Life Sciences Seminar

Mechanistic studies of Rab GTPase membrane targeting and cycling in cells

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Rab GTPases are key regulators of intracellular vesicle transport in eukaryotic cells. Rab family members (>60 Rabs in human) localize to distinct intracellular compartments and regulate multiple steps of vesicular transport. Intracellular membrane trafficking requires correct and specific localization of Rab GTPases. The hypervariable C-terminal domain (HVD) of Rabs is posttranslationally modified by isoprenyl moieties that enable membrane association. To elucidate the function of the HVD, we have substituted this region with an unnatural polyethylenglycol (PEG) linker by using oxime ligation. Through localization studies and functional analyses of semisynthetic PEGylated Rab1, Rab5, Rab7, and Rab35 proteins, we demonstrate that the role of the HVD of Rabs in membrane targeting is more complex than previously understood. In our studies, we reveal the mechanism of Rab35 plasma membrane targeting. We find that Rab35 cycles between the plasma membrane and the Golgi apparatus via endocytic trafficking and GDI-mediated recycling. The C-terminal polybasic region (HVD) of Rab35, DENN1A, OCRL1 and PRA1 (GDF) play an important role in spatial cycling of Rab35, thereby its plasma membrane localization and function. We show that OCRL1 mutants lead to disruption of Rab35 plasma membrane localization and function in neurite outgrowth, suggesting a link of Rab35 to the Lowe syndrome. Our findings suggest that Rab membrane targeting is dictated by a complex mechanism involving GEFs, GAPs, effectors, and C-terminal interaction with membranes to varying extents, and possibly other binding partners.

Monday, May 7, 2018 04:00pm - 05:15pm

Meeting room 2nd floor / Bertalanffy Bldg. (I04.2OG - LAB)

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