Cent. Eur. J. Biol. • 5(1) • 2010 • 1–10
DOI: 10.2478/s11535-009-0061-x

VERSITA

Central European Journal of **Biology**

CLERC and centrosomal leucine-rich repeat proteins

Mini-Review

Yoshinori Muto[1]*, Yukio Okano[2]

[1]*Department of Functional Bioscience, Gifu University School of Medicine, 501-1193 Gifu, Japan*

[2]*Department of Molecular Pathobiochemistry, Gifu University Graduate School of Medicine, 501-1194 Gifu, Japan*

Received 18 June 2009; Accepted 12 October 2009

Abstract: The centrosome functions as the microtubule-organizing center and plays a vital role in organizing spindle poles during mitosis. Recently, we identified a centrosomal protein called CLERC (Centrosomal leucine-rich repeat and coiled-coil containing protein) which is a human ortholog of *Chlamydomonas* Vfl1 protein. The bibliography as well as database searches provided evidence that the human proteome contains at least seven centrosomal leucine-rich repeat proteins including CLERC. CLERC and four other centrosomal leucine-rich repeat proteins contain the SDS22-like leucine-rich repeat motifs, whereas the remaining two proteins contain the RI-like and the cysteine-containing leucine-rich repeat motifs. Individual leucine-rich repeat motifs are highly conserved and present in evolutionarily diverse organisms. Here, we provide an overview of CLERC and other centrosomal leucine-rich repeat proteins, their structures, their evolutionary relationships, and their functional properties.

Keywords: *Centrosome • CLERC • Leucine-rich repeat • SDS22-like • Chlamydomonas • Centriolin • CEP97 • LRRC6 • Seahorse*

© Versita Warsaw and Springer-Verlag Berlin Heidelberg.

1. Introduction

The centrosome, first described by Van Beneden and Boveri in 1876, has attracted the interest of cell biologists and remained a focus of attention for over a century [1]. It functions as the major microtubule-organizing center in most animal cells. The core of the centrosome is comprised of a pair of centrioles, cylindrical structures composed of nine groups of triplet microtubules [2,3]. Each centriole is surrounded by pericentriolar material or centrosome matrix, which nucleates the growth of new microtubules [4]. By nucleating and anchoring microtubules, the centrosome influences most microtubule-dependent processes, including cell division, shape, polarity and motility, as well as intracellular transport and positioning of organelles [5-8]. The centrosome also anchors regulatory molecules and may serve as a central site that receives, integrates, and transmits signals that regulate fundamental cellular functions [9].

Progress has been made toward understanding the complex architecture of mammalian centrosomes using mass-spectrometric proteome analyses, which have identified several hundred polypeptides [10]. It was suggested that proteins with known functional domains or motifs are rarely found among human centrosome components. Instead, there is a tendency for proteins to adopt coiled-coil structures, which likely constitute the structural scaffold of the centrosome matrix [11]. Although many of the centrosomal proteins identified by proteomic analysis remain uncharacterized, several proteins essential for the centrosomal function have been analyzed in detail. Using gene knockdown technology, several laboratories have demonstrated that a number of centrosomal proteins perform essential functions in centrosome reproduction and cell division [12-20].

* *E-mail: ymuto@gifu-u.ac.jp*

Unauthenticated
Download Date | 11/12/19 5:06 AM

Recently, we identified a centrosomal protein called CLERC (**C**entrosomal **le**ucine-rich **r**epeat and **c**oiled-coil containing protein) which is a human ortholog of *Chlamydomonas* Vfl1 protein [21]. The bibliography as well as database searches provided evidence that the human proteome contains additional centrosomal leucine-rich repeat proteins other than CLERC. Given the importance of leucine-rich repeat as a protein recognition motif [22], it is quite interesting to elucidate the nature of CLERC and other leucine-rich repeat proteins in the centrosome. Here, we review recent findings on the structure and function of CLERC and other human centrosomal leucine-rich repeat proteins. We also describe the functional properties of some leucine-rich repeat protein homologs present in lower organisms.

2. Structure of Centrosomal LRR proteins

The leucine-rich repeat (LRR) is a widespread structural motif that has been identified in thousands of protein sequences in a broad range of organisms. The LRR, usually present in tandem array, was first recognized in the leucine-rich glycoprotein [23] and subsequently defined as a protein motif by Kobe and Deisenhofer [24]. Each LRR motif is typically 20-30 amino acids long and generally rich in the hydrophobic amino acid leucine. The common feature of the LRR motif is a conserved 11-residue segment with the consensus sequence LxxLxLxxN/CxL (x can be any amino acid and L positions can also be occupied by valine, isoleucine and phenylalanine) [22]. The crystal structures of LRR proteins have revealed that LRR motifs form a horseshoe-shaped curved solenoid structure (LRR domain) [25,26]. The concave surface of the LRR domain is a parallel β-sheet to which each LRR motif contributes one β strand. The outer convex side is composed of any one of the structural elements: α-helices, 3_{10} helices, polyproline II helices and β-turns. The curved LRR domain structure appears to be well suited for building a structural framework for protein interactions. Many LRR proteins are associated with a variety of biologically important processes [27,28], including signal transduction and transmembrane receptors [29,30], RNA processing [31,32], neuronal development [33,34], immune response [35,36] and extracellular matrix assembly [37]. Despite their involvement in diverse biological processes, the common function among LRR domains is that they form complexes with other proteins. Thus, the primary function of LRRs appears to be to provide a versatile structural module for protein-protein interactions. Presence of LRR motifs in a centrosomal protein can be considered as a hallmark of its ability to interact with another protein.

In order to identify LRR-containing centrosomal proteins, we searched the protein assembly from CentrosomeDB (a human centrosomal proteins database) recently compiled

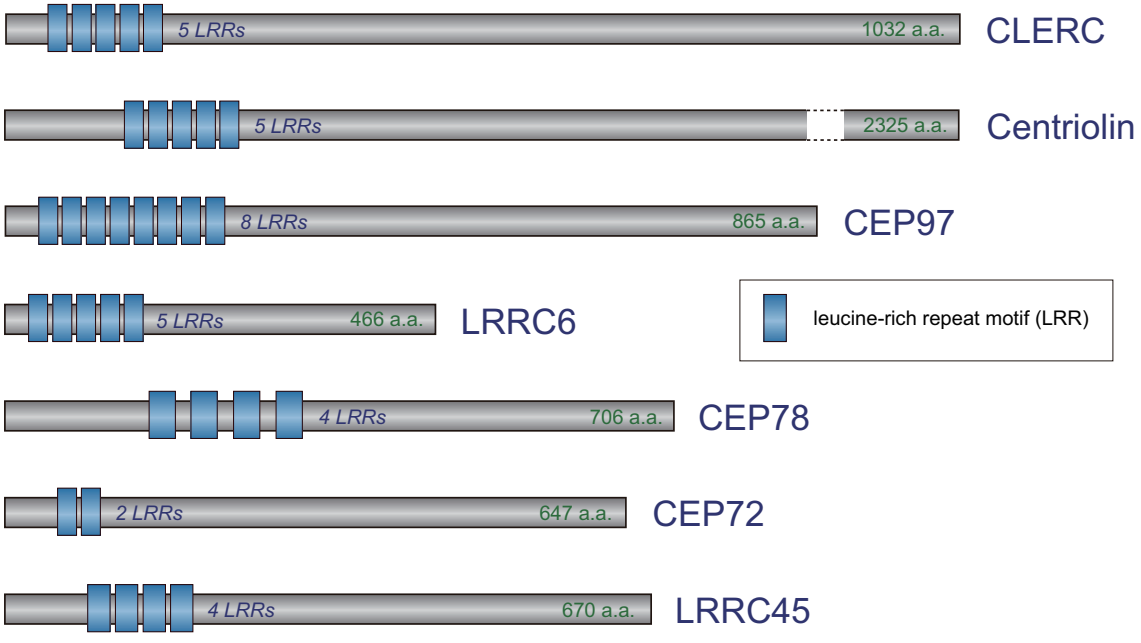

Figure 1. Schematic representation of the human centrosomal LRR proteins, illustrating the range of LRR motifs they contain. Note that the number of LRR motifs among proteins is variable, ranging from 2 to 8.

Unauthenticated
Download Date | 11/12/19 5:06 AM

Protein	Size (kDa)	Location of gene	LRR subtype	Accession number	Reference
CLERC	120	8q21.2	SDS22-like	FAA00427	[21]
Centriolin	270	9q33-q34	SDS22-like	AAP43846	[14]
CEP97	97	3q12.3	SDS22-like	NP_078824	[64]
LRRC6	54	8q24.22	SDS22-like	NP_036604	[66]
CEP78	78	9q21.2	cysteine-containing	NP_115547	-
CEP72	72	5p15.33	SDS22-like	NP_060610	[73]
LRRC45	76	17q25.3	RI-like	NP_659436	-

Table 1. Properties of human Centrosomal LRR proteins.

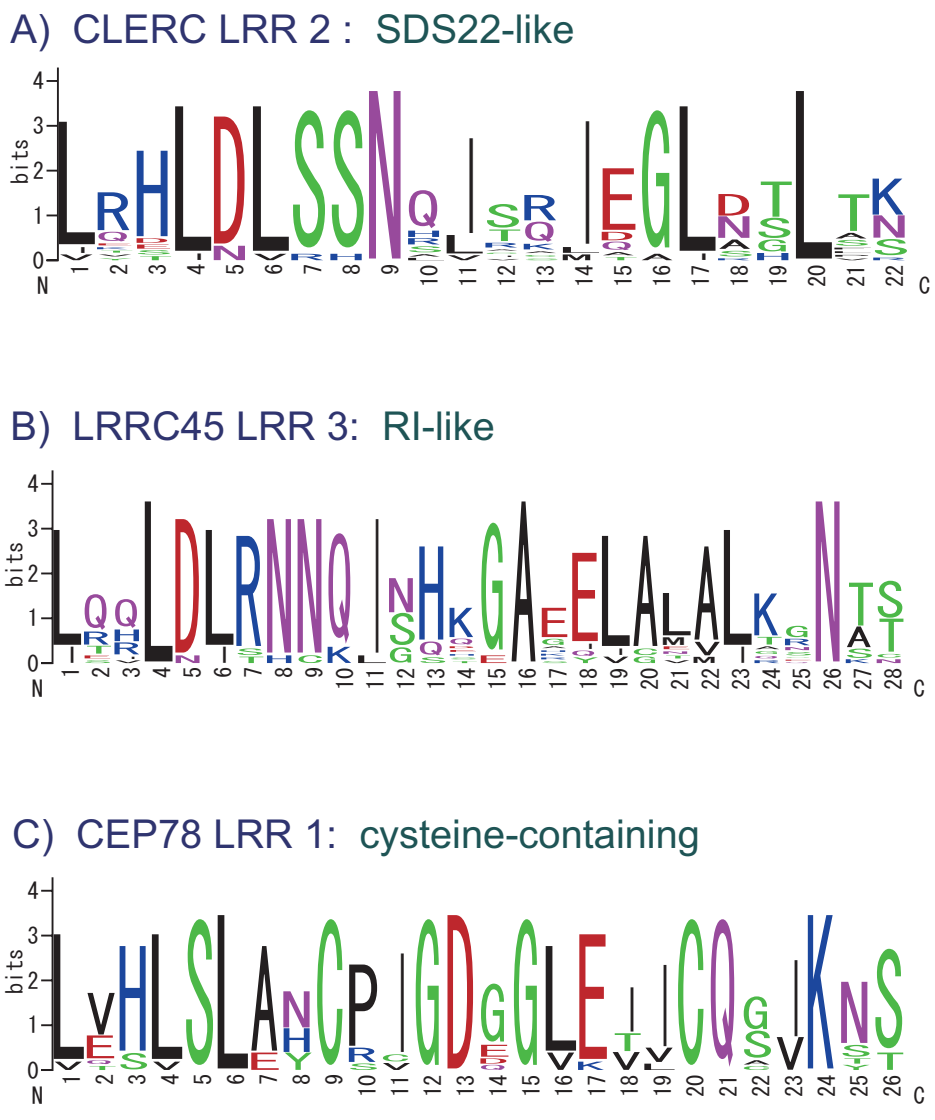

Figure 2. Sequence logo of the alignment of LRR sequences in the representative centrosomal LRR proteins. The height of a residue symbol is proportional to its frequency. The x-axis designates residue position in the multiple sequence alignment, and the y-axis the information content in bits. Only one LRR motif from each representative protein was selected for Sequence logo analysis. (A) A logo representation of the second LRR motif in the CLERC proteins collected from phylogenetically diverse organisms of 18 species. (B) A logo representation of the third LRR motif in the LRRC45 proteins collected from phylogenetically diverse organisms of 15 species. (C) A logo representation of the first LRR motif in the CEP78 proteins collected from phylogenetically diverse organisms of 13 species.

Unauthenticated
Download Date | 11/12/19 5:06 AM

by Nogales-Cadenas *et al*. [38]. This database contains a total of 383 human genes integrated on the basis of several types of evidence supporting centrosomal localization. A Hidden Markov Model (HMM) profile for LRR motif was obtained from Pfam database (http://pfam.sanger.ac.uk/) and was used to identify LRR-containing proteins with *hmmsearch*, a HMMER program (http://hmmer.janelia.org/) [39]. The HMMER search within the set of 383 human proteins identified a total of 6 centrosomal LRR proteins. In addition, we also identified a protein with LRR motifs, based on evidence in the literature. Although this protein (LRRC6) was not present in the CentrosomeDB, its localization to the basal body, a centrosome-related organelle, merits its consideration as a centrosomal LRR protein here. Table 1 shows a total of 7 LRR-containing centrosomal proteins retrieved. The human genes for centrosomal LRR proteins were found randomly dispersed across chromosomes in the genome, with the exception of chromosome 8, on which two LRR protein genes are located close to each other (Table 1). Of the 7 LRR proteins, 4 have already been described in the literature. As depicted in Figure 1, the number of LRR motifs in tandem ranges from 2, in the CEP72 protein, to 8, in the CEP97 protein. All the LRR motifs are clustered in the N-terminal half regions of the proteins (Figure 1).

Kajava and co-workers [22,40] have proposed seven classes for LRR motif subfamilies on the basis of sequence patterns. They are as follows: (I) RI-like, with α-helical conformation in their convex sides; (II) SDS22-like, with typical LRR motifs 22 residues long and 3_{10} conformation in the convex side; (III) cysteine-containing, with LRR motifs usually 26 residues long; (IV) bacterial, with short LRR motifs; (V) typical, the most populated subfamily; (VI) plant specific, with LRR motifs similar in length to the typical subfamily; and (VII) TpLRR, with 23-residue LRR motifs containing specific consensus pattern. Sequence analyses of centrosomal LRR proteins suggest that LRR motifs of CLERC, Centriolin, CEP97, CEP72 and LRRC6 all belong to the SDS22-like LRR subfamily (Table 1). Blast searches with these human centrosomal LRR proteins further allowed us to identify various homologs in evolutionarily divergent organisms. By using homologous LRR protein sequences, sequence logos [41] from relative entropy were generated on the WebLogo server (http://weblogo.berkeley.edu/) [42]. As shown in Figure 2A, inspection of LRR residues using the sequence logos further confirms that SDS22-like consensus sequences of the centrosomal proteins are highly conserved among divergent organisms. On the other hand, LRRC45 contains RI-like LRR motifs, which are comprised of longer amino acid sequences (Figure 2B). Finally, cysteine-containing LRR motifs are found in CEP78 (Figure 2C). At present, it remains unclear as to the evolutionary relationships of these LRR motifs in the centrosomal proteins. However, it is possible that the SDS22-like LRR motifs most frequently found in centrosomal proteins have a common and early evolutionary origin.

3. Functional and evolutional Features

3.1 CLERC

Chlamydomonas reinhardtii, the biflagellate unicellular alga, serves as a valuable genetic model system to better understand the molecular structure and regulation of centrioles/basal bodies [43]. Genetic approaches in *Chlamydomonas* allowed identification of the variable flagella number mutant, *vfl1*, which was observed to have defects in the number and localization of basal bodies and in their associated striated fibers [44]. Silflow and colleagues [45] extensively studied the *vfl1* gene that encodes a protein of 128 kDa with five leucine-rich repeat motifs near the NH_2 terminus and a large coiled-coil domain at the COOH terminus. The mutant phenotype, together with the localization results, suggested that Vfl1 protein plays a role in establishing the correct rotational orientation of basal bodies. The human protein CLERC was originally identified as an ortholog of *Chlamydomonas* Vfl1 protein by using iterative PSI-BLAST searches [21]. The CLERC gene maps to 8q21.2 and database analyses suggest the existence of potential isoforms. One of the isoforms, which is most closely related to Vfl1, consists of 19 exons and encodes one predicted open reading frame of 1032 amino acids, with a predicted molecular mass of 120 kDa. Although the global alignment of the *Chlamydomonas* Vfl1 and human CLERC sequences showed an identity of only 22%, the two proteins share a coiled-coil region distributed over its C-terminal two-thirds and a LRR domain comprised of five LRR motifs near the N-terminus (Figure 1). Blast searches with the CLERC sequence further identified homologs in various organisms, including the protist *Tetrahymena* (Figure 3). Members of this protein family have a relatively conserved size and structure, with the LRR domain located towards the N terminus, followed by one predicted coiled-coil domain in the C-terminal half. A multiple alignment using Clustal W indicated that LRR domain is highly conserved [21]. These features suggest that the CLERC protein family has an ancient origin.

In a proteomic analysis of the human centrosome [10], CLERC was listed as KIAA1764 and predicted to be a centrosomal protein by a protein correlation profiling

Unauthenticated
Download Date | 11/12/19 5:06 AM

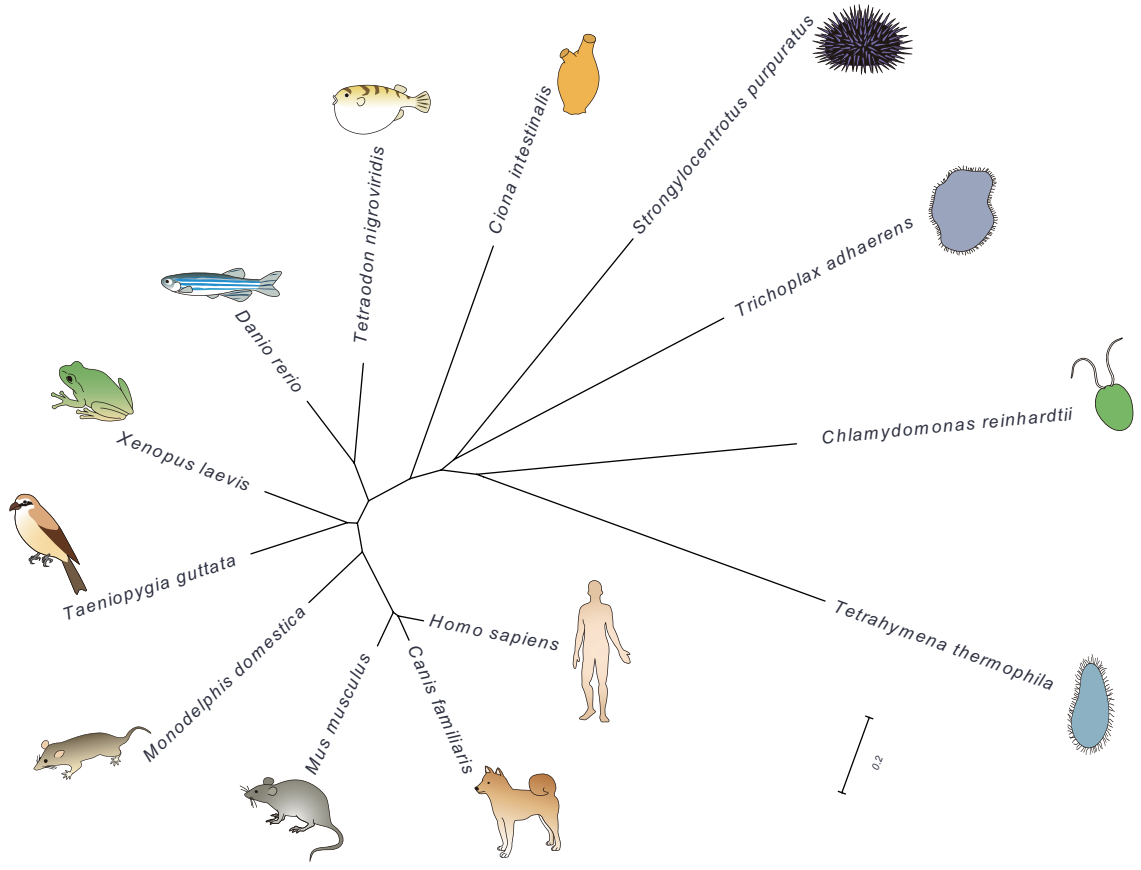

Figure 3. Phylogenetic tree of CLERC family proteins constructed using Neighbor-joining method in the MEGA4.02 package. The sequences used were *Homo sapiens* (NP_208325), *Canis familiaris* (XP_544157), *Mus musculus* (Q69ZB0), *Monodelphis domestica* (XP_001376791), *Taeniopygia guttata* (XP_002198373), *Xenopus laevis* (NP_001084885), *Danio rerio* (XP_690381), *Tetraodon nigroviridis* (CAF88490), *Ciona intestinalis* (XP_002122133), *Strongylocentrotus purpuratus* (XP_001185066), *Trichoplax adhaerens* (XP_002108289), *Chlamydomonas reinhardtii* (XP_001701335), and *Tetrahymena thermophila* (XP_001032550).

algorithm [10,11]. Immunofluorescence microscopy further demonstrated that endogenous CLERC protein associated with the centrosomes throughout the cell cycle and accumulated during mitosis in cultured human cells. CLERC expression appeared to be cell cycle-dependent and its levels behaved similarly to those of cyclin B. CLERC exhibited extremely low levels at the G_1 cells, but started to express an abundant level at the S phase and peaked at the mitotic phase. When cells moved out of the mitotic phase, CLERC levels decreased to a very low level. RNAi-mediated depletion of CLERC in HeLa cells resulted in a high percentage of mitotic cells that had three or four spindle poles [21], which indicates that CLERC is necessary for the bipolar organization of the mitotic spindle. The formation of multiple spindle poles can result from several different routes that can be distinguished by the number of centrioles found at the individual poles [46,47]. The results obtained by using centrin staining revealed that many of the spindle poles in CLERC depleted cells contained only one centriole, indicating that centrosomes split into fractions containing a single centriole. Thus, the depletion of CLERC is considered to induce the aberrant centriole disengagement during spindle pole formation or during mitosis [48-50], and the major function of CLERC might be to maintain the centriole engagement during mitosis, thereby contributing to spindle bipolarity [21].

Vfl1 protein from *Chlamydomonas* is the founding member of the evolutionarily related CLERC protein family and database searches detect various CLERC homologs in the genomes of distant organisms (Figure 3). Interestingly, a CLERC homolog is present in eukaryotes that have basal bodies or centrioles, whereas none is apparent in fungi or plants, which have structurally distinct spindle poles and no centrioles. In addition, homologs are also absent from the genomes of *Caenorhabditis elegans* and *Drosophila melanogaster*, which contain atypical centrioles [51-53]. This characteristic distribution suggests that CLERC family proteins have a crucial role specifically related

Unauthenticated
Download Date | 11/12/19 5:06 AM

to centriole/basal body function in diverse organisms. Although implication of CLERC in the basal body function, such as cilium formation in human cells, remains to be elucidated, further investigations to define the molecular mechanisms underlying CLERC-mediated centrosome integrity during mitosis will greatly advance our understanding of spindle formation.

3.2 Centriolin

Gromley and coworkers [14] used sera from patients with the autoimmune disease scleroderma to screen a human cDNA library for genes encoding centrosomal proteins. They identified a novel 270 kDa polypeptide, termed centriolin, which associates with centrioles [14]. This protein contains five LRR motifs near the NH_2 terminus (Figure 1) and shows sequence similarity to several previously identified proteins. These include two regions of homology with the human oncogenic transforming acidic coiled-coil proteins (TACCs) [54], the human oncogenic protein stathmin [55], and a region near the COOH terminus with homology to the centrosomal protein CEP110 [56]. In addition, a region near the NH_2 terminus shared homology with Nud1p and Cdc11p, budding and fission yeast spindle pole body proteins that anchor components of the yeast MEN and SIN, respectively [57]. Since this N-terminal region of centriolin and the corresponding regions of Nud1p and Cdc11p all have LRR motifs, homology detected among these proteins might be mainly derived from the similarity of the LRR motifs.

Immunofluorescence microscopy demonstrated that centriolin was localized to centrosomes and associates specifically with the mother centriole. Localization of centriolin to the mother centriole was confirmed by inducing growth of a primary cilium, which is assembled using the mother centriole as a template [58]. Interestingly, centriolin sometimes appeared adjacent to the intercellular bridge during cytokinesis, suggesting that the centriole had moved to this site. As cytokinesis progressed, centriolin ultimately became concentrated at the midbody. When centriolin expression was reduced using siRNAs, a dramatic increase in the percentage of late-stage mitotic cells was observed [14]. Moreover, cells with reduced centriolin appeared to be arrested in the final stages of cytokinesis and most cells retained intercellular bridges of varying length and thickness. These observations and the localization of centriolin at midbody suggest that centriolin is required for terminal events of cytokinesis to occur, especially at the stage of cell abscission.

In a more recent study, Gromley and colleagues [59] demonstrated that centriolin interacts with proteins of vesicle-targeting exocyst complexes and vesicle-fusion SNARE complexes. These complexes require centriolin for localization to a unique midbody-ring structure, the Flemming body [60]. Reduction of exocyst levels by siRNA causes an abscission defect similar to that caused by centriolin depletion [61]. In addition, depletion of the SNARE-associated protein snapin also causes a similar abscission defect. Based on these extensive analyses, Gromley and colleagues [59] proposed that centriolin anchors protein complexes required for vesicle targeting and fusion, and integrates membrane-vesicle fusion with abscission in mammalian cells.

3.3 CEP97

CP110 is a centrosomal coiled-coil protein that interacts with two small calcium-binding proteins, calmodulin and centrin [62,63]. Depletion of CP110 exhibits premature centrosome separation in S phase arrested cells [62] and cytokinesis defects [63]. Using immunoaffinity purification and mass spectrometric sequencing, Spektor and colleagues [64] have analyzed proteins associated with CP110 and identified several uncharacterized proteins reported in a recent proteomic analysis of human centrosomes [10]. Among those human centrosome proteins, they recognized a novel protein, leucine-rich repeats and IQ motif containing 2 (LRRIQ2). They renamed this protein CEP97 based on its centrosomal localization and predicted molecular mass of 97 kDa. CEP97 contains eight LRR motifs predicted by HMM profile of the Pfam database (Figure 1), an IQ CaM-binding motif, and a short coiled-coil domain. The CEP97-CP110 binding appears not to be mediated by calmodulin, but is likely to be direct, based on *in vitro* translated proteins and immunoprecipitation experiments [64].

Immunofluorescence analysis revealed that CEP97 localized exclusively to centrosomes, consistent with its ability to interact with CP110. Since CEP97 staining overlapped extensively with centrin, it was suggested that CEP97 colocalizes with CP110 at centrioles. Cell cycle analysis indicated that CEP97 localized to the centrosomes throughout the cell cycle and its level was low in G_0 cells and increased on cell-cycle entry. Spektor and colleagues [64] further examined the consequences of CEP97 knockdown in U2OS cells, using siRNAs targeting CEP97. They observed a remarkable increase in the number of cells with monopolar and multipolar mitotic spindles in CEP97-depleted cells as compared to controls. Moreover, some of the cells with abnormal mitotic spindles exhibited a markedly long microtubular structure that emanated from a centrosome. This long and aberrant microtubular structure was reminiscent of a primary cilium [65]. In order to elucidate the ciliary structures formed after CEP97 depletion, they further

Unauthenticated
Download Date | 11/12/19 5:06 AM

examined cells for a well-established primary cilium marker, acetylated tubulin, after transfection with control and CEP97 siRNAs. Indeed, long cilia-like structures containing acetylated tubulin appeared in cells depleted of CEP97. The simple explanation for these data is that primary cilia assemble in cells lacking CEP97, or that CEP97 inhibits the ability of centrioles to form cilia. Spektor *et al*. [64] suggested that loss of CEP97 function relieves an inhibitory barrier, activating a switch that sets in motion a ciliary assembly program in proliferating somatic cells.

3.4 LRRC6

LRRC6 was first identified as a mammalian testis-specific protein of unknown function, which most abundantly expressed in pachytene and diplotene cells in meiosis I from mice and human testis [66]. Morgan and coworkers [67] cloned its ortholog, TbLRTP, in the flagellated protozoan *Trypanosoma brucei*. TbLRTP is a protein of 383 amino acids with a predicted molecular mass of 43.3 kDa and contains five LRR motifs near the NH_2 terminus (Figure 1). This protein also contains several glutamic acid-rich acidic regions near the COOH terminus and a predicted small coiled-coil domain. Immunofluorescence analysis confirmed the close localization of TbLRTP to both the mature basal body and the probasal body. In order to elucidate the TbLRTP function in *Trypanosoma*, Morgan and coworkers [67] performed overexpression and RNAi experiments. In TbLRTP overexpressing cells an increase in cell size was observed, while RNAi of TbLRTP resulted in reduced cell length. There was also a direct correlation between flagellum length and cell size. In some of the overexpressing cells, mitosis occurred in the absence of basal body duplication, whereas RNAi resulted in additional basal bodies free in the cytoplasm. According to these findings, Morgan *et al*. [67] concluded that TbLRTP suppresses basal body replication and subsequent flagellar biogenesis and plays a critical role in the control of the cell cycle.

The LRRC6 family is highly conserved throughout evolution, and homologs are present in phylogenetically diverse organisms, such as protozoan, insects and mammals. Significantly, the zebra fish homologue of LRRC6, Seahorse, has been reported to be involved in ciliary function and, further, was implicated as having a role in the development of polycystic kidney disease [68]. Recently, Kishimoto and colleagues [69] reported the cloning and characterization of *seahorse* mutants. They demonstrated that *seahorse* is required for establishing left-right asymmetry and for preventing kidney cyst formation. Moreover, *seahorse* transcript is highly enriched in heavily ciliated tissues, and it genetically interacts with the ciliary gene *inversin*. There is also evidence that Seahorse associates with Dishevelled, one of the multi-module proteins working in the Wnt pathway. Taken together, these data suggest that Seahorse may provide a link between ciliary signals and Wnt pathways. More recently, Serluca and colleagues [70] cloned and characterized other alleles of *seahorse* mutants, and provided the experimental evidence that LRRC6/Seahorse is required for ciliary motility *in vivo*.

At present, it remains unclear as to the physiological function of human LRRC6 protein. It is possible that human LRRC6 also plays an essential role in cilia related function. However, its high expression in the meiotic cells from testis suggests another function for the LRRC6 [66].

3.5 CEP78, CEP72 and LRRC45

CEP78, CEP72 and LRRC45 were all previously listed in a proteomic analysis of the human centrosome and predicted to be centrosomal proteins by a protein correlation profiling algorithm used in a mass spectrometry-based proteomic study [10]. However, no publications are available on the detailed characterization of these proteins. Only recently have there been preliminary descriptions of CEP72 as an binding partner of Kizuna [71], but detailed description is not available (Oshimori N., Ohsugi M., Yamamoto T., presented at the Biochemistry and Molecular Biology BMB2008, Kobe, Japan, 9-12 December 2008).

4. Concluding Remarks

In this minireview, we addressed the members of centrosomal leucine-rich repeat proteins and summarized recent observations that implicate the LRR proteins in centrosomal and mitotic functions in mammalian cells. Although significant progress has been made towards elucidating the functional properties of several centrosomal LRR proteins, virtually nothing is known about the functions of CEP78 and LRRC45. Moreover, despite the critical role of LRR motifs as a structural framework for protein-protein interactions, relatively little is known about the binding partners for these motifs present in the individual centrosomal LRR proteins. Therefore, one of the essential fields for future research is to identify the proteins that interact directly with LRR motifs of individual centrosomal LRR proteins. In this context, it is intriguing that the Nud1p-like domain of centriolin binds Bub2p [14], the budding yeast GTPase-activating protein that regulates the mitotic exit network (MEN) [72]. The Nud1p-like domain of centriolin is mainly constituted of LRR motifs, as

Unauthenticated
Download Date | 11/12/19 5:06 AM

described above. Thus, it may be rewarding to explore a possible connection between the LRR motifs of centrosomal LRR proteins and the components of small G protein cascade. The study of the centrosomal LRR proteins has considerably advanced our understanding of centrosome dynamics, and future studies in this field will also be exciting and illuminating.

Note added in proof: During revision of this article, functional characterization of CEP72 was described by Oshimori *et al*. [73]. The authors showed that CEP72 was the key protein essential for maintaining microtubule-organizing activity and structural integrity of the centrosome.

Acknowledgments

Y.M. is indebted to Professor Emeritus Dr. M. Ishikawa of Ehime University for introducing him to the field of centrosome biology. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

[1] Wilson E.B., The cell in development and inheritance, Macmillan & co., ltd., 1896
[2] Chretien D., Buendia B., Fuller S.D., Karsenti E., Reconstruction of the centrosome cycle from cryoelectron micrographs, J. Struct. Biol., 1997, 120, 117-133
[3] Piel M., Meyer P., Khodjakov A., Rieder C.L., Bornens M., The respective contributions of the mother and daughter centrioles to centrosome activity and behavior in vertebrate cells, J. Cell Biol., 2000, 149, 317-330
[4] Bobinnec Y., Khodjakov A., Mir L.M., Rieder C.L., Edde B., Bornens M., Centriole disassembly in vivo and its effect on centrosome structure and function in vertebrate cells, J. Cell Biol., 1998, 143, 1575-1589
[5] Bornens M., Centrosome composition and microtubule anchoring mechanisms, Curr. Opin. Cell Biol., 2002, 14, 25-34
[6] Fukasawa K., Introduction. Centrosome, Oncogene, 2002, 21, 6140-6145
[7] Rieder C.L., Faruki S., Khodjakov A., The centrosome in vertebrates: more than a microtubule-organizing center, Trends Cell Biol., 2001, 11, 413-419
[8] Zhong X., Pfeifer G.P., Xu X., Microcephalin encodes a centrosomal protein, Cell Cycle, 2006, 5, 457-458
[9] Doxsey S., Zimmerman W., Mikule K., Centrosome control of the cell cycle, Trends Cell Biol., 2005, 15, 303-311
[10] Andersen J.S., Wilkinson C.J., Mayor T., Mortensen P., Nigg E.A., Mann M., Proteomic characterization of the human centrosome by protein correlation profiling, Nature, 2003, 426, 570-574
[11] Wilkinson C.J., Andersen J.S., Mann M., Nigg E.A., A proteomic approach to the inventory of the human centrosome, In: Nigg E.A., (Ed.), Centrosomes in Development and Disease, Wiley InterScience, Weinheim, 2005, 125-142
[12] Gomez-Ferreria M.A., Rath U., Buster D.W., Chanda S.K., Caldwell J.S., Rines D.R., et al., Human cep192 is required for mitotic centrosome and spindle assembly, Curr. Biol., 2007, 17, 1960-1966
[13] Graser S., Stierhof Y.D., Nigg E.A., Cep68 and Cep215 (Cdk5rap2) are required for centrosome cohesion, J. Cell Sci., 2007, 120, 4321-4331
[14] Gromley A., Jurczyk A., Sillibourne J., Halilovic E., Mogensen M., Groisman I., et al., A novel human protein of the maternal centriole is required for the final stages of cytokinesis and entry into S phase, J. Cell Biol., 2003, 161, 535-545
[15] Guarguaglini G., Duncan P.I., Stierhof Y.D., Holmstrom T., Duensing S., Nigg E.A., The forkhead-associated domain protein Cep170 interacts with Polo-like kinase 1 and serves as a marker for mature centrioles, Mol. Biol. Cell, 2005, 16, 1095-1107
[16] Salisbury J.L., Suino K.M., Busby R., Springett M., Centrin-2 is required for centriole duplication in mammalian cells, Curr. Biol., 2002, 12, 1287-1292
[17] Strnad P., Leidel S., Vinogradova T., Euteneuer U., Khodjakov A., Gonczy P., Regulated HsSAS-6 levels ensure formation of a single procentriole per centriole during the centrosome duplication cycle, Dev Cell, 2007, 13, 203-213
[18] Xie Z., Moy L.Y., Sanada K., Zhou Y., Buchman J.J., Tsai L.H., Cep120 and TACCs Control Interkinetic Nuclear Migration and the Neural Progenitor Pool, Neuron, 2007, 56, 79-93
[19] Zhao W.M., Seki A., Fang G., Cep55, a microtubule-bundling protein, associates with centralspindlin to control the midbody integrity and cell abscission during cytokinesis, Mol. Biol. Cell, 2006, 17, 3881-3896

Unauthenticated
Download Date | 11/12/19 5:06 AM

[20] Zou C., Li J., Bai Y., Gunning W.T., Wazer D.E., Band V., et al., Centrobin: a novel daughter centriole-associated protein that is required for centriole duplication, J. Cell Biol., 2005, 171, 437-445
[21] Muto Y., Yoshioka T., Kimura M., Matsunami M., Saya H., Okano Y., An evolutionarily conserved leucine-rich repeat protein CLERC is a centrosomal protein required for spindle pole integrity, Cell Cycle, 2008, 7, 2738-2748
[22] Kobe B., Kajava A.V., The leucine-rich repeat as a protein recognition motif, Curr. Opin. Struct. Biol., 2001, 11, 725-732
[23] Takahashi N., Takahashi Y., Putnam F.W., Periodicity of leucine and tandem repetition of a 24-amino acid segment in the primary structure of leucine-rich alpha 2-glycoprotein of human serum, Proc. Natl. Acad. Sci. U.S.A., 1985, 82, 1906-1910
[24] Kobe B., Deisenhofer J., The leucine-rich repeat: a versatile binding motif, Trends Biochem. Sci., 1994, 19, 415-421
[25] Kobe B., Deisenhofer J., Crystal structure of porcine ribonuclease inhibitor, a protein with leucine-rich repeats, Nature, 1993, 366, 751-756
[26] Kobe B., Kajava A.V., When protein folding is simplified to protein coiling: the continuum of solenoid protein structures, Trends Biochem. Sci., 2000, 25, 509-515
[27] Bella J., Hindle K.L., McEwan P.A., Lovell S.C., The leucine-rich repeat structure, Cell. Mol. Life Sci., 2008, 65, 2307-2333
[28] Matsushima N., Tachi N., Kuroki Y., Enkhbayar P., Osaki M., Kamiya M., et al., Structural analysis of leucine-rich-repeat variants in proteins associated with human diseases, Cell. Mol. Life Sci., 2005, 62, 2771-2791
[29] Hohenester E., Hussain S., Howitt J.A., Interaction of the guidance molecule Slit with cellular receptors, Biochem. Soc. Trans., 2006, 34, 418-421
[30] Matilla A., Radrizzani M., The Anp32 family of proteins containing leucine-rich repeats, Cerebellum, 2005, 4, 7-18
[31] Liker E., Fernandez E., Izaurralde E., Conti E., The structure of the mRNA export factor TAP reveals a cis arrangement of a non-canonical RNP domain and an LRR domain, EMBO J., 2000, 19, 5587-5598
[32] Price S.R., Evans P.R., Nagai K., Crystal structure of the spliceosomal U2B"-U2A' protein complex bound to a fragment of U2 small nuclear RNA, Nature, 1998, 394, 645-650
[33] Chen Y., Aulia S., Li L., Tang B.L., AMIGO and friends: an emerging family of brain-enriched, neuronal growth modulating, type I transmembrane proteins with leucine-rich repeats (LRR) and cell adhesion molecule motifs, Brain Res Rev, 2006, 51, 265-274
[34] Ko J., Kim E., Leucine-rich repeat proteins of synapses, J. Neurosci. Res., 2007, 85, 2824-2832
[35] Gay N.J., Gangloff M., Structure and function of Toll receptors and their ligands, Annu. Rev. Biochem., 2007, 76, 141-165
[36] Pancer Z., Cooper M.D., The evolution of adaptive immunity, Annu. Rev. Immunol., 2006, 24, 497-518
[37] Hocking A.M., Shinomura T., McQuillan D.J., Leucine-rich repeat glycoproteins of the extracellular matrix, Matrix Biol., 1998, 17, 1-19
[38] Nogales-Cadenas R., Abascal F., Diez-Perez J., Carazo J.M., Pascual-Montano A., CentrosomeDB: a human centrosomal proteins database, Nucl. Acids Res., 2009, 37, D175-D180
[39] Eddy S.R., Profile hidden Markov models, Bioinformatics, 1998, 14, 755-763
[40] Kajava A.V., Structural diversity of leucine-rich repeat proteins, J. Mol. Biol., 1998, 277, 519-527
[41] Schneider T.D., Stephens R.M., Sequence logos: a new way to display consensus sequences, Nucl. Acids Res., 1990, 18, 6097-6100
[42] Crooks G.E., Hon G., Chandonia J.M., Brenner S.E., WebLogo: a sequence logo generator, Genome Res., 2004, 14, 1188-1190
[43] Dutcher S.K., Elucidation of basal body and centriole functions in Chlamydomonas reinhardtii, Traffic, 2003, 4, 443-451
[44] Adams G.M., Wright R.L., Jarvik J.W., Defective temporal and spatial control of flagellar assembly in a mutant of Chlamydomonas reinhardtii with variable flagellar number, J. Cell Biol., 1985, 100, 955-964
[45] Silflow C.D., LaVoie M., Tam L.W., Tousey S., Sanders M., Wu W., et al., The Vfl1 Protein in Chlamydomonas localizes in a rotationally asymmetric pattern at the distal ends of the basal bodies, J. Cell Biol., 2001, 153, 63-74
[46] Keryer G., Ris H., Borisy G.G., Centriole distribution during tripolar mitosis in Chinese hamster ovary cells, J. Cell Biol., 1984, 98, 2222-2229
[47] Sluder G., Rieder C.L., Centriole number and the reproductive capacity of spindle poles, J. Cell Biol., 1985, 100, 887-896
[48] Di Fiore B., Ciciarello M., Mangiacasale R., Palena A., Tassin A.M., Cundari E., et al., Mammalian RanBP1 regulates centrosome cohesion during mitosis, J. Cell Sci., 2003, 116, 3399-3411
[49] Thein K.H., Kleylein-Sohn J., Nigg E.A., Gruneberg U., Astrin is required for the maintenance of sister chromatid cohesion and centrosome integrity, J. Cell Biol., 2007, 178, 345-354

Unauthenticated
Download Date | 11/12/19 5:06 AM

[50] Wang X., Yang Y., Duan Q., Jiang N., Huang Y., Darzynkiewicz Z., et al., sSgo1, a major splice variant of Sgo1, functions in centriole cohesion where it is regulated by Plk1, Dev. Cell, 2008, 14, 331-341

[51] McDonald K., Morphew M.K., Improved preservation of ultrastructure in difficult-to-fix organisms by high pressure freezing and freeze substitution: I. Drosophila melanogaster and Strongylocentrotus purpuratus embryos, Microsc. Res. Tech., 1993, 24, 465-473

[52] Moritz M., Braunfeld M.B., Fung J.C., Sedat J.W., Alberts B.M., Agard D.A., Three-dimensional structural characterization of centrosomes from early Drosophila embryos, J. Cell Biol., 1995, 130, 1149-1159

[53] Perkins L.A., Hedgecock E.M., Thomson J.N., Culotti J.G., Mutant sensory cilia in the nematode Caenorhabditis elegans, Dev. Biol., 1986, 117, 456-487

[54] Lee M.J., Gergely F., Jeffers K., Peak-Chew S.Y., Raff J.W., Msps/XMAP215 interacts with the centrosomal protein D-TACC to regulate microtubule behaviour, Nat. Cell Biol., 2001, 3, 643-649

[55] Andersen S.S., Spindle assembly and the art of regulating microtubule dynamics by MAPs and Stathmin/Op18, Trends Cell Biol., 2000, 10, 261-267

[56] Guasch G., Mack G.J., Popovici C., Dastugue N., Birnbaum D., Rattner J.B., et al., FGFR1 is fused to the centrosome-associated protein CEP110 in the 8p12 stem cell myeloproliferative disorder with t(8;9)(p12;q33), Blood, 2000, 95, 1788-1796

[57] McCollum D., Gould K.L., Timing is everything: regulation of mitotic exit and cytokinesis by the MEN and SIN, Trends Cell Biol., 2001, 11, 89-95

[58] Vorobjev I.A., Chentsov Yu S., Centrioles in the cell cycle. I. Epithelial cells, J. Cell Biol., 1982, 93, 938-949

[59] Gromley A., Yeaman C., Rosa J., Redick S., Chen C.T., Mirabelle S., et al., Centriolin anchoring of exocyst and SNARE complexes at the midbody is required for secretory-vesicle-mediated abscission, Cell, 2005, 123, 75-87

[60] Paweletz N., On the function of the “Flemming body” during division of animal cells, Naturwissenschaften, 1967, 54, 533-535

[61] Fielding A.B., Schonteich E., Matheson J., Wilson G., Yu X., Hickson G.R., et al., Rab11-FIP3 and FIP4 interact with Arf6 and the exocyst to control membrane traffic in cytokinesis, EMBO J., 2005, 24, 3389-3399

[62] Chen Z., Indjeian V.B., McManus M., Wang L., Dynlacht B.D., CP110, a cell cycle-dependent CDK substrate, regulates centrosome duplication in human cells, Dev. Cell, 2002, 3, 339-350

[63] Tsang W.Y., Spektor A., Luciano D.J., Indjeian V.B., Chen Z., Salisbury J.L., et al., CP110 cooperates with two calcium-binding proteins to regulate cytokinesis and genome stability, Mol. Biol. Cell, 2006, 17, 3423-3434

[64] Spektor A., Tsang W.Y., Khoo D., Dynlacht B.D., Cep97 and CP110 suppress a cilia assembly program, Cell, 2007, 130, 678-690

[65] Wheatley D.N., Wang A.M., Strugnell G.E., Expression of primary cilia in mammalian cells, Cell Biol. Int., 1996, 20, 73-81

[66] Xue J.C., Goldberg E., Identification of a novel testis-specific leucine-rich protein in humans and mice, Biol. Reprod., 2000, 62, 1278-1284

[67] Morgan G.W., Denny P.W., Vaughan S., Goulding D., Jeffries T.R., Smith D.F., et al., An evolutionarily conserved coiled-coil protein implicated in polycystic kidney disease is involved in basal body duplication and flagellar biogenesis in Trypanosoma brucei, Mol. Cell. Biol., 2005, 25, 3774-3783

[68] Sun Z., Amsterdam A., Pazour G.J., Cole D.G., Miller M.S., Hopkins N., A genetic screen in zebrafish identifies cilia genes as a principal cause of cystic kidney, Development, 2004, 131, 4085-4093

[69] Kishimoto N., Cao Y., Park A., Sun Z., Cystic kidney gene seahorse regulates cilia-mediated processes and Wnt pathways, Dev. Cell, 2008, 14, 954-961

[70] Serluca F.C., Xu B., Okabe N., Baker K., Lin S.Y., Sullivan-Brown J., et al., Mutations in zebrafish leucine-rich repeat-containing six-like affect cilia motility and result in pronephric cysts, but have variable effects on left-right patterning, Development, 2009, 136, 1621-1631

[71] Oshimori N., Ohsugi M., Yamamoto T., The Plk1 target Kizuna stabilizes mitotic centrosomes to ensure spindle bipolarity, Nat. Cell Biol., 2006, 8, 1095-1101

[72] Pereira G., Hofken T., Grindlay J., Manson C., Schiebel E., The Bub2p spindle checkpoint links nuclear migration with mitotic exit, Mol. Cell, 2000, 6, 1-10

[73] Oshimori N., Li X., Ohsugi M., Yamamoto T., Cep72 regulates the localization of key centrosomal proteins and proper bipolar spindle formation, EMBO J., 2009, 28, 2066-2076

Unauthenticated
Download Date | 11/12/19 5:06 AM