Universität Basel

Research Project

Regulation of endosomal transport and maturation

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Principal Investigator(s) Spang, Anne ;
Organisation / Research unit
Departement Biozentrum / Biochemistry (Spang)
Department
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Endocytosis is an essential pathway in eukaryotes to receive signals and regulate the protein composition of the plasma membrane. Proteins that are removed from the plasma membrane can either be recycled back, go to the trans-Golgi network (TGN) or be degraded in the lysosome. Inappropriate sorting at endosomes can lead to a variety of cancers, and many factors involved in these processes are oncogenes. In addition, the endosomal pathway is often highjacked by pathogens for their cell entry and infectivity. Moreover, a plethora of other diseases are linked to defects in the endosomal pathway. Therefore, understanding the endosomal pathway is of pivotal importance. Rather than concentrating on a specific disease, we work towards the elucidation of the regulation of the endosomal pathway. This knowledge can then be applied to many instances. Our starting point was the discovery of endosomal maturation. Even though, maturation had been proposed earlier, we were the first to show that endosomes mature from early to late before fusing with the lysosomes. Since then, we have been interested in understanding the regulation and coordination of processes that take place during maturation. Recently, we identified FERARI, a platform on sorting endosomes that recruits Rab11 recycling structures to the sorting endosomes, promotes fusion -without membrane flattening- and then fission of these Rab11 compartments from the sorting endosome. We surmise that during this process cargo destined for recycling is taken up. Thus, we discovered a kiss-and-run mechanism in endocytic recycling. Surprisingly, the residence time of recycling structures on sorting endosomes was quantal in 7 sec intervals, which we interpreted as the time of fusion pore opening and closing. To investigate this unexpected finding further, we propose to (1) determine the structure of FERARI by cryoEM and to reconstitute FERARI function in vitro. (2) to analyse the regulation of FERARI and sorting in vivo using mammalian cell lines and C. elegans as a model animal. (3) In order to better understand the regulation of endosome maturation, we have set up and in vivo assay system in mammalian cells, in which we can enlarge endosome about 40x without harming cells and follow endosome mature with ease under a widefield microscope. We want to explore this unpublished assay (manuscript in preparation) to first describe the coordination of different processes during endosome maturation and then use genetic engineering as well as acute perturbances to understand the regulation of endosome maturation. Thus, we use a balanced mix of high-risk, high-gain parts and very attainable goals to provide unprecedented data on endosomal transport.

Keywords C. elegans, structure, tissue culture, small GTPase, microscopy, in vivo assays, intracellular traffic, Rab GTPases, endoscopes, intracellular transport, in vitro assays
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