Molecular Insights Into Rab-Dependent Tethering At Endosomal And Vacuolar Membranes

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Protein and lipid transport in the endomembrane system occurs via vesicle carriers that form at one compartment and fuse with the receiving organelle. Over the last decade, the molecular players of membrane fusion have been identified. Fusion is initiated by a contact step, where a switch-like Rab GTPase present on the vesicle binds a tethering factor on the receiving membrane. After tethering, membrane-embedded SNARE proteins on both vesicle and target membrane form a SNARE complex, and its formation is accompanied by mixing of the two membrane bilayers.

We have analyzed the fusion machinery in the endolysosomal system, in particular at the yeast vacuole. The vacuole is the final destination of several trafficking pathways, and is particularly important for the degradation of membrane proteins and membrane lipids. Its fate is also closely linked to the preceding endosome, where membrane proteins are sorted into intraluminal vesicles prior to the fusion of endosomes with lysosome. In fact, endosomes can only fuse efficiently with vacuoles once all membrane proteins that are marked for degradation have been sorted into intraluminal vesicles of the maturing endosome. We have therefore focused our attention on the machinery involved in fusion of endosomes with the vacuole, and could identify many of the involved proteins, including the required SNAREs, the HOPS tethering complex and the Rab7 nucleotide exchange factor, the Mon1-Ccz1 complex. Interestingly, many of these factors act on both vacuole and endosome.

In this presentation, I will focus on the molecular events that take place during the maturation of the endosome and will discuss our recent observations on the control of Rab GTPase activity during this process.