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Department of Medical Genetics, University of British Columbia, Vancouver, Canada. E-mail: conibear@cmmt.ubc.ca

Mutations in each of the four human VPS13 (VPS13A-D) proteins are associated with distinct neurological disorders: chorea-acanthocytosis, Cohen syndrome, early-onset Parkinson's disease, and spastic ataxia. Recent evidence suggests that the different VPS13 paralogs transport lipids between organelles at different membrane contact sites. However, how each VPS13 isoform is targeted to these different sites is not known. Yeast has a single Vps13 protein whose localization depends on developmental stage or nutrient conditions. We have found that the membrane localization of yeast Vps13 requires a conserved six-repeat region, the Vps13 Adaptor Binding (VAB) domain, which binds to organelle-specific adaptors. Our results suggest that all adaptors compete for a single binding site in the VAB domain. Using a systematic mutagenesis strategy to define the contribution of each repeat, we have identified the putative adaptor binding site. Importantly, a missense mutation in VPS13D that causes spastic ataxia is predicted to impact this binding site, suggesting a conserved adaptor binding role for the VAB domain. Current efforts are focused on identifying novel VAB binding partners in both yeast and humans.

CB-03
MECHANISM OF ORGANELLE IDENTITY WITHIN THE ENDOLYSOSOMAL PATHWAY

Ungermann C
University of Osnabrück, Department of Biology/Chemistry, Osnabrück, Germany. E-mail: cu@uos.de

Eukaryotic cells have an elaborate endolysosomal system of interconnected organelles, much similar to our digestive tract. Proteins, in particular, membrane proteins such as nutrient transporters, which need to be degraded during cellular adaptation, travel along this pathway from the plasma membrane by being incorporated into endocytic vesicles to the early endosome. These then mature into late endosomes, where intraluminal vesicles form to remove selected proteins from the endosomal surface. These vesicles are then degraded with their entire luminal content, once late endosomes fuse with the lysosome, called vacuole in yeast. Likewise, autophagosomes are formed during autophagy as a major catabolic pathway and deliver proteins and organelles in double-membrane vesicles by fusing directly with lysosomes. This poses the question, how each organelle gains identity to become fusion competent. Using yeast as a model system, we have now evidence that both endosomes and autophagosomes use comparable mechanisms to acquire the machinery to fuse with vacuoles. A first requirement during this process is the recruitment of the small Rab7 GTPase to the surface of each organelle. Rab GTPases can be kept soluble in the GDP-bound form in the cytosol. They require a guanine nucleotide exchange factor (GEF) for their membrane localization and activation into the active GTP-form. The principles of GEF localization to the right membrane are mostly unknown. We have identified and characterized the Rab7 GEF, called Mon1-Ccz1, and I will present evidence on its function and regulation. Once on the membrane, Rab7 binds in its GTP-form to effectors, in our case to the HOPS tethering complex. This large complex acts like a bridge between endosomes (or autophagosomes) and lysosomes, but can also catalyze fusion. This unique ability is due to one of its subunits, which can assemble SNAREs as the fusion machinery present on both endosomes (and autophagosomes) and lysosomes. I will present a working model, how both processes—endosome and autophagosome fusion with lysosomes—can be studied *in vivo* and *in vitro*. Our analysis provides, in addition, insights into the regulation of metabolic adaptations of yeast cells—and these also occur in human cells.

CB-04
IN SILICO TESTING THE FUNDAMENTAL MECHANISMS AND LOGIC OF INTRACELLULAR TRAFFIC

Cebrián I, Pavarotti M, Mayorga LS
IHEM -CONICET, Universidad Nacional de Cuyo, Facultad de Ciencias Exactas y Naturales, Mendoza. E-mail: lmayorga@fcm.uncu.edu.ar

Intracellular traffic is a central process in cellular physiology. Numerous macromolecules must be transported in the endocytic and exocytic pathways for the correct function of eukaryotic cells. However, the way by which macromolecules are transported between compartments is still a matter of intense debate. Our group has developed a simulation platform, based on a combination of agent-based modeling and ordinary differential equations, for processes that occur in dynamic organelles that merge, divide, and change position and shape, while altering their composition by complex networks of molecular interactions and chemical reactions. We have already described how this modeling strategy successfully reproduces transport in the endocytic pathway. Our next objective is to apply this modeling approach to the trafficking within the Golgi apparatus. It is worth mentioning that several hypotheses regarding this issue are still in conflict, despite the abundance of experimental results and the development of ingenious probes to assess transport. Interestingly, our modeling strategy is flexible enough to simulate all these hypotheses and test the agreement between the different models and experimental data. At present, we have successfully modeled the transport of small and large membrane-associated cargos using the "cisternal progression/maturation" hypothesis. We expect that the active dialogue between simulations and experimental results will foster our understanding of the logic underlying the transport mechanisms that efficiently sort a large number of macromolecules to their final destination inside and outside the cell.

RN-01
TRANSLATION AFFECTS MRNA STABILITY IN A CODON DEPENDENT MANNER IN HUMAN CELLS AND ZEBRAFISH EMBRYOS