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Septin complexes assemble during a kinetic window of opportunity

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Septins are a family of cytoskeletal proteins that were discovered by Lee Hartwell and colleagues in the early 1970s in budding yeast based on their essential role in cytokinesis.[1] Despite the fact that they were later found to be highly conserved in the eukaryotic kingdom, and misregulation of the 13 human septin genes is associated with many debilitating diseases, basic questions about their form and function remain unanswered.[2] For perspective, a pubmed search of "septin" reveals reveals just under 1000 entries, while in contrast searches for "actin" and "microtubule," reveals >100,000, and ~65,000 respectively. Fortunately, in the last several years, numerous studies have started to begin to make substantial progress in understanding how septins tick. In yeast, it is known that 5 mitotic septin genes come together to form heteromeric rod-shaped complexes that then assemble into filaments on the plasma membrane at sites of micron-scale curvature.[2,3,4] These filaments are thought to organize into complex higher-order structures which function in cytokinesis and other critical cellular processes.[2] While numerous studies have deciphered the structure and organization of the septin rod complex, and how these complexes elongate into filaments, little is known about how the rod complex itself is assembled. In this issue, Schaefer and colleagues make their second contribution to understanding the early steps of septin complex assembly and extrapolate their results to protein oligomerization in general.[5]

Previously, the authors showed that mutant alleles of septin proteins were excluded from incorporation into complexes when a wild-type copy of the same gene was present.[6] What prevents incorporation of mutant septin proteins? Considering the precise stoichiometry and composition of septin complexes, Schafer and colleagues use mathematical modeling to explore the possibility that septin subunits are likely translated and folding during a kinetic "window of opportunity." In their model, if a mutant septin allele folds more slowly than wild type, it will miss any chance of incorporation into heteromeric complexes. To test this idea, the authors show experimentally that mutant cdc3 *(G365R)* is incorporated into the higher-order structure at the bud-neck more slowly than the WT protein. Next, the authors argue that changing the duration of the "window of opportunity" should alter the amount of folded mutant protein competent for inclusion into septin complexes. The authors elongate G1 by limiting nitrogen and find that *cdc3 (G365R)* cells actually grow faster and display less extreme morphology defects than cells of the same genotype in rich media. This result suggests that elongating G1 at least partially rescues mutant septin defects, likely by extending the amount of time allowed for septin folding. If this is true, the authors argue that shortening G1 should exacerbate mutant septin phenotypes. Indeed, when the length of G1 was reduced, it was found that *cdc3 (G365R)* cells were even more elongated and grew significantly slower than cells with normal G1 duration. Taken together, this work argues that septin complex assembly occurs in a temporally limited manner, and opens up many interesting avenues of work including biophysical characterization of septin protein folding and analysis of translation timing and localization.

Another recent study showed that septins are co-translated on endosomes traveling toward sites of growth in the pathogenic fungus *Ustilago maydis*.[7] Together, these 2 pieces of work further demonstrate how central septin heterooligomerization is to function. Septins are effectively born as a complex and likely remain that way until they are degraded. How does complex assembly work in more complicated systems? Considering that humans have 13 septin genes and multiple splice variants, the combinatorial possibilities of protein composition in septin complexes is enormous. Does the timing and spatial distribution of translation dictate the composition of these subunits? Although we are far from understanding complex assembly at this level of complexity, this work by Schafer and colleagues is a major advance and demonstrates, on a broader level, how simple kinetic differences can dictate the composition of protein oligomers.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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