Intrinsically disordered region of Talin's FERM domain functions as an initial PIP_2 recognition site

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ABSTRACT Focal adhesions mediate the interaction of the cytoskeleton with the extracellular matrix (ECM). Cell-ECM adhesion is used by almost all cells both during development and homeostasis and ranges from dynamic to permanent. As such, it is an important process in health and disease alike. Talin is a central regulator and adaptor protein 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. This work presents the dynamics of the interaction and identifies key residues. Further, we surveyed the effect of a physiological PIP_2 enrichment at focal adhesion sites on the dynamics of talin through force-probe molecular dynamics simulations. The results provide backing for the direct involvement of PIP_2 in the localization and activation of talin.

SIGNIFICANCE TODO Each manuscript must also have a statement of significance or no more than 120 words.

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