Universität Basel

Research Project

Morphological dynamics of the permeability barrier in yeast nuclear pore complexes

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Project title Morphological dynamics of the permeability barrier in yeast nuclear pore complexes
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Phenylalanine-glycine nucleoporins (FG Nups) are intrinsically disordered proteins thatăgenerate the permeability barrier within nuclear pore complexes (NPCs). NPCs areăremarkable sorting machines that mediate nucleocytoplasmic transport (NCT) inăeukaryotic cells. On one hand, NCT is rapid and selective for cargo-carrying nuclearătransport receptors termed karyopherins (Kaps). On the other, the permeability barrierăobstructs the passage of non-specific cargoes. Importantly, NPC function isăunderscored by, amongst others, neurodegenerative disorders and viral pathogenesisăthat are linked to FG Nup/Kap dysfunction.ăDespite being central to NPC function, we do not understand the spatiotemporalăbehavior of the FG Nups in the NPC and the permeability barrier remains highlyădebated. Due to their conformational flexibility, a structural characterization of theăpermeability barrier remains lacking and lags significantly behind advances in ourăunderstanding of NPC scaffold structure. Likewise, it remains unclear how Kap-cargoăinteractions with the FG Nups might alter the behavior of the permeability barrier toătraverse the NPC. This is further related to the question of whether the permeabilityăbarrier plays a role in influencing large-scale conformational changes in the NPC suchăas to accommodate large cargoes.ăIn this work, we will tackle these two major themes: (i) FG Nup dynamics within theăNPC permeability barrier; and (ii) to explore its links to conformational changes in theăNPC. To do so, we will employ high-speed atomic force microscopy (HS-AFM) toăinvestigate the permeability barrier within NPCs isolated from S. cerevisiae (buddingăyeast) nuclei at the single NPC level, at transport-relevant length scales (nm) andătimescales (100 ms). Specifically we will characterize FG Nup dynamic behavior in theăabsence and presence of Kap-cargo complexes in both native NPCs and ÄFG mutantăNPCs. In addition, we will evaluate how the permeability barrier might act as aămechanosensor that induces large-scale conformational changes in the NPC. This willăinvolve a systematic study using different ÄFG mutant NPCs that exhibit differentădegrees of FG Nup cross-linking within their respective permeability barriers. On thisăbasis, we hypothesize that disrupting inter-FG Nup interactions (e.g., by FG-domainădeletions, amphipathic alcohols, large cargo complexes, etc.) facilitates pore dilation byăreducing the amount of tension imposed by the FG Nups on the NPC scaffold. Finally,ăwe will substantiate our NPC-level findings at the individual FG Nup-level byăinvestigating the permeability barrier generated by FG Nups tethered within artificialănanochannels (also termed NPC mimics).

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