KEMIJSKI INŠTITUT

Predavanje / Lecture

Leucine Aminopeptidase LyLAP enables lysosomal degradation of membrane proteins

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Velika predavalnica, 1. nadstropje / Great Lecture Hall, 1st floor

Transmembrane proteins represent ~20-30% of the human proteome and are subjected to turnover by endocytic uptake and delivery to the lysosome, where their degradation poses a unique challenge due to their hydrophobic, phospholipid-embedded α-helical domains that are inaccessible to endopeptidases. In this talk, I answer the long-standing question of how lysosomes degrade transmembrane proteins - a key missing piece in the life cycle of this important class of proteins that mediate signal transduction, nutrient import, adhesion, and migration. Combining lysosomal proteomics with functional genomic data mining, untargeted metabolomics, and biochemical reconstitution, we find that a previously mischaracterized enzyme that we rename Lysosomal Leucine Aminopeptidase (LyLAP) is most tightly associated with elevated endocytic activity and enables transmembrane protein degradation. LyLAP performs a unique function not found among known lysosomal hydrolases, namely, processive disassembly of hydrophobic α-helices triggered by their N-terminal hydrophobic (often Leucine) residues. Importantly, LyLAP is upregulated in pancreatic ductal adenocarcinoma (PDA), an aggressive cancer that relies on macropinocytosis for nutrient uptake. Strikingly, loss of LyLAP activity has catastrophic consequences for lysosomes, ultimately leading to PDA cell death. Thus, LyLAP enables lysosomal degradation of membrane proteins, and may represent a targetable vulnerability in highly endocytic cancer cells.

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Vljudno vabljeni / Kindly invited