Open/Close the Jackknife

Dynamics of the full-length intramembrane protease GlpG

T. Utesch[1], H. Sun[1,2], *[1]Leibniz-Forschungsinstitut fuer Molekulare Pharmakologie, [2]Technische Universitaet Berlin*

In Short

- Intramembrane protease
- Opening-closing dynamics
- Domain interaction
- Allosteric regulation

GlpG is an intramembrane rhomboid protease that is involved in many physiological processes, such as cell signaling and growth. GlpG has thus been considered as a promising therapeutic target. Many active molecules that interact with the active site have been developed to date. These achievements have strongly benefited from the well-understood substrate binding process at the active site, which involves a serine-histidine diad that is deeply buried in the hydrophobic environment of the lipid bilayer. For catalysis, GlpG must undergo structural changes to allow substrate access to the active site[1]. Many different 3D structures have been resolved in recent years, validating that GlpG can adopt closed and open states. These states differ in the conformation of transmembrane helix 5 (TM5), which can open and enable substrate access to the catalytic center (figure 1). All these known 3D structures show only the transmembrane core domain. However, the missing N-terminal domain was thought to be crucial for the opening-closing equilibrium.

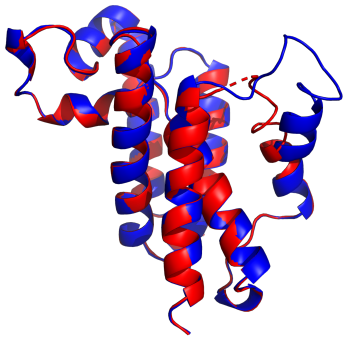

Figure 1: *Comparison of the open (blue; PDB 2NRF chain A[2]) and closed (red; PDB 2NRF chain B[2]) states of GlpG. While the overall structure is maintained, TM5 (righ side) undergoes a notable structural rearrangement.*

This lack of structural knowledge together with the fact that the mechanism how the function of GlpG is regulated make the search for allosteric regulators a challenging task. Motivated by these facts, our current project aims at understanding the opening-closing dynamics and, in particular, the role of the N-terminal domain on the dynamics of TM5. We assume that the N-terminal domain acts as regulator and shifts the opening-closing equilibrium by adopting different orientations with respect to the core domain.
This question will be investigated through microsecond molecular dynamics (MD) simulations, using GlpG embedded in a solvated lipid bilayer (figure 2). To achieve this, simulations starting from the open and closed states of both, truncated and full-length GlpG, will be conducted. First, homology models guided by NMR data from the group of Adam Lange (Leibniz-Forschungsinstitut fuer Molekulare Pharmakologie, Berlin) have been generated. The challenge in building these models is, among other things, the unknown orientation of the N-terminal domain relative to the transmembrane core domain of GlpG. These two domains are connected by a structurally uncharacterized and possibly very flexible linker.

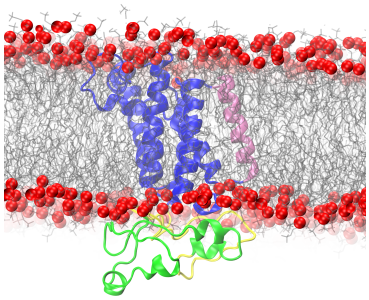

Figure 2: *Model of full-length GlpG embedded in a lipid bilayer. The protein and the lipids are shown in the cartoon and sticks representations, respectively. The core domain is colored in blue, the linker in yellow, and the N-terminal domain in green. Additionally, TM5 is highlighted in pink. The phosphorus atoms of the lipid head groups are indicated as red spheres.*

In the course of the project, we hope to also gain access to cryo-EM data and structures from our cooperation partners (Adam Lange and Daniel Roderer, Leibniz-Forschungsinstitut fuer Molekulare Pharmakologie) to increase the accuracy of our model.

In the future, we plan to investigate (a) the role of the lipid composition in the dynamics of the N-terminal domain, and (b) how small molecules can alter the behavior of the N-terminal domain. However, these steps are strongly dependent on the outcome of the first stage of the project described here.

WWW

https://leibniz-fmp.de/de/research/research-areas/chemical-biology/han-sun

More Information

[1] C. Shi, C. Oester, C. Bohg et al. *J. Am. Chem. Soc* **141**, 43 (2019). doi:10.1021/jacs.9b08952

[2] Z. Wu, N. Yan, L. Feng et al. *Nat Struct Mol Biol* **13**, 1084 (2006). doi:10.1038/nsmb1179

Project Partners

Adam Lange, Leibniz-Forschungsinstitut fuer Molekulare Pharmakologie
Daniel Roderer, Leibniz-Forschungsinstitut fuer Molekulare Pharmakologie

Funding

DFG supported Cluster of Excellence Unifying Systems in Catalysis, project number: 390540038

DFG Subject Area

201-02