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MPI-NAT SEMINAR SERIES

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How chemical scars mark proteins for degradation

Human cells have the remarkable ability to identify and remove individual damaged proteins among a sea of intact ones. But how do cells surveil the highly diverse human proteome for damaged, excess or mislocalized proteins?

In recent work, I discovered that human cells scan protein C-termini for a minimal chemical modification that marks damaged proteins following oxidative fragmentation (Muhar, Farnung et al. 2025, Nature). By precisely modelling protein damage using chemical biology tools, I identified that cells selectively degrade C-terminal amide-bearing proteins (CTAPs). A genome-wide CRISPR screen identified SCF/FBXO31 as the reader of C-terminal amidation which directly recognizes and ubiquitylates CTAPs. SCF/FBXO31 binds diverse C-terminal sequences with high affinity, yet exquisite selectivity over unmodified ones. A mutation found in cerebral palsy patients shifts client selection towards unmodified C-termini, thereby forming a toxic ubiquitin ligase.

This work demonstrates how a chemical mark enables broad yet selective proteome surveillance, which could represent a common strategy by which cells maintain protein homeostasis. In my future work, I will explore how recognition of CTAPs and similar modifications shapes the human proteome. I will dissect how cells toggle global proteome turnover during developmental transitions and how different cell types tailor the proteome to their specialized functions.

Wednesday, 16 April 2025, 11:00 a.m.

Hosts: Christian Griesinger & Sonja Lorenz

Large Seminar Room
Fassberg Campus

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