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REVIEW

The evolution, complex structures and function of septin proteins

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Abstract The septin family is a conserved GTP-binding protein family and was originally discovered through genetic screening for budding yeast mutants. Septins are implicated in many cellular processes in fungi and metazoa. The function of septins usually depends on septin assembling into oligomeric complexes and highly ordered polymers. The expansion of the septin gene number in vertebrates increased the complex diversity of septins. In this review, we first discuss the evolution, structures and assembly of septin proteins in yeast and metazoa. Then, we review the function of septin proteins in cytokinesis, membrane remodeling and compartmentalization.

Keywords Septin · Cytokinesis · Membrane remodeling · Diffusion barriers · Vesicle targeting

Introduction

The septin family was originally discovered in 1971 through genetic screening for budding yeast mutants defective in cell-cycle progression [1, 2]. Over the next 2 decades, septins were found in all animals and fungi, but not in plants [3, 4]. It was demonstrated that septins are a family of conserved GTP-binding proteins that act as dynamic, regulatable scaffolds for recruitment of other proteins in yeast and metazoans [5–11]. The septin gene numbers in vertebrates are expanded mainly by the duplication of pre-existing genes [12], and this expansion contributes to septin functional complexity in vertebrates.

In yeast, septins usually assemble as rings in the bud neck. Septin rings are thought to function as scaffolds and diffusion barriers for the localization of yeast proteins to the bud neck [6]. Studies of yeast suggested that the septin collar (or hourglass) in the bud neck might serve as a scaffold for many proteins involved in diverse cellular processes such as bud site selection [6, 13], chitin deposition [14], mitotic spindle positioning [15, 16], polarized growth [17, 18], cytokinesis [6, 19], the morphogenetic checkpoint [17, 20] and a diffusion barrier formation [21, 22]. In addition, septins were also implicated in cell-cycle control [17, 20] and the coordination of the DNA-damage response and cellular morphology [23, 24].

In contrast to yeast septins, which polymerize mainly at cortical sites of the mother–bud neck, mammalian septins localize not only to the plasma membrane, but also throughout the cytoplasm together with the microtubule and actin cytoskeletons [8]. Human septins have been implicated in many cellular processes, including microtubule and actin function [25, 26], DNA damage-related checkpoint response [27], cytokinesis [28–30], membrane associated cell movement [31, 32] and vesicle trafficking [32]. Another function of septins is to prevent the degradation of proteins like HIF1 and c-Jun-N-terminal kinase (JNK) and the aggregation of synuclein [33–35].

Recently, much progress has been achieved in elucidating the septin and its complex structures. Electron microscopy (EM) studies have revealed the order of septin subunits in the core septin complex in *Caenorhabditis elegans* and *Saccharomyces cerevisiae* [36, 37]. The crystal structures of the dimer of the human SEPT2 G domain and human SEPT2–SEPT6–SEPT7 complex have also been resolved [38].

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In this review, we will discuss the evolution, structures, assembly and function of septin proteins in yeast and metazoa.

Septin members and its evolution

The septin family is a conserved GTP-binding protein family and was originally discovered through genetic screening for budding yeast mutants [1, 2]. Septins are found in animals and fungi, but not plants [3, 4]. Based on the evolution analysis, it was found that septins belong to the GTPase superclass of P-loop NTPases, which includes the Ras-type superfamily of small GTPases, translation factors, the OBG/HflX superfamily, and the structurally related myosin–kinesin superfamily of ATPases [3]. Paraseptins, the septin-like proteins, are found in bacteria, and it was speculated that the emergence of septins among eukaryotes was initiated by an ancestral protein (probably the paraseptin) transferring laterally from bacteria to eukaryotes and subsequently evolved in fungi and metazoans [3].

The *S. cerevisiae* genome encodes seven septins (Cdc3, Cdc10, Cdc11, Cdc12, Shs1/Sep7, Spr3 and Spr28). Fission yeast also has seven septins (Spn1, Spn2, Spn3, Spn4, Spn5, Spn6 and Spn7). *Candida albicans, Eremothecium gossypii, aspergillus nidulans and Neurospora crassa* also encode several septins [7, 10, 39]. Interestingly, the genomes of aquatic green algae (*Chlamydomonas reinhardtii*) and marine phytoplankton (*Nannochloris* spp.) encode *bona fide* septin orthologs [7].

Among metazoans, the nematode (*C. elegans*) contains two septin genes (Unc-61, Unc-59), and the fruit fly (*Drosophila melanogaster*) contains five septin genes (sep1, sep2, sep4, sep5, and pnut) [6, 7]. The human genome encodes 14 septin genes, mouse (*Mus musculus*) encodes 13, chicken (*Gallus gallus*) encodes 10, frog (*Xenopus laevis*) encodes 9, zebrafish (*Danio rerio*) encodes 17 and the deuterostome echinoderm sea urchin (*Strongylocentrotus purpuratus*) and non-vertebrate chordate Ciona (*Ciona intestinalis*) each have four [4, 7, 12].

Pan et al. [39] did phylogenetic analysis of the septin family across kingdoms (fungi, microsporidia, and animals). Based on their analysis, all septins from fungi, microsporidia, and animals clustered into five groups: Group 1 and group 2 contain septin sequences from fungi and animals, group 3 and group 4 contain septin sequences from fungi and microsporidia, and group 5 contains septin sequences from filamentous fungi. This evolutionary analysis based on the septin proteins sheds light on the clear evolutionary links between septins from fungi and those from metazoans [39].

While the analysis work of Pan et al. was mainly on fungal septins, evolutionary analysis by Kinoshita et al. and Cao et al. focused on metazoan septins, within which human septins were classified into four groups: SEPT2, SEPT3, SEPT6 and SEPT7 groups [4, 12]. Cao et al. [12] collected 78 septin sequences from representative metazoan organisms including *D. melanogaster, C. elegans*, *C. intestinalis, S. purpuratus*, *G. gallus*, *X. laevis*, and *D. rario,* and proposed a detailed evolutionary map of metazoan septin proteins, focusing on the expansion of the septin gene in vertebrates. Possible functional redundancy is one of challenges to elucidate the function of human septins. Detail evolutionary analysis of septins in vertebrates will be helpful for further functional studies.

The metazoan septin grouping information is shown in Table 1 [4, 12]. The SEPT7 group includes human SEPT7 and human SEPT13, *D. melanogaster* septin pnut, *C. elegans* septin unc-59, and septins of invertebrate deuterostomes and *S. purpuratus* (gi: 115720187). The SEPT2 group includes human SEPT1, SEPT2, SETP4, SEPT5 and the *D. melanogaster* septins sep1 and sep4. A direct homologue of SEPT2 can be found in *S. purpuratus* (gi: 115951499). The SEPT6 subgroup includes human SEPT6, 8, 10, 11 and 14; *D. melanogaster* septins sep2 and sep5; *C. elegans* septin unc-61; and a septin of invertebrate deuterostome *S. purpuratus* (gi: 115770370). The SEPT3 group includes human SEPT3, SEPT9 and SEPT12, and is different from other subgroups. All members of the SEPT3 subgroup lack the coiled-coil domain. No septins from fly or worm belong to the SEPT3 group, but *S. purpuratus* (gi: 115715387) is present. In the SEPT2 group, it was found that the direct orthologue of human SEPT1 can only be found in mammals, but not in other vertebrates (such as *G. gallus, X. laevis* and *D. rario*) [12]. In the SEPT7 group, the direct homologue of human SEPT13 was not found in *M. musculus* and *G. gallus* [12].

One important finding from Cao's analysis is that a representative homologue of every group is present in the deuterostome echinoderm sea urchin (*S. purpuratus*) and in the non-vertebrate chordate Ciona intestinalis. This clearly indicates that the emergence of the four septin groups must have occurred prior to the divergence of vertebrates and invertebrates, and the expansion of the septin gene number in vertebrates was mainly by the duplication of pre-existing genes, rather than the appearance of a new septin group [12].

The expansion of the septin gene number in vertebrates also induced the expansion of septin complexes and functions in these organisms. At the same time, possible functional redundancy might also have emerged in vertebrates and is one of main challenges to elucidating the function of septins in these organisms. Detailed analysis of septins in vertebrates will be helpful for further septin

Table 1 The metazoan septin grouping information

Organisms	SEPT2 group	SEPT7 group	SEPT6 group	SEPT2 group
Homo sapiens	SEPT2-Hs; SEPT4-Hs; SEPT5-Hs; SEPT1-Hs	SEPT7-Hs; SEPT13-Hs	SEPT6-Hs; SEPT8-Hs; SEPT10-Hs; SEPT11-Hs; SEPT14-Hs	SEPT3-Hs; SEPT9-Hs; SEPT12-Hs
Mus musculus	SEPT2-Mm;SEPT4-Mm; SEPT5-Mm; SEPT1-Mm	SEPT7-Mm	SEPT6-Mm; SEPT8-Mm; SEPT10-Mm; SEPT11-Mm; SEPT14-Mm	SEPT3-Mm; SEPT9-Mm; SEPT12-Mm
Gallus gallus	gi:50752104-Gg; gi:57525156-Gg; gi:71897193-Gg	gi:60302768-Gg	gi:71895629-Gg; gi:118090250-Gg; gi:118097603-Gg; gi:118084362-Gg	gi:118082695-Gg; gi:71897123-Gg
Xenopus laevis	gi:52354788-Xl; gi:111598420-Xl	gi:49256249-Xl	gi:504118014-Xl; gi:51703480-Xl; gi:47683059-Xl; gi:68534806-Xl	gi:71679814-Xl; gi:34784614-Xl
Danio rario	gi:115313325-Dr; gi:45709377-Dr; gi:125836845-Dr; gi:82658250-Dr; gi:57524587-Dr; gi:41152396-Dr	gi:115313325-Dr; gi:45709377-Dr; gi:125836845-Dr; gi:82658250-Dr; gi:57524587-Dr; gi:41152396-Dr	gi:47086783-Dr; gi:32822794-Dr; gi:134133316-Dr; gi:62955083-Dr;	gi:66773110-Dr; gi:62122803-Dr; gi:38181410-Dr; gi:125812510-Dr
Ciona intestinalis	gi:198428956-Ci	gi:198436549-Ci	gi:198432765-Ci	gi:198417201-Ci
Strongylocentrotus purpuratus	gi:115951499-Sp	gi:115720187-Sp	gi:115770370-Sp	gi:115715387-Sp
Drosophila melanogaster	Sep1-Dm Sep4-Dm	Pnut-Dm	Sep2-Dm, Sep5-Dm	
Caenorhabditis elegans		Unc-61	Unc-59	

function studies. *S. purpuratus* has only four septin genes [12] and is thus a good model organism for studying cell division.

Septin structures

Septins belong to the GTPase superclass of P-loop NTPases. The P-loop GTPases, including kinesin, myosin and ras proteins, share at least five conserved motifs within the GTP-binding domain, designated G1–G5 [3]. Septins clearly contain the G1, G3 and G4 motifs [5]. The G1 motif, defined by the consensus element GxxxxGK [ST], forms a flexible loop that interacts with the phosphate group of the nucleotide [40, 41]. The G3 motif contains several hydrophobic residues followed by DxxG. This region binds Mg^{2+} and can interact with β and γ phosphates of GTP. The G4 motif, NKxD, is important for GTP binding specificity [3, 39]. The G5 motif is found in some, but not all, members of the P-loop GTPase class [3, 39]. The N-terminal to the GTPase domain of septin contains a polybasic region that has been shown to bind phosphoinositides [40, 41]. C-terminal to the GTPase domain, a 53-amino-acid septin element conserved among many septins, has been previously identified [42]. Most septins also contain a C-terminal extension predicted to form coiled coils, which were essential to the interactions between certain septins [7, 41].

Septins usually assemble into oligomeric complexes and highly ordered polymers [36–38]. Analysis of filaments formed in vitro by the *C. elegans* septin proteins revealed that UNC-59 and UNC-61 are aligned in a striking linear pattern of four densities, and the septin core structure is composed of the G domains of these proteins in the order UNC-59–UNC-61–UNC-61–UNC-59. This analysis indicated that the filaments must be non-polar along the direction of filament extension [36].

A complex of recombinant *S. cerevisiae* septins—Cdc3, Cdc10, Cdc11 and Cdc12—forms an elongated linear octamer. EM imaging of wild-type and mutant yeast septin oligomers revealed that the order of subunits within the yeast core octamer was Cdc11p–Cdc12p–Cdc3p–Cdc10p–Cdc10p–Cdc3p–Cdc12p–Cdc11p [37]. The septin core structure in *S. cerevisiae* is composed by the G domains of these proteins, with the coiled-coil domains flexible and extending away from the core octamer. Similarly,

reconstruction of the complex of mammalian SEPT3–SEPT5–SEPT7 also created a linear hexamer [43]. Therefore, septin complexes may commonly form linear filaments.

The G domain of human SEPT2 was solved to a resolution of 3.4 Å, revealing a canonical GTPase fold that is similar to that of the small Ras-type GTP-binding proteins [38]. SEPT2 could form a dimer with alternating G-dimer interfaces and NC-dimer interfaces [38].

The crystal structure of the human SEPT2–SEPT6–SEPT7 complex (Fig. 1) revealed that the same basic interaction surfaces of the SEPT2 G-domain filament are present in an oligomeric assembly of full-length septins [38]. The arrangements in the SEPT2–SEPT6–SEPT7 filament are similar to those observations from the SEPT2 G-domain filament, with alternating G-dimer interfaces and NC-dimer interfaces. The structure revealed that complex and filament formation was dependent on the GTPase domains rather than, as had been previously proposed, on the coiled-coil domains [4]. In fact, the coiled-coil domains of SEPT2, SEPT6 and SEPT7 appear to be flexible and are therefore disordered in the crystal lattice [38].

Bound guanine nucleotide was also observed in the SEPT2–SEPT6–SEPT7 filament; both SEPT2 and SEPT7 are GDP-bound, and SEPT6 is GTP-bound [38]. This arrangement results in two different nucleotide states at the two different G-dimer interfaces: the SEPT2–SEPT6 interface is a GDP–GTP interface, whereas the SEPT7–SEPT7 interaction contains two GDP molecules [38]. The observation indicates that the nucleotide is required for dimerization across the G-dimer interface and that different nucleotide states are present in the two distinct G-dimer interfaces in the filament.

It was also viewed by EM that at least a fraction of the septin complexes (the human hexamer or the nematode tetramer) were bent [36, 38]. The source of the bend in the human hexamer is located at the SEPT2–SEPT2 interface in the center of the complex [38]. This bend might mediate the curvature observed in many higher order septin structures, such as the yeast septin collars or self-assembling septin structures [10, 44].

Septin assembling and its highly ordered structure

Septin assembling

The biological functions of septins are generally thought to stem from their intrinsic ability to assemble into oligomeric complexes and highly ordered polymers. Septin complexes can serve as diffusion barriers for the compartmentalization of the cell membrane and form scaffolds for interacting proteins at specific intracellular locations.

Purified septins have been observed to polymerize into filaments in vitro [44–47]. However, *X. laevis* Sept2 and human Sept2 can assemble in vitro [38, 47]. Septins are thought to usually polymerize in filaments composed of two or more different septins. In most cases examined, the capacity to polymerize into filaments requires the presence of the complexes containing at least three types of septins. For example, in budding yeast, septins assemble at the mother–bud neck in a filamentous collar, which contains five septins (Cdc3, Cdc10, Cdc11, Cdc12 and Shs1) [48]. Septin ring formation in *Schizosaccharomyces pombe* requires a minimum of three complexed septins, either Spn3p–Spn4p–Spn1p or Spn4p–Spn1p–Spn2p [49]. Spns1-4p, present throughout interphase as a diffusely localized complex containing two copies of each septin, linked together as a chain in the order Spn3p–Spn4p–Spn1p–Spn2p [49]. In flies, the septin complex Sep2–Pnut–Sep1 was found [45]. In mammals, the septin complex Sept6–Sept7–Sept2 was found in human HeLa cells and in vitro

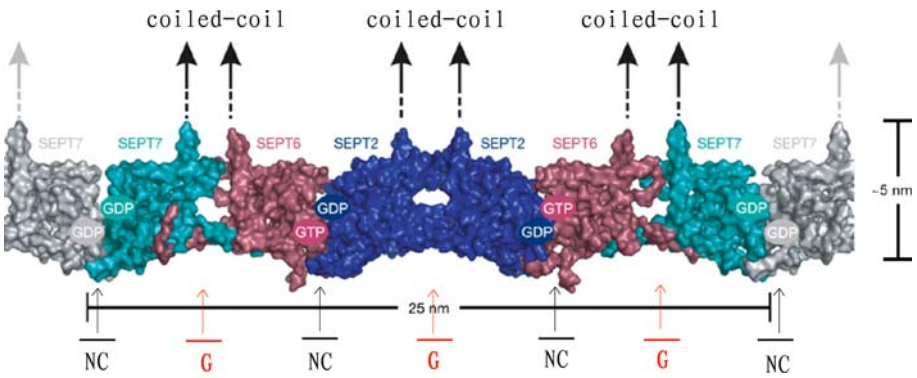

Fig. 1 X-ray structure of the human septin complex SEPT2–SEPT6–SEPT7. SEPT2–SEPT6–SEPT7 filament is arranged with alternating G-dimer interfaces and NC-dimer interfaces. Bound guanine nucleotide is also observed in the SEPT2–SEPT6–SEPT7 filament; both SEPT2 and SEPT7 are GDP-bound, while SEPT6 is GTP-bound. The NC-dimer interfaces and the G-dimer interfaces are indicated with *black arrows* and *red arrows*, respectively. The *dashed arrows* indicate the position and orientation of the coiled-coil domain. This figure is reproduced with the kind permission of the authors Sirajuddin et al. [38]

[44, 50]. The SEPT7–SEPT11–SEPT9_v3α complex was found in rat embryonic fibroblast REF52 cells [51]. The SEPT3–SEPT5–SEPT7 complex presented in rat brain [43]. However, *C. elegans* contains only two septins, UNC-59 and UNC-61, which form a UNC-59/UNC-61/UNC-61/UNC-59 complex [36].

Human have 14 septin genes (SEPT1–SEPT14) that can be classified into four groups (SEPT2, SEPT3, SEPT6 and SEPT7) [4, 12]. Though it was reported that sept2 can form a dimer in vitro [38], monomeric septins are not stable in vivo and are prone to form insoluble aggregates in vitro [44, 50]. Recombinant septins that form stable heterodimers in vitro usually are composed of three different septins [44, 50, 52]. Previously, SEPT7 was thought to be a unique and perhaps irreplaceable subunit that binds proteins of the SEPT2 (SEPT1, SEPT4, SEPT5) and SEPT6 (SEPT8, SEPT10, SEPT11, SEPT14) groups in the sept2/6/7 complex. This homology-based classification agreed well with their compatibility in the recombinant complex formation tested in insect cells, which found that SEPTx/6/7 complexes of $\sim$1:1:1 stoichiometry ($x = 1$, 2, 4 or 5) could be formed and that SEPT6 in the SEPT2/6/7 complex was replaceable with SEPT8, SEPT10 and SEPT11 [53, 54].

Because SEPT13 is now classified into the septin 7 group [12], it is possible that septin 7 can be replaced with SEPT13 in some situations. The finding of a SEPT7-SEPT11-SEPT9_v3α complex [51] and a SEPT3–SEPT5–SEPT7 complex [43] indicated that our knowledge about septin assembly in mammals is still very limited. More new mammalian septin complexes will be investigated in further studies.

Highly ordered septin structures

Septins can form high-order structures that can be viewed in EM. The well-ordered septin rings had been observed via EM in budded cells [2, 46, 55]. In negative-staining EM, septins appear as filaments 7–9 nm in width and of variable length [46]. The septin filaments were also found in *Drosophila* [45] and rat [31] via EM. Using the shadowing technique, the septin ring was found to elongate into an hourglass-shaped stable collar during budding yeast cytokinesis [56].

Septins are first recruited to the presumptive bud site as unorganized septin clouds or patches, which are then transformed into the septin ring within minutes [57]. A cortical septin ring was reported to form in the late G_1 phase, approximately 15 min before bud emergence. Around emergence of the bud, the septin ring expanded into a collar spanning the whole bud neck. During cytokinesis, the collar was split into two distinct rings, marking the division sites at both the mother and daughter sides [58]. FRAP studies indicate that the septin structures prior to bud emergence are highly dynamic. Upon bud emergence, the septin collar at the bud neck is stabilized. During cytokinesis, the split septin rings become dynamic again [59, 60]. This dynamic cell cycle-regulated septin explains why septin-containing rings are found by EM only in small- to medium-budded cells, but not in unbudded cells or cells in cytokinesis [2].

The average orientation of septin filaments at the bud neck has been recently determined using polarized fluorescence microscopy to observe septins in live yeast cells [61, 62]. The authors observed two important characteristics of septin filaments in vivo. First, neither the hourglass nor the ring structures have polarity along the mother–bud axis, in agreement with the structural data. Second, upon cytokinesis, the orientation of the GFP undergoes a 90° rotation in the plane of the membrane, with filaments rotating from a longitudinal alignment along the bud neck to a circumferential arrangement around the bud neck [61, 62].

Using fluorescence-based pulse-chase methods to visualize the fate of pre-existing (old) and newly synthesized (new) molecules of two septins, it was found that Cdc10 and Cdc12 were recycled through multiple mitotic divisions, and old and new molecules were incorporated indistinguishably into the collar [63].

In fission yeast, it was also found that septins assembled first during mitosis into a single ring and then developed into double rings during septation as the septum forms [64–66].

In mouse and human spermatozoa, SEPT4 and other septins are found in the annulus, a cortical ring that separates the middle and principal pieces, which could be visualized by EM [67, 68]. The annulus is an atypical septin ring, because it is a durable subcellular structure in a nondividing cell.

In general, metazoan septin assembly throughout the cell cycle is very complex, and even appears to vary among cell lineages within a species [28, 69]. It was found that septin could be co-localized with midbody, membrane, actin or MT in mammals [8, 9]. Interestingly, in mammalian cells, SEPT2-containing filaments and rings are also highly dynamic, exhibiting rapid exchange of cytoplasmic SEPT2 molecules in and out of their respective polymers [70].

Regulation of septin polymerization

GTP and/or GDP binding affect septin assembly

Most septins from yeast and animals are reported to bind and hydrolyze GTP, except yeast Cdc3 and Cdc11, and fly

Sep2 previously reported [45, 47, 48, 50]. Recently, Cdc3p, Cdc10p, Cdc11p and Cdc12p have all been reported to bind GTP, with GTP-binding by all four septins needed for formation of the septin ring [71].

For many septins, mutation of residues that contribute to GTP binding could alter the formation, appearance, localization and/or function of septin filaments [28, 41, 72–75]. P-loop and G4 motif mutations in septins affect nucleotide binding and result in temperature-sensitive defects in septin localization and function. For Cdc3p, Cdc10p, Cdc11p and Cdc12p, nucleotide binding is important for septin–septin interactions and complex formation [71]. In the absence of complete complexes, septins do not locate to the cortex, suggesting septin localization factors interact only with complete complexes [71]. However, there is no evidence demonstrating that nucleotide binding is specifically involved in the interaction of septins with septin-associated proteins [71]. Bound guanine nucleotides are also observed in SEPT2–SEPT6–SEPT7 filament crystals; both SEPT2 and SEPT7 are GDP-bound, while SEPT6 is GTP-bound [38]. The rates of nucleotide exchange and hydrolysis in septin are slow in vitro, and the turnover of GTP in septin complexes in vivo is also very slow [46, 76, 77]. Mammalian septin polymers have little or no GTPase activity in vitro [44, 50].

Cdc42 and phosphorylation regulate septin assembly

Septin complexes assembled at the mother–bud neck of a filamentous collar contain five septins (Cdc3, Cdc10, Cdc11, Cdc12 and Shs1). It was demonstrated that a small, Rho-family GTPase, Cdc42p played a crucial role in septin assembly in yeast [59, 78, 79].

Cdc42p, a highly conserved Rho-type small GTPase, is required for polarized growth in *S. cerevisiae* [80]. The Cdc42p GTPase module includes Cdc42p, the Cdc24p GEF that activates Cdc42p by catalyzing the exchange of GDP for GTP and the GAPs (Bem3p, Rga1p and Rga2p) that inactivate Cdc42p by enhancing its intrinsic GTPase activity. Mutations in CDC42p or CDC24p result in defects in the polarized localization of both the actins and the septins to the presumptive bud site [56, 81].

Though the septin collar assembly is a continuous and efficient process, recent studies on live cells suggested that septin collar formation involved at least three steps: septin recruitment, septin ring assembly and septin ring maturation [57, 59, 80].

Cdc42p-GTP was suggested to be needed for the whole process of septin collar formation. Septin recruitment requires Cdc42p-GTP and two Cdc42p-GTP effectors, Gic1p and Gic2p [67]. Gic1p and Gic2p are two Cdc42/Rac interactive binding (CRIB) domain-containing effectors of Cdc42p-GTPase that promote polarized cell growth in *S. cerevisiae*. After septin recruitment, Cdc42p, its GAPs (Rga1p, Rga2p, and Bem3p) and the PAK Cla4p, an effector of Cdc42p, are thought to play a role in septin ring formation. Mutations of cdc42p that affect the cycling of Cdc42p between its GDP- and GTP-bound states confer profound defects in septin ring assembly [78]. Deletion of all Cdc42 GAPs, rga1pΔ rga2pΔ bem3pΔ, delays septin ring formation without affecting septin recruitment [57, 78].

Several yeast kinases, such as Cla4p, Gin4p [82] and Elm1p [83], as well as septin-interacting proteins such as Bni5p [84], locate to the bud neck in a septin-dependent manner and are also involved in septin collar formation.

Cla4p mutant cells fail to assemble a normal septin ring [48, 85, 86], suggesting that Cla4p plays a role in the initial septin ring assembly. In yeast containing Bni1p and Cla4p mutants, septins were recruited to the incipient budding site. However, the septin ring was not assembled, and septins remained at the polarized growing sites [86]. Cla4p, a p21-activated protein kinase, phosphorylates Cdc10p, Cdc3p and Cdc11p. Mutation of at least one of the Cla4p sites in Cdc10p (Ser256 to Ala) has readily discernible effects on cell morphology and septin architecture [48]. Cla4p is activated through binding of Cdc42p–GTP to an N-terminal Cdc42p and/or Rac-interactive-binding (CRIB) domain. Because Cdc42p function is implicated in bud emergence, stimulation of Cla4p activity by Cdc42p provides a mechanism to link the timing of this event to assembly of the septin collar [48].

Gin4p, one of the Nim1-related protein kinases, is recruited to the septin ring and reported to function in septin ring assembly. Mutation of three genes (*GIN4*, *CLA4* and *NAP1*) produces perturbations of septin organization associated with a Swe1p-dependent cell cycle delay [18]. Gin4p was found to be directly phosphorylated by the neck-associated Ser/Thr kinase Elm1 and Gin4p phosphorylates yeast septin Shs1p in vitro. Septin assembly-dependent cellular events can also be regulated by Elm1 directly phosphorylating and activating the Gin4-dependent pathway. Gin4 can phosphorylate Shs1p and regulate septin ring formation [87, 88]. Cdc42p and Cla4p are required for the activation of the Gin4 kinase, indicating another route through which Cla4p regulates septin collar assembly [80].

In mammalian cells, Cdc42 also seems to have dual roles in promoting the organization of the actin cytoskeleton and the septin complexes [52]. Macara et al. [52] have demonstrated direct binding of mammalian septin complexes (SEPT2-SEPT6-SEPT7) to a downstream effector of Cdc42 called Borg3, which contains a CRIB motif. Overexpression of Borg3 disrupted the assembly of septins into fibrillar structures, and the effect was ameliorated by expression of a constitutively active mutant of Cdc42,

which inhibited the Borg3–septin interaction [52]. Septin was also suggested to be regulated by the Rho family of GTPases. Rhotekin is a Rho effector molecule [89]. SA-RhoGEF, a Rho-guanine nucleotide exchange factor (GEF), was reported to associate with septin complexes [90].

Several studies have shown that mammalian septins could be phosphorylated by kinases such as protein kinase C (PKC), cGMP-dependent protein kinase I, Aurora-B kinase and dual-specific kinase DYRK1A in mitotic cells [91–94]. Wild-type Sept2 revealed a unique phosphorylation site at residue Ser248 in vivo [95]. It was found that Cdk5/p35 phosphorylated SEPT5 in vitro and in vivo, and Cdk5 phosphorylation of human septin SEPT5 at Ser327 played a role in modulating exocytotic secretion [96].

Sumoylation regulate septin assembly

Septins are also major sumoylation targets [97–99]. At least three septins, Cdc3p, Cdc11p and Shs1p, become sumoylated specifically during mitosis. This modification occurs before anaphase and is removed at cytokinesis, probably playing a role in the disassembly of the septin ring [97, 99]. The sumoylation of the septins during M phase requires the E3 ligase Siz1p, which is located in the nucleus during interphase [97, 99]. At a point before anaphase, coincident with septin sumoylation, Siz1p is phosphorylated and leaves the nucleus to accumulate at the septin ring [98]. These changes in the localization of Siz1p require Ulp1p [100, 101]. Recently, the kaps Kap95p, Kap121p and Kap142p/Msn5p were demonstrated to play specific roles in mediating the movement of Siz1p and Ulp1p in controlling the cell cycle oscillation of septin sumoylation [102].

Similarly, two-hybrid interactions have been found between *Drosophila* septins and the ubiquitin-activating (E1) and -conjugating (E2) enzymes Dmuba2 and Dmubc9, which catalyze the conjugation of the SUMO1-like protein Smt3 [103]. DmSmt3 was observed to localize in the midbody during cytokinesis, both in tissue-culture cells and in *Drosophila* embro [103].

Anillin regulates septin assembly

Anillin, a member of a conserved family of pleckstrin homology (PH)-domain proteins, is required for spatial control of metazoan septin organization. Vertebrate and nematode orthologs of anillin have three distinct domains, one of which interacts with septin complexes [44, 69]. Overexpression of a septin-interacting fragment of anillin can perturb septin organization and cause loss of actin bundles in cells [44].

An important role for anillin is as scaffolding for cleavage furrow components. Mutations that result in amino acid changes in the C-terminal PH domain of anillin cause defects in septin recruitment to the furrow canal and contractile ring and also alter the timing and rate of furrow ingression [104]. Direct binding of the nuclear transport receptors importin α and β to anillin was found to prevent the binding of Peanut to anillin, and the GTPase Ran was required for the localization of the septin Peanut to the pseudocleavage furrow [105].

Mid1 and Mid2, anillin homologs in fission yeast, are important for organization of the septin rings at the medial cortex at the end of anaphase, and Mid2 binds septins directly [64–66]. FRAP studies show that septins are stable in wild-type cells, but the exchange rate is 30-fold more rapid in *mid2*Δ cells. Mid2p colocalized with septins and required septins for its localization [64]. Overproduction of Mid2p depolarizes cell growth and affects the organization of both the septin and actin cytoskeletons. In the presence of a nondegradable Mid2p fragment, the septin ring is stabilized, and cell cycle progression is delayed [49, 65]. The closest counterpart of Mid2 in budding yeast appears to be Bud4, which localizes to the bud neck and associates with other markers of the bud neck, such as IQGAP (Iqg1).

The septin assembly in yeast and metazoan was a complex process and was regulated by many factors. Here we summarize what we discussed in this section about the possible regulatory mechanism of septin assembly in yeast and metazoa (Fig. 2).

Septin function

Septin function in yeast

Studies of yeast suggest that the septin collar (or hourglass) at the bud neck may serve as a diffusion barrier and scaffold for many proteins involved in diverse cellular processes [5, 6]. Here we will mainly discuss the septin function in cell division, membrane remodeling and compartmentalization in yeast.

Septin function in cell division in S. cerevisiae

Septins are best known for their role in cytokinesis. However, their requirement in this process varies tremendously from one organism to another. For example, septins play an essential role in cytokinesis in *S. cerevisiae*, presumably by functioning as a scaffold that tethers cytokinetic components, such as those involved in the formation of the actomyosin contractile ring and of the septum at the bud neck [19, 106]. In contrast, deletion of all

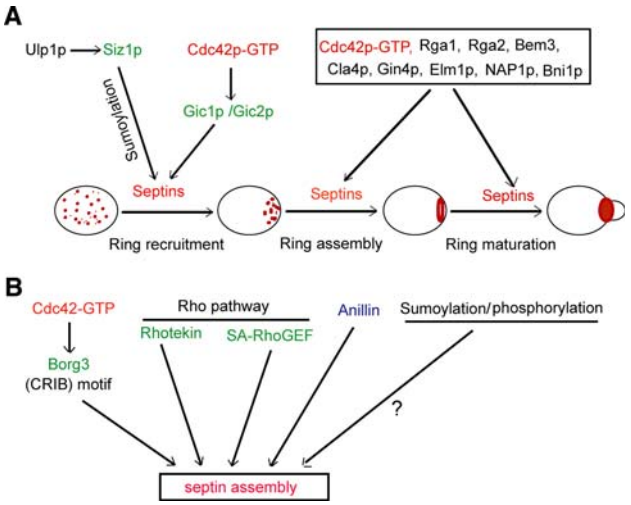

Fig. 2 Septin assembly in yeast and metazoa. **a** Septin assembly in yeast, Cdc42-dependent septin assembly. In yeast, assembly of the septin ring appears to have at least three steps: septin recruitment, septin ring assembly and septin ring maturation. Cdc42-GTP was required for the whole process of septin collar formation, which depends on activated Cdc42p and at least two partially redundant effector Gic1p and Gic2p. After septin recruitment, Cdc42, its GAPs (Rga1, Rga2 and Bem3), Cla4p, Gin4p, Elm1p, NAP1p and Bni1p are all required for septin ring assembly and maturation. Siz1p-related septin sumoylation is also involved in septin recruitment. **b** Metazoan septin assembly. Borg3, a CRIB motif containing protein and a Cdc42 effector, is required for metazoan septin assembly. Anillin, a conserved family of pleckstrin homology (PH)-domain proteins, is required for spatial control of metazoan septin organization. A Rho-guanine nucleotide exchange factor (GEF) SA-RhoGEF and a Rho effector Rhotekin are also involved in septin assembly. Whether the phosphorylation and/or sumoylation of septin could regulate septin assembly is still unknown

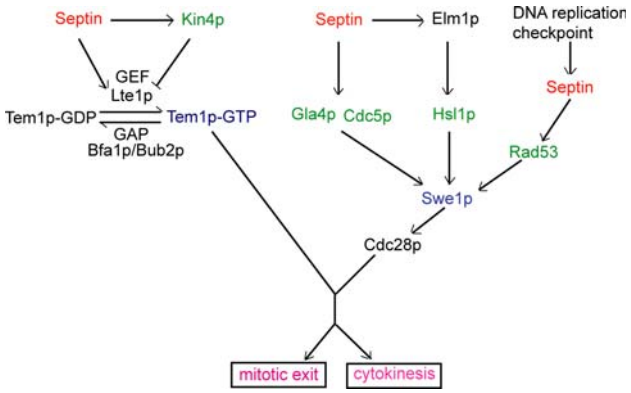

Fig. 3 Role of septins in mitotic exit and cytokinesis in yeast. In *S. cerevisiae*, Tem1p and Swe1p are involved in two important pathways regulating mitotic exit and cytokinesis separately. The activation of Tem1 by Lte1p leads to the activation of a kinase cascade, resulting in mitotic exit and cytokinesis. The Kin4ps provide additional layers of regulation by inhibition of the activation of Tem1p in the bud. This cell-cycle is also regulated by Swe1p protein kinase, which causes the inactivation of complexes of Cdc28p and mitotic cyclins. Several proteins were reported to function in septin regulating cytokinesis by controling Swe1p protein degradation. Protein kinases Gla4p and Cdc5p are located in the bud neck. If the septin collar is disturbed, Swe1p phosphorylation by Gla4p and Cdc5p were delayed and in turn promote the down-regulation of Swe1p. Another kinase Hsl1p could also promote Swe1p degradation and itself could be activated by relief of autoinhibition in response to septin interaction or phosphorylation promoted by the septin-associated kinase Elm1p. Septins may also function in the DNA replication checkpoint by interacting with Rad35, which could control the timely degradation of Swe1p during replication stress

four vegetatively expressed septins in the fission yeast *S. pombe* causes only a mild defect in cell separation [64, 65].

Septin assembly in bud neck in *S. cerevisiae* is temporally linked to G1-specific cell cycle signals and is regulated by the Ras-like Cdc42 signaling module, the Cdc42p GAPs (Rga1, Rga2, and Bem3), Galp, Gin4p, Hsl1p and Em1Lp [78, 107]. Septin assembly is discussed in the previous section. Here we will mainly focus on how septins regulate yeast cell cytokinesis (Fig. 3).

Septins were involved in spindle orientation in *S. cerevisiae*. During *S. cerevisiae* mitosis, the nuclear envelope remains intact, and the spindle pole bodies (SPBs) are located in the nuclear envelope. After DNA replication and SPB duplication, the daughter-bound SPB and mother-bound SPB must be correctly positioned [15]. Septins are also involved in positioning the spindle apparatus in yeast, for disturbing the septin organization at the neck would disrupt the correct positioning of SPB in yeast [15].

Septins were also involved in cell-cycle checkpoints in *S. cerevisiae*. The spindle-position checkpoint in budding yeast monitors the position of SPB to ensure that cells do not exit mitosis until the nucleus is properly positioned in the neck. Tem1 GTPase activity and the spatial separation of mitosis exit network (MEN) components provide an attractive model for how mitotic exit is temporally and spatially coordinated with spindle positioning. Bfa1/Bub2 stimulates Tem1 GTPase activity as a GAP. Lte1, which is the GEF for tem1p, is sequestered predominantly at the bud cortex, whereas Bfa1, Bub2 and Tem1 colocalize preferentially to the SPB directed toward the bud [108, 109]. Hence, mitotic exit is activated only when the nucleus is pulled into the bud and Tem1 encounters Lte1 [108]. In cells with compromised septin structures, Lte1p failed to restrict bud cortex localization, which in turn induces inappropriate Tem1p activation and inappropriate mitotic exit [110–112]. The spatially restricted activation of the MEN is further safeguarded by the protein kinase Kin4, which localizes to the SPB and the cortex of the mother cell in anaphase [109, 113]. Kin4 is thought to inhibit MEN activation by counteracting the activity of the polo kinase Cdc5, which activates Tem1 by inhibiting its GAP [114].

The morphogenetic checkpoint plays a key role in coordinating cellular morphogenesis (or budding) with nuclear progression of the cell cycle in budding yeast. In this checkpoint response, cell-cycle delay is mediated by

stabilization of the Swe1p protein kinase, which causes the inactivation of complexes of Cdc28p and mitotic cyclins. In unperturbed cells, the septin-dependent localization of both Swe1p and its negative regulators to the daughter side of the neck is important in the inactivation and degradation of Swe1p [17, 18]. Perturbations of the septin collar at the bud neck lead to the disturbance of the Gla4/PAK and Cdc5/Polo location in neck. In turn, phosphorylation of Swe1p by Gla4 and Cdc5 was delayed, and Swe1p expression was down-regulated as well [115].

Septins may also function at the DNA replication checkpoint by interacting with Rad35. The checkpoint kinase Rad53 acts at the DNA replication checkpoint, which maintains replication fork stability and prevents precocious chromosome segregation. Rad53 shows genetic interactions with septin ring pathway components and controls the timely degradation of Swe1p during replication stress along with other checkpoint proteins, thereby facilitating proper bud growth [23, 24].

Hsl1p, one of Nim1-related protein kinases, is also concentrated at the mother–bud neck through association with septin filaments, [17], and it was reported that Hsl1p activation involved relief of autoinhibition in response to septin interaction [116]. Another group reported that Hsl1p activation involved the phosphorylation of Thr273, promoted by the septin-associated kinase Elm1p [117]. It was suggested that septins were important to provide a scaffold upon which Swe1p could be targeted for degradation. Elm1p phosphorylates Hsl1p at Thr273, in turn activating Hsl1p to promote Swe1p degradation [117].

Septin function in compartmentalization and diffusion barriers in yeast

Besides septin function in cytokinesis in yeast, septin also functions in compartmentalization and diffusion barriers. The plasma membrane of many cell types displays domains with distinct composition and properties. This polarization allows vectorial transport of solutes across epithelia and unidirectional propagation of signals by neurons. Association of septins with phospholipids [41] is crucial to the formation and maintenance of membrane domains. Barral et al. demonstrated that septins compartmentalize yeast cell membranes during interphase and mitosis [21, 22]. In interphase cells, during isotropic bud growth, disruption of the septin collar at the bud neck failed to maintain the exocytosis and morphogenesis factors Spa2, Sec3, Sec5 and Myo2 in the bud during isotropic growth, resulting in passive diffusion of bud-restricted membrane proteins into the mother cell [21]. In wild-type cells, the septin collar splits into two rings, demarcating a distinct membrane compartment at the plane of cytokinesis during cell division where septins act as diffusion barriers for the concentration of cortical factors that mediate actomyosin contraction, membrane growth and abscission at the mother–bud neck [22].

Septins also function in the ER, restricting diffusion of ER membrane proteins through the bud neck [118]. In budding yeast, septin-dependent diffusion barriers function in asymmetric cell division. The septin-dependent, lateral diffusion barrier forms in the nuclear envelope and limits the translocation of pre-existing nuclear pores into the bud. This confines aging factors such as carbonylated proteins and DNA circles to the mother cell [119].

Septin function in metazoa

In contrast to yeast septins, which polymerize mainly at cortical sites of the mother–bud neck, mammalian septins localize not only to the plasma membrane, but also throughout the cytoplasm with the microtubule and actin cytoskeletons [8]. Human septins are especially implicated in many cellular processes [8–10].

Septins function in cytoskeleton organization and cell division in metazoa

In metazoans, septin polymers, being diverse, discontinuous and relatively static, seem suited to form discrete scaffolds. It is possible that the septin system might be redefined as discrete scaffolds that are conditionally united to behave like cytoskeleton [8–10].

In *Drosophila*, a mutation in the septin gene *pnut* results in a lethal phenotype with multinucleated cells [120], and Pnut and another *Drosophila* septin, Sep1, have been shown to colocalize with the contractile ring of dividing cells [120]. In *C. elegans*, mutations in the septin UNC-59 and UNC-61 result in some postembryonic cell division defects, and immunofluorescence studies on wild-type organisms revealed colocalization of septins at the leading edge of the cleavage furrow [29].

In dividing mammalian cells, the septin SEPT2 is localized to the cleavage furrow along with actin, and inhibitory antibody microinjection experiments further suggested a role for Nedd5 in cytokinesis [28]. During cytokinesis in mammal cells, septins were found to colocalize with actin in the cleavage furrow with microtubules in the midbody and central spindle [25, 28, 32]. Interfering septin expression results in binucleate cells [25, 28, 32].

In 2005, Dr. Spiliotis reported that Sept2 localized to the midbody, the ingressing cleavage furrow and the central spindle of cells during cytokinesis. Septin depletion resulted in chromosome loss from the metaphase plate, lack of chromosome segregation and spindle elongation, and incomplete cytokinesis upon delayed mitotic exit. These data suggested that mammalian septins might form a novel

scaffold at the midplane of the mitotic spindle that coordinates several key steps in mammalian mitosis [30]. Recently, it was found that SEPT7 can bind directly to CENP-E and stabilizes the kinetochore. In SEPT7-suppressed cells, the tension at kinetochores of bi-orientated chromosomes was reduced, and the mitotic spindle checkpoint was activated [121].

SEPT2 directly binds nonmuscle myosin II (myosin II), and this association is important for fully activating myosin II in interphase of dividing cells. Inhibition of the SEPT2-myosin II interaction in interphase cells results in loss of stress fibers in interphase cells and causes instability of the ingressed cleavage furrow and dissociation of the myosin II from the Rho-activated myosin kinases ROCK and citron kinase in dividing cells [122].

In mammalian cells, DNA damage was found to induce actin and septin rearrangement and rapid nuclear accumulation of NCK and SOCS7; thus, the septin-SOCS7-NCK axis might link with the canonical DNA damage cascade downstream of ATM/ATR and p53 Ser15 phosphorylation [27].

It was found that the recombinant SEPT2–SEPT6–SEPT7 could bind directly to microtubule-associated protein 4 (MAP4) [123]. This interaction might inhibit MAP4 binding to MTs and reduce the stability of cellular MTs. In contrast, loss of septins will increase the availability of MAP4, which will cause an inappropriate stabilization of the MT cytoskeleton [123]. It was also reported that SEPT2 regulates the efficiency of vesicle transport by antagonizing MAP4, and tubulin-associated SEPT2 facilitates vesicle transport by maintaining poly-Glu microtubule tracks and impeding tubulin binding of microtubule-associated protein 4 (MAP4) [125]. We summarized the recent results on septin function in metazoan cell cytokinesis (Fig. 4).

Septin filaments were reported to interact in vivo with assemblies of actin [28, 44, 89] and tubulin [25, 30, 32, 123]. A first indication that septins might interact with microtubules (MTs) was the observation that *Drosophila* septins Pnut, Sept1 and Sept2 could bind to MTs in vitro [124]. Mammalian septins form filamentous structures throughout the cell in interphase. These filaments align along actin stress fibers and/or microtubules (MTs), dissipate during mitosis and associate with the midbody at telophase [28, 32, 52]. Sept2 and Sept9 can align along MTs during interphase in PC12 and HeLa cells [25, 32, 72]. In epithelial cells, it was found that Sept2 fibers colocalize with a subset of microtubule tracks composed of polyglutamylated (polyGlu) tubulin. It was found that Sept2 binding to polyglutamylated MTs specifies a functionally distinct subset of MT tracks on which "fast track" vesicle transport occurs without slowing down due to MAP "speed bumps" [125].

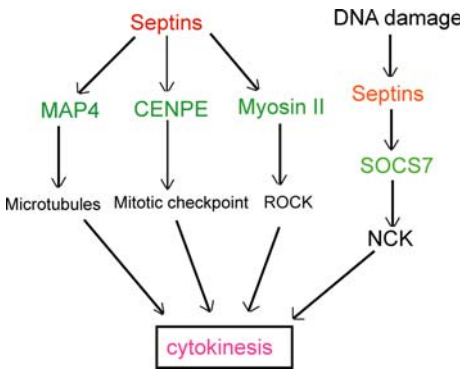

Fig. 4 Role of septins in cell dividion in metazoa. Septins could function in cell division by several pathways. Septins could directly bind to CENP-E and stabilize the kinetochore and function in forming the correct tension at kinetochores of bi-orientated chromosomes. Septins bind directly to nonmuscle myosin II and are involved in the myosin II and the Rho-activated myosin kinases ROCK pathway. In addition, septins can reduce the stability of cellular microtubules (MTs) by binding to microtubule-associated protein 4 (MAP4). Septin rearrangement induced by DNA damages could induce rapid nuclear accumulation of NCK and SOCS7. All these pathways could function during cell cytokinesis

Septins in membrane organization and vesicle targeting

In postmitotic cells, mammalian septins are thought to be involved in the secretory pathway, guiding vesicles to points of exocytosis [26]. SEPT3 is specifically enriched in synaptosomes and in peripheral membrane extracts, and is involved in synaptic vesicle recycling [32, 92]. SEPT3 (G-septin) and SEPT5 (CDCrel-1) are highly expressed in neurons. SEPT2 and SEPT11 are found colocalized with submembranous actin-rich structures during phagocytosis [126].

Mammalian septins associate with biological membranes through a highly conserved polybasic region at the N-terminus of the GTP-binding domain. Through this region, recombinant SEPT4 specifically binds phosphatidylinositol (4,5)-bisphosphate [PtdIns(4,5)P_2] and phosphatidylinositol (3,4,5)-trisphosphate [PtdIns(3,4,5)P_3] [40, 41].

In mammalian cells, sequestration of PtdIns(4,5)P_2 and reduction of its overall level at the membrane lead to loss of SEPT4 filaments. Lipid-based signaling events and PtdIns(4,5)P_2-mediated regulation of the actin cytoskeleton might indirectly influence septin polymerization [40]. Alternatively, septins might bind to membranes through adaptor proteins such as anillin. In *Drosophila*, anillin mutations disrupted septin localization, resulting in the collapse of newly formed plasma membranes during cellularization [104].

Human septins might function as possible diffusion barriers in neuronal cells [127, 128]. They were reported to specifically localize to the base of dendritic protrusions and

dendritic branch points, and downregulation of septin-7 (*SEPT7*) expression causes defects in dendritic spine morphology. This suggests that septins may be important in regulating the growth and morphology of these structures [127, 128]. Photobleaching-based assays in NRK cells also suggested that septins may have a compartmentation function in the plasma membrane and the cleavage furrow of mammalian cells [129].

In spermatozoa from male *Sept4*-knockout mice, both cortical organization and intraflagellar transport are disrupted [67, 68]. Sept12 was also a component of the mammalian sperm tail annulus [130].

Mammalian septins interact with the Sec6–Sec8 complex (called the 'exocyst' in yeast), which is involved in the tethering and/or fusion of exocytic vesicles to the plasma membrane [72]. SEPT5 has been shown to interact directly with the syntaxin SNARE protein, which is involved in the fusion of vesicles with membranes [131, 132]. It was found that Ser17 of Sept5_v1 is phosphorylated in mouse brains, possible by Cdk5. It was demonstrated that the phosphorylation of Sept5_v1 by Cdk5-p35 decreased the binding ability of Sept5_v1 to syntaxin-1, a component of the SNARE complex [133]. Recently, it was found that Cdk5 can phosphorylate SEPT5 at Ser327, which is involved in modulating exocytotic secretion [96].

SEPT3 and SEPT5 are highly expressed in neurons and associated with synaptic vesicles. Overexpression of SEPT5 could inhibit exocytosis in insulin-secreting cells [131, 132], and the release of serotonin in platelets was upregulated in *Sept5*-knockout mice compared to wild-type mice [134]. However, $Sept5^{-/-}$ mice did not show any overt neurological phenotypes, while the $Sept3^{-/-}$ and $Sept3^{-/-}$ $Sept5^{-/-}$ mice are also normal in the gross morphology and synapses of the hippocampus [135]. One possible reason for these results might be the possible septin functional redundancy in neurons.

Human IQGAP1 functions in organizing cytoskeletal architecture through unclear mechanisms, although recently human IQGAP1 was reported to bind to the exocyst–septin complex and influence the localization of the exocyst as well as the organization of septin. Activation of CDC42 GTPase abolished the association between IQGAP1 and the exocyst-septin complex, and inhibited secretion in pancreatic β-cells [136].

Septins were also required for efficient FcγR-mediated phagocytosis. SEPT2 and SEPT11 colocalize with submembranous actin-rich structures during the early stages of FcγR-mediated phagocytosis [126]. Septins have also been demonstrated to function in transforming phospholipid-based liposomes through interacting with giant liposomes [137].

Conclusion future directions

Septins play fundamental roles in cytokinesis, membrane remodeling and compartmentalization. In this review, we have described the evolution, structures, assembly and function of septin proteins in yeast and metazoa. The relationship between septin proteins and disease was also mentioned.

The function of septins depends on their assembly into oligomeric and highly ordered polymers. Various structures of septins are found in yeast, *D. melanogaster* and mammals. Though several septin complexes in mammals, such as SEPT2–SEPT6–SEPT7, SEPT7–SEPT11–SEPT9_v3α and SEPT3–SEPT5–SEPT7 complexes, are reported, more septin complexes in mammals are still needed to be unraveled to better elucidate septin assembling rules and functions. EM and crystal studies of septin complexes provide important knowledge about septin core complexes. However, how septin core complexes are assembled into filaments and higher order complexes still remains unclear. Our knowledge about how septin assembly is regulated is rather limited. There is not enough information about septin interacting proteins and the regulation of septin dynamics.

The shared domain structure of fungal and animal septins implies that the basic mechanisms of septin-complex assembly and function are shared among septins. Nevertheless, the expansion of the septin gene number in vertebrates increased septin complex diversity in vertebrates. At the same time, possible functional redundancy of septins became one of challenges to elucidate the function of human septins. For example, SEPT3 and SEPT5 are highly expressed in neurons and associated with synaptic vesicles; however, $Sept5^{-/-}$, $Sept3^{-/-}$ and $Sept3^{-/-}$ $Sept5^{-/-}$ mice did not exhibit overt neurological phenotypes. Knock-down of septin genes based on the evolutionary relationship in vertebrates may be helpful for further septin functional studies.

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