Determinants of substrate specificity of SPP/SPPL intramembrane proteases

Our group works on intramembrane proteolysis which links protein degradation with signal transduction and thus represents an important regulatory mechanism for cellular homeostasis. We are especially interested in the SPP/SPPL family of intramembrane proteases, which are mechanistically related to the γ-secretase complex that is involved in Alzheimer disease. One member of this protease family, SPPL2a, represents a promising therapeutic target for the treatment of autoimmunity. Recently, human patients with SPPL2a deficiency were identified to lack certain dendritic cells and to be susceptible to mycobacterial infections. Nevertheless, the substrate spectrum of these proteases as well as their regulatory impact are insufficiently characterized. In particular, the integration of these proteases into alternative pathways for membrane protein degradation within the endocytic system (ESCRT, MVB pathway) is currently not well characterized and is one of our key interests.

In the planned summer project, we would like to further characterize the substrate determinants of SPP/SPPL intramembrane proteases. It is still not very well understood why certain type II transmembrane proteins or tail-anchored proteins are cleaved and others are not. A type II membrane orientation (N-terminus in the cytosol) as well as a small size of the luminal or ectodomain are necessary requirements. However, these are not sufficient. Even closely related tail anchored proteins differ in their cleavability. Not being cleaved by these intramembrane proteases means on the other hand that these proteases are degraded by other pathways in the cell. We would like to understand the molecular switch between these different pathways. We aim to narrow down which determinants define a substrate of SPP/SPPL intramembrane protease or render it a non-substrate. The major approach will be substrate mutagenesis and the generation of chimeric proteins between substrate and non-substrates. These different variants will be tested in protease cleavage assays as well be assessed with regard to the impact on subcellular localization and interaction with the proteases. In the summer project you will be able to learn and apply a broad spectrum of molecular biology, biochemical and cell biological techniques.

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