VAMP4 is a new factor involved in membrane remodeling of immature secretory granules during maturation

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Insulin secretory granules (ISGs) named as dense-core vesicles (DCVs), a group of distinguishing organelles in pancreatic β cells[1], are responsible for storage and secretion of insulin to maintain blood glucose homeostasis[1, 2]. Although the molecular mechanism of ISG exocytosis has been well characterized in the past few decades[3, 4], the molecular mechanism of ISG maturation is largely unknown because of its high dynamics. In this study, we focused on the vesicle-associated membrane protein 4 (VAMP4) and demonstrated that it participated in the membrane remodeling during ISG maturation. By using lattice light sheet microscopy and other live cell imaging, we identified that VAMP4 was packaged into the clathrin-coated vesicles (CCVs) budding from the immature ISGs. The VAMP4-anchored CCVs were transported to the lysosomes and underwent fusion with lysosomes facilitated by VAMP4 and other SNARE proteins, releasing unwanted ISG cargoes carried by the CCVs for degradation. We further demonstrated that VAMP4 deficiency led to the failure of insulin processing and other abnormities of ISG maturation.

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