Molecular Mechanisms of Sphingolipid Homeostasis in the Endolysosomal System

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Sphingolipids (SLs) are abundant and essential molecules in eukaryotes that have crucial functions as signaling molecules and as membrane components. They are important for many processes, including endocytosis and surface receptor function. Pathological changes in sphingolipid levels are associated with many common pathologies, ranging from obesity to cancer, asthma, and atherosclerosis, and to neuro-degenerative diseases. Therefore, cells have to maintain sphingolipid homeostasis. How sphingolipid levels are regulated and maintained is a long standing, fundamental problem in biology.

We use a combination of mass spectrometry based proteomics and lipidomics, combined with functional genetic screening in *Saccharomyces cerevisiae* to identify genes and their protein products that are important regulators of sphingolipid homeostasis. This has let us to discover important processes such as retrograde endosome to Golgi transport dependent on a functional Golgi associated Retrograde Protein Trafficking (GARP) Complex [1,2]. Our analysis of the GARP complex as a crucial factor of sphingolipid homeostasis has now led us to the discovery of a novel membrane contact site between the Golgi and mitochondria that is formed upon phosphorylation of the GARP subunit Vps53 in response to increased AMPK signaling. Now we are trying to understand how this contact site contributes to sphingolipid homeostasis in cells.

[1] Eising, S., Thiele, L., Fröhlich, F., A Systematic Approach to Identify Recycling Endocytic Cargo Depending on the GARP Complex Abstract. *Elife* 2019.

[2] Fröhlich, F., Petit, C., Kory, N., Christiano, R., et al., The GARP complex is required for cellular sphingolipid homeostasis. *Elife* 2015, 4.