LS21-029 - Using activity-based probes to study the mechanism and regulation of the giant E3 ligase Huwe1

Zusammenfassung

The E3 ligase HUWE1 is an essential component of the ubiquitin-proteasome system (UPS), marking a broad variety of cellular proteins for degradation. Though being linked with severe human diseases, the molecular mechanism of Huwe1, a giant 500 kDa protein, is little understood. Our project addresses the important question of how Huwe1 activity is controlled and directed towards a particular substrate that needs to be degraded in a cell-context specific manner. To this end, we will study how Huwe1 mediates the selective targeting and degradation of the cell-fate determining transcription factor Ascl1 in adult Neural Stem Cells (aNSCs). By monitoring Ascl1 stability, we will screen for cellular signals that modulate Huwe1 function in aNSCs. The functional status of Huwe1 will be reported by activity-based probes (ABPs) that selectively label active E3 enzymes in cells. ABPs will be also used in complementary in vitro and cryo electron microscopy (cryoEM) studies, visualizing the activated Huwe1 in atomic detail. Together, our data will provide an in-depth molecular characterisation of how Huwe1 is regulated in aNSCs to ensure the controlled elimination of Ascl1. Aside revealing very basic concepts underlying targeted protein degradation, our unique and interdisciplinary Chemical Biology approach will serve as a blueprint to characterize the intricate regulation of E3 systems that promote protein degradation in diverse signaling pathways.

Wissenschaftliche Disziplinen:
Chemical biology (30%) | Biochemistry (40%) | Cell biology (30%)

Keywords:
Targeted Protein Degradation, Ubiquitin Proteasome System, E3 ligases, Activity Based Probes, Huwe1, Ascl1

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Weiterführende Links zu den beteiligten Personen und zum Projekt finden Sie unter
https://wwtf.at/funding/programmes/ls/LS21-029/