Mini-Review

Dynamin and FtsZ: Missing Links in Mitochondrial and Bacterial Division

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FtsZ forms the cytoskeletal framework of the cytokinetic ring in bacteria, and appears to play the major role in constriction of the furrow at septation. Until recently, FtsZ had been found in every eubacterium and archaebacterium, and was thought to be the major and essential component of the division machine (Erickson, 1997). FtsZ has also been found in chloroplasts (Osteryoung et al., 1998), which was expected since these plastids originated from bacterial ancestors. An apparent missing link was that FtsZ was absent from mitochondria, which are also of prokaryotic origin. There is no FtsZ in the completed genomes of *Saccharomyces cerevisiae* and *Caenorhabditis elegans*, and none in the extensive EST databases from human and animals. Now the mystery of mitochondrial cell division seems well on its way to resolution: most mitochondria have replaced FtsZ with dynamin for division. An important missing link is the recent discovery by Beech et al. (2000), of a mitochondrion that still uses FtsZ. But even as the division of mitochondria is being resolved, a new paradox has appeared, as several prokaryotes have now been discovered to have no FtsZ.

Chloroplasts Use FtsZ for Division

Chloroplasts appear to have conserved the bacterial division machine, with an interesting new twist (described below). Two *ftsZ* genes have been discovered in *Arabidopsis*, both encoded at genomic loci. One of these, *ftsz1*, has a signal peptide that transports it into the chloroplast. The other, *ftsz2*, does not, remaining on the cytoplasmic side of the chloroplast (Osteryoung et al., 1998). Antisense experiments showed that both *ftsZ* genes are essential for chloroplast division in *Arabidopsis* (Osteryoung et al., 1998). A homologue of *ftsz2* was discovered in the moss *Physcomitrella*, and chloroplast division was completely blocked when the gene was knocked out (Strepp et al., 1998). There are now several chloroplast *ftsZ* genes, which all show closest similarity to those of cyanobacteria, from which chloroplasts were derived (Osteryoung et al., 1998; Beech et al., 2000). Chloroplasts have also retained other bacterial division genes, including *ftsI*, *ftsW*, *minC*, and *minD* (Turmel et al., 1999).

Most Mitochondria Use Dynamin for Division

The apparent absence of FtsZ in mitochondria raises two questions: where in the evolution of eukaryotes did mitochondria lose their FtsZ, and how do they now divide? The second question has seen great progress in the past year. Two laboratories, working from different directions, have found that *S. cerevisiae* Dnm1, a dynamin-related protein, is responsible for division of mitochondria (Bleazard et al., 1999; Sesaki and Jensen, 1999). In *dnm1* mutant cells, the mitochondria coalesce to form a net of interconnected tubules. The Dnm1 protein has no mitochondrial import sequence, and was localized to the outside surface of the mitochondria, primarily at sites of constriction or at the tips of mitochondria that may have recently divided. A comprehensive study in *C. elegans* showed similar mitochondrial disruptions for mutations in DRP-1 (Labrousse et al., 1999). A gene knockout of *dynA* in *Dictyostelium* blocked division of mitochondria, and also had pleiotropic effects on cytokinesis and nuclear and endosomal morphology (Wienke et al., 1999). The human dynamin-related protein, Drp1/DLP1, seems to be essential for mitochondrial division, and may affect other membrane processes (Smirnova et al., 1998; Pitts et al., 1999). There are multiple dynamins in most species. The dynamins identified above may be orthologs, but they have some important differences in phenotype. Some of them appear to operate primarily on mitochondria, while others affect additional membrane systems. In addition, other dynamin-like proteins are known that affect mitochondrial morphology. Regardless of this complexity, the function of dynamin in mitochondrial division appears to be widespread in eukaryotes.

The two laboratories working on yeast both made the fascinating discovery that another gene, *fzo1* (not a dynamin homologue), works antagonistically to *dnm1*, by causing the fusion of mitochondria (Bleazard et al., 1999; Sesaki and Jensen, 1999). Thus, in the absence of *dnm1*, fusion dominates and mitochondria coalesce into a network. In the absence of *fzo1*, there is no fusion and mitochondria divide into small fragments. Remarkably, a double mutant of both *dnm1* and *fzo1* has largely normal mitochondrial morphology. These two genes operating together generate a balance of division and fusion, creating a dynamic mitochondrial network (Bleazard et al., 1999; Sesaki and Jensen, 1999; Yaffe, 1999).

Pulling from the Inside, Squeezing from the Outside

In bacteria, the ring of FtsZ on the inner membrane is thought to constrict and pull the membrane inward. In

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chloroplasts, FtsZ1 seems to play the same role, constricting the chloroplast membrane from within. However, there is a new twist, as FtsZ2 is on the outside of the mitochondrion. In this position it would appear to be squeezing or pinching the division furrow from the outside. Dnm1 appears to function like the FtsZ2, squeezing or pinching from the outside. This is similar to how dynamin works in endocytosis, where it forms rings or helices around membrane protrusions and pinches off vesicles. A remarkable observation in *C. elegans* was that division of the inner mitochondrial compartment continued when DRP-1 mutants blocked division of the outer membrane (Labrousse et al., 1999). This suggests that a dual division mechanism, squeezing from the outside and constricting from the inside, may operate in both mitochondria and chloroplasts.

The Missing Link: A Mitochondrion that Uses FtsZ

The bacterial ancestor of mitochondria must have used FtsZ for division, but animal cells and yeast appear to have replaced FtsZ with dynamin. Are their any eukaryotes that still use FtsZ for mitochondrial division? The answer is yes, and Beech and colleagues (2000) have now discovered this missing link. The golden-brown alga *Mallomonas splendens* has a genomic *ftsZ* most closely related to *ftsZ* of α-proteobacteria, the ancestors of the mitochondrion. The FtsZ protein is located in patches on the mitochondrial membrane, near the center or at the ends of mitochondria, similar to the location of Dnm1. This FtsZ is translocated into the mitochondria, and therefore appears to operate by constriction from within. It was even able to modulate the structure of yeast mitochondria when expressed transgenically in *S. cerevisiae*, a remarkable observation since yeast doesn't use or express FtsZ.

This discovery should spur a search for FtsZ in other mitochondria. A spectrum of eukaryotes may be found, some using FtsZ, some using dynamin, and perhaps some using both, for mitochondrial division. Beyond the question of mitochondrial division, the spectrum of FtsZ- and dynamin-based mechanisms should provide a new tool for looking at the evolution of eukaryotes (Martin, 2000).

The mechanism by which FtsZ and dynamin operate in division is not known, but an intriguing observation is that both form rings or spirals (Fig. 1). Dynamin spirals form at the neck of endocytic vesicles, and the vesicles may be pinched off by constriction (Sweitzer and Hinshaw, 1998) or by a change in the helical pitch (Stowell et al., 1999). An alternative proposal is that dynamin may be a signaling molecule, recruiting another, force-generating molecule to the complex (Sever et al., 1999). FtsZ may power constriction by switching from a mostly straight protofilament to a curved conformation (Lu et al., 2000).

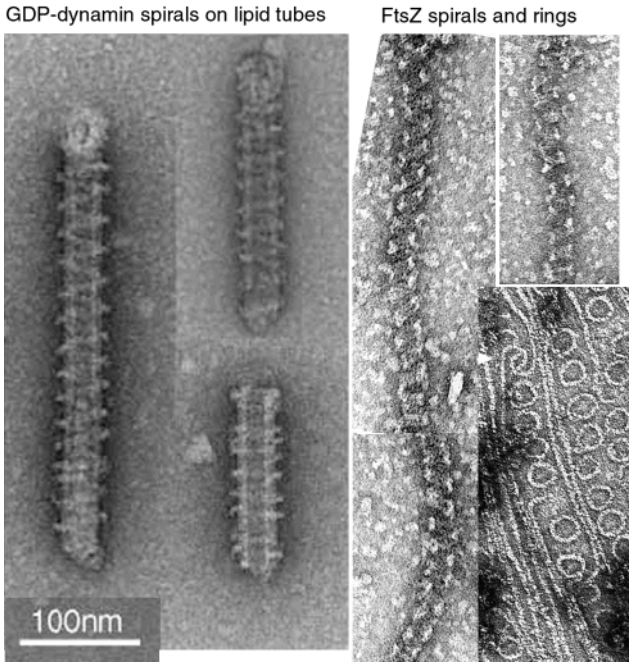

Figure 1. Rings and spirals assembled by dynamin on the left (Stowell et al., 1999), and FtsZ on the right (Lu et al., 2000; Erickson et al., 1996). The dynamin spirals are ~50-nm diameter, and FtsZ is ~23-nm diam.

The New Paradox: Prokaryotes with No FtsZ

Just as the missing link of mitochondrial FtsZ is falling into place, a new paradox has appeared. Until recently it seemed a simple story that all eubacteria and archaea used FtsZ for cell division. Last year the genomic sequences of two *Chlamydia* species showed a surprising absence of FtsZ (Stephens et al., 1998; Kalman et al., 1999). However, these bacteria are obligate parasites that live in membrane-bound inclusions in their host cells. One possibility is that they may use the host cell's machinery for vesicle trafficking for their own division. Consistent with this possibility, Boleti et al. (1999) found that a dominant negative dynamin transfection inhibited the proliferation of *Chlamydia.* But an intriguing study by Brown and Rockey (2000) demonstrated sharp localization of an antigen, perhaps a peptidoglycan, at the cleavage furrows of *Chlamydia.* This implies that the bacteria play some active role in the division process, and may divide independently of the host.

Even more puzzling is the recent discovery of two free-living prokaryotes with no FtsZ. *Aeropyrum pernix* is an archeon that lives at 90°C in ocean thermal vents. The cells from laboratory culture are irregular cocci with some sharp edges, ~1 μm in diameter (Sako et al., 1996). Clearly, they must have some efficient system for division to maintain this size and shape. Yet the genomic sequence shows no *ftsZ*, nor any other known cell division protein (Kawarabayasi et al., 1999). Just as surprising, the genome of *Ureaplasma urealyticum* has no *ftsZ* (Glass and Lefkowitz, http://genome.microbio.uab.edu). This is a mycoplasma that lives primarily in its host, but can be cultured in defined medium, so it must have a mechanism for cell division. These two examples, and perhaps *Chlamydia*, suggest the possibility of a completely novel mechanism for bacterial cell division, still to be discovered.

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