Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

Fungal pathogens are platforms for discovering novel and conserved septin properties

Andrew A Bridges and Amy S Gladfelter

Septins are filament-forming GTP-binding proteins that act as scaffolds in diverse cell functions including division, polarity and membrane remodeling. In a variety of fungal pathogens, it has been observed that septins are required for virulence because cells are unable to survive or are misshapen when septins are mutated. Cell morphology is interconnected with pathogenesis and thus septin mutants displaying aberrant cell morphologies are commonly deficient in host tissue invasion. The degree to which septins orchestrate versus maintain changes in fungal cell morphology during pathogenesis remains to be determined. Aside from the importance of septins in the process of pathogenesis, animal and plant fungal pathogens display complexity in septin form, dynamics, and function not seen in *Saccharomyces cerevisiae* making these organisms important models for uncovering diversity in septin behavior. Additionally, host septins have recently been implicated in the process of *Candida albicans* invasion, motivating the need to examine host septins in fungal pathogenesis. Understanding the role of septins in the host–pathogen interaction not only illuminates pathogenesis mechanisms but importantly also expands our understanding of septin biology in general.

Addresses
Department of Biological Sciences, Dartmouth College, 78 College Street, Hanover, NH 03755, United States

Corresponding author: Gladfelter, Amy S (amy.gladfelter@dartmouth.edu)

Current Opinion in Microbiology 2014, **20**:42–48

This review comes from a themed issue on **Host-microbe interactions: fungi**

Edited by **Jay C Dunlap** and **Jean Paul Latgé**

1369-5274/$ – see front matter,

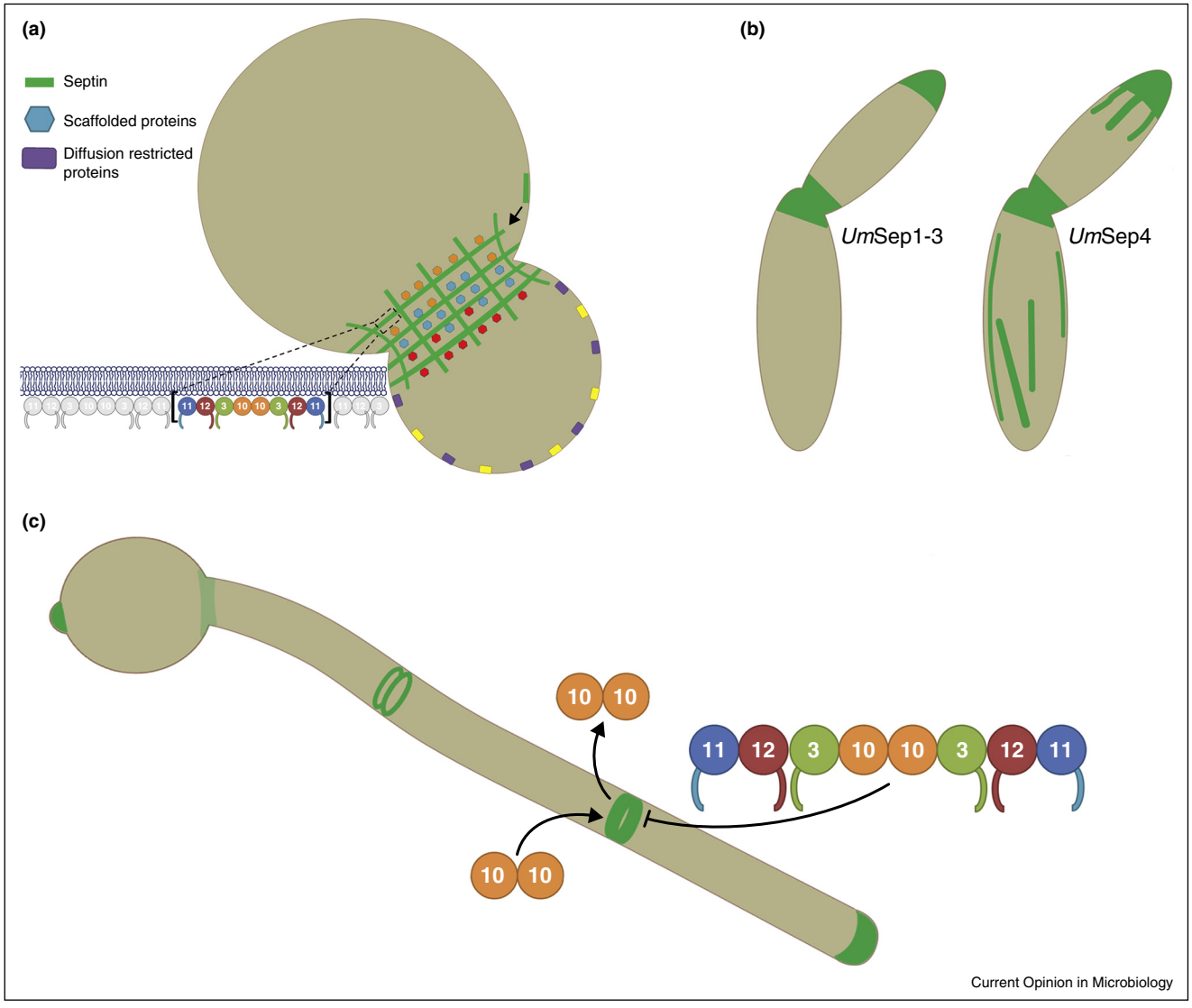
http://dx.doi.org/10.1016/j.mib.2014.04.004

How is septin function linked to assembly of filaments?

Septins are a family of filament-forming GTP-binding proteins that function in eukaryotic cell compartmentalization [1,2,3,4]. In *Saccharomyces cerevisiae*, the organism in which septins were discovered and have been most intensively studied, five mitotic septin proteins (Cdc3, Cdc10, Cdc11, Cdc12, Shs1) form an hourglass structure associated with the plasma membrane at the mother-bud neck (Figure 1a) [5,6]. At this junction they act as a scaffold for proteins involved in cell division and septation [3,7]. Additionally, both in yeast and at the base of primary cilia, higher order septin structures can compartmentalize membranes by acting as diffusion barriers [8,9,10]. Recently, septins have been also been implicated in cell functions as diverse as calcium signaling, membrane remodeling, and cell morphology [11,12,13]. Additionally, both host and microbial septins have newly emerging roles in pathogenesis that are related to cell shape and invasion of host tissues [14]. How a single class of proteins touches on such diverse cell functions remains a critical open question.

The number of septin genes varies widely between eukaryotic organisms, from two in nematodes to 13 in humans [15,16,17]. Despite this variability in number, septins have been found to assemble into soluble hetero-oligomeric rod shaped complexes, typically containing two copies of each septin protein when immunoprecipitated from different cell types (Figure 1a) [18,19,20,21]. Septins interact with one another via two interfaces, one of which is a surface created by the N-termini and C-termini that are brought into proximity when the polypeptide is folded, and the other surface is the GTP binding domain [18]. In the formation of higher order structures such as rings and hourglasses involved in cytokinesis, septin rods associate with the plasma membrane then diffuse and collide to form short filaments by end-on association, termed annealing. These short filaments subsequently merge together in the plane of the membrane to form the functional higher order structure [22]. Transmission electron microscopy and electron tomography of septin higher-order structures in *S. cerevisiae* has revealed that septin filaments may be paired and run in two orthogonal arrays, forming assemblies resembling 'gauzes' (Figure 1a) [5,6,23]. At cytokinesis, the septin hourglass rapidly rearranges, as demonstrated by fluorescence polarization microscopy and fluorescence recovery after photobleaching (FRAP), likely by a process that involves the loss of a large proportion of septins via filament fragmentation [24,25,26,27]. How the fundamental characteristics of septin complexes and filaments relate to their broad cellular functions remains to be described.

Figure 1



Septin localization and dynamics. **(a)** In *S. cerevisiae*, septins localize to the bud-neck plasma membrane in a gauze-like arrangement of filaments that act as molecular scaffolds for many proteins, some of which preferentially localize to one side of the bud-neck [4]. Septin higher-order structures assemble from palindromic rod subunits via a process involving filament annealing and once assembled are capable of restricting membrane associated proteins to one side of the cell [3,22]. **(b)** In the plant pathogen *U. maydis*, septins Sep1, Sep2, and Sep3 localize to the cell middle and at growing tips [30]. Notably, Sep4 also localizes at these sites but additionally forms fibers structures running throughout the cell, which partially colocalize with, but do not depend on, microtubules [30]. **(c)** Though all septins colocalize in *C. albicans* hyphae, their dynamics are separable. While Cdc3, Cdc11, Cdc12 and Shs1 assembled into higher order structures do not readily exchange with cytoplasmic septins as determined by FRAP, Cdc10 does. Interestingly, Cdc10, the only septin lacking a c-terminal coiled-coil domain, was found to recover after photobleaching only when Shs1 was not mutated [29].

The links between septin properties such as filament formation and functions such as scaffolding are ready to be investigated at both the molecular and biophysical level. For example, what role, if any does the GTPase cycle play in dynamic rearrangements of septin structures? Is there exchange of either rods or individual monomers within filaments? Why is a filament-forming protein that makes flexible filaments used to build scaffolds and barriers [22]? What direct interactions occur at septin assemblies and what is the molecular basis for scaffolding? Do septins restrict membrane-associated protein to specific regions of the cell by influencing membranes or by acting as a physical barrier? Functions have been ascribed mostly based on phenotypes observed upon deletion of septin genes, many of which could be indirect consequences of losing septins. Thus, many questions regarding the molecular mechanism of septin function are ripe for examination.