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MPI-NAT SEMINAR SERIES

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Voltage-gated ion channel assembly at the human endoplasmic reticulum

Nearly half of all ~5,000 human membrane proteins need to assemble into defined oligomeric complexes to function. How do thousands of newly synthesized membrane proteins navigate the crowded ER membrane environment and avoid promiscuous interactions, aggregation or premature degradation to find their correct binding partners? How are hydrophilic subunit interfaces protected within the hydrophobic lipid bilayer prior to assembly? We propose that membrane protein assembly does not occur through chance encounters of randomly diffusing subunits; rather, it is highly regulated and requires assembly factors that collaborate with membrane insertion machinery.

To begin exploring the diversity of factors and mechanisms controlling membrane protein assembly at the ER, we are using the large family of *voltage-gated ion channels (VGICs)* as important model complexes. VGICs fulfill many essential functions; for example, they mediate excitation-contraction coupling in heart and muscle cells, and trigger hormone and neurotransmitter release in secretory and neuronal cells. Mutations that impair VGIC biogenesis or function cause severe cardiological, neuropsychiatric, and neurodevelopmental diseases. A better understanding of ion channel assembly and quality control pathways could therefore reveal critically needed therapeutic targets to modulate their cellular levels.

In my seminar, I will present our latest findings showing that the assembly of heterotrimeric voltage-gated calcium channels is highly regulated and requires the abundant and highly conserved ER membrane protein complex (EMC) as an assembly factor at the ER membrane. The EMC is well known for its function in inserting membrane proteins into the lipid bilayer (1-4), but had long been speculated to have additional roles in membrane protein biogenesis. Combining cell-based calcium channel reporter assays, inhibitory anti-EMC nanobodies, and reconstruction of early calcium channel assembly events in an *in vitro* translation and ER membrane insertion system, we could provide first direct evidence for a chaperone function of the EMC. We found that the EMC engages nascent calcium channels co-translationally at the multipass translocon to prevent their pre-mature degradation. Our work highlights a sophisticated network of biogenesis factors that collaborate dynamically to ensure membrane protein folding and assembly intermediates are protected from otherwise wasteful premature degradation or toxic aggregation.

Monday, 17.03.2025, 1 pm

Host: Dirk Görlich

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