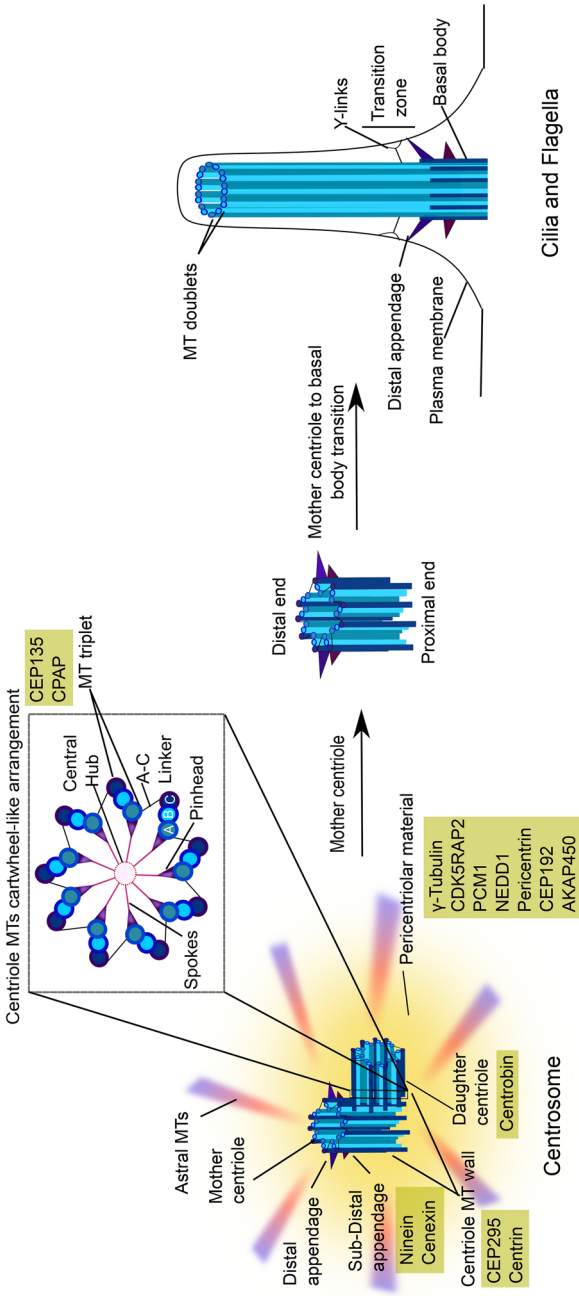

Figure 1: *Centrosome structure*: Centrosome is a microtubule-based structure, consisting of a centriole pair (mother and daughter centriole) embedded in pericentriolar material. Several ultra-structures are labelled. The schematic also indicates names of Table 1 proteins (green box) next to the centrosome ultra-structures where they are known to be localized. The box highlights the 9 + 0 symmetric arrangement of centriole microtubule triplets arranged in cartwheel-like fashion. In resting cells, the mother centriole transitions to become the basal body which generates axoneme of other cellular structures like cilia and flagella. *MTs* Microtubules.

the centrosome where it is further activated by Aurora A–mediated phosphorylation of the activation loop. Alternatively, PLK1 could also bind to another site *i.e.* phosphorylated serine-995 of CEP192 which is also sufficient to recruit PLK1 at the centrosome. Thereafter, PLK1 further phosphorylates CEP192 to enhance the γ-tubulin recruitment capacity of CEP192-Aurora A-PLK1 complex[64]. Interestingly, the centriole duplication protein CPAP has also been shown to be required for efficient PCM organization[35, 46]. Aurora A mediated phosphorylation of CPAP protein is required for maintaining the integrity of PCM during mitosis[11]. CPAP orthologue in *Drosophila* (SAS4) is also involved in direct interaction with Polo (PLK1, human orthologue)[71] which suggest a possible mechanism which could explain its role in centrosome maturation. However, in certain organisms, depletion of γ-tubulin does not completely inhibit MT nucleation function of PCM, thereby suggesting existence of alternative mechanisms of MT nucleation at the PCM[84, 94]. Accordingly, the kinase activity of PLK1 is also known to be required for the recruitment of PCM protein CDK5RAP2/CEP215 (vertebrate orthologue of *Drosophil*a CNN) at the centrosome which offer binding site for the γ-TuRC[24, 31]. However, CNN can also recruit MT-associated protein TACC (Transforming Acidic Coiled-Coil) (Jiuli[108] which in turn brings MT stabilizing XMAP215/ch-TOG (Colonic and hepatic Tumour Overexpressed Gene) protein at the centrosomes possibly suggesting an alternative route for spindle organization[26]. Similarly, Aurora-A kinase is also known to phosphorylate MT-associated proteins TPX2 (targeting protein for the Xenopus kinesin-like protein 2)[52] and TACC[80] at the centrosomes which also influence their MT nucleating function.

Additionally, distinct adaptor proteins are involved in recruitment and activation of γ-TuRCs to different MTOCs, whereas certain adaptor proteins can function at multiple locations in a cell. For instance, NEDD1 is known to be involved in recruitment of γ-TuRCs to the centrosome and as well as to spindle MTs. The phosphorylation of NEDD1, increases the affinity of NEDD1 to the γ-TuRC and enables the interaction with proteins at the PCM and spindle MTs[27]. However, Grip71, NEDD1 homologue in *Drosophila* has been shown to be involved in γ-TuRC at spindles but not at centrosomes, thereby suggesting possible functional differences among organisms[82]. Non-centrosome MT nucleation pathways relies on Augmin (HAUS in mammals), a multi-protein complex. Augmin is comprised of eight protein subunits and mediates MT nucleation from the lateral surface of pre-existing spindle MTs using NEDD1 as an adaptor. This mechanism amplifies the density of MT arrays in neurons, mitotic spindle and plant cell cortex. Accordingly, it is found to be a prevalent mechanism during the early embryonic cell divisions and female meiosis in various species[62, 63].

Other additional protein identified in γ-TuRC activation is a nucleoside diphosphate kinase, NME7, which is mostly expressed in tissues with motile cilia and in sperms. It interacts with soluble inactive γ-TuRCs and also with centrosome-bound active γ-TuRCs[37], Pengfei[62, 63]. Recently, Mozart1 has been identified as an additional component of γ-TuRC which directly interacts with the N-terminus of GCPs[12]. Its paralogue Mozart2, is involved in the centrosomal recruitment of γ-TuRCs via NEDD1 exclusively during interphase[97]. In mammals, several other centrosome associated factors aid in the recruitment and activation γ-TuRCs, including pericentrin (PCNT/kendrin)[105], ninein (GSK3B-interacting protein)[55], ninein-like protein (NLP)[7], A-kinase anchoring (AKAP450/AKAP9/CG-NAP) protein[96] and centrosomal P4.1-associated protein (CPAP)[81]. These proteins associate together forming molecular scaffolds to cluster γ-TuRCs. It is of interest to explore whether all of these proteins randomly recruit γ-TuRCs or whether these proteins individually regulate the binding process. For instance, PCNT and AKAP450 directly interact with GCP2 and GCP3 and hence with γ-TuRC without the involvement of NEDD1[96, 111]. The centrosome duplicating factor, CPAP has been shown to be associated with the γ-tubulin in yeast-two-hybrid screening. Furthermore, MT destabilizing motifs have also been identified in CPAP[36]. Additional work has revealed that Aurora-A mediated phosphorylation of CPAP is required for maintaining spindle pole integrity[11]. Several proteins affecting the structural integrity of PCM also influence its MT nucleation function. For example, Lectin galactoside-binding soluble 3 binding protein (LGALS3BP) plays a crucial role in maintenance of centriole integrity and biogenesis. Disrupted levels of the protein cause PCM dispersion with abnormal γ-tubulin recruitment and defects in MT aster formation[23]. Similarly, depletion of Centrobin, a daughter centriole specific protein enhances the recruitment of PCM proteins to the centrosome and result in abnormal MT organization[41]. Moreover, centrosomal MT nucleation can also be regulated by signalling proteins including Protein Kinase D 3 (PKD 3)[109], G protein-coupled receptor kinase-interacting protein 1 (GIT1), p21 protein [Cdc42/Rac]-activated

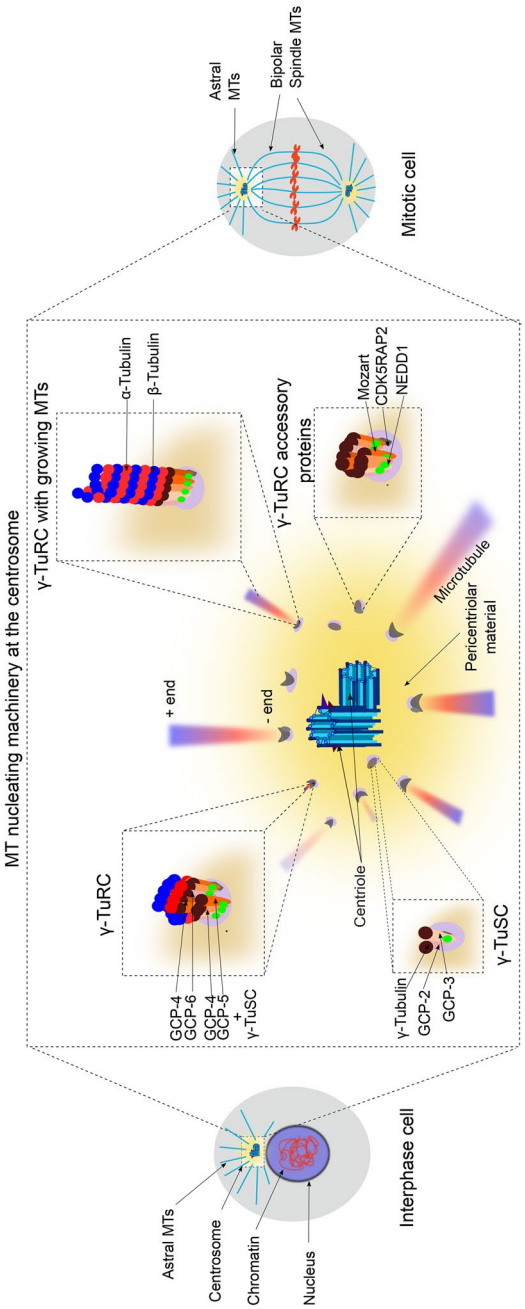

Figure 2: *γ-TuRC involved in MT nucleation at the centrosome:* the schematic represents astral and spindle microtubules (MTs) emanating from centrosome at different stages of the cell-cycle (interphase and mitotic cell). The box highlights γ-TuRC involved in MT nucleation at the centrosome. γ-TuSC: involves Y-shaped arrangement of GCP-2/GCP-3 dimers, where each GCP is associated with γ-tubulin protein. γ-TuRC: involves association of γ-TuSC and additional GCPs (GCP4/5 and GCP4/6 dimers). γ-TuRC with growing MTs: indicate α/ß-tubulin dimers arranged on γ-TuRC. γ-TuRC accessory proteins: indicates additional proteins involved in γ-TuRC activation at the centrosome (Mozart, NEDD1 and CDK5RAP2)

Table 1: List of centrosome-localized proteins and their microtubule-associated function

S. no	Protein	Centrosome localization	Centrosome function	Centrosome-associated microtubule function	References
1	AKAP450/AKAP9/CG-NAP	PCM	Centrosome duplication	Microtubule nucleation via γ-TuRC	Keryer et al.[45], Takahashi et al.[96])
2	CDK5RAP2/CEP215/CNN	PCM	Centrosome maturation	Spindle organization via γ-TuRC and TACC	Fong et al.[24], Haren et al.[31], Jiuli Zhang & Megraw[108]
3	Cenexin	Sub-distal appendages	Centrosome positioning	Astral MTs length and Spindle organization	Hung et al.[34]
4	Centrin	Distal lumen of centriole/basal bodies	Centrosome duplication	MT severing	Paoletti et al.[75]
5	Centrobin	Daughter centriole	Centrosome duplication and elongation	Nucleation and stabilization of mitotic spindles	Jeffery et al.[2010]
6	CEP135/Bld10p	Centriole-cartwheel protein	Centrosome elongation and PCM organization	Microtubule binding; central axoneme of cilia/flagella	Mottier-Pavie & Megraw[69], Ohta et al.[74]
7	CEP192	PCM	Centrosome duplication and PCM integrity	Spindle organization via γ-TuRC	Gomez-Ferreria et al.[28], Joukov et al.[43], Meng et al.[64]
8	CEP295	Centriole MT wall	Centrosome elongation	Post-translational modification of centrosome MTs	Chang et al.[10]
9	γ-Tubulin	PCM	Centrosome maturation; forms γ-TuRC	Astral and spindle MT nucleation	Moritz et al.[67],[68]
10	NEDD1	PCM	Centrosome duplication	γ-TuRC targeting to centrosome and spindle assembly	Haren et al.[30]
11	Ninein	Sub-distal appendages	Centrosome maturation	MT Nucleation	Stillwell et al. [93]
12	PCM-1	Centriolar-satellite enriched around centrosome (PCM)	Centrosome maturation	Astral MT organization	Dammermann & Merdes [14]
13	Pericentrin/PLP	PCM	Centrosome elongation and PCM integrity	MT organization via CNN and SAS4	Lee & Rhe[56], Richens et al.[83], Singh et al.[90]
14	SAS4/CENPJ/CPAP	Centriole-cartwheel protein	Centrosome duplication, elongation and maturation	MT organization via CNN and γ-tubulin	Ramani et al.[81]

* The localization of listed proteins is also indicated in Fig. 2. PCM pericentriolar material, MT microtubule

kinase 1 (PAK1)[8] and p21-activated kinase interacting exchange factor (βPIX)[95] which require further studies to enhance the understanding of complex molecular networks at the centrosome.

3.2 Aberrant Centrosome-Mediated MT Nucleation Cause Human Diseases

Defects in centrosome structure or number in animal cells is often accompanied by MT nucleation and organization abnormalities. Dysfunctional MTs cause loss of cell polarity and cytoskeletal malformations, eventually affecting organelle positioning and protein cargo movements. Any abnormalities in MT organization function of centrosomes could give rise to a wide range of human cancers, ciliopathies and neurodevelopmental disorders.

The two centrosomes in a dividing cell generate bipolar mitotic spindle which ensure proper DNA segregation between the resulting daughter cells. Increase in the number of centrosome which is referred as centrosome amplification, could cause either a multipolar spindle or an abnormal clustering of spindle poles. Such

abnormalities in a dividing cell subsequently result in mitotic defects and genomic instability which is often associated with wide range of cancers. Consequently, increased expression of a number of core centriole duplicating proteins like Polo-like kinase 4 (PLK4)[58], SAS6[89] and STIL[19] have been observed in a wide range of cancers like breast, prostate, kidney, brain, liver, colorectal and bone[9].

Not just the centrosome number, but their positioning also plays an important role in correct divisions of certain cell types. During the brain development, centrosome positioning with respect to cell polarity in dividing neural stem cells decides the spindle axis and thereby the segregation of cell-fate determinants among resulting daughter cells. During the early stages of neurodevelopment, positioning of the two centrosomes creates a spindle axis which is perpendicular with respect to the polarity axis of a neural stem cell. This results in symmetric division and generates two daughter cells with self-renewing capacity. However, during the later stages of embryonic development, centrosomes are positioned at an angle to the polarity axis which causes asymmetric division of stem cells. The switch to asymmetric mode of division results in a daughter cell with self-renewing capacity and another one differentiates to neuron. Centrosome-related defects in these cells could disrupt this timely switch from symmetric to asymmetric division thereby affecting the pool of stem- and neural cells in a developing brain. In agreement, centrosome-related defects have been reported in neurodevelopmental disorders such as autosomal recessive primary microcephaly (MCPH) and seckel syndrome (SCKL)[40]. Patients with these neurodevelopmental disorders have small brain size, distinct morphological features and intellectual disability. As per OMIM (Online Mendelian Inheritance in Man) database, currently 8 centrosome-associated gene loci have been mapped in patients with MCPH and 4 centrosome-associate gene loci have been mapped in patients with SCKL syndrome. This include several core centriole and PCM associated genes like, *ASPM*, *CDK5RAP2*, *CEP63*, *CEP135*, *CEP152*, *CPAP/CENPJ*, *SAS6*, *STIL*, *NIN* and *WDR62*[38].

In resting cells, centrosomes act as basal bodies of other MT based structures like cilia (primary/non-motile or motile) and flagella which are involved in cell signalling and motility, respectively[88]. Nearly all animal cells have primary cilia, so their dysfunction affect majority of organs system resulting in diverse disorders collectively refereed as ciliopathies. Different mutations at the centriole/basal body associated genes like *ALSM1*, *NEK2*, *PLK4*, *OFD1* and *KIA00556* which result in non-functional proteins have been identified in patients with ciliopathies[38].

4 Perspective

MT organization is one of the principle functions of centrosomes. Centrosome proteins influence the stability and dynamics of MTs through various mechanisms. The advancement in proteomics has successfully identified several centrosome proteins that regulate MT nucleation, activation and stability. Despite our knowledge on diverse centrosome proteins associated with MT dynamics, their mechanism of action is not entirely clear. The field will benefit from further studies providing coherent picture of molecular mechanisms involved in centrosome-mediated MT nucleation. Elucidating these mechanisms will pave ways towards deciphering new targets to combat diseases associated with MT organization.

Abbreviations

MTOC: Microtubule Organizing Center; MT: Microtubule; PCM: Pericentriolar material; γ-TuRC: Gamma-tubulin ring complex; γ-TuSC: Gamma-tubulin small complex; MAP: Microtubule-associated protein; GCP: Gamma complex protein.

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Compliance with ethical standards

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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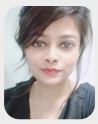

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