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Role of endoplasmic reticulum domains in determining secretion routes

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Abstract

Distinct domains of the endoplasmic reticulum (ER) can function as entry points into different protein-sorting routes. In addition to using the classical ER-Golgi pathway, one of these unconventional routes utilizes different combinations of machinery of the classical secretory pathway and components of the autophagosomal system.

Introduction and context

Secretion of membrane proteins and the majority of soluble proteins involves translocation through or into the membrane of the endoplasmic reticulum (ER), followed by exportation via coat protein complex II (COPII)-coated vesicles [1]. In yeast, these vesicles exit the ER at evenly distributed sites and fuse directly with dispersed Golgi units. Higher eukaryotes employ the same core machinery for transport but produce spatially organized ER exit sites. COPII vesicles and recycling COPI vesicles form tubular structures that deliver cargo to a centralized Golgi apparatus. In addition to this well-conserved function of the ER as an entry point into the classical secretory pathway, specialized ER domains may function as entry points into more unconventional secretion routes. We are at the beginning of a mechanistic understanding of these alternative transport routes.

Major recent advances

Most metazoan cell types contain cortical ER domains, which are aligned with the plasma membrane. Ultra-structural analysis in HeLa cells has revealed the presence of cortical ER – thin, ribosome-free structures – and precortical ER [2]. Upon ER calcium depletion, these cortical ER domains form ER-plasma membrane contacts, which function in store-operated calcium entry (SOCE). This signaling process depends on the function of calcium sensors in the ER lumen: the ER-located type I membrane proteins STIM1 (stromal interaction molecule 1) and STIM2 [3]. Recruitment of STIMs to membrane contacts during store depletion involves a dual-targeting mechanism with recognition of phosphatidylinositol phosphate (PIP) species at the cytosolic face of the plasma membrane [4-6] and interaction with the calcium channel in the plasma membrane [7,8]. Transient interaction of STIM1 with growing microtubule tips contributes to cortical localization but this process is not required for SOCE [9].

Recognition of PIPs at the cytosolic face of the plasma membrane by integral ER membrane proteins is a conserved mechanism in ER-plasma membrane contact formation. The accumulation of the polytopic yeast membrane protein Ist2 at cortical ER depends on a basic sorting signal that recognizes $PI(4,5)P_2$ [10,11]. A similar mechanism results in the accumulation of Ist2 at cortical ER domains in mammalian cells and this leads to a large extension of this organelle [5,12]. Formation of cortical ER and accumulation of proteins at cortical ER in mammalian cells depend on COPI and microtubules [12], suggesting that coatomer and its interaction with microtubules play a role in the clustering of proteins in domains of ER membranes. Further studies are necessary in order to

determine the role of coatomer in the formation of cortical ER, and it remains an open question whether coatomer function contributes to the formation of the abundant cortical ER in yeast as well.

It has recently been proposed that cortical ER domains may function as entry points into unconventional secretion routes. We have suggested that yeast Ist2 travels directly from cortical ER to the plasma membrane [13,14], but it remains to be solved whether Ist2 indeed reaches the plasma membrane or whether the protein resides completely in plasma membrane-associated cortical ER. Moreover, this postulated unconventional secretion route is not conserved. Expression of Ist2 in mammalian cells leads to the induction of cortical ER [5,12], but it has been shown that the protein does not reach the cell surface [5]. However, vesicles that bud off from the cortical ER may bypass the central Golgi in order to reach the neighboring plasma membrane. Such a pathway may play a role in neurons, where the ER forms subsurface cisternae in the soma and extends into dendrites and the axon. This close association between ER and plasma membrane regulates a number of neuronal signaling processes [15] and may play a role in unconventional secretion of locally synthesized proteins. Dendrites contain Golgi outposts that are required for dendritic growth [16] but axons lack these structures. Therefore, in axons, locally translated proteins may travel directly from ER domains to the plasma membrane, bypassing Golgi.

A complete bypass of the Golgi has been described for the secretion of α-integrins in *Drosophila* during epithelial cell remodeling [17]. This and other transport routes depend on Golgi reassembly stacking protein (GRASP). Deletion of the GRASP homologue GrhA in *Dictyostelium discoideum* abolishes unconventional secretion of soluble acyl-coenzyme A-binding protein (ACBP) [18], and ACBP-containing vesicles accumulate at the cell cortex with no docking or fusion with the plasma membrane [19]. In α-integrin and ACBP secretion, GRASP functions as a cortical organizer of trafficking routes [17,18,20,21].

ACBP is a highly conserved small (10 kDa) protein that binds long-chain acyl-CoA esters with very high affinity and this interaction plays a role in the transport of these molecules [22,23]. Recent work employing an elegant bioassay revealed the first mechanistic insights into unconventional secretion of ACBP [20,21]. The morphological development of slime mold depends on the secretion and proteolytic processing of small amounts of the cellular ACBPs [24], and a secreted Acb1 protein fraction from starved yeast cells was sufficient to induce encapsulation of *D. discoideum* [20,21]. This secretion of ACBPs requires the function of autophagosomes [20,21], which otherwise mediate the degradation of cytosolic content in response to environmental changes (e.g., starvation). Instead of fusing with the lysosome/vacuole, the ACBP-containing autophagosomes are re-routed to the plasma membrane [20,21]. This unconventional secretion occurs independently of the function of many steps of the classical secretory pathway [20] but requires Sec18/NSF, the plasma membrane SNARE Sso1 [20], fatty acyl-CoA generated by peroxisomes [21], multivesicular bodies (MVBs) and the endosomal compartment but not transport from endosomes to vacuoles [20]. ACBPs containing autophagosomes may fuse first with endosomes or MVBs en route to the plasma membrane [20]. However, the precise function of endosomes and MVBs in unconventional secretion of ACBPs remains an open question.

Future directions

Two exciting questions are how autophagosome-like vesicles specifically recruit ACBPs and where this branch of autophagosome formation occurs. Since ACBPs localize in a ligand-dependent manner to the ER [25], the loaded long-chain acyl-CoA ester may organize ACBP loading and autophagosome formation. This is consistent with the requirement of long-chain acyl-CoA production for unconventional ACBP secretion [21]. The second question addresses the source of the donor membrane for this autophagosome generation. This remains a matter of debate in the autophagy field [26], but it has been suggested that mammalian phagosomes originate from an ER-associated location enriched in PI(3)P [27] and that PI3-kinase and PI3-phosphatase activities determine autophagy initiation [28,29]. Electron tomographic analyses support the idea of a direct connection between ER and growing phagosomes [30,31]. Specific PIPs at ER domains in cis and trans may recruit machinery that allows secretion by different mechanisms. Given the high degree of conservation between ACBPs in different species, it is conceivable that human ACBPs use a similar unconventional route to the extracellular space.

Abbreviations

ACBP, acyl-coenzyme A-binding protein; CoA, coenzyme A; COP, coat protein complex; ER, endoplasmic reticulum; GRASP, Golgi reassembly stacking protein; MVB, multivesicular body; NSF, *N*-ethylmaleimide-sensitive factor; PIP, phosphatidylinositol phosphate; SNARE, soluble NSF attachment protein receptor; SOCE, store-operated calcium entry; STIM, stromal interaction molecule.

Competing interests

The author declares that he has no competing interests.

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