Membrane traffic in endosomes – how is targeting specificity achieved?

Reinhard Jahn and Seiichi Koike*

Department of Neurobiology, Max-Planck-Institute for Biophysical Chemistry, 37077 Göttingen/Germany

Present affiliation:

Intracellular membrane traffic operates by vesicles that bud from precursor organelles and are transported to their target compartment where they dock and fuse. Targeting requires tethering factors recruited by small GTPases and phosphoinositides whereas fusion is carried out by SNARE proteins. However, some SNAREs also bind tethering factors. Moreover, specific sets of SNAREs appear to be specialized for specific fusion reactions but it is controversial how this specificity is achieved. To disentangle the role of SNAREs in targeting, we have prepared artificial vesicles with a defined phospholipid composition that contained specific SNAREs as the only proteins and injected them into mammalian cells. We found that liposomes containing the four SNAREs mediating fusion of early endosomes as the only proteins dock and fuse with endogenous early endosomes, whereas liposomes containing the four SNAREs mediating fusion of late endosomes are specifically targeted to late endosomes. Further analysis revealed that the Q-SNAREs syntaxin 13 (Stx13) and syntaxin 6 (Stx6) suffice for early endosomal targeting whereas liposomes containing only Stx6 are targeted to a different endosomal compartment. These differences are mediated by different tethering factors recruited by the SNAREs. Targeting by Stx6 requires Vps51, a component of the GARP/EARP tethering complexes. In contrast, targeting by both Stx6 and Stx13 is governed by Vps13B, a novel tethering factor functioning in transport from early endosomes to recycling endosomes. Vps13B specifically binds to Stx13/Stx6 as well as to Rab14, Rab6, and PtdIns(3)P_2. We conclude that SNAREs use a combinatorial code for recruiting tethering factors which is governed by the N-terminal domains of the SNAREs, revealing a key function in targeting that is independent of SNARE pairing during fusion. Thus, specificity in intracellular membrane trafficking is governed by a combination of SNAREs, Rab proteins and phosphoinositides that operate by panels of effectors, thus allowing for precise fine-tuning that would be difficult to achieve with only a single class of targeting molecules.