Novel roles for mammalian septins: from vesicle trafficking to oncogenesis

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Summary

In recent years a convergence of various aspects of cell biology has become apparent, and yet investigators are only beginning to grasp the underlying unifying mechanisms. Among the proteins that participate in diverse aspects of cell biology are the septins. These are a group of novel GTPase proteins that are broadly distributed in many eukaryotes except plants. Although septins were originally identified as a protein family involved in cytokinesis in yeast, recent advances in the field have now ascribed additional functions to these proteins. In particular, the number of known mammalian septin family members has increased dramatically as more data has become available through genome analyses. We suggest a classification for the mammalian septins based on the sequence homologies in their highly divergent N- and C-termini. Recent work suggests novel functions for septins in vesicle trafficking, oncogenesis and compartmentalization of the plasma membrane. Given the ability of the septins to bind GTP and phosphatidylinositol 4,5-bisphosphate in a mutually exclusive manner, these proteins might be crucial elements for the spatial and/or temporal control of diverse cellular functions. As the functions of the septins become unraveled, our understanding of seemingly different cellular processes may move a step further.

Key words: Cytokinesis, Cell polarity, Cytoskeleton, Exocytosis, GTPase

Introduction

Septin genes were first identified in a genetic screen for *Saccharomyces cerevisiae* mutants defective in cytokinesis (Hartwell, 1971). The name septin was chosen to reflect the role of these proteins in separation of mother and daughter cells. The originally identified septins (Cdc3p, Cdc10p, Cdc11p and Cdc12p) localize to the division plane between mother and daughter cells (Haarer and Pringle, 1987; Kim et al., 1991; Ford and Pringle, 1991). Because they can also form filaments in vitro (Field et al., 1996; Frazier et al., 1998) and co-localize with previously discovered neck filaments (Byers and Goetsch, 1976) believed to be required for mother-daughter separation during cytokinesis, it was suggested that septins actually constitute these neck filaments. For some time, researchers in the field then assumed that the sole function of septins is to aid in cytokinesis, although structures similar to neck filaments are not visible in other organisms. The identification of septin homologues in higher eukaryotes that also localize to the cleavage furrow in dividing cells supported the idea of an orthologous function in cytokinesis (Flescher et al., 1993; Neufeld and Rubin, 1994; Fares et al., 1995; Kinoshita et al., 1997). However, both the identification of new septin family members in budding yeast that are specifically involved in sporulation (DeVirgilio et al., 1996; Fares et al., 1996), in positioning of chitin synthase and bud-site-selection markers (DeMarini et al., 1997; Flescher et al., 1993) in cell cycle control (Barral et al., 1999) and in the expression of septin homologues in post-mitotic cells (Longtine et al., 1996; Trimble, 1999) have now suggested additional roles for these proteins. Here, we concentrate on very recent findings about mammalian septins that place these proteins into novel cellular contexts; other aspects of septin function have been described previously, and we mention these only briefly (Longtine et al., 1996; Cooper and Kiehart, 1996; Field and Kellog, 1999; Trimble, 1999).

Septins, a rapidly growing protein family

Septins are broadly expressed throughout the animal kingdom, and yet seem to be absent from plants (Longtine et al., 1996). To date, numerous mammalian homologues of the yeast septins are known, some of which were given independent names despite sequence identity (Fig. 1). The primary structure of these 40-50 kDa proteins is well conserved between different species. Besides a conserved central core domain (>35% sequence identity between yeast and mammalian septin homologues) common to all septins, most septins possess in their N-terminal half a P-loop motif characteristic of GTP/ATP-binding proteins (Flescher et al., 1993; Cooper and Kiehart, 1996; Field and Kellog, 1999). Only one exception devoid of a P-loop motif has been reported to date: a septin homologue from the phytopathological fungus *Pyrenopeziza brassicae* (Singh et al., 2000). Indeed, GTP binding and GTPase activity have been demonstrated for some of the septins in vitro (Field et al., 1996; Frazier et al., 1998). Thus, septins are a novel group of GTPases that are distinct from the small Ras-like GTPases or any of the other known GTPase proteins (Field and Kellog, 1999). The N- and C-termini surrounding the core domain of the septins are divergent, but most C-termini from lower eukaryotes and some of the mammalian septins (Fig. 1) have a C-terminal predicted coiled-coil domain, which could be involved in protein-protein

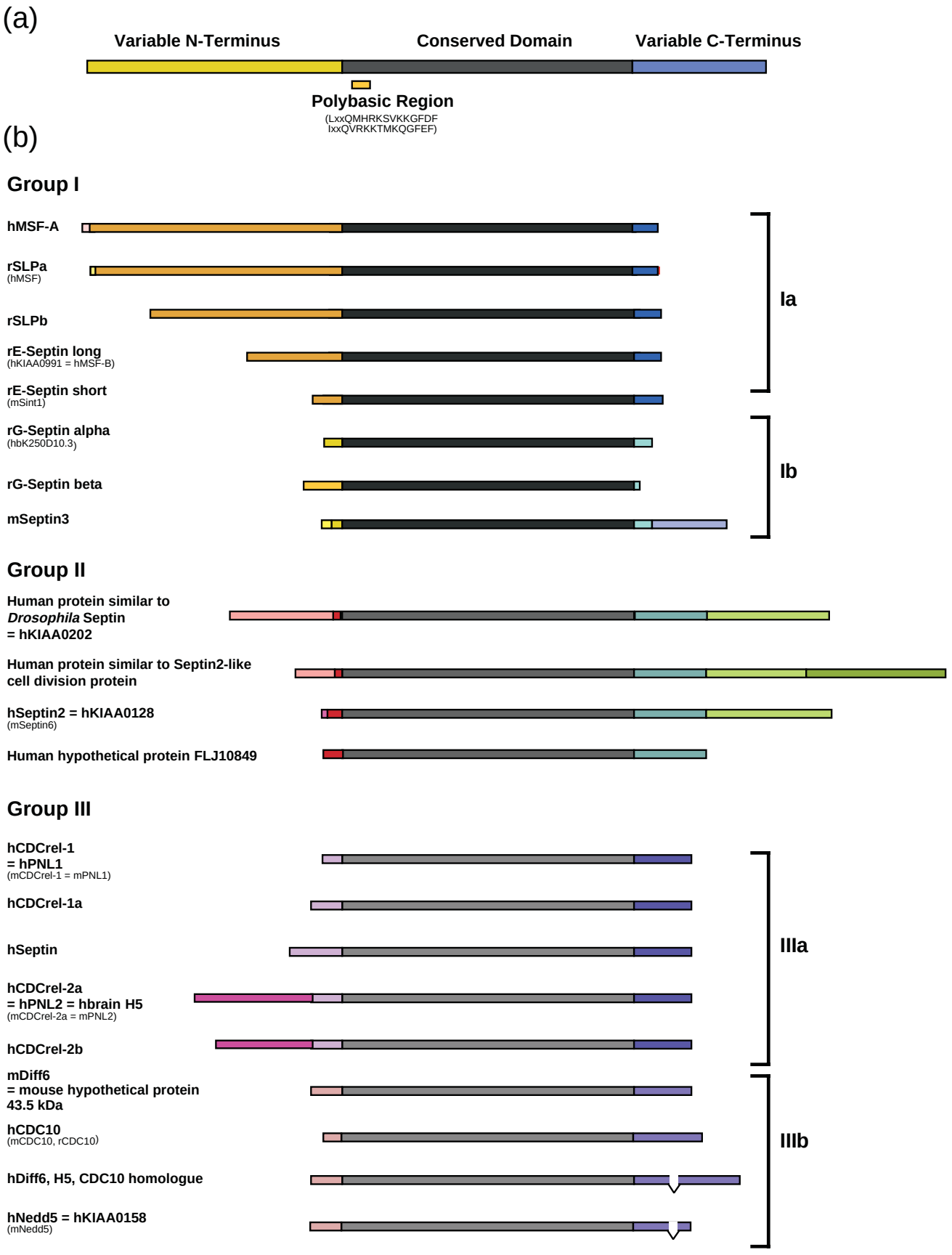
(a)
Variable N-Terminus
Conserved Domain
Variable C-Terminus
Polybasic Region
(LxxQMHRKSVKKGFDF
IxxQVRKKTMKQGFEF)
(b)
Group I
hMSF-A
rSLPa
(hMSF)
rSLPb
rE-Septin long
(hKIAA0991 = hMSF-B)
rE-Septin short
(mSint1)
rG-Septin alpha
(hbK250D10.3)
rG-Septin beta
mSeptin3
Ia
Ib
Group II
Human protein similar to
Drosophila Septin
= hKIAA0202
Human protein similar to Septin2-like
cell division protein
hSeptin2 = hKIAA0128
(mSeptin6)
Human hypothetical protein FLJ10849
Group III
hCDCrel-1
= hPNL1
(mCDCrel-1 = mPNL1)
hCDCrel-1a
hSeptin
hCDCrel-2a
= hPNL2 = hbrain H5
(mCDCrel-2a = mPNL2)
hCDCrel-2b
mDiff6
= mouse hypothetical protein
43.5 kDa
hCDC10
(mCDC10, rCDC10)
hDiff6, H5, CDC10 homologue
hNedd5 = hKIAA0158
(mNedd5)
IIIa
IIIb

Fig. 1

Fig. 1. Classification of the mammalian septins. (a) The domain structure of the septins. (b) Domain structures of the main representatives of the individual groups. Group I septins are characterized by large N-termini and short C-termini, the latter being devoid of coiled-coil regions. Two subgroups can be distinguished on the basis of their homology in the N- and C-terminal extensions. Group II septins possess a large C-terminal region that forms a long coiled-coil domain (>80 residues) at the extreme C-terminus. Septins from other species show clear homology to mammalian group II septins, particularly Sep2 and Sep5 from *Drosophila* (>75% sequence identity). Group III comprises the largest number of members. This group has two subgroups, which are defined by their high sequence identities in the C-termini. In addition, Pnut from *Drosophila* and septin B from *Aspergillus nidulans* show strong homology to mammalian group III septins. Some of the septins will probably turn out to represent alternative splice forms. Black and grey boxes indicate the conserved central domain. Identical colours represent sequence identities of >90%. Names in small type indicate homologues in other mammalian species. Homologies within a single septin group are >75%. Abbreviations for species names: h, human; r, rat; m, mouse.

interactions (Longtine et al., 1996). Mammalian septins display the same overall domain structure; however, they exhibit even greater variations in the length and primary structure of the N- and C-termini. Computational analysis has nonetheless revealed distinct subclasses that allowed classification of all presently known sequences for mammalian septins into three groups (I, II and III) (Fig. 1). Members of each subgroup have similar characteristics with respect to the length of N- and C-terminal extensions and overall sequence identity. A similar phylogeny resulting in the classification of the mammalian septins into the same three groups was also recently reported (Xue et al., 2000). This classification was based on eight of the mammalian septins and derived from sequence homologies within the GTPase consensus domain.

Too little is known about the mammalian septins to allow their classification on a functional level. However, group III septins in particular are characterized by a well-conserved polybasic region that binds phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P_2) (Zhang et al., 1999). PtdIns(4,5)P_2 binding might confer plasma membrane association, as reported for the group III septin H5 (Xie et al., 1999). Importantly, PtdIns(4,5)P_2 binding to septins might regulate their binding to GTP, because the PtdIns(4,5)P_2- and GTP-binding sites are in close proximity in the primary structure, and the binding of PtdIns(4,5)P_2 and GTP to septins is mutually exclusive (Zhang et al., 1999). This implies that the binding of PtdIns(4,5)P_2 to septins at the plasma membrane occurs only in the GDP-bound conformation whereas the GTP-bound form is prevented from localizing to the plasma membrane. Consequently, septin activity might be tightly regulated (spatially and/or temporally) by the guanine-nucleotide state of the septin and the level of PtdIns(4,5)P_2 within the cell (Fig. 2A).

A role in vesicle transport and exocytosis?

In yeast and other organisms, numerous septin-interaction partners have been identified; many are components of the bud-site-selection machinery, of kinase cascades or part of the ubiquitination pathway (Longtine et al., 1996; Trimble, 1999; Field and Kellog, 1999). Septins might thus act as a protein scaffold that provides a spatially defined interaction matrix for other proteins. In mammals, the situation appears different because the only interaction partners identified to date are components of the exocytic machinery, except for protein kinase G, which phosphorylates the so-called G septins (named after their interaction with cGMP-dependent protein kinase) (Xue et al., 2000) and is more likely to regulate septin activity. Other interaction partners might, however, be found in the future. The components of the exocytic machinery that interact with mammalian septins are (1) components of the so-called exocyst complex (Hsu et al., 1998; Fung and Scheller, 1999), which is present in yeast and mammals (TerBush et al., 1998;

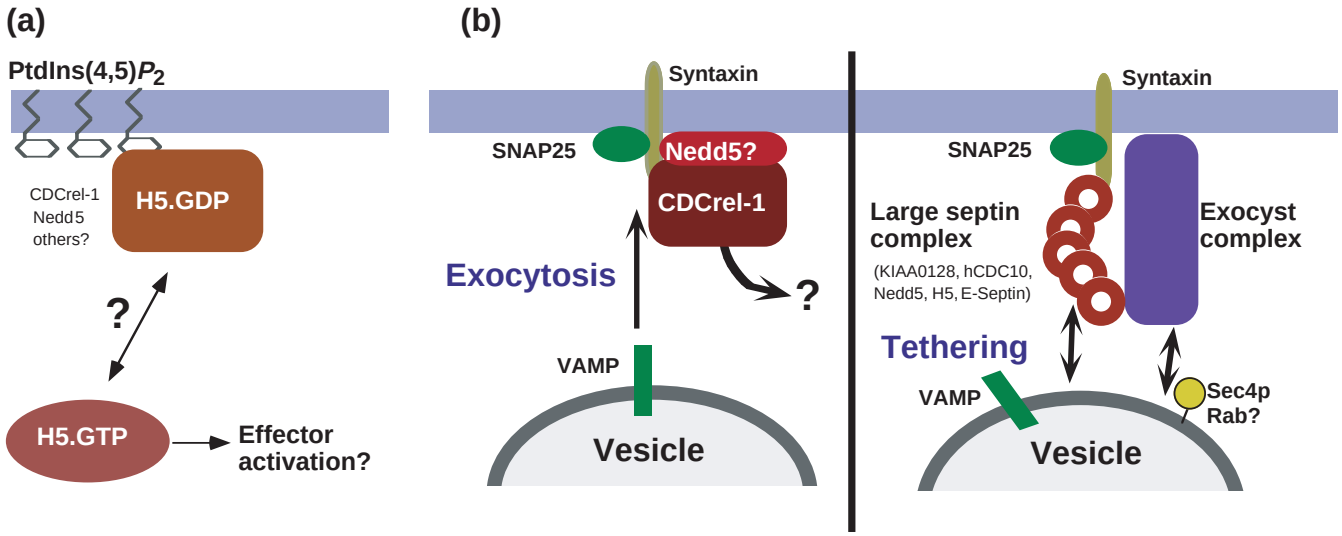

Fig. 2. Septin regulation and functions in vesicle trafficking. (a) Potential spatial regulation of septin activity by mutually exclusive binding of PtdIns(4,5)P_2 and GTP to septins. (b) Alternative models for septin function in exocytosis. Left panel: CDCrel-1 blocks vesicle fusion by binding to syntaxin and thus inhibiting SNARE interactions. Right panel: the large septin complex helps to tether vesicles to sites of exocytosis that have been marked by the exocyst complex.

Hsu et al., 1996) and may be involved in vesicle targeting or tethering, and (2) syntaxin (Beites et al., 1999), a SNARE protein predominantly present on the plasma membrane that is essential for membrane fusion.

Hsu et al. initially isolated a large septin complex consisting of KIAA0128, hCDC10, Nedd5, H5 and E-Septin by co-immunoprecipitation with Sec8 (Hsu et al., 1998), a component of the multi-subunit exocyst complex. In yeast, subunits of the exocyst complex are essential for post-Golgi transport (Finger and Novick, 1998; Guo et al., 2000). In rat brain, the exocyst complex seems to play a role in synaptogenesis by accumulating or retaining vesicles at active zones (Hazuka et al., 1999; Hsu et al., 1999). Exocyst immunoreactivity localises to sites of immature Golgi-derived vesicles along the axon in developing neurons. Once stable synaptic sites are formed, this localization is lost (Hazuka et al., 1999). The interaction and partial co-localization of septins and the exocyst complex in rat brain (Hsu et al., 1998) suggest that the large septin complex helps tether vesicles to specialized regions of the plasma membrane that have been marked to receive synaptic vesicles by the exocyst complex (Hsu et al., 1998; Hsu et al., 1999). However, the large septin complex might not localize exclusively to presynaptic sites, because one of its subunits, hCDC10, is also present in postsynaptic density fractions (Walikonis et al., 2000), whereas localization of the exocyst to postsynaptic sites has not been reported.

The second known interaction partner of mammalian septins is the SNARE protein syntaxin. SNARE proteins are essential for the fusion of vesicles with the plasma membrane (Söllner et al., 1993). Vesicle-resident SNAREs tightly interact with plasma membrane SNAREs prior to the final membrane-fusion event. This interaction has to be carefully controlled to avoid unwanted fusion events. Two septins, CDCrel-1 and Nedd5, directly interact with syntaxin, and all three proteins can be precipitated as a single complex (Beites et al., 1999). This interaction could be important for the regulation of fusion events: proteins that bind to individual SNARE proteins, such as these septins, are interesting candidates that might regulate SNARE protein interactions and thereby membrane fusion events. However, at least in the case of Nedd5, interaction with the plasma-membrane-resident SNARE syntaxin may not be its sole function. As mentioned above, Nedd5 is also a component of the large septin complex that interacts with the exocyst complex. Nedd5 therefore appears to form alternative complexes with either set of protein partners, which presumably is governed by as-yet-unknown factors.

Although the majority of CDCrel-1 co-fractionates with synaptic vesicle proteins rather than with the plasma membrane fraction (Caltagarone et al., 1998), the majority of syntaxin is present at the plasma membrane. It thus remains to be shown to which pool of syntaxin – vesicle or plasma membrane – CDCrel-1 binds, although an interaction at the plasma membrane seems favourable, since the interaction of CDCrel-1 with syntaxin appears to play a direct role in regulating exocytosis (Beites et al., 1999). Overexpression of CDCrel-1 inhibits exocytosis from insulin-secreting cells almost completely (Beites et al., 1999). Interestingly overexpression of a dominant negative mutant of CDCrel-1 (CDCrel S58N), which is equivalent to the S17N mutation of Ras (Polakis and McCormick, 1993), enhances exocytosis. Co-expression of tetanus toxin light chain, a treatment known to cleave syntaxin and prevent SNARE complex formation, abolishes this enhancement (Beites et al., 1999). The region of syntaxin that binds to CDCrel-1 is the same C-terminal region that is otherwise engaged in interactions with two other SNARE proteins, SNAP-25 and synaptobrevin (Beites et al., 1999; Fig. 2B). The binding of CDCrel-1 to syntaxin could determine the availability of syntaxin for SNARE complex formation and consequently for membrane fusion. The mechanism underlying the effects on exocytosis of wild-type or dominant negative CDCrel-1 is not known. However, the ability of another septin (Nedd5) to assemble into filament-like structures is inhibited by overexpression of the Nedd5 S51N mutant (Kinoshita et al., 1997), a mutant similar to the CDCrel-1 mutant used by Beites et al. (Beites et al., 1999). Septins might therefore tether vesicles to the plasma membrane through their ability to form filaments. The binding of septins to syntaxin might also prevent syntaxin from interacting with the other SNARE proteins; this process could be controlled by the GTPase activity of the septins (Fig. 2B). Thus, currently, evidence exists for a dual role of septins in exocytosis: as potential regulators of SNARE protein interactions and thereby membrane fusion events, and as additional tethering or targeting proteins that interact with the exocyst complex during the transport of vesicles to sites of membrane fusion at the plasma membrane. The question of whether these functions are carried out by different septin members and of what roles the state of the bound guanine nucleotide or PtdIns(4,5)P_2 play, remain interesting areas of future investigation.

A role for septins in oncogenesis?

Repeatedly, some septins have been identified as in-frame fusions with parts of the so-called MLL (mixed lineage leukaemia or also called acute lymphocytic leukaemia 1 (ALL1)) protein. De novo leukaemias in children and therapy-related acute leukemias in patients who were previously treated with topoisomerase II inhibitors frequently show chromosomal rearrangements of the MLL coding region with target regions on other chromosomes (Felix et al., 1995). Two septins, CDCrel-1 and MSF (MLL-septin-like fusion protein), are among the targets for MLL fusions (Megonigal et al., 1998; Taki et al., 1999; Osaka et al., 1999). MSF is a putative septin that was cloned as a partner gene for MLL. The predicted protein is highly homologous to CDCrel-1. Northern blot analysis revealed three transcripts for MSF, two of which are ubiquitously expressed and one of which is specific to hematopoietic tissues. The partner protein of CDCrel-1 and MSF for these chromosomal rearrangements, MLL, is a DNA-binding protein that is believed to be the human homologue of the Trithorax gene product, which is involved in segment determination in *Drosophila* (Ziemin-van der Poel et al., 1991). The MLL/septin fusion proteins contain the N-terminus of MLL, including the DNA-binding regions, and almost the entire septin protein except for a few N-terminal residues (Osaka et al., 1999). Neither the localization nor the function of the MLL-septin fusion proteins is clear. However, mouse knock-in models provide strong evidence for the idea that the fusion partners of MLL themselves play an important role in the generation of leukaemias (Corral et al., 1996). When a fusion oncogene of MLL with different marker genes was

introduced in mice, only mice that produced a fusion of MLL and one of its known partner genes developed leukaemia (Corral et al., 1996). Furthermore, the chromosomal region in which the gene encoding MSF is located is deleted in some ovarian and mammary tumours (Kalikin et al., 2000). Because this region contains an as-yet-unidentified tumour suppressor gene, MSF itself could be such a tumour suppressor (Kalikin et al., 2000).

At this point, all hypotheses regarding the roles of septins in oncogenesis remain speculative. However, recent findings in yeast have revealed a connection between the regulation of mitosis and septins (Barral et al., 1999; Shulewitz et al., 1999; Longtine et al., 2000). In budding yeast, septins can function in a morphogenetic checkpoint pathway by controlling the activity of the Nim1-related kinase Hsl1p, an upstream regulator of a kinase cascade that controls entry of cells into mitosis. The activity of Hsl1p strictly depends on proper septin localisation; cytokinesis is therefore delayed in septin mutants, which results in abberantly growing cells (Barral et al., 1999; Shulewitz et al., 1999; Longtine et al., 2000). Given that homologues of Nim1-related kinases are present in mammals, an orthologous control mechanism through which a septin-dependent checkpoint controls mitosis and thus oncogenesis may exist in mammals.

Septins, a final frontier?

Despite the first discovery of septin mutants over three decades ago, the seemingly pleiotropic functions attributed to the septins have raised more questions than answers. Barral et al. have now suggested yet another way of thinking about the mechanisms of septin function in yeast, which could also apply to their functions in other organisms (Barral et al., 2000). This is based on the finding that septin mutants cannot maintain the distinct distribution of cortical protein factors required for ordered cell growth and vesicle delivery (Barral et al., 2000). The authors suggest that the septin complex provides a way to compartmentalize the cell cortex, because proteins that are required for morphogenesis (e.g. components of the bud emergence machinery, such as Cdc42p and Bud6p, the exocyst complex, or Spa2p, a component of the so-called polarisome (Sheu et al., 1998)), are no longer localized exclusively to the daughter cell but also redistribute into the mother cell in septin mutants. Thus, the distinct compartmentalization of mother and daughter cells seems crucial for proper cell growth during isotropic bud growth. Furthermore, the asymmetric localization of at least one mRNA also depends on the integrity of the septin diffusion barrier (Takizawa et al., 2000). In addition, a morphogenetic checkpoint that controls the timing of entry into mitosis is activated in the mutant cells; consequently they cannot undergo cytokinesis (Barral et al., 1999; Longtine et al., 2000). Whether septins constitute a physical diffusion barrier or compartmentalize regions of the plasma membrane in some other way – for example, by establishing a certain spatially restricted lipid environment (possibly by binding and localizing PtdIns(4,5)P_2) – is left for future investigations.

Summary and perspectives

The compartmentalization of the plasma membrane into specialized regions is an important aspect of cell polarity in all cell types, ranging from the simple yeast cell to highly differentiated cell types such as epithelial cells and neurons. Septins seem to play an integral part in this process. (1) They bind to PtdIns(4,5)P_2, which is likely to be contained in specialized lipid domains within the plasma membrane (Czech, 2000). (2) They interact with components of the vesicle targeting and fusion machinery, which is essential for creating cell polarity. (3) They set up a diffusion barrier for other cytosolic components, which is required for asymmetric distribution of proteins and mRNA. In addition, their intrinsic GTPase activity is likely to control the timing of downstream events or their interaction with partner proteins. Certainly, septins seem unlikely to function solely in establishment of cell compartments, which their roles in oncogenesis or cytokinesis suggests. The diversity of expressed septin family members in most eukaryotes may help us to understand their diverse functions, and it is clear from recent findings that these proteins are key players in processes that go beyond cytokinesis.

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