Structural and functional regulation of the Focal adhesion kinase by mechanical force

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Focal adhesion kinase (FAK) is a crucial component of focal adhesion sites, by transducing signals between the cytosol and the extra-cellular matrix. The translocation of FAK to focal adhesions and its functional activation by tyrosine phosphorylation lead to the formation of enormous multimolecular complexes, which trigger lots of signaling pathways, including Ras-dependent MAPK/ERK pathway.

FAK comprises a central tyrosine kinase domain and two large non-catalytic regions, one of which, the FERM domain, auto-inhibits the kinase by blocking a phosphorylation site (Tyr576/577). [1] We hypothesized that FAK acts as a force sensor, translating mechanical forces in the focal adhesion site into a biochemical signal. Force-induced partial unfolding should lead to the exposure of the hidden Tyr576/577 phosphorylation site, and thereby to a sequence of force-triggered downstream signaling events. We tested this by forced-probe Molecular Dynamics simulations (FPMD) to monitor the force dependent conformational transition of FAK. Only if force is applied to physiologically relevant protein domains, we observe the selective exposure of the hidden Tyr576/577 site.

Our study will serve as a reference for a MAPK/ERK mechanotransduction model, thereby providing insight into the force-sensoring function of FAK for guiding gene expression and cell differentiation.

[1] D. Lietha, X. Cai, D.F.J. Ceccarelli, Y. Li, M. D. Schaller and M. J. Eck. *Cell*, **2007(129)**, 1177-1187