Intrinsically disordered region of talin's FERM domain functions as an initial PIP2 recognition site

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Abstract

Focal adhesions mediate the interaction of the cytoskeleton with the extracellular matrix (ECM). Talin is a central regulator and adaptorprotein of the multiprotein focal adhesion complexes and is responsible for integrin activation and force-sensing. We evaluated direct interactions of talin with the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2) by means of molecular dynamics simulations. A newly published autoinhibitory structure of talin, where common PIP_2 interaction sites are covered up, sparked our curiosity for a hitherto less examined loop as a potential site of first contact. We show that this unstructured loop in the F1 subdomain of the talin1 FERM domain is able to interact with PIP_2 and can facilitate further interactions by serving as a flexible membrane anchor.

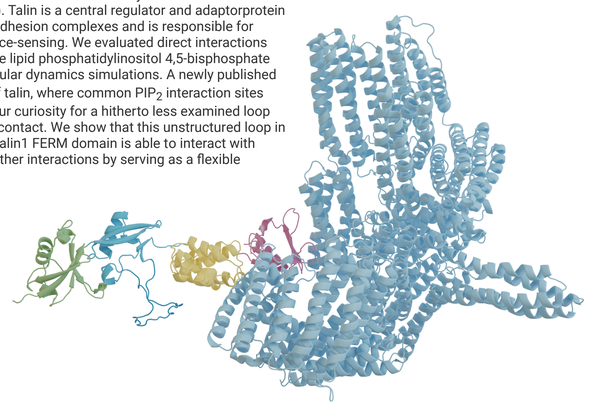


Figure 1. The autoinhibited (Cryo-EM) structure of Talin1 found by Dedden et al. (2019) aligned with the structure of the FERM domain by Elliott et al. (2010) and the modelled flexible loop in F1 (darker cyan)

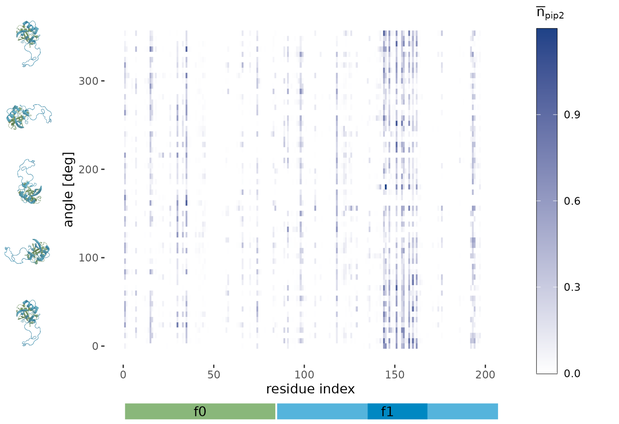


Figure 2. A rotational sampling of the F0F1 domain reaveals the strong propensity of the F1 loop to interact with the membrane. Even in the most unfavorable position, the loop still has a high probability to find the membrane and interact with PIP_2 due to the large search space it can cover.

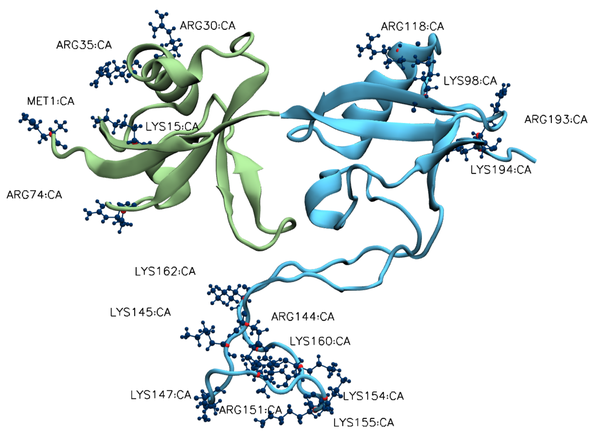
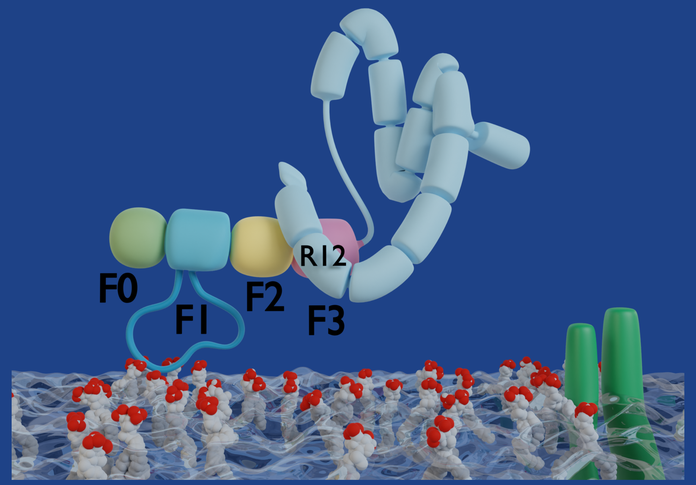


Figure 3. The residues of F0F1 interacting with PIP_2 are highlighted in blue, with their CA-atoms labelled

Unstructured loop of Talin's FERM domain can serve as a flexible membrane anchor

This allows for interaction with PIP_2 even in Talin's autoinhibited form and paves the way to establish known binding surfaces.



Follow the QR code or visit https://github.com/hits-mbm-dev/paper-talin-loop for the repository of the paper draft. Or even better yet, talk to me in front of the poster!

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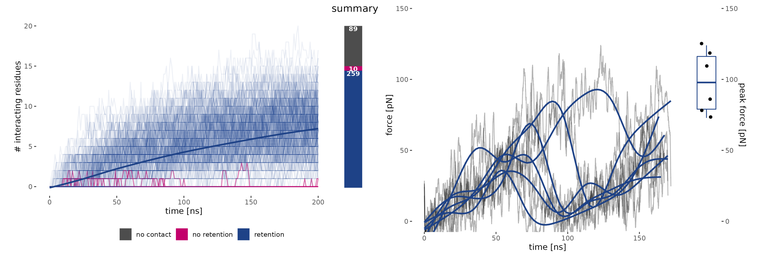

Figure 4. Left: Once a certain number of residues are interacting, it becomes highly unlikely for F0F1 to dissociate from the membrane. **Right**: Pulling bound F0F1 from the membrane does need some force, but the most important aspect for remaining bound is its flexibility. This allows it to remain in contact with PIP_2 even at large distances.

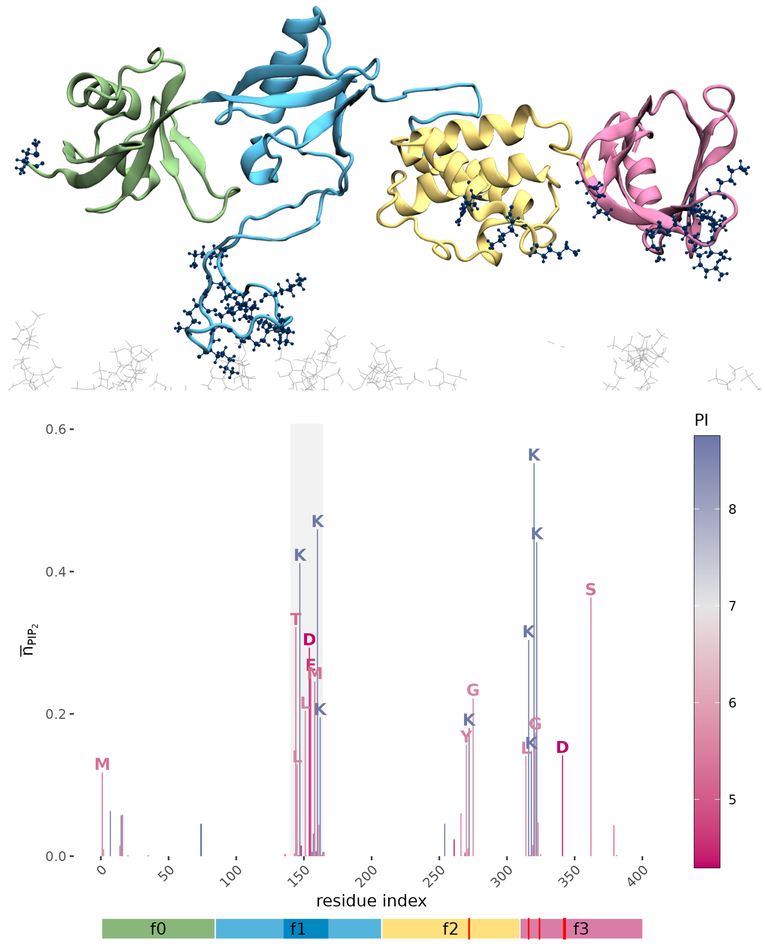

Figure 5. Once contact has been established via the loop, simulations with the full lenght FERM domain show that known PIP_2 interaction sites are recovered. The location of binding surfaces found by Chinthalapudi, Rangarajan, and Izard (2018) are highlighted with red lines on the schematic: K272 of F2 and K316, K324, E342, and K343 of F3.

Acknowledgments

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