Universität Basel

Research Project

Sinergia: Regulation of early to late endosomal traffic

Third-party funded project

Project title Sinergia: Regulation of early to late endosomal traffic
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Endocytosis is a fundamental process in eukaryotic cells. It describes the uptake of fluids, macromolecules, plasma membrane localized proteins, and particles from the plasma membrane. The membrane invaginates at sites of endocytosis, allowing the formation of carriers that are released from the plasma membrane by scission. Those endocytic carriers then fuse with early endosomes. In metazoan cells, the cargo that can be endocytosed ranges from solutes over surface receptors to bacteria and viruses. By sorting, processing, recycling, storing, activating, silencing, and degrading incoming substances and receptors, endosomes are responsible for regulation and fine-tuning of numerous pathways in the cell. Some of the endocytosed material is recycled to the plasma membrane, while another subset travels to the Golgi apparatus. The factors that are not sorted away from the early endosomes enter the degradation pathway via the late endosome to the lysosome, whereby they either remain on the limiting membrane or are sequestered away from the cytoplasm by being deposited into intralumenal vesicles (ILVs).

The transition from early-to-late endosomes occurs through a maturation process during which multiple processes have to take place: sorting and recycling of cargo, the lipid and protein composition of the limiting membrane has to change, ILVs have to form, the pH has to drop, the lumenal ion concentration has to change, the endosome has to move from the cell periphery to the cell center, and Rab conversion –the change of Rab5 to Rab7- has to occur. All these events have to take place to ensure that only material that should be degraded in the lysosome ends up in the late endosome, which ultimately will fuse with lysosomes. Moreover, the lumenal milieu in the late endosome should be such that upon fusion with the lysosome, the then newly created endolysosome still retains the ability to degrade the endosomal content.

How is endosome maturation regulated? This is the major question, we will address in this proposal by studying mammalian tissue culture cells and different tissues in life C. elegans. The goal of the proposal is to increase the knowledge of this critical process at the molecular level, and at the same time to understand the underlying logic. What are the various changes that take place during the maturation process, and to what extent are they interdependent? Why are they necessary? How are the different changes during maturation regulated? How are viruses able to exploit the maturation process for infection?

We expect to generate biochemical, molecular and systems-based information about the life and regulation of endosomes by combining the strengths of each of the three involved groups. We will show genetic interactions of components involved in endosome maturation in a live multicellular organism, and we will device new technology to characterize endosomes. Our approach will clarify questions about endosome function and maturation, and address issues regarding the design of the pathway. Our results will have an impact on the fields of signaling, cancer, organ growth, differentiation and development, and strongly

influence infection biologists working on host-pathogen interactions with an interest towards new therapies.

Keywords genetic interaction network, high-end imaging, endocytosis, systems analysis , tissue cuture & C. elegans, early-to-late endosome transport, coordination of maturation process, Rab GTPases, RNAi screen, endosome maturation, viruses, Rab conversion

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