COPII with ALG2 and ESCRTs control lysosome-dependent microautophagy of ER exit sites

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ER exit sites (ERESs) are tubular outgrowths of endoplasmic reticulum (ER) that serve as the earliest station for protein sorting and export into the secretory pathway. How these structures respond to different cellular conditions remains unclear. Here, we report that ERESs undergo lysosome-dependent microautophagy when Ca^{2+} is released by lysosomes in response to nutrient stressors such as mTOR inhibition or amino acid starvation. The pathway occurred downstream of macroautophagy and involved LC3-labeled lysosomes. Once associated with such lysosomes, ERESs were encapsulated, internalized into intraluminal structures, and subsequently degraded. The mechanism underlying ERES microautophagy was ESCRT-dependent and required ubiquitinated Sec31, ALG2 and ALIX. Knockout of ALG2 or function-blocking mutations of ALIX prevented lysosomal engulfment of ERESs. ERES microautophagy could be reconstituted *in vitro* using lysosomal lipid mimicking vesicles and purified recombinant components. Together, our results describe a novel pathway involving ERESs for bulk turnover of secretory proteins under nutrient stress.