Septin localization across kingdoms: three themes with variations

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Septins are GTPases that form filaments in fungi and animals. In addition to their original role in cell division, septins have been shown to have roles in coordinating nuclear division, membrane trafficking and organizing the cytoskeleton. Many recent studies have examined subcellular localization of septins in a wide range of fungi and animals. Septin localization shows three patterns, which generally correspond to function across kingdoms. Septins that localize to projections shape and compartmentalize emerging growth. Septins that localize to partitions compartmentalize pre-existing cellular material. Septins that localize to the whole cell are involved in membrane trafficking and organizing the cytoskeleton and are most often in animals. The difference in localization pattern frequency between kingdoms will probably disappear as more septins are examined in diverse organisms and tissues.

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Introduction

Septins were first observed 30 years ago associated with filamentous rings at the mother-bud neck in *Saccharomyces cerevisiae* [1]. During the next two decades, septins were found in other fungi and some animals. With the increased availability of genome sequences, it is now clear that septins are found in fungi, animals and microsporidia, and that they are absent from plants. The number of septin proteins in a single organism ranges from two in *Caenorhabditis elegans* to 13 in humans [1–7] (F Pan, RL Malmberg, M Momany, submitted). Septins are members of the P loop GTPase family, and septin heteropolymers form filaments. The combination of GTPase activity and filament formation has led to comparisons between the septins and the cytoskeletal elements actin and tubulin [8,9].

Recent reviews have focused on septins in fungi [10•,11] and mammals [7], on the scaffolding role of septins [9] and on septin filament formation [12]. Here, we focus on the subcellular localization of septins. All fungi and animals have multiple septin genes (F Pan, RL Malmberg, M Momany, submitted) and splice variants have also been reported [7]. Further complicating matters, septin localization is dynamic, changing during development and the cell cycle [7,11]. In the past few years, many studies have examined septins in fungi and animals, yielding a bewildering array of subcellular localization patterns. However, upon closer examination, subcellular septin localization falls into variations of three distinct patterns: localization to projections, to partitions or to whole cells (Figure 1).

Projections

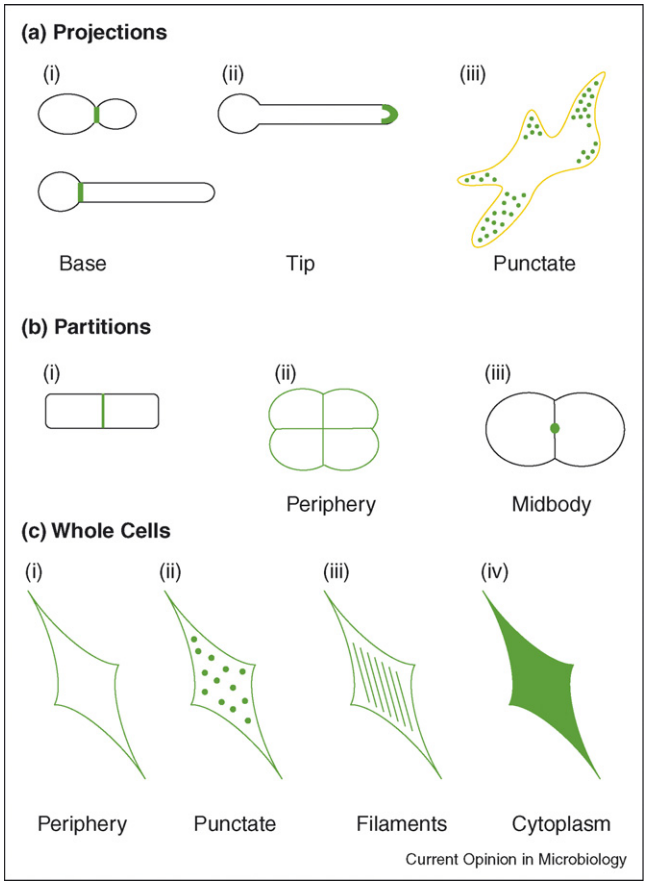
Septins localize to projections, outgrowths from a larger cell, in fungi and animals (Figure 1a; Table 1). Projections can be round (e.g. yeast buds and fungal spores) or tubular (e.g. fungal hyphae and mammalian neurites) and arise from cells of any shape.

Septins at the projection base

Septin localization to the base of a projection is common in fungi, where round projections include buds, reproductive structures and spores, and tubular projections include germ tubes, hyphae and branches. Indeed, the first septin structure observed was the prominent ring formed by Cdc3p, Cdc10p, Cdc11p and Cdc12p at the base of the projecting daughter bud in *S. cerevisiae* [1]. Later work showed that the septin ring forms on the mother cell along with an actin ring late in the G_1 phase, circumscribing the site where the bud will emerge in the S phase [13]. As the bud emerges through the ring, the septins broaden at the neck and remain there for the rest of the cell cycle. Septins at the neck form a barrier to diffusion of products between mother and daughter cells (described in this elegant study [14]), and are part of the morphogenesis checkpoint that monitors the progression of budding and the spindle checkpoint that monitors chromosome segregation [11].

In the filamentous fungi *Aspergillus nidulans* and *Ashbya gossypii*, a similar pattern is seen in branching [15,16•]: the septin ring appears, the branch emerges within the circumference of the ring and nuclear division occurs. Although the details are not yet clear, it appears that septins have a role in coordinating branch emergence and mitosis. In hyphae of *Candida albicans*, a broad diffuse septin band appears at the base of the emerging germ tube before nuclear division [17,18]. In the *A. nidulans* reproductive structure (the conidiophore [15]) septins localize to the base of round projections although, in this case, many projections emerge in synchrony, forming multiple layers of cells before spores are made.

Figure 1



Septins localize in three basic patterns in fungal and animal cells. Septins localize to: **(a)** projections at the base, tip or throughout; **(b)** partitions between cells; **(c)** whole cells at the periphery or throughout in a punctate, filamentous or cytoplasmic pattern. Green shading represents septin labeling.

In animals, sperm cells furnish the only example of septin localization to the base of a projection. In mice, Sept4, along with other septins, forms the annulus, a cortical ring separating the sperm into two segments: the midpiece and the primary piece. Sperm from mice lacking Sept4 also lack the annulus and are sterile [19•,20•]. Although the septins have not yet been localized during early sperm development, electron micrographic studies have followed the annulus, now thought to be composed of septins [21]. Early in sperm development, before the tail is made, an electron-dense rudimentary annulus appears near the centrosome. The flagellum develops within the annulus, much as a bud or branch emerges from the septin ring in fungi. During flagellum development the sperm nucleus is reorganized, although it is not clear if the septins have anything to do with this process. After the flagellum is made the annulus moves down the tail to serve as a barrier between the midpiece and primary piece. Interestingly septins remain at the mature annulus making this the only clear case of a permanent septin ring [20•].

Septins at the base of a projection define its circumference before it emerges from the main cell. These septins appear to couple growth with nuclear division. Septins at the base of a projection serve as diffusion barriers, although in some cases the barrier function occurs long after the projection is made.

Septins at the projection tip and punctate throughout the projection

Septins are at the tips of *C. albicans* and *A. gossypii* hyphae. The tip is where all growth occurs in fungal hyphae [22], thus tip-localized septins are well positioned to have a role in the addition of new membrane and cell wall.

Table 1

Subcellular localization of septins.

Species	Septin	Pattern[a]	Cell type[b]	Localization[c]	Refs
Fungi					
A. nidulans	AspB (Cdc3)	Partition	Hyphae	Septa	[15]
		Projection, base	Hyphae	Emerging branches	[15]
		Projection, base	Conidiophores	Layers	[15]
		Projection, base	Conidiospores	Ring at neck	[15]
C. albicans	Cdc3, Cdc10,	Projection, base	Yeast	Neck[d]	[2,17,18]
	Cdc11, Cdc12,	Projection, base	Hyphae	Emerging germ tubes	[2,17,18,49]
	Sep7	Projection, tip	Hyphae	Emerging germ tubes	[17,18,49]
		Partition	Hyphae	Septa	[2,17,18,49]
	Cdc10, Cdc12	Projection, base	Chlamydospores	Ring at neck	[37]
		Whole, periphery, filaments	Chlamydospores	Periphery	[37]
A. gossypii	Sep7	Projection, base	Hyphae	Emerging branches	[16]
		Projection, tip	Hyphae	Tips	[11,16]
		Partition	Hyphae	Septa	[11,16]
S. cerevisiae	Cdc3, Cdc10, Cdc11, Cdc12, Sep7	Projection, base	Yeast (budding)	Neck	[1]

Table 1 (*Continued*)

Species	Septin	Pattern[a]	Cell type[b]	Localization[c]	Refs
	Cdc3, Cdc10, Cdc11, Spr3, Spr28	Partition, periphery	Ascospores	Leading edge of prospore membrane	[1,35,50]
S. pombe	Spn1, Spn2, Spn3, Spn4	Partition	Yeast (fission)	Septa	[1,25,26,51]
Animals					
C. elegans	unc59, unc61	Partition, midbody	Embryo	Cleavage furrow	[5,28]
D. melanogaster	Pnut, Sep1, Sep2	Partition	Embryo and S2	Cleavage furrow	[6,27,36]
		Partition, periphery	Embryo	Cellularization front	[27]
Mammals[e]	Sept1	Partition, midbody, sp	HeLa	Cleavage furrow, midbody and spindle poles	[29]
	Sept1, Sept4, Sept6, Sept7	Projection, base	Sperm	Annulus	[19•,20•]
	Sept2	Partition, midbody	COS7, ERC, HeLa, MDCK	Cleavage furrow	[30–32]
		Whole, periphery	Neuron, HeLa, MDCK, PC12	Cell periphery/plasma membrane	[7,40,41]
		Whole, filaments	ERC, HeLa, NRK	Actin stress fibers	[33]
	Sept2, Sept6, Sept7	Whole, filaments	NIH3T3	Actin stress fibers	[44]
	Sept2, Sept6, Sept9	Whole, filaments	HeLa, MDCK	Cytoplasmic microtubules, spindle	[31–33]
	Sept3	Projection, punctate	Neuron	Cell processes, nerve termini	[24]
		Whole, punctate	Neuron	Cell body	[24]
	Sept4	Whole, punctate	COS7	Cytoplasm, mitochondria	[38]
		Partition	COS7	Cleavage furrow	[30]
		Whole, filaments	COS7	Actin stress fibers	[30]
	Sept5, Sept6	Whole, filaments	Platelet	Circumferential microtubule band	[42•,52]
	Sept5, Sept6	Whole, punctate		Cytoplasm	[42•,52]
	Sept5	Projection, tip	PC12	Plasma membrane of neurites, concentrated in tip	[40]
		Whole, periphery	Platelet, COS7	Cytoplasm, granules	[42•,43]
	Sept6	Partition, midbody	ERC	Cleavage furrow	[33]
	Sept9	Partition			
	Sept6, Sept7, Sept9, Sept11	Whole, filaments	HeLa, HMEC, MDCK, COS7, REF52	Actin stress fibers	[31,45,46]
	Sept7	Partition	MDCK	Cleavage furrow	[34]
		Whole, periphery	Neurons	Cytoplasm	[34,39]
	Sept8	Whole, periphery	COS-7	Cytoplasm, vesicles	[43]
	Sept9	Whole, filaments	ERC	Cytoplasmic microtubules	[33]
	Sept10	Whole, cytoplasm	HEK 293	Cytoplasm, nucleus	[48]
	Sept11	Whole, filaments	HeLa, REF52	Cytoplasmic microtubules	[46]

[a] Patterns illustrated in Figure 1: **a**, projection, (i), base; (ii), tip; (iii), punctuate. **b**, (i), cleavage furrow or septum; (ii), periphery of dividing cells; partition: (iii), midbody after completion of cleavage; sp, spindle pole. **c**, whole cell: (i), periphery; (ii), punctuate; (iii), filaments; (iv), cytoplasm.
[b] Fungal or animal cell type. Cell culture sources: COS-7, African green monkey kidney fibroblast; ERC, embryonic rat cardiomyocytes; HeLa, human epithelial; HEK 293, human embryonic kidney; HIT T15, hamster insulinoma; HMEC, human mammary epithelial; MDCK, Madin–Darby canine kidney epithelial; NIH 3T3, mouse embryonic fibroblast; N18, mouse neuroblastoma; NRK, normal rat kidney; PC12-rat pheochromocytoma; REF52, rat embryo fibroblasts; S2, fly.
[c] Only localization resolved at the individual cell level is included. Localization at the tissue level is not included. Most septin localization is transient.
[d] Septin was overexpressed.
[e] Most mammalian septin localizations used antibodies raised against heterologous protein and are listed with the cell type examined. The mammalian septin-naming convention is described by Macara *et al*. [53] and Martinez and Ware [54].

Mammalian Sept5 is localized to plasma membranes and concentrated in the tips of neurites, where it associates with vesicles and is thought to regulate vesicle targeting and fusion [23]. The single example of punctuate localization to a projection is also consistent with a role in secretion and membrane fusion. Sept3, a septin expressed in the brain, localizes to synaptic vesicles in mammalian neurons [24].

Septins localized at projection tips and throughout the cytoplasm in a punctate pattern appear to direct new growth through membrane trafficking.

Partitions

Septins localize to partitions, barriers that divide existing cytoplasm, in animals and fungi (Figure 1b; Table 1). Septins at the base or tip of projections also form barriers;

however, we consider this a different pattern because in projections, septins shape the new growth they circumscribe, whereas in partitions septins do not alter the overall shape of the cell, only its organization. When fungal septa and animal cleavage furrows separate cytoplasm into two compartments that will occupy the same plane, septins localize only to the partition between the cells, not to the periphery of the cells. During cellularization of embryos, partitions separate the cytoplasm into multiple compartments that form a network extending in all directions, and septin localization is peripheral, forming a cage around the new compartment.

Septins at partitions

In the fission yeast *Schizosaccharomyces pombe*, septins form a ring late in mitosis at the center of the elongated, tubular cell. As the contractile ring constricts, the septin ring splits [25,26]. In the filamentous fungus *A. nidulans*, septins form rings that partition the tubular hypha into compartments after mitosis is complete [15]. Septins partition the hyphae of *C. albicans*, although in this case mitosis occurs after the septin ring appears [17]. Septins also partition the hyphae of *A. gossypii*, where septation and mitosis appear to be much less coordinated [16•].

Similarly, *C. elegans* and *Drosophila melanogaster* septins localize to cleavage furrows during partitioning of cells. After cleavage, septins are often found at the midbody, an intercellular bridge of interdigitated spindle microtubules seen in animal cell cytokinesis [5,6,27,28]. This same pattern of septin localization to constricting cleavage furrows, often followed by localization to the midbody, has been reported for a variety of mammalian cell types [29–34]. Interestingly, in addition to its localization at the cleavage furrow and midbody, Sept1 in HeLa cells localizes to the spindle poles throughout mitosis [29]. This association of septins with both spindle and cleavage plane led to the suggestion that mammalian septins form a scaffold that coordinates chromosome segregation and division plane specification [29,32]. In *S. cerevisiae* ascospore formation and *D. melanogaster* embryo cellularization, partitions divide compartments in more than one plane, and septins localize to the periphery of compartments [6,27,35,36].

Septins localized to partitions do not alter the overall shape of the cell, only its organization into compartments. Although the mechanisms are not clear, septins in partitions appear to relay information between sites of nuclear division and sites of cell division.

Whole cells

Septins localize throughout the cell most often in animals, although examples from a single fungus have been reported (Figure 1c; Table 1).

Septins at the whole cell periphery and punctate throughout

The single published example of septin localization to the periphery of a fungal cell is found in *C. albicans* chlamydospores, where short septin filaments localize to the cortex [37]. Because no divisions occur in the spore, it is thought that these septins direct vesicles carrying cell wall biosynthetic enzymes to the plasma membrane. Peripheral and punctate septin localization has been seen in several mammalian cell types [7,24,34,38–41,42•,43], where it is also thought to be involved in membrane trafficking. In platelets, punctate Sept5 and Sept6 have been associated with secretion [42•,43], and rat brain septins coprecipitate with proteins needed for vesicle delivery [34]. One interesting exception is the punctate localization of a Sept3 splice variant to mitochondria in neurons, where it is thought to be involved in neural development [38].

Septin filaments throughout the whole cell

The only published report of septin filaments in fungi comes from *C. albicans* chlamydospores [37]. Although the filament pattern is reminiscent of actin or tubulin, no colocalization experiments were reported. Septin filaments have been reported in a variety of mammalian cell types [30–33,44–46], and in all cases they colocalize with actin stress filaments and/or cytoplasmic microtubules throughout the cytoplasm. One interesting variation on filament localization is seen in platelets. Platelets are formed by the extrusion of cytoplasm from larger proplatelets. This process is driven by microtubules, which remain coiled around the platelet, forming a circumferential band [47]. Septins colocalize with this cortical microtubule band, where they help to maintain the discoid shape of resting platelets [42•].

The colocalization of septin filaments with actin and/or microtubules led to the question of whether actin or microtubules were serving as templates for septin, or vice versa. Disruption of mammalian actin caused septins to shift from filaments to small circles similar to septins reconstituted *in vitro*, suggesting that actin directs the formation of septin filaments and that circles might be the default septin organization when actin is absent [44]. However, other work has shown that disruption of actin or microtubules causes septins to lose their filamentous form in some cell types and not in others [46].

There is only a single report of septin localization to the cytoplasm, and its physiological significance is not yet clear [48].

Septins that localize to the cell periphery or cytoplasm in a punctate pattern are mostly involved in membrane trafficking. Septins that localize as filaments colocalize with actin or microtubules, where they are thought to organize the cytoskeleton through interactions with cytoskeletal binding proteins [32].

Conclusion: septin form and function across kingdoms

Examples of septin localization to partitions (Figure 1b) are common in both fungi and animals; however, most examples of localization to projections (Figure 1a) are in fungi, and most examples of localization to whole cells (Figure 1c) are in animals. This has led to the assumption that, except for cytokinesis, fungi and animals use septins in very different ways. However, the apparent differences in septin localization between fungi and animals probably have more to do with experimental systems than with septin function.

Fungi have between five and seven septins (F Pan, RL Malmberg, M Momany, submitted). The full complement of fungal septins has been examined only in the budding yeast *S. cerevisiae* and its close relative *C. albicans*. *S. cerevisiae* is unicellular and microtubules have little or no role in its growth. Thus, septin localization specific to the coordination of multiple cells or transport over long distances would not be expected in budding yeast. In this context, it is significant that the only published examples of whole cell septin localization (Figure 1c) in fungi are from *C. albicans* – a dimorphic fungus that can grow in a hyphal form and undergoes several developmental programs. Further, in our unpublished work, we have seen punctuate and filamentous whole cell septin localization in the multicellular fungus *A. nidulans*. Undoubtedly, more examples of whole cell localization will be uncovered as other septins are investigated in multicellular fungi.

Septin localization data in animals are similarly skewed, with mammalian cell culture furnishing most examples. In humans, there are thirteen septin genes, many with alternate splice forms [32]. Given the probable number of septin isoforms and complexity of tissue types, it is not surprising that no one has localized the full complement of septins in any mammal. Studies of septins in the early development of cells that form projections would be especially informative. In fungi, the septin ring circumscribes the region from which the bud or germ tube will emerge. It seems likely that studies of early sperm and neuron development will reveal similar septin localization.

Although the classification of septin localization into three patterns is undoubtedly an oversimplification, it does point to trends across kingdoms. Septins that show similar localization patterns have been implicated in similar processes. On the basis of what we know so far, we predict that the following will hold true across kingdoms: (i) septins at the base of projections (Figure 1a, part i) shape emerging growth and serve as barriers, although shape determination and barrier functions might be temporally separated; (ii) septins at partitions (Figure 1b) compartmentalize previously existing cytoplasm without affecting its overall shape; (iii) septins at the base of projections (Figure 1a, part i) and at partitions (Figure 1b) coordinate nuclear division with cell division, although the mechanism is not always clear; (iv) septins at the cell periphery (Figure 1c, part i) or throughout the cytoplasm in a punctate pattern (Figure 1c, part ii) are involved in membrane trafficking or, less commonly, development of mitochondria or other organelles; (v) septins that form filaments (Figure 1c, part iii) co-localize with actin and/or tubulin. These septins either organize the other elements of the cytoskeleton or are organized by them.

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