Modulating the conformation of the Sec61 protein translocation pore

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The Sec complex is a central component of the cellular machinery that translocates nascent peptides synthesized by the ribosome into the endoplasmic reticulum (ER). The Sec complex also assists membrane protein insertion into eukaryotic ER membranes and protein secretion. Its α-subunit forms the channel pore. The N-termini of Sec61 subunits α, β and γ are typically not fully resolved in atomistic structures. However, there is experimental evidence that the N-terminus of Sec61α is required for post-translational protein import and complex stability [1]. Hence to understand its conformational dynamics and its interaction with other subunits, we modeled the missing N-terminal part of Sec61α by molecular modeling and explored its conformational space using enhanced sampling molecular dynamics simulations. Our results suggest that the N-terminal amphipathic helix (F10-S15) of Sec61α is stable and the N-terminus of its β subunit (sbh1) is disordered. Furthermore, Sec63 of yeast contributes to post-translational protein translocation. Recent crystallographic data demonstrated that binding of Sec62-Sec63 to Sec61 caused a wide opening of the lateral gate and assists in post-translational import [2]. MD simulations indeed revealed that binding of Sec63 affects the conformations of lateral gate and plug region of Sec61α. Finally, by molecular docking we delineate putative binding locations of the Sec61 inhibitor *Mycolactone*.

[1] Elia, Francesco, et al. "The N-terminus of Sec61p plays key roles in ER protein import and ERAD." *PloS one* 14.4 (2019): e0215950

[2] Itskanov, Samuel, and Eunyong Park. "Structure of the posttranslational Sec protein-translocation channel complex from yeast." *Science* 363.6422 (2019): 84-87.