Multiscale modeling of the yeast mitofusin Fzo1

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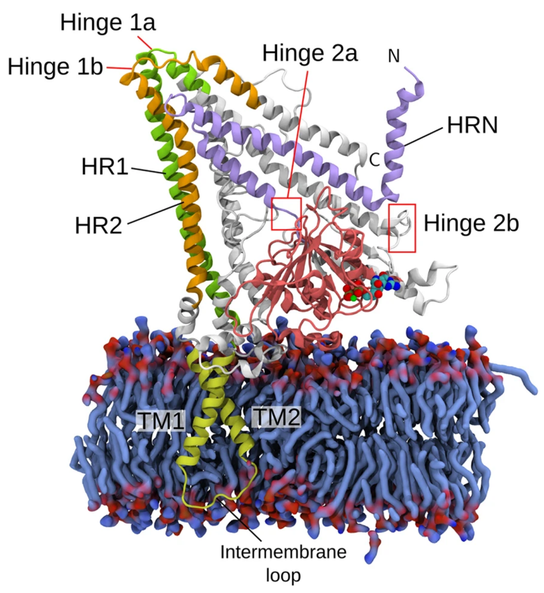
Background

Mitochondria are dynamic organelles whose ultrastructural organization is essential in maintaining their quality control and ensuring functional efficiency. The mitochondrial network is the result of both fusion and fission of inner and outer membranes. Tethering and homotypic fusion of mitochondrial outer membranes is mediated by large GTPases of the dynamin-related proteins family called the mitofusins. Their full-length structures remain unknown, which is a limiting factor in the study of outer membrane fusion.

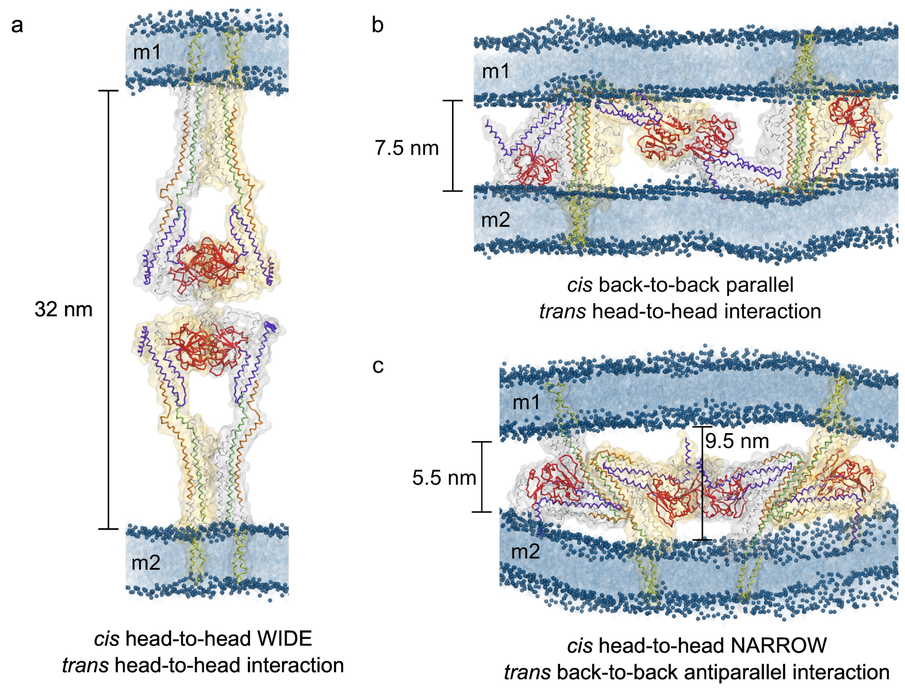
Monomer modeling

The yeast mitofusin, Fzo1, was modeled by homology with the mitofusin related bacterial dynamin-like protein (BDLP) as a template [2].



Oligomers

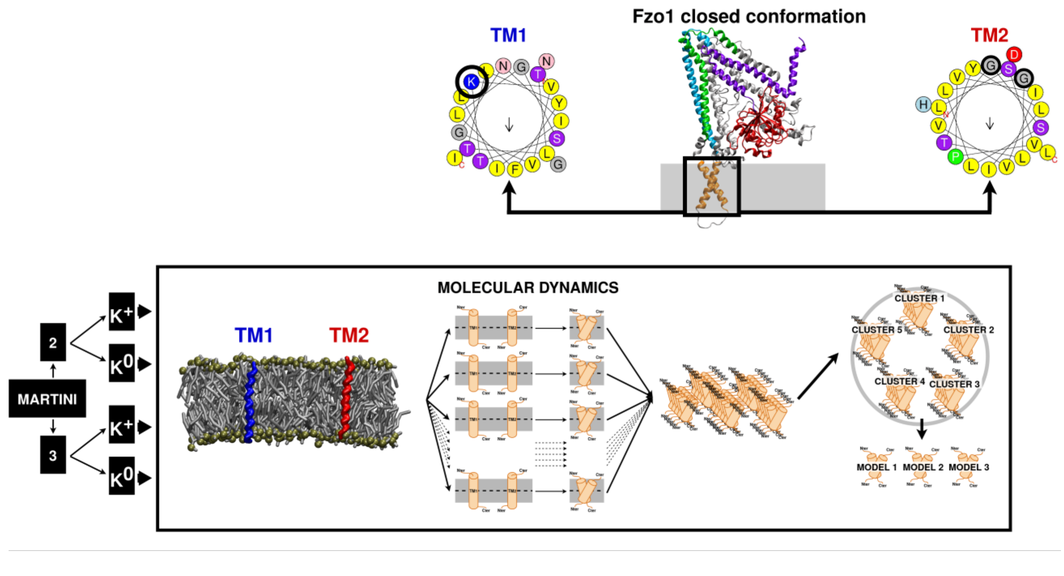
Noteworthy, mitofusins form oligomers, in both cis (on the same lipid bilayer) and trans, to mediate membrane attachment and fusion. We have built three distinct cis-assembly Fzo1 models that gave rise to three distinct trans-oligomeric models of mitofusin constructs [1]. Each model involves two main components of mitofusin oligomerization: the GTPase and the trunk domains.



MD analysis of the oligomers. The oligomeric models were assessed for stability and dynamics in a membrane environment using a coarse-grained molecular dynamics (MD) simulation approach.

Transmembrane helices

Noteworthy, BDLP used to construct the model presented above does not possess any transmembrane part. Thus, the structure of the Fzo1 transmembrane domain, made of two putative helices TM1 and TM2, had to be determined using *ab initio* methods. Furthermore, TM1 has a lysine (Lys716) located inside the membrane which could either be protonated or deprotonated.



MD analysis of the transmembrane helices Coarse-grained representations, with the MARTINI force field, were used in order to sample the association of TM1 and TM2, as well as the different protonation states of the TM1.

Conclusions

- A narrow opening 'head-to-head' cis-oligomerization (via the GTPase domain) followed by the antiparallel 'back-to-back' trans-associations (via the trunk domain) appears to be in agreement with all of the available experimental data.
- We found the TM1/TM2 model with the largest sampling to be different from the model used to construct the previous model of Fzo1.

Author representation

We note gender inequality in the author list (2F/4M). We are committed to achieve an always better balanced representation of minorities in our future work.

References

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