A Class of Membrane Proteins Shaping the Tubular Endoplasmic Reticulum

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SUMMARY

How is the characteristic shape of a membrane bound organelle achieved? We have used an in vitro system to address the mechanism by which the tubular network of the endoplasmic reticulum (ER) is generated and maintained. Based on the inhibitory effect of sulfhydryl reagents and antibodies, network formation in vitro requires the integral membrane protein Rtn4a/NogoA, a member of the ubiquitous reticulon family. Both in yeast and mammalian cells, the reticulons are largely restricted to the tubular ER and are excluded from the continuous sheets of the nuclear envelope and peripheral ER. Upon overexpression, the reticulons form tubular membrane structures. The reticulons interact with DP1/Yop1p, a conserved integral membrane protein that also localizes to the tubular ER. These proteins share an unusual hairpin topology in the membrane. The simultaneous absence of the reticulons and Yop1p in S. cerevisiae results in disrupted tubular ER. We propose that these “morphogenic” proteins partition into and stabilize highly curved ER membrane tubules.

INTRODUCTION

Many organelles have characteristic shapes that often deviate significantly from spheres, likely the energetically most stable form of a membrane bound object. An example is the endoplasmic reticulum (ER), which consists of two major, differently shaped domains: the nuclear envelope (NE) and the peripheral ER (Baumann and Walz, 2001; Du et al., 2004; Voeltz et al., 2002). The NE consists of two continuous sheets of membranes, the inner and outer nuclear membrane, connected to one another at nuclear pores. The approximately spherical shape of the NE is stabilized by interactions between inner nuclear membrane proteins and the underlying chromatin and—in higher eukaryotes—the nuclear lamina (Holmer and Worman, 2001). The peripheral ER consists of a network of membrane tubules connected by three-way junctions. It also contains membrane sheets (cisternae), particularly close to the nucleus, which are prominent in secretory cells (Baumann and Walz, 2001). In mammalian cells, the peripheral ER extends from the NE throughout the entire cell, while in S. cerevisiae, it is located beneath the plasma membrane, linked by a few tubules to the NE (Prinz et al., 2000). The entire ER is a continuous membrane system enclosing a single luminal space.

The mechanism by which the tubular ER is generated and maintained is unclear. One idea is that membrane tubules are generated by being pulled out by molecular motors as they move along microtubule or actin filaments or by the tips of filaments as these grow by polymerization (for review, see Du et al., 2004). Although the cytoskeleton is indeed required for dynamic movements of the ER network, the alignment of membrane tubules with microtubules in mammalian cells and with actin in plants and yeast is not perfect (Prinz et al., 2000; Staehelin, 1997; Terasaki et al., 1988), and the network only retracts slowly upon depolymerization of microtubules (Terasaki et al., 1986). Thus, the cytoskeleton does not seem to be essential to maintain ER tubules. In addition, when ER networks are formed in vitro from small vesicles, an intact microtubule or actin network is not required (Dreier and Rapoport, 2000). Other models of ER network formation and maintenance postulate the existence of abundant scaffolding proteins inside or outside of the ER or the regulation of internal ER volume by ion pumps and water flow restriction (Voeltz et al., 2002). However, scaffolds are not obvious in electron microscopy pictures and would be difficult to reconcile with the dynamic nature of the ER tubules, and the ER membrane is permeable to small molecules (Le Gall et al., 2004). Perhaps the most plausible models for tubule formation and maintenance are based on mechanisms that generate or stabilize high curvature in membranes. For example, the high curvature in cross-sections of the tubules could be generated if the two leaflets of a membrane had different lipid compositions (for review, see Farsad and De Camilli, 2003; Sprong et al., 2001). Proteins would be required to keep the lipid imbalance or to create curvature on their own.