HIGHLIGHTS

CELL ADHESION

A FERM interaction

To ensure that they're in the right place, phosphoinositides often rely on the precise localization of their synthesizing enzymes. Phosphatidylinositol phosphate kinase type Iγ (PtdInsPKIγ) catalyses the formation of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P_2), a key regulator of the assembly of focal adhesions. Two groups, led by De Camilli and Anderson, now report in *Nature* that PtdInsPKIγ is targeted by talin to focal adhesions, which defines a mechanism for the spatial generation of PtdIns(4,5)P_2 at these sites.

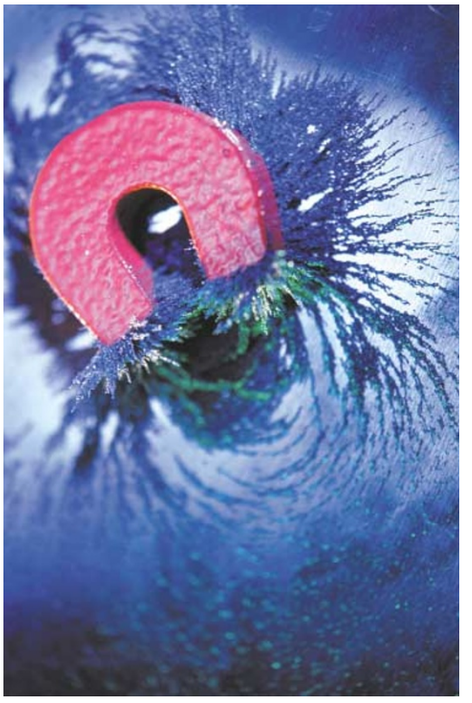
PtdInsPKIγ is alternatively spliced, and both groups found that the longer isoform — PtdInsPKIγ-90 (defined on the basis of its molecular weight; also known as PtdInsPKIγ661 on the basis of its carboxy-terminal amino acid sequence) — was targeted to focal adhesions. The carboxy-terminal amino acids that were missing from the shorter isoform were required for both focal adhesion targeting and association with talin.

They took slightly different approaches to identify proteins that interacted with the longer isoform of PtdInsPKIγ, but both groups isolated talin — an important component of focal adhesions — as a direct binding partner and mediator of its localization. Further analysis by the De Camilli group mapped the binding site to the third lobe of the clover-shaped FERM (for 4.1/ezrin/radixin/moesin) domain in the amino-terminal globular head region of talin. Conversely, the amino-acid sequence WVYSPL comprises the minimal binding sequence in the carboxy-terminal tail of PtdInsPKIγ-90.

Once recruited to focal adhesions, then, what might PtdInsPKIγ-90 do? Both groups reasoned that the talin-mediated recruitment of PtdInsPKIγ-90 to focal adhesions might increase the local production of PtdIns(4,5)P_2, which might, in turn, regulate the assembly of focal adhesions. So, De Camilli's group looked to see whether talin binding increased PtdInsPKIγ-90 kinase activity. They found that it did, in a dose-dependent manner.

Anderson's group showed that PtdInsPKIγ-90 kinase activity is regulated by its ability to be tyrosine phosphorylated. Focal adhesion kinase (FAK) is a key tyrosine kinase that regulates focal adhesions, and Anderson's group showed a positive correlation between FAK activity and the tyrosine phosphorylation (and so the activity) of PtdInsPKIγ-90. Furthermore, FAK-induced tyrosine phosphorylation enhances the binding of PtdInsPKIγ-90 to talin.

Anderson's group then showed that a kinase-inactive form of PtdInsPKIγ-90 inhibited the targeting of talin to focal adhesions, consistent with results from both groups showing that PtdInsPKIγ-90 affects focal adhesions. Moderately overexpressing PtdInsPKIγ-90 gave rise to larger talin-containing focal adhesions in well-spread cells, whereas cells expressing high levels of PtdInsPKIγ-90 were rounded and loosely attached and had fewer focal adhesions with less talin.



So both groups propose a positive-feedback mechanism that controls cell adhesion. Talin recruits PtdInsPKIγ-90 to focal adhesions, and the resultant increase in PtdIns(4,5)P_2 regulates other focal adhesion proteins, such as FAK, vinculin and α-actinin, in a highly localized manner at cell adhesion sites. The De Camilli group have extended this model to apply to the synapse — highly specialized cell adhesion sites — after finding PtdInsPKIγ-90–talin interactions in neurons, too.

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References and links

ORIGINAL RESEARCH PAPERS Di Paolo, G. *et al.* Recruitment and regulation of phosphatidylinositol phosphate kinase type 1γ by the FERM domain of talin. *Nature* **420**, 85–89 (2002) | Ling, K. *et al.* Type Iγ phosphatidylinositol phosphate kinase targets and regulates focal adhesions. *Nature* **420**, 89–93 (2002)