The structure and global distribution of the endoplasmic reticulum network is actively regulated by lysosomes

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KEY WORDS: Living cells imaging, Fast-SIM, machine-learning based segmentation, *in vivo* labelling, optogenetics, Endoplasmic Reticulum dynamics, multiple organelle tracking.

Abstract

The endoplasmic reticulum (ER) comprises morphologically and functionally distinct domains, sheets and interconnected tubules. These domains undergo dynamic reshaping, in response to changes in the cellular environment. However, the mechanisms behind this rapid remodeling within minutes are largely unknown. Here, we report that ER remodeling is actively driven by lysosomes, following lysosome repositioning in response to changes in nutritional status. The anchorage of lysosomes to ER growth tips is critical for ER tubule elongation and connection. We validate this causal link via the chemo- and optogenetically driven re-positioning of lysosomes, which leads to both a redistribution of the ER tubules and its global morphology. Lysosomes sense metabolic change in the cell and regulate ER tubule distribution accordingly. Dysfunction in this mechanism during axonal extension may lead to axonal growth defects. Our results demonstrate a critical role of lysosome-regulated ER dynamics and reshaping in nutrient responses and neuronal development. A range of techniques, including live-cell super-resolution imaging, machine learning-based segmentation, chemo-/optogenetic control of organelle motions, and gene silencing by RNAi have been applied in our study.

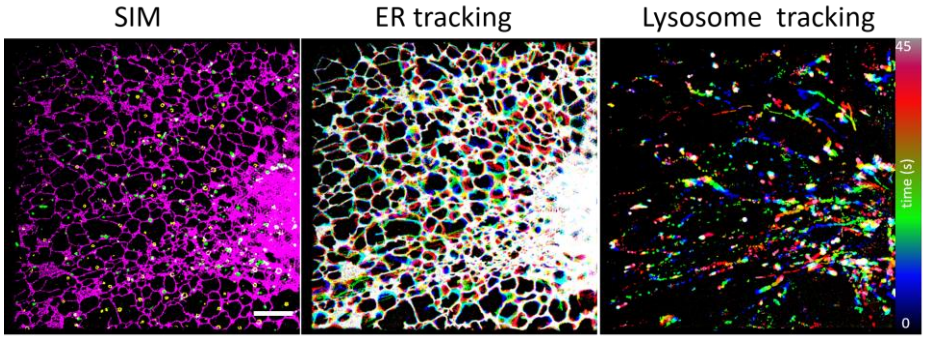

Fig. Organelle dynamics recorded by live-cell SIM.
SIM image from a time-lapse recording of a COS-7 cell expressing mApple-Sec61b-C1 (magenta), stained with SiR-lysosome (green). From second left to right: merged image of ER and lysosomes, ER tracking in the time window of 45 s, lysosome tracking in the time window of 45 s.