1072
doi:10.1017/S1431927610055480
Microsc. Microanal. 16 (Suppl 2), 2010
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Dynamin Family members and their Role in Membrane Remodeling

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Dynamin, a 100 kDa GTPase, is involved in the final stages of fission during clathrin-mediated endocytosis in all cell types including synaptic membrane retrieval in neurons [1]. Other dynamin family members are involved in organelle division, such as the dynamin-related protein, Drp1, that is required for mitochondrial fission. During membrane fission, dynamin family members are believed to self-assemble into short helices around sites of constriction and drive fission upon GTP hydrolysis. In support of this model, both purified dynamin and the yeast Drp1 (Dnm1) readily form protein-lipid tubes, which further constrict the membrane upon GTP addition [2,3]. However, the dimensions of the protein assemblies and the extent of constriction is tailored to the proteins function. Dynamin forms helices with a diameter of 50 nm , which is ideal for wrapping around the necks of budding vesicles, and constricts the membrane by 10 nm (outer diameter of 50 nm to 40 nm). Dnm1 assembles into significantly larger helices with an outer diameter of ~110 nm, which exactly matches mitochondrial constricted sites observed in vivo [4], and constricts the membrane by 60 nm (110 nm to 50 nm). To further understand the mechanism of constriction, we solved the 3D structure of both dynamin [5] and Dnm1 by cryo-electron microscopy and Iterative Helical Real Space Reconstruction (IHRSR) methods. The structures reveal differences in their architecture that lead to slight variations in the mechanism of constriction. The 3D maps of dynamin in the constricted and non-constricted states revealed a twisting motion between subunits that suggests a corkscrew model for dynamin constriction. The 3D map of Dnm1-lipid tubes revealed a 2-start helix, instead of a 1-start helix observed for dynamin, and lacked a direct interaction with the lipid bilayer, which correlates with the absence of a pleckstrin homology domain in Dnm1. Overall, the Dnm1 features allows for a more flexible helix, a characteristic that may be necessary for the large conformational change required for organelle division. In summary, these results suggest that although dynamin family members share common mechanochemical properties, the structure of each member varies to fit their unique function.

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https://doi.org/10.1017/S1431927610055480 Published online by Cambridge University Press

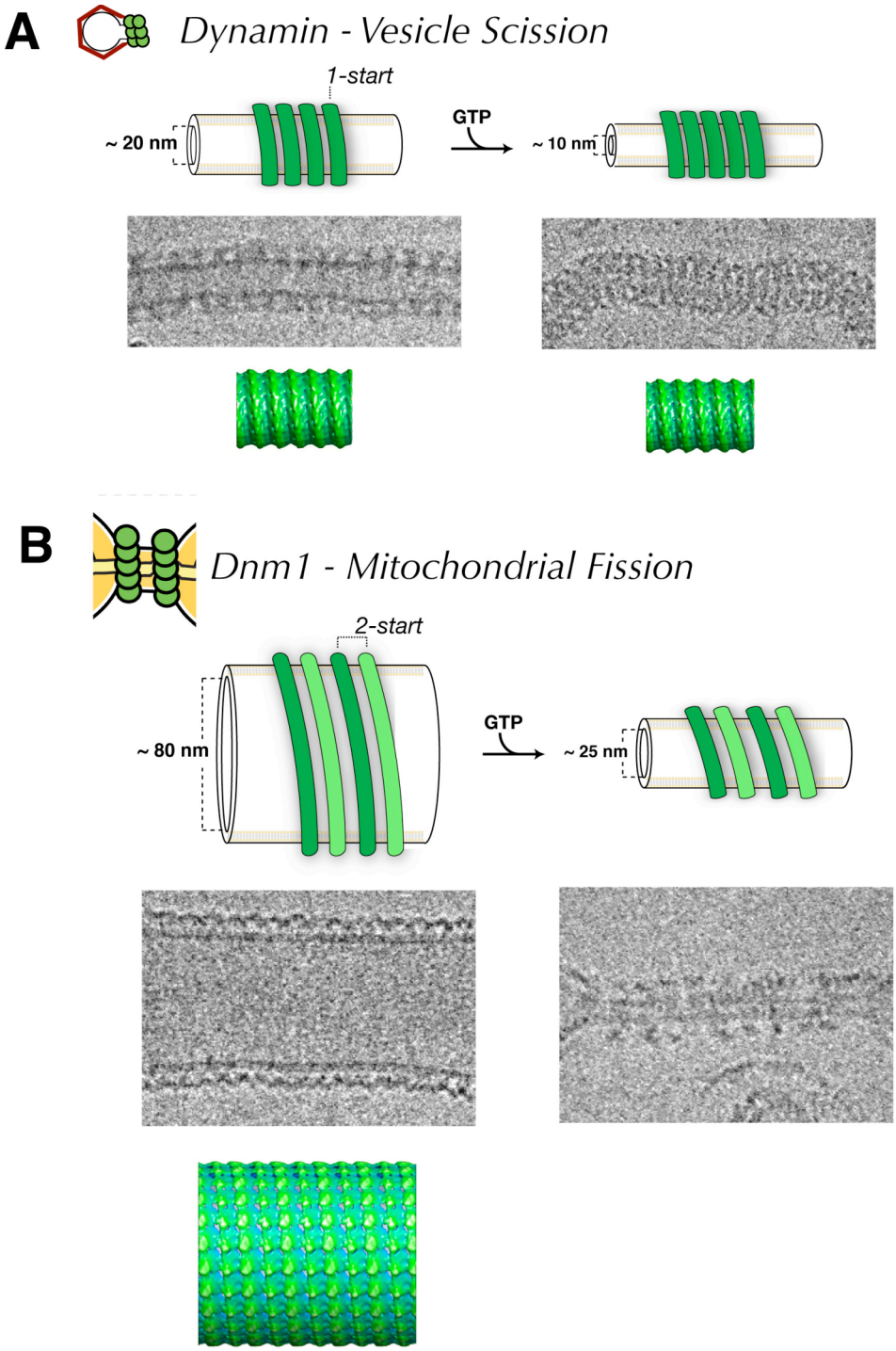

Figure 1. Dynamin family members are involved in membrane fission events during endoytosis (A) and mitochondria division (B). **A**. Schematic diagram of the role of dynamin during membrane fission, cryo-EMs and 3D maps before and after GTP addition. **B.** Schematic diagram of the role of Dnm1 during mitochondria division, cryo-EMs and a 3D map of Dnm1 in the non-constricted state.

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