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REVIEW

The Centrosome Is a Polyfunctional Multiprotein Cell Complex

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Abstract—Contemporary knowledge about centrosome proteins and their ensembles, which can be divided into several functional groups—microtubule-nucleating proteins, microtubule-anchoring proteins, centriole-duplication proteins, cell cycle control proteins, primary cilia growth regulation proteins, and proteins of regulation of cytokinesis—is reviewed. Structural–temporal classification of centrosomal proteins and the scheme of interconnection between the different centrosomal protein complexes are presented.

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The centrosome, a cellular organelle visible under a light microscope as a dense granule, possesses a complex ultrastructure common for most animal cells studied. It is composed of a pair of centrioles (cylindrical structures consisting of nine microtubule (MT) triplets) surrounded by a pericentriolar material (Fig. 1). It is worth noting that MT triplets of centriolar cylinders are very stable and, unlike the cytoplasmic MTs, are not disassembled under the action of mitostatics and cold [1-3]; the disassembly only occurs in isolated centrioles at high salt concentrations [4]. The centriole keeps its form after removal of the triplets; the structure obtained was named the centriolar rim [4]. Hence, the centriolar matrix, rather than MTs, comprises the basis of centriolar cylinders.

Centrioles of the pair are different: one of them is mature or maternal, and, unlike the second one, immature or daughter, bears additional structures, such as pericentriolar satellites and appendages. Another difference of maternal centriole is in its ability to form the primary cilium, which is often associated with striated rootlets. The mature centriolar cylinder is about 0.3-0.5 μm in length and 0.2 μm in diameter. Together with the abovementioned components, the centrosomes of some types of cells may contain additional structures, such as free foci of microtubule convergence. The elements comprising the centrosome themselves possess a complex constitution. A detailed analysis of all morphological aspects of the centrosome structure was presented in previous papers [5, 6].

Here we present a summary of data on proteins and protein complexes found in the centrosome, analysis of which is necessary for comprehension of principles of the functioning of this organelle in the cell.

CLASSIFICATION OF CENTROSOMAL PROTEINS

The centrosomal proteins can be classified by several parameters. First, there are the structural proteins either directly involved in the centriolar structure or localized in the pericentriolar matrix. Second, the centrosomal proteins may be either permanently associated with the centrosome or appear in its structure in distinct stages of the cell cycle. Third, the centrosomal proteins can be classified by their functions: protein motors, regulatory proteins of the cell cycle, components of MT nucleation complex, etc. Any centrosomal protein will fall into one or another isolated group by classification corresponding to a chosen parameter. Thus, it is impossible to elaborate a universal classification encompassing all presently known centrosomal proteins. This situation creates a certain intrigue in this field of research and enforces us to reinterpret all the wealth of data accumulated from early light- and electron-microscopic experi-

Abbreviations: AB) antibody; MT) microtubule.

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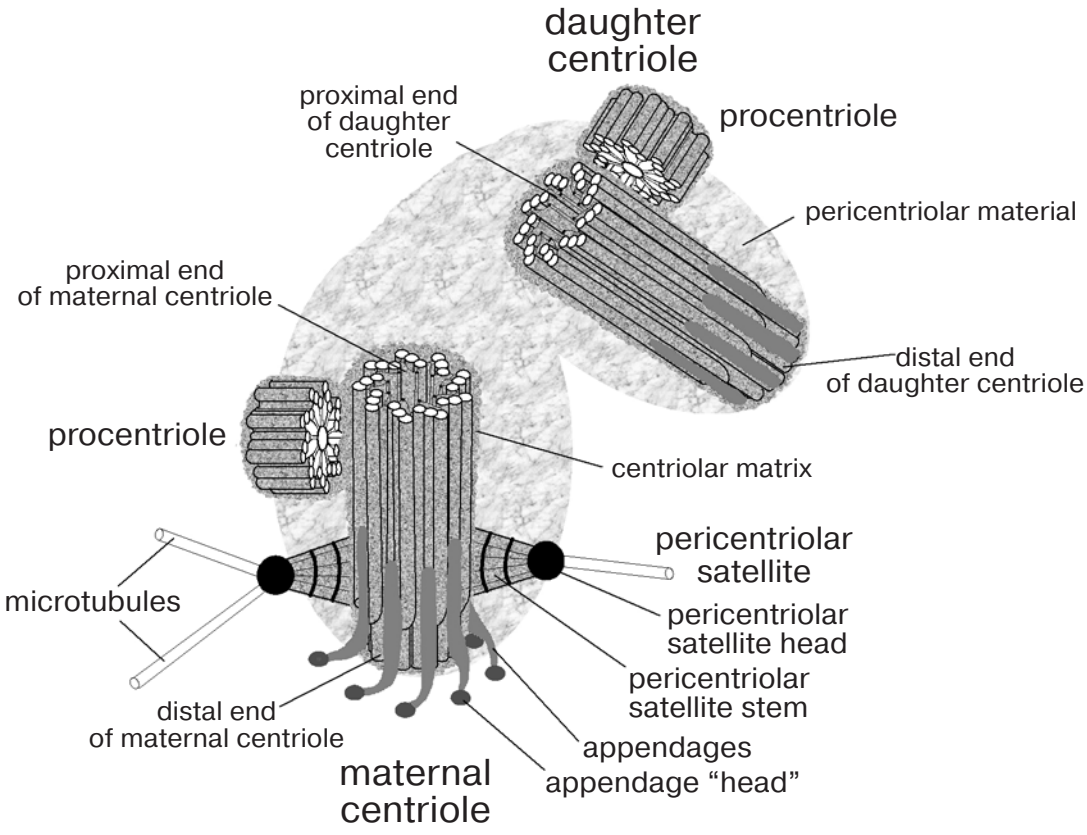

Fig. 1. Simplified scheme of centrosome structure in interphase mammalian cells at the beginning of S-phase of the cell cycle: both maternal and daughter centrioles and procentrioles growing from them are surrounded by a pericentriolar material; pericentriolar satellites and appendages are localized on the maternal centriole. The primary cilium and striated rootlets are not shown (from [6] with modifications).

ments up to the current epoch of molecular identification of proteins.

Relying of analysis of known facts, we have proposed a structural–temporal classification of proteins that is based on different affinity of proteins to the main centrosome components. This classification results from the data of experiments in which the proteins of isolated centrosomes were sequentially removed [7], as well as from observations on formation of the centrosome functioning as the MT nucleation center [8]. In the first case, the sequential loss of centrosomal proteins correlated with the loss of functional activity of the centrosome, and in the second case—the nucleation activity of the centrosome was restored with accumulation of proteins. Unlike of the classification of Andersen [9] based on the analogous principle, we do not equate centriole and centrosome, reasoning that the former is the basal component of the latter and that the centriolar matrix and pericentriolar material are distinct components. However, we do not exclusively accent the MT-polymerizing activity of the centrosome, but offer a polyfunctional approach. Since sufficient data (obtained by protein synthesis inhibition by short interfering RNAs) has been accumulated to date on the dependence of centrosomal localization of some proteins on the presence of others in the centrosome, we use for our classification data on protein–protein interactions in addition to data of experiments on resistance of centrosomal proteins to salt and carbamide extraction. Hence, our classification makes possible the inspection of centrosome not only for MT nucleation, but also for its other intrinsic activities.

Thus, one can recognize three protein groups. The first comprises MT triplet and centriolar matrix proteins, the second—proteins of pericentriolar material, and third—proteins whose association with the centrosome is labile (table). Some of these proteins from the second and third groups is only associated with the centrosome at distinct stages of the cell cycle. These proteins are classified as facultative (table). In our opinion, such classification allows a maximal generalization of the presently known data on centrosomal proteins and has a developing potential for accumulation of new data.

PROTEINS OF CENTRIOLAR TRIPLETS

Classical proteins of the tubulin family. The first characterized centrosomal proteins were, naturally, α- and β-

Structural–temporal classification of main centrosomal proteins

Proteins of triplets and centriolar matrix	Proteins of pericentriolar material	Centrosome-associated proteins
α-Tubulin*	**γ-tubulin**	**CDK 1 kinase**
β-Tubulin*	**γ-TuSC-complex**[1]	**Xklp2 motor**
Tektins*	**γ-TuRC-complex**[2]	**dynein**
γ-Tubulin	**δ-tubulin**	**dynactin complex**[3]
Centrin	**ε-tubulin**	γ-tubulin**
Pericentrin	**η-tubulin**	katanin
Ninein	**centrosomin A**	NuMA
Cenexin	**PCM-1**	**duplication complex**[4]
hsp73	**Nek2 kinase**	p53
TCP-1	centrosomin B	Aurora-A kinase
CEP110	CP190	PLK-kinase
Centriolin	CP60	Eg5 motor
Centrobin	Nlp	B23
	CG-NAP/ACAP450	cyclin A
		CDK2/cyclin E
		D-TACC
		MSPS
		XMAP215
		Ajuba
		HEF1

Note: Facultative proteins whose presence or concentration in centrosome depends on the cell cycle stage are given in normal (not bold) font. The table does not display proteins whose localization in centrosome is uncertain.

* Proteins of MT triplets.

** Additional pool recruited from cytoplasm in mitosis.

[1] γ-TuSC complex is composed of two γ-tubulin molecules, one molecule of GCP2-, and one molecule of GCP3-protein.

[2] γ-TuRC complex contains several copies of γ-tubulin and at least five other proteins—GCP2, GCP3, GCP4, GCP5, and GCP6.

[3] Dynactin complex contains the following proteins: EB1, $p150^{Glued}$, $p135^{Glued}$, p62, dynamitin (p50), Arp1 (centractin), p37 (CapZα), p32 (CapZβ), p27, and p24.

[4] The centriole duplication complex contains proteins SPD-2, ZYG-1, SAS-6, SAS-5, SAS-4, or their homologs.

tubulins forming a dimer with molecular mass of 110 kD (50-55 kD per each of the tubulins) and comprising a framework for MT triplets of centriolar cylinders. Even in evolutionarily distant organisms, the amino acid sequences in tubulin molecules share about 40% homology. Tubulins of birds and mammals are virtually identical [10-12]. Internal homology (α–α or β–β) between the sequences of tubulins from different organisms is about 60%, and achieves 97% for α-tubulin and 95% for β-tubulin in animals [13]. The universality of MT architecture on one hand and diversity of cell structures including MTs on the other hand imply modifications of MTs or tubulins comprising them depending on their functions.

First, each organism contains several isoforms of α- and β-tubulins. In vertebrates, their number is from two through seven for each tubulin [14, 15]. A resemblance between corresponding isoforms from different species is higher than that between different isoforms from one species [11, 16]. It was demonstrated that MTs might simultaneously contain all isoforms expressed in the cell [17]. On the other hand, data exists on heterogeneous distribution of different isoforms in MT-structures, which is likely associated with different ability of isoforms to post-translational changes [18] and with their interaction with MT-associated proteins [19].

Second, the tubulin molecules undergo posttranslational modifications, preferably near the variable C-end [15, 20]. Detyrosylation, polyglutamylation, and polyglycylation are only characteristic of this protein [21]. Acetylation of α-tubulin was found in centrioles and centriole-associated cilia [22-24]. The common acetylation site is lysine, particularly Lys40 [25]. Polyglycylation of β-tubulin may be necessary for normal sperm motility [26] and for regulation of cytokinesis [27].

Polyglutamylation, that is, addition of one through seven glutamate residues to the γ-carboxylic group of glutamyl residues, was described for α-tubulin [28-31]. It is necessary for the interaction of MTs with MT-associated proteins and calcium and probably plays an important role in regulation of MT polymerization and depolymerization dynamics [28]. Already at early stages of procen-

triole growth, MTs of triplets undergo polyglutamylation, which increases their stability [32, 33].

In the steady state, all the cellular pool of monomeric tubulins become tyrosylated [34, 35], because tubulin-tyrosine ligase is only active towards monomeric tubulin [36]. What is important about MTs is that the tyrosylation level depends on their lifetime [34, 37, 38]. In the long-lived MTs, tubulin-carboxypeptidase, which is only active towards polymerized tubulin [39], catalyzes detachment of the C-terminal tyrosine [40], so the centriole triplet MTs are detyrosylated. α-Tubulin, both in nerve tissue cells and in MTs of cilia and flagella, can exist in a form lacking two terminal residues (Glu450 and Tyr451). This modified form was named Δ2-tubulin [41, 42]. The loss of two terminal residues results in that Δ2-tubulin is no longer a substrate for tubulin-tyrosine ligase. This tubulin abandons the tyrosylation–detyrosylation cycle, and MTs containing Δ2-tubulin become considerably more stable [43].

β-Tubulin phosphorylation can occur at serine residues [29, 44, 45], particularly at Ser444 [46, 47], and at tyrosine residues [48]. Stability of MTs comprising centriolar and ciliar triplets to depolymerizing agents is significantly associated with posttranslational modifications of β-tubulin, such as polyglutamylation, acetylation, and phosphorylation.

Moreover, tubulins can interact with various MT-associated proteins, which significantly alter properties of centrosomal, ciliar, and flagellar MTs.

Tektins are proteins that are constantly present in centrioles, cilia, flagella, and basal bodies [49-51]. Tektins were first isolated from MT duplets of sea urchin sperm flagella. There are three types of proteins of this family: tektin A (~53 kD), tektin B (~51 kD), and tektin C (~47 kD) [49, 52]. Tektins of different types are now characterized for a broad spectrum of organisms [53]. Tektins possess secondary structure very similar to that of intermediate filaments [54, 55] but have very little homology with them in amino acid sequences. Tektins comprising a flagellum form thin filaments of 2-3 nm in diameter, which are identified by immunoelectron microscopy after removal of tubulins. This suggests localization of tektins in the inner space of MTs in intact flagella [56]. Tektins A1 and B1 were shown to form stable heterodimers and tektin C homodimers [52, 57] forming at least one protofilament in MT duplets of the flagellum [58]. High expression level of tektins is found in tissues such as testicles, trachea, and lung, whose cells have cilia or flagella [53, 59]. In the centrosome, tektins were found in the cells of strains CHO and HeLa [51, 60]. Electron microscopic immunolocalization revealed tektin B in pericentriolar material [51]. Antibodies (AB) against tektin B stained it in centrioles isolated from CHO cells, that is, its localization was not associated with the centrosomal MTs [51]. Tektin B localization in the centrosomal area depended on the stage of the cell cycle: this protein appeared in prometaphase and disappeared in late telophase [51]. It is hypothesized that the function of centriolar tektins is stabilization and regulation of the length of centriolar cylinders [50, 61].

PROTEINS OF CENTRIOLAR MATRIX

Centrin, or **caltractin**, is an acidic protein with molecular weight of ~21 kD. It was found in centrioles, basal bodies, and mitotic spindle poles of various cell types from algae, higher plants, and invertebrates to mammals [62-65]. As first demonstrated by the example of alga cells, centrin can form a new class of filaments of 3-8 nm in diameter that are capable of calcium-dependent contraction [66-69]. Unlike motility associated with actomyosin complex, which is based on sliding of one filament along others, and motility based on interaction of mechanochemical motors with MTs, the centrin-associated motility is based on filament supercoiling [66, 70]. Centrin is a calcium-binding protein that can be phosphorylated by kinases A and $p34^{cdc2}$ [65]. Although the functional significance of centrin phosphorylation is unclear, it was found to correlate with increase in amount of centrin-containing filaments [67, 71]. Like γ-tubulin, centrin is only partly localized in the centrosome (Fig. 2, see color insert); its largest part is dissolved in cytoplasm [72]. The centrin amount in mature centriole is greater than in daughter centriole [73] and differs between the mitotic spindle poles [74]. In the yeast *Saccharomyces cerevisiae*, the protein Cdc31p (a centrin homolog in yeasts) encoded by the *CDC31* gene is necessary for duplication of the spindle pole body (SPB, the centrosome analog in yeasts) [75, 76]. Mutations in the *VFL2* gene encoding centrin (Crcentrin) of green alga *Chlamydomonas reinhardtii* led to impairment of centriole and basal body duplications [77]. Recently, the role of centrin (centrin 2p) in centriole duplication in mammals was directly demonstrated for HeLa cells. Suppression of centrin expression by injection of antisense RNA blocked centriole replication, but such cells entered mitosis in which one centriole was present in each spindle pole [78]. Surprisingly, the daughter cells, each inheriting one centriole, could complete one or even two subsequent cell cycles with formation of mitotic spindle (however, with apparent dysmorphic features). As a result, the cells without mature or even both centrioles were incapable of proper cytokinesis and eventually died [78]. In mammals, four different centrins—1p, 2p, 3p, and 4p [62, 74, 79, 80]—are presently characterized. A comparative analysis of amino acid sequence has revealed a close homology of centrin 3p to the yeast centrin ScCdc31p, whereas centrins 1p and 2p exhibit more homology to *Chlamydomonas* centrin [77, 79]. Unlike centrin 1p, which is preferably expressed in male gametes, centrins 2p and 3p are expressed in most mammalian cell types and found (as

mentioned above) in centriolar lumen and in the area of initiation of procentriole formation [72, 81]. Centrin 4p resembles centrin 2p, but it is only expressed in cells of brain, kidney, lung, and testis and specifically associated with cilium formation [80]. Thus, in various taxonomic groups centrins play an important role in centrosome duplication, regardless of whether the centrosome contains centrioles or not.

Pericentrin, like many other centrosomal proteins, was found using autoimmune ABs (in this case isolated from serum of patients suffering from sclerodermitis) and subsequently cloned [82, 83]. This 220-kD protein is an integral protein of the centrosome, which cannot be separated from it even using high salt concentrations [84]. Later, the second pericentrin isoform with molecular mass of 350 kD was characterized [85]. The first isoform was named pericentrin A, and the second—pericentrin B (or kendrin [85]). The investigation of sequences of pericentrin A and pericentrin B (kendrin) has demonstrated that the two proteins are products of alternative splicing of the same gene [86]. Like pericentrin A, pericentrin B is detected in centrosome composition during the continuance of the cell cycle, even after experimental MT depolymerization [85]. The transport of pericentrin into the centrosome depends on MT; pericentrin can be transported by the protein motor dynein due to binding with its light chain [87, 88]. As demonstrated by high-resolution immunofluorescence, in pericentriolar material pericentrin form centrosomal scaffold [83] that other proteins can be attached to. Pericentrin can bind with the PCM-1 protein, being colocalized with it in interphase centrosome to form small (70-100 nm in size) electron-dense granules, which were previously characterized morphologically as "non-centriolar focuses" [89] or "centriolar satellites" [85, 90, 91]. These granules can move along MTs in the direction of their minus-ends and concentrate near the MT-organizing centers [91, 92]. It is not yet entirely known whether pericentrin is directly associated with MT nucleation or not. On one hand, ABs against this protein do not block the nucleating capability of the centrosome [82], but on the other hand, pericentrin can form complexes with γ-tubulin, although independently from γ-TuRC formation [83].

Ninein is a very acidic (calculated p*I* 4.8) self-helicized protein with molecular mass of 220-245 kD [93, 94] that is localized in centrosomes of most cells possessing the radial system of MTs. In mitosis, ABs against ninein, besides the centrosome, stain also the mitotic spindle MTs [93]. This protein has a potential site for GTP binding [93]. Ninein (Fig. 2) is preferably found on the maternal centriole [73]. It appears on the distal (distant from the maternal centriole) end of daughter centriole only during transition from telophase to G_1-phase of next cell cycle [95]. In the centrosome, ninein is colocalized with CEP110 and CEP250/C-Nap1 [95-98]. Ultrastructural studies [93, 99] have demonstrated ninein localization both on the head of pericentriolar satellite and on the surface of centrioles, especially near the proximal ends. Moreover, this protein binds with the minus-ends of MTs; it is not directly involved in their nucleation, but is important for MT stability, distribution, and attachment [99]. In specialized cells (such as the cells of polar epithelium lining the inner ear), ninein is presumed to be the basis of the anchoring complex maintaining MTs in basal–apical orientation [100].

Cenexin, a protein with molecular mass of 96 kD, is only detected on one of two centrioles in early interphase cells (Fig. 2) and only on one of four centrioles (elder of maternal ones) in the late interphase [101, 102]. This protein appears on the maturing centriole only in the early prophase of mitosis, later than all known centrosomal proteins (together with centriolin). As shown earlier, the mitotic centrosome (from prophase) can nucleate a significantly greater amount of MTs than can the interphase centrosome [103, 104]. Ultrastructural analysis of cenexin-defective cells has shown that their centrosomes do not contain pericentriolar satellites and appendages [105]. The growth of primary cilium is impossible in such cells. Thus, cenexin is involved in functional maturation of the centrosome upon transition from interphase to mitosis, "allowing" transformation of daughter centriole to maternal one in the next cell cycle.

Molecular chaperones, which play an important role in maturation of many newly synthesized proteins [106], can also participate in regulation of MT assembly on the centrosome [84]. Two molecular chaperones, hsp73 (Mw ~70 kD) and TCP-1 (50-60 kD) are integral components of the eukaryotic cell centrosome, which are colocalized with pericentrin [84, 107]. Both preincubation of isolated centrosomes with anti-TCP-1 AB *in vitro* and microinjection of these ABs into the living cells inhibit MT growth on the centrosome, whereas ABs against hsp73 do not block MT nucleation on the centrosome [84]. Likewise, it was demonstrated for some other centrosomal proteins that most portions of hsp73 and TCP-1 are distributed in cytoplasm. TCP-1, which is present in the cytoplasm in the form of 25S-complex with at least eight additional subunits, is involved in posttranslational folding of tubulin [108]. Hsp73 is the heat shock protein. It is supposed to be also involved both in centrosome maturation and centrosome reparation after heat shock. Functions of molecular chaperones in centrosome may be a facilitation of protein movement in and out of the organelle, as well as catalysis of spatial alterations of proteins in pericentriolar material during the cell cycle [9].

Protein CP110 (110 kD, 991 amino acids, Acc. No. NCBI NP_055526; http://www.ncbi.nlm.nih.gov/). Initially, this protein was named Cep110 [109], which has led to significant misunderstandings and mishmash, because in subsequent publications in was renamed CP110 [110]. At the same time, another centrosomal protein with similar molecular mass was described, named

CEP110 (in upper case) ([111]; 994 amino acids, Acc. No. NCBI AF083322). The name CEP110 is now used for the protein identical to the C-terminal end of centriolin [113]. CP110 has two coiled-coil domains at both ends and two cyclin-binding sites in the middle. It was demonstrated that this protein can be phosphorylated by complexes CDK2/cyclin E, CDK2/cyclin A, and CDK1/cyclin B [110]. Suppression of the synthesis of this protein leads to both impairments in centriole replication and cell polyploidization [110, 112]. It is presumed that the growth of procentriole due to MT triplet elongation occurs with direct involvement of CP110, which forms the "cap" on its distal end [112].

Protein CEP110 has a molecular mass of 110 kD ([111]; 994 amino acids, Acc. No. NCBI AF083322). Localization of this protein depends on the stage of centriolar and cell cycles. In G_1-phase of cell cycle, CEP110 is only present on the more mature centriole: on its distal end near pericentriolar satellites and appendages and on the proximal end on the face of the centriolar cylinder, analogically to ninein. In the course of centriole duplication and disjunction, CEP110 first appears only on the proximal end of daughter centriole, whereas in the distal end it is only found after completion of mitosis [95]. In the course of mitosis, while amounts of many centrosomal proteins increase, the amount of CEP110 in the centrosomal area decreases and begins to increase only after completion of mitosis [95], which correlates with disappearance and appearance of pericentriolar satellites in the centriolar cycle. Microinjection of anti-CEP110 ABs into metaphase HeLa cells leads to impaired localization of several centrosomal proteins [95], hence, one can suppose that CEP110 may function as the binder.

Centriolin is a coiled-coil centrosomal protein (molecular mass 270 kD), which is localized both on the mature centrosome and midbody and required for normal cytokinesis in vertebrates. As mentioned above, its C-end is identical to that in Cep110 [113], which sometimes leads to identifying these proteins and using the term "centriolin/CEP110" [114]. The ultrastructural analysis of localization of this protein has shown that in interphase cells it is associated with the head of pericentriolar satellite. Unlike ε-tubulin, which appears on the second centrosome during the G_2-phase of the cell cycle, centriolin, like cenexin [101], is only detected on the second centrosome in prophase–metaphase of mitosis. The protein amounts in both spindle poles therewith become evened only in metaphase. In the anaphase-to-telophase transition, the centrosomal level of centriolin dramatically decreases. Disjunction of centrioles occurs in some cells during cytokinesis, and one of the centrioles (more mature, maternal) is displaced into the area of constriction. In this case, centriolin is only found on this displaced centriole rather than on the younger centriole, remaining in the middle of the cell. Suppression of centriolin synthesis by transfection with corresponding interfering RNA led to arrest of cells in the terminal stage of cytokinesis. The delay was so long that some cells entered the next mitosis in non-divided state to form syncytia of three to four cells connected by cytoplasmic bridges. Suppression of centriolin synthesis did not affect both MT nucleation on the centrosome and general organization of MT system at all stages of the cell cycle. No defects in centrosomal localization of γ-tubulin and other marker centrosomal proteins were detected [113]. The far consequence of the inhibition of centriolin synthesis was blocking of centrosome duplication in such cells; the cells either abandoned the cell cycle before the beginning of S-phase and remained in G_1-phase for a long time or exit to G_0 [113].

Centrobin (centrosomal BRCA2 interacting protein), another recently described protein with molecular mass of 100 kD, contrariwise, is only localized on the daughter centriole before the beginning of replication [115]. When replication begins, at the end of G_1- and beginning of S-phase, the protein is only detected on the newly-formed procentrioles (Fig. 2). Inhibition of the synthesis of this protein by transfection with corresponding interfering RNA blocked centriole duplication with following impairment of cytokinesis, which is indicative of the involvement of centrobin in regulation of these processes. In this case, the level of γ-tubulin did not decrease, and MT-nucleating ability of the centrosome, at least in interphase cells, was not noticeably affected [115].

PROTEINS OF THE PERICENTRIOLAR MATERIAL

Minor proteins of tubulin family. The tubulin family has now been significantly enlarged: after **γ-tubulin** [116, 117], several proteins with molecular masses of 50-55 kD, such as δ-, ε-, ζ-, η-, θ-, ι-, and κ-tubulins, have been characterized [118].

γ-Tubulin with molecular mass of 55 kD was first identified in *Aspergillus nidulans* [116] and has now been found in cells of many other organisms [119, 120]. This protein has 30% common amino acid sequence with α- and β-tubulins and is greatly conservative among various organisms. γ-Tubulin comprises about 1% of total cell tubulins [121]. The centrosomal pool of γ-tubulin (about 20%) is in dynamic balance with the cytoplasmic pool of this protein (about 80%) [122, 123]. Immunoelectron microscopic data suggests association of some part of centrosomal γ-tubulin with pericentriolar material [123, 124] (Fig. 2). This observation is in good agreement with biochemical data suggesting that half of the centrosomal γ-tubulin is tightly bound with centrosomes, whereas the other half can be easily extracted [123]. Quantitative analysis of γ-tubulin content in the centrosomal area after various treatments [125], as well as direct study of its dynamics using a

cell strain expressing a chimeric protein γ-Tu-GFP consisting of γ-tubulin and green fluorescent protein [126] support the idea of the existence of three pools of γ-tubulin (cytoplasmic, centriolar, and perocentriolar) in the cell. Both the pericentriolar and the cytoplasmic γ-tubulins initiate growth and stabilize the minus-ends of centrosomal and free cytoplasmic MTs, respectively.

For MT nucleation, γ-tubulin forms complexes with several additional proteins [127, 128] (Fig. 3, see color insert). The first described is a complex found in the yeast *S. cerevisiae* and formed by the proteins tub4p, Spc97p, and Spc98p [129], which are localized in mitotic spindle poles (spindle pole body—SPB—analog of the centrosome in yeast). Two proteins, Spc10p and Spc72p, bind this triple complex with the inner and outer SPB lamina, respectively [130, 131]. The transport of this complex into the nucleus occurs with involvement of a special site of Spc98p protein with this protein only phosphorylated in the nucleus rather than in cytoplasm. This phosphorylation depends on the cell cycle and is realized after SPB duplication by kinase Mps1p, which is also responsible for mitotic checkpoint control [132].

Two γ-tubulin complex types were found in animal cells. The first "small" complex γ-TuSC (tubulin small complex, ~280 kD) is composed of two molecules of γ-tubulin and one molecule of GCP2 and GCP3 proteins each—the human homologs of *S. cerevisiae* proteins Spc97p and Spc98p (Dgrip84 and Dgrip91 in *Drosophila*) [133, 134]. The second "large" (~2200 kD) complex γ-TuRC (γ-tubulin ring complex) contains several copies of γ-tubulin and at least five other proteins (in *Drosophila* they are called D-grips and have molecular masses 163, 128, 91, 84, and 75 kD) [127, 133-135]. Both complexes can nucleate MTs, but the nucleating efficacy of complex γ-TuRC is higher [134].

The study of *Xenopus laevis* egg extract has shown that during mitotic aster formation γ-Tu-GFP aggregates in small granules, which move along MTs into the center of the aster; this movement depends on activity of cytoplasmic dynein [136]. Inhibition of γ-tubulin activity with specific ABs does not allow MTs to form asters (the function is restored upon overexpression of γ-Tu-GFP), thus confirming the necessity of the presence of γ-tubulin on MTs forming asters. The study of mutant γ-tubulins has shown that the middle part of the protein causes formation of atypical mitotic asters with unattached MT minus-ends. The use of γ-tubulin devoid of the N-terminal area prohibited the assembly of MT into asters; this effect was the same as the effect of anti-γ-tubulin ABs [136].

δ-Tubulin (molecular mass 51 kD) was first characterized in *Chlamydomonas* [137]. Besides the original amino acid sequence, δ-tubulin has distinctive localization in the cell: it is found in the flagellar basal body [138]. The study of mutants in the δ-tubulin gene has shown that they are characterized by abnormal architecture of the centriolar cylinder: instead of MT triplets, their centrioles contain duplets even in the proximal part due to the loss of exterior MT of the triplet [137]. Genomic analysis has allowed characterization of δ-tubulin in human, mouse, and trypanosome [139, 140]. In the yeast *S. cerevisiae*, δ-tubulin analog is absent [139], possibly because of the absence of centrioles in this organism. In human cells, δ-tubulin was found in the area between centrioles before the beginning of their replication and, later, between two replicating centrosomes (Fig. 2); both accumulation and localization of δ-tubulin were not dependent on whether MTs were intact or not [139].

ε-Tubulin (molecular mass 53 kD) was independently found in mammalian [139] and trypanosomal [140] cells. Like δ-tubulin, this fifth member of the tubulin family plays an important role in assembly of MT duplets and triplets in *Chlamydomonas* [141]. Like δ-tubulin, ε-tubulin has no analogs in yeast cells [139]. Unlike δ-tubulin, ε-tubulin is found in pericentriolar material [139]; in the beginning of centrosome duplication, the protein is only localized near the "old" centrosome (Fig. 2) and appears in the other centrosome after completion of S-phase, that is, in G_2-phase [139, 142]. The portion of ε-tubulin measured in U2OS cells was ~0.02% of the total protein [139], which is about the cellular level of γ-tubulin [121, 127]. As is characteristic of γ-tubulin [123, 143], most ε-tubulin comprises the cytoplasmic pool of this protein [139].

Ultrastructural analysis has shown that ε-tubulin is localized on pericentriolar satellites [142]. Removal of ε-tubulin from *Xenopus laevis* extract, in which centrioles can normally replicate, leads to the blocking of centrosome duplication; moreover, MT nucleation focuses which are not associated with centrosomes become observed in mitosis [142]. However, as demonstrated earlier [139], ε-tubulin is not a part of the 32-S γ-TuRC complex, although the authors did not exclude the possibility of direct interaction between ε- and γ-tubulins. In experiments on MT nucleation on the centrosome after their complete depolymerization in the cell by nocodazole followed by washing off this drug, nearly equal numbers of MTs were found in both duplicated centrosomes significantly differing in amount of ε-tubulin. In this case, both the difference in ε-tubulin content and resemblance in MT amount did not depend on the distance between the centrosomes [139]. These data show that maturation of centrosomes associated with accumulation of ε-tubulin is not directly associated with their MT-nucleating capability, at least in interphase.

ζ-Tubulin (molecular mass ~52 kD) was first found in trypanosomes, and its amino acid sequence is known for *Trypanosoma brucei* and *Leishmania major* [140]. However, it is very probably that this member of the tubulin family is present in cells of other organisms [141]. Immunofluorescence and electron microscopy immunolocalization studies have shown that ABs against

ζ-tubulin stain the area of basal body in trypanosomes and centriolar area in animal cells [144].

η-Tubulin was first found using genetic methods in *Paramecium* as the protein encoded by the *SM19* gene [145]. Mutation in this gene (sm 19-1) led to the blocking of basal body duplication, which reduced the oral apparatus of *Paramecium* and simultaneous caused improper localization of γ-tubulin. These data suggest that η-tubulin may play the role of a connecting link between γ-tubulin (or γ-TuRC) and the basal body. Ultrastructural study of sm 19-1 mutants has shown the absence of MT triplets in some (~3%) basal bodies.

θ-, **ι-**, and **κ-tubulins** were recently found in *Paramecium* sp. [118]. Their analysis has shown that κ-tubulin closely resembles α-tubulin, whereas θ-tubulin belongs to the β-tubulin branch. The data on these minor tubulins are still fragmentary, and the role of these proteins in cell organization is unknown.

PCM-1 protein with molecular mass of ~220 kD was first characterized using autoimmune ABs [146]. PCM-1 is a very acidic protein that has no apparent homology with other known proteins, and whose amino acid sequence suggests its interaction with ATP and/or GTP. PCM-1 is found in the centrosomal area during the continuance of the cell cycle; however, its level is lower during mitosis [9]. Anti-PCM-1 ABs do not block MT nucleation on isolated centrosomes, but accumulation of this protein requires MT integrity [85]. Suppositions were proposed that PCM-1 may serve as inhibitor of MT nucleation: due to its high acidity, it inhibits binding of acidic tubulin with microtubule nucleation sites [9]. PCM-1 can form complexes with pericentrin-B [85], which is probably associated with its anchoring in the pericentriolar area.

Nek2-kinase (NIMA-related kinase 2) is one of the very well-studied kinases of the NIMA (Never In Mitosis A) family (molecular mass 52 kD). During the continuance of the cell cycle, this protein is found on the centrosome, although only about 10% of this protein is localized on this organelle [97, 147]. MT depolymerization with nocodazole did not change the centrosomal localization of Nek2; moreover, Nek2-kinase was only detected in the nucleation focuses associated with centrosomes upon induction of additional MT nucleation centers with Taxol [147]. These data, together with the data on the presence of Nek2 in isolated centrosomes, suggest that Nek2 is an integral protein of pericentriolar material. Nek2-kinase phosphorylates C-Nap1 protein (Fig. 3) localized on the proximal ends of the two centrioles [97] (Fig. 2). Since the overexpression of C-Nap1 stimulated premature disjunction of centrosomes [147], one can suppose that the protein can be a component of the connective link between the proximal ends of the centrioles, which is disrupted after phosphorylation of this protein by Nek2 or other kinases activated before mitosis [97]. Overexpression of recombinant inactive kinase led to nondisjunction of centrosomes and formation of monopolar spindle [148], which supports a hypothesis on the role of C-Nap1 phosphorylation in the process of centrosome separation. Besides Nek2 itself, a shorter protein exists in which 70 amino acids from the C-end are absent [149, 150]. The first protein was named Nek2a and the second—Nek2b [149]. In human cells, both proteins are localized in the centrosomal area, but unlike Nek2a, overexpression of Nek2b did not stimulate separation of centrosomes. The cellular synthesis of both proteins was low in G_1-phase of the cell cycle, but increased in the course of cell progression through the S- and G_2-phases [150]. However, Nek2a quickly underwent degradation, whereas the Nek2b level remained high in cells arrested in prometaphase. Nek2a and Nek2b may play differing roles in mitosis [150].

Centrosomin is a 150-kD centrosomal protein that was first described in *Drosophila melanogaster*. Mutants in the centrosomin gene were viable but sterile [151, 152]. At late stages of embryogenesis of these mutants, multipolar divisions and formation of giant nuclei were observed, suggesting the necessity of centrosomin for the proper distribution of mitotic spindles in cyncytium. The spindle poles contained significantly lower amounts of the centrosomal proteins CP60, CP190, and γ-tubulin, and had no astral MTs at late stages of embryogenesis. Thus, centrosomin is necessary for the proper organization and functioning of centrosomes during syncytial divisions [151]. Later, a protein was described that has a large region identical to centrosomin, but it is localized in the nucleus. The new protein named centrosomin B and previously described centrosomin (named centrosomin A) are the products of alternative splicing of one gene [153]. The longer centrosomin B has an additional NLS region (nuclear location signal) on the C-end, which provides its corresponding localization in the cell nucleus.

CG-NAP/ACAP450, a large integral protein of the centrosome (molecular mass of 450 kD), which also found in Golgi complex, binds with many regulatory molecules associated with the centrosome and thus serves as a peculiar structural platform (Fig. 3). CG-NAP/ACAP450 is bound with the dynactin complex via the protein named $p150^{Glued}$, and its accumulation in the centrosome depends on dynein activity [154]. This protein was shown to associate with PKC family kinases [155], CK1 [156], PKN, and also with PP2A phosphatase [157]. Moreover, this protein interacts with the proteins Cep55 [158] and calmodulin [159] comprising the functional cytokinesis regulatory complex, as well as with γ-tubulin and GCP2 protein [160] of MT nucleation complex. The protein is fixed on the centrosome via its C-terminal domain, which is significantly homologous to the GCP2 domain of pericentrin B (kendrin) [160]. The interaction of CG-AP/ACAP450 with the complex of cyclin E and cdk2 is of fundamental importance in regulation of centriole duplication [161].

CP60 and CP190, two proteins with centrosomal localization and molecular masses of 60 and 190 kD, respectively, were first described in *Drosophila* and named DMAP60 and DMAP190, respectively [162, 163]. It was later found that the protein CP190 corresponds to the previously found centrosomal antigen stained with mABs of the clone Bx63 [164]. Accumulation of both CP60 and CP190 in the centrosome does not depend on whether or not MTs are intact [165, 166]. There are data suggesting that protein CP190 is a component of a large complex of about ten proteins including CP60 and γ-tubulin. In turn, CP60 without CP190 can form a firm complex with γ-tubulin [167]. However, according to the data of other authors, neither CP60, nor CP190 form complexes with γ-tubulin [133]. Nonetheless, a significant decrease in amount of CP190 associated with the spindle poles was observed in cells of *Drosophila* mutants in the gene of one of the γ-TuRC complex proteins (a homolog of yeast Spc98) [168]. The observed effect may be either a direct result of impaired interaction between γ-TuRC and CP190 or a mediated effect of significant decrease of MTs nucleated by the centrosome in such mutants. In interphase cells, CP190 is detected in the nucleus and localized in the centrosome only in mitosis [165], in which case the sequence of the protein contains NLS (nuclear localization signal) domain. When NLS-domain is deleted, CP190 is found in the centrosome during the continuance of the whole cell cycle [163]. Like CP190, CP60 is localized in the nuclei of interphase cells, and in mitosis it is localized in the centrosome. The maximum level of centrosomal CP60 is observed in anaphase and telophase of mitosis, whereas it dramatically falls upon transition into interphase, which is possibly associated with specific degradation: the protein contains a sequence homologous to the "destruction box" of cyclins [169].

Nlp (ninein-like protein), a recently discovered protein with molecular mass of 240 kD, is, according to the authors describing it, the key regulator of centrosome maturation, which is necessary for chromosome segregation and cytokinesis [170]. At present the mechanism controlling Nlp expression is not well investigated, but it was demonstrated that expression of this protein depends on the stage of the cell cycle—the peak of expression corresponds to the end of G_2-phase. Nlp is a short-lived protein; the APC/c (anaphase-promoting cyclosome complex) is involved in its degradation.

CENTROSOME-ASSOCIATED PROTEINS

The proteins of a third group according to our spatial–temporal classification (table), the proteins associated with the centrosome, are the most numerous characterized proteins. This group also includes multiple protein complexes responsible for distinct functions of the centrosome (Fig. 3).

Many regulatory (kinases, phosphatases, and cyclins) and motor proteins are found to be components of the centrosome, but most are weakly associated with it. One exception is the above-described Nek2-kinase, which is not lost upon isolation of centrosomes.

Centrosomal kinases and phosphatases. For a long time CDK1 ($p34^{cdc2}$) kinase was recognized as the key mitotic kinase [171]. It was found in the centrosome during the continuance of the cell cycle [172]. The level of CDK1 in the centrosome achieves a maximum in late interphase and mitosis before the beginning of anaphase, just while the MT-nucleating capability of the centrosome increases and the level of phosphorylated centrosomal proteins undergoes significant increase [173-175]. Besides CDK1, several other kinases involved in mitotic regulation are described to date, such as mitogen-activated kinases [176], kinases of the Polo family [175, 177, 178], kinases of Aurora family [179, 180], LOSK/SLK [181], and some others (Fig. 3). Among phosphatases, centrosomal localization was shown for the type A2 phosphatase PPX [182] and PP1 [183].

Polo (Polo-like kinases, PLK). Kinases of this family were named after the Polo-kinase, which was first described in *Drosophila* [179], and the corresponding human protein was named PLK1 (molecular mass of 68 kD) [184]. In mitotic cells, these kinases are localized both in the spindle poles and kinetochores, and in telophase they are also found in MTs of the midbody. Such localization of the protein is indicative of multiplicity of its functions in mitosis. Association of PLK-kinases with motor proteins of the KLP (kinesin-like-protein) family suggests possible association of PLK functions with regulation of motor protein activities [185, 186].

Aurora A, another kinase of fundamental importance for cell cycle regulation, belongs to a protein family that also contains the Aurora B and Aurora C kinases [187]. Aurora A (molecular mass of 46 kD) is found in interphase in the centrosomal area (Fig. 2) and in mitosis in the mitotic spindle poles [179, 180]. Kinase activity of this protein is necessary for segregation of centrosomes and maintenance of the mitotic spindle stability [188, 189]. Aurora A accumulates in cytoplasm during oogenesis, and its level in blastomers progressively falls during embryogenesis; first this protein concentrates in the centrosomal area after actuation of the embryonal genome [190]. In this case, accumulation of Aurora A does not depend on CDK1, whereas its kinase activity does [191].

In somatic cells Aurora A appears in the centrosome at the late S- or at the beginning of G_2-phase and disappears soon after mitosis [180, 188, 192-194]. Degradation of this protein at the beginning of G_1-phase of the cell cycle occurs via a ubiquitin-dependent mechanism [195].

When the activity of Aurora A kinase is inhibited by the injection of specific AB, the transition of the cells from interphase to mitosis is allowed but delayed by 2 h. Hence, the minimum activity of the Aurora A kinase after

the microinjection of AB is sufficient for the ongoing into mitosis [196]. The inhibition of the Aurora A kinase synthesis by the injection of interfering RNA in *Caenorhabditis elegans* resulted in decrease by 60% in amount of MTs associated with centrosome and hindered the accumulation of additional mitotic γ-tubulin as well as Zyg-9 and CeGrip, two other proteins of pericentriolar material [197]. The injection of interfering RNA in HeLa cells inhibited the synthesis of Aurora A kinase and hindered the entry into mitosis [198]. The cells synthesized cyclin B1 but were incapable of its accumulation in centrosomes [198].

Overexpression of Aurora A kinase also leads to a disturbance of normal cell division. The increase in Aurora A kinase content described in cells of various tumors was accompanied by centrosome amplification [199-202]. The increase in the centrosome number in cells overexpressing Aurora A kinase was not a result of additional cycles of their duplication, but a consequence of cell tetraploidization induced by the disturbance of chromosomal divergence [203].

Aurora A interacts with a number of proteins in the centrosome (Fig. 3); some of them apparently act as its activators. Activation of Aurora A depends on the presence of Ajuba protein, which stimulates autophosphorylation of Aurora A kinase [198] and TPX2 protein (Targeting Protein for *Xenopus* kinesin-like protein 2) [204], the presence of which is crucial for Aurora A localization on mitotic spindle MTs, but not in the centrosome [205]. Centrosomin is another centrosomal protein interacting with Aurora A kinase. Aurora A binds with the C-terminal domain of this protein, and its N-terminal domain interacts with γ-tubulin [206]. Thus, centrosomin is the link binding the regulatory and MT nucleating functions of the centrosome.

Aurora A kinase interacts *in vivo* with D-TACC protein (*Drosophila* Transforming Acidic Coiled Coil), the phosphorylation substrate for Aurora A kinase [207]. Cells injected with AB against D-TACC, as well as carrying mutation in *D-TACC* gene, had anomalous short astral MTs associated with the centrosome. D-TACC was shown earlier to be found in the mitotic spindle poles, and its link with MSPS (minispindles) protein is important for stabilization of centrosomal MTs [208]. In *Drosophila* embryos with mutant *AURORA* gene, as well as with blocked synthesis of Aurora A kinase by the injection of interfering RNAs, had centrosomes devoid of D-TACC protein, and their spindles also had anomalous short astral MTs [207]. Thus Aurora A kinase participates in regulation of MT polymerization mediated by the control of D-TACC protein accumulation and MT-associated MSPS/XMAP215 protein [207], which accelerates the rate of MT elongation on plus- and minus-ends of MT [209, 210]. The phosphorylation of HEF1 protein by Aurora A kinase plays a key role in the process of primary cilium resorption before mitosis [211].

Experiments on fluorescence recovery after photobleaching of GFP-conjugated recombinant protein have demonstrated that Aurora A kinase is characterized by very high renovation rate—the half-regeneration time was about 3 sec [212]. The centrosomal localization of Aurora A is disturbed when it is deleted in its central stem domain; it is this part of the molecule that apparently interacts with the structural proteins of pericentriolar material [212]. Deletions at its C- and N-terminal domains did not interrupted the centrosomal localization of Aurora A but substantially decreased the rate of its regeneration in the centrosome [212].

Cell motors localized in the centrosomal region. The protein motors play a crucial role in the processes of intracellular transport and the mitotic spindle composition. However, only some of them are shown to be localized in the centrosome. Particularly, the disjunction of centrosomes preceding the mitosis of XL2 cells is accompanied by the appearance of kinesin-like protein XlEg5 (molecular mass 130 kD) between the two centrosomes, whereas the protein is localized around centrosomes in prophase cells and on spindle MTs in metaphase cells [188]. This protein is phosphorylated by Aurora A kinase and participates in centrosome disjunction, probably due to the interaction of MT ends growing from one centrosome, with motors localized in the vicinity of the other centrosome [188]. The result of inhibition of Eg5 functioning under the addition of AB against this protein is very similar to the result of the inhibition of Xklp2, another centrosomal kinesin-like protein (molecular mass ~160 kD): chromosomes are ordered in "rosette" or form a monopolar spindle [213, 214]. Xklp2 binds to centrosomes by its C-terminal (tail) domain, and peptides devoid of the motor domain act as dominant negative mutants [214]. Centrosomal localization of this protein in XL177 cells in mitosis and interphase was independent on whether MTs were intact or not. However, in mitosis Xklp2 was detected not only at spindle pole but also on adjacent MTs [214].

Some protein motors participate in accumulation of specific centrosomal proteins on centrosome. In particular, it has been shown that the transport of pericentrin into the centrosome depends not only on MT, but also on dynein, the light chains of which interact with pericentrin [87, 88] (Fig. 3). Dynein also participates in pericentrosomal localization of cisterns of Golgi complex [215].

Dynactin. Interstitial and light chains of cytoplasmic dynein bind with another multiprotein complex named dynactin [216, 217]. Dynactin contains several proteins in its composition: $p150^{Glued}$, $p135^{Glued}$, p62, dynamitin (p50), actin-binding protein 1 (other names of this proteins are Arp1, p45, and centractin), α- and β-subunits of actin-capping protein p37 (another name CapZα), and p32 (another name CapZβ), p27, and p24 (Fig. 3). The stoichiometric ratio of these proteins in dynactin is 1 : 1 : 1 : 4(5) : 9(8-13) : 1 : 1 : 1 : 1, respectively. Heterodimer

$p150^{Glued}$–$p135^{Glued}$ forms a side protuberance of Arp1-actin short (37 nm) filament and contains two globular domains carrying the MT-binding site [218]. The N-terminal domain $p150^{Glued}$ interacts with interstitial 74-kD chains of dynein [219, 220]. Dynamitin, on one hand, binds $p150^{Glued}$ with centractin filament, and, on the other hand, interacts with the light chains of dynein, thus acting as a connecting link between dynein and centractin filament.

Katanin. The phenomenon of MT cutting was found in 1991 [221], when MTs polymerized *in vitro* and stabilized with Taxol were incubated with mitotic (but not interphase) extract of *Xenopus laevis* ova. It was demonstrated later that the MT cutting is catalyzed by katanin, a protein component of mitotic extract. Katanin is a heterodimer containing two subunits: MT-stimulated ATPase with molecular mass of 60 kD and 80-kD protein, which is able to fix the complex to centrosome and regulate the MT-cutting activity of the 60-kD subunit [222, 223]. The maximum ATPase activity of katanin *in vitro* is observed at tubulin dimer concentration of 2-10 μM [223]. Katanin belongs to the widely distributed multifunctional AAA protein family (ATPases Associated with various cellular Activities) [222]. The protein members of this family participate in cellular processes that involve assembly and disassembly of protein complexes: transcription, DNA replication, proteolysis, motor activity associated with dynein [224]. The mechanism of the effect of katanin on MT assembly is supposed as follows: katanin binds to tubulin molecules in MT wall and captures and tears out the tubulin dimers on its subsequent dissociation [225-227]. The MT damaged in this way becomes less stable, depolymerization of protofilaments adjacent to the damaged ones occurs, and MT breaks. MTs inside the cell are protected from cutting by various MT-associated proteins, hindering the binding of katanin to the MT surface.

The minus-ends of MT are fixed at the pole region in mitosis, and the binding of γ-TuRC complexes, as demonstrated *in vitro* experiments, protects the minus-ends from depolymerization [128, 228]. On the other hand, MT "flow" exists directed to the pole [229], hence a mechanism of MT detaching from γ-TuRC complexes acts at the region of the centrosome. Since katanin is concentrated at mitotic spindle poles in mitosis [225], one possible variant of explanation for MT depolymerization at minus-ends may be their cutting near the centrosome. A substantial amount of γ-tubulin spread in the cytoplasm observed by many authors can be explained by the localization of this protein at MT ends cut by katanin from the centrosome of MT. This supposition is directly confirmed by data on inhibition of katanin leading to prophase-like staining of centrosome with AB against γ-tubulin [230]. In addition, the inhibition of katanin retards MT disassembly under the action of nocodazole [230], which is probably associated with the decrease in amount of free ends of MT in such spindles.

The katanin activity in the cell cycle is negatively regulated by ubiquitin-like protein Nedd8, which putatively modifies cullin protein, which is a constituent of E3 complex of ubiquitin ligase responsible for katanin degradation during the transition from meiosis to mitosis [231].

NuMA protein. NuMA (Nuclear Mitotic Apparatus protein) is one of the more fully characterized centrosomal autoantigens, whose activity is necessary for the formation of mitotic and meiotic spindles [232]. NuMA is a 220-kD protein that can be revealed in interphase nucleus and at mitotic spindle poles in mitosis; the accumulation of this protein in spindle depends on MTs [232]. In the nucleus, NuMA is associated with importin protein, and after the decomposition of the nuclear membrane at the beginning of mitosis prometaphase this complex decays involving Ran protein [233, 234]. NuMA is revealed at the spindle poles in mitotic pericentriolar halo, where it forms a complex with cytoplasmic dynein. Dynein is supposed to displace NuMA to MT minus-poles, where NuMA participates in attachment of spindle MTs [235]. NuMA facilitates the stabilization of MT bundle orientation by the formation the cross-links between bundles of spindle MT at the side of the centrosome facing the chromosomes [33].

Some proteins formerly found in cytoplasm and other cellular organelles have been revealed as components of centrosomes as well. Particularly, p53 protein involved in apoptosis regulation and cell cycle control is found as a component of the centrosome [236], and it effects centriole duplication [237]. A nucleolus component, B23 protein playing an important role in regulation of centriole duplication, was found initially at the poles of mitotic spindle [238, 239] and later as a component of centrosomes at G_1-phase of the cell cycle [240]. The non-phosphorylated B23 protein is localized at the centrosome after mitosis. The complex CDK2/cyclin E phosphorylates B23 at the restriction point and stimulates the escape of this protein from the centrosome, with simultaneous initiation of centriole replication [240].

STUDIED PROTEIN COMPLEXES COMPRISING THE CENTROSOME

To conclude, it should be noted that studies have presently achieved the level of revealing of protein complexes responsible for distinct functions of the centrosome (Fig. 3). A complex consisting of centriolin, Cep55, CP110, and BBS6 is described, which apparently plays a substantial role in cytokinesis [158, 241-243]. The MT nucleation γ-TuRC complex is carefully studied in various organisms [243, 244]. A complex is revealed consisting of CAP350, FOP, and EB1, which is putatively responsible for MT anchoring to the centrosome [244]. A similar function is possibly fulfilled by the complex of pericentrin-bound PCM/BBS4, ninein, and centrin, the compo-

nents of pericentriolar material, wherein BBS4 functions as an adaptor between PCM and $p150^{Glued}$ [245]. The anchoring complex consisting of ninein, and apparently ODF2/cenexin, Cep170, centriolin, and ε-tubulin is described as a component of the pericentriolar satellite heads [246]. The data of these studies indicate that the function of MT anchoring (as well as the other functions of the centrosome) can be actualized not only by different protein complexes—these complexes can be localized on different components of the centrosome.

Protein cascades described for a number of organisms are involved in different types of functional activity of the centrosome (Fig. 3). Five proteins identified in *C. elegans* are sequentially executing in the process of centriole duplication: SPD-2 is the primary protein appearing at the maternal centriole after fertilization and recruiting ZYG-1 kinase, which, in turn, is responsible for accumulation of complex consisting of two proteins, SAS-6 and SAS-5, involved in the formation of procentriole central hub, the structure on which radii the MT triplets are formed later with involvement of SAS-4 (centrosome-associated component, whose amount determines the centriole sizes) [8, 247, 248]. Homologous proteins of the centriole replication complex have been identified in *Drosophila* (DSAS-4, DSAS-6, and Plk4/DSAK kinase) and human (hSAS-6 and Plk4/SAK) [249-251], as well as their homologs and BLD-10 protein in *Chlamydomonas* [252], but cascades of interacting proteins are still incompletely described in these organisms [246]. The proteins of this group participating in centriole biogenesis are presently under comprehensive study. The involvement of DSAS-6 in the process of centriolar cylinder assembly and the linkage formation between centrioles has been directly shown. This protein is able to organize tubular structures, precursors of centrioles, and its excessive expression in embryos leads to the formation *de novo* of multiple centers of MT organization. Note that these centers did not contain centrioles, which was described earlier upon SAK/PLK4 overexpression [253]. Data on the formation of tubular structures supports the hypothesis that states that the centriole assembly begins with the formation of tubular scaffold, and this process depends on DSAS-6. A mutation resulting in the loss of DSAS-6 functional activity deprives the centriole of its ability to accomplish the formation and elongation of its structure along all nine axes. This suggests that the process of centriole formation is modular: the forming tubular structures are built of subunits, joint both laterally and along their whole length, and represent peculiar modules aggregating gradually to form a structure resembling a coreless lamellar pie [253].

In the process of ciliogenesis, the interaction between the HEF1/Cas-L/NEDD9 protein complex and Aurora A kinase at the ciliary basal body induces the phosphorylation and activation of HDAC6 protein (Fig. 3), a tubulin deacetylase, which results in the disassembly of the cilium [211]. SAS-6 protein is found at the basal body and proximal region of ciliar axonema, as well as being involved in ciliogenesis of ciliated epithelium cells [254].

Centrosome proteins are involved in cytokinesis process as well. So, already mentioned Cep55, the self-involuted 55-kD protein, is localized in interphase at the maternal centriole. Cep55 is bound with γ-TuRC-anchoring protein CG-NAP and kendrin, but in spite of this it is not necessary for MT nucleation. It has another function: Cep55 abandons the centrosome after the beginning of mitosis (thus providing a signal to Erk2/Cdk1-dependent phosphorylation at S425 and S428) and consequently localizes in the midbody being involved in cytokinesis; the exhaustion of Cep55 using short interfering RNAs leads to the arrest of cytokinesis [158]. Phosphorylation at S425/428 is required for the interaction with Plk1 and subsequent phosphorylation of Cep55 at S436. Cytokinesis does not occur in cells expressing mutant incompletely phosphorylated Cep55 forms. Thus, the complexes organized on the centrosome provide phosphorylation of Cep55 required for its dislocation to the midbody, where it participates in mitosis outgoing and in cytokinesis [158].

The ways of MT nucleation and anchoring as well as realization of other functions of the centrosome up to its self-replication can be duplicated by the work of several protein cascades possessing their own activator systems [255-257]. Thus, the execution of many centrosomal functions is provided not only by various protein complexes comprising the centrosome. Different protein assemblies often localized in different structural components of the centrosome can be responsible for the same function: this interchangeability provides a substantial hardiness and stability of the operation of the whole system.

The analysis of the data presented in this review suggest a contemporary structure–functional characteristic of the centrosome—a multiprotein and polyfunctional complex of the cell.

MT triplets consisting of α- and β-tubulin and centriolar matrix comprise the basis for the maintenance of the centrosome integrity. Posttranslational modification of tubulins in centriolar triplets provides them with unequalled stability along the whole cell life cycle. The centriolar cylinders represent a peculiar stable platform on which additional structures are formed, which are typical for the interphase or mitotic centrosome functioning at the distinct cell cycle moment. The group of structural proteins of centriolar matrix, such as pericentrin and CG-NAP/ACAP450, due to their ability to interact with functional and regulatory proteins (Fig. 3), provide their anchoring and concentration at the centrosome region and enable execution of the processes of intracellular regulation in a very small cell volume. The proteins of the γ-tubulin complex realize the MT nucleation of a radial system; in dependence on "cell needs", they are kept at the

centrosome region via the mechanism executed by ninein complex or, alternatively, are separated from centrosome due to the katanin activity. The choice between these two variants of development of events is controlled by the regulatory protein complex, particularly, kinases and phosphatases, as well as various activators and inhibitors of their own activity. The regulation like this is more apparently seen during the cell transition from interphase to mitosis. Substantial increase in number of MTs bound with the centrosome, on one hand, is a consequence of the elevation of γ-tubulin amount in the centrosome, and, on the other hand, leads to the accumulation in its composition of numerous specific mitotic proteins. Disjunction of centrosomes, the formation of division poles on their basis, spindle assembly—all these processes comprise the coordinated action of kinases, protein motors, and proteins-stabilizers of the MT network, such as NuMa. Rapid and drastic alterations in biochemical composition of the centrosome take place after the beginning of anaphase, and multiple specific mitotic proteins are actively consumed by the cell due to the action of the ubiquitin-dependent proteolysis system. The role of the centrosome in regulation of cytokinesis is not obvious, but apparently a number of centrosomal proteins participate in regulation of this process. Temporary migration of maternal centriole to the region of midbody is a fact not yet explained, but distinctly indicating the link between the centrosome activity and cytokinesis process. The MT system generated by the centrosome not only supports the cell form in dormant state and directionally alters it during the cell movement or other morpho-functional changes of the cell, but also provides the directed intracellular transport of substances and whole cellular organelles due to the action of motors associated with MTs. It is this feature, the ability to concentrate the regulator proteins in extremely small volume (about 0.1% of total cell volume) due to the directed transport along the monocentric MT system, that enables the centrosome to execute regulatory control, in particular, the cell cycle—rapidly, exactly, and accurately. To execute this fine regulation it is necessary to accumulate together two, three, and sometimes more molecules, thus the concentration of these molecules in the centrosome is more beneficial from thermodynamics consideration, than, for instance, their collocation in the cellular membrane plane, or, furthermore, their even distribution in the total cell volume.

The sensor and locomotor functions of the centrosome associated with cilia or flagella are not regarded in the present review, but the concentration of signal and regulatory molecules and the presence of a branched system of "transport" pathways are crucial for realization of these functions.

To conclude, one can surely state that the centrosome takes a central place in the cellular regulation system, executing, being the cellular processor, the constant dynamic control of the activity of the whole cell.

With the beginning of the XXI century, the possibility has appeared to study the protein composition of centrosome directly, due to the progress in proteomic analysis, that has enabled revealing about 60 new centrosomal proteins [258, 259], the functions of which are to be elucidated. Even the described earlier centrosomal proteins are yet insufficiently investigated from the point of view of their ultrastructural localization, dynamics in cell cycle, and functional links.

This fact is obvious: to elucidate the principles of centrosome functioning in the cell, it is necessary to join and combine two groups of accumulated data—the ultrastructural studies and the results of biochemical analysis. A simplified approach to the analysis of localization of centrosomal proteins limited by their revealing using specific AB at the light optical level does not allow elucidation of what distinct structure composing centrosome is associated with the given protein. Reappearance of interest in the study at the ultrastructural level in combination with immunochemical approaches must enable mapping all centrosomal structures in their protein compositions. The knowledge of exact ultrastructural localization of all centrosomal proteins, their dynamics in the cell cycle, and interactions with other cellular proteins must help not only to decipher functions of each of these proteins and protein complexes, but, finally must result in detailed understanding of the whole functioning of the centrosome.

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