The cytoskeletal protein talin binds to a short C-terminal sequence in phosphatidylinositol phosphate kinase type Iγ (PIPKIγ), activating the enzyme and promoting the local production of phosphatidylinositol 4,5 bisphosphate, which regulates focal adhesion dynamics as well as clathrin-mediated endocytosis in neuronal cells. Here we show by crystallographic, NMR, and calorimetric analysis that the phosphotyrosine binding (PTB)-like domain of talin engages the PIPKIγ C terminus in a mode very similar to that of integrin binding. However, PIPKIγ binds in the canonical PTB-peptide mode with an SPLH motif replacing the classic NPXY motif. The tighter packing of the SPLH motif against the hydrophobic core of talin may explain the stronger binding of PIPKIγ. Two tyrosine residues flanking the SPLH motif (Tyr-644 and Tyr-649) have been implicated in the regulation of talin binding. We show that phosphorylation at Tyr-644, a Src phosphorylation site in vivo, has little effect on the binding mode or strength, which is consistent with modeling studies in which the phosphotyrosine makes surface-exposed salt bridges, and we suggest that its strong activating effect arises from the release of autoinhibitory restraints in the full-length PIPKIγ. Modeling studies suggest that phosphorylation of Tyr-649 will likewise have little effect on talin binding, whereas phosphorylation of the SPLH serine is predicted to be strongly disruptive. Our data are consistent with the proposal that Src activity promotes a switch from integrin binding to PIPKIγ binding that regulates focal adhesion turnover.

The integrin family of cell adhesion molecules provide a mechanical link between the extracellular matrix and the cytoskeleton and form the nuclei of structural and signaling complexes that regulate cell migration, proliferation, and survival, typically in concert with receptors for soluble ligands (1, 2). Integrins are initially activated by intracellular (“inside-out”) signals; following ligation to the extracellular matrix, “outside-in” signals lead to reorganization of the cytoskeleton and activation of intracellular signal transduction pathways. Until recently, rather little was known about the membrane-proximal events involved in integrin activation and signaling. Recent studies have demonstrated a critical role for the cytoskeletal protein talin, which binds to the integrin β subunit cytoplasmic tail, disrupting αβ tail association and promoting a conformational change in the extracellular domains that leads to enhanced affinity for extracellular matrix proteins and the subsequent clustering of integrins on the cell surface (3–5). For outside-in signaling, a critical role has been revealed for Src, which binds constitutively to the C terminus of the integrin β-tail and is activated by intermolecular phosphorylation upon integrin clustering (6).

The interplay between inside-out and outside-in signaling is less well understood. Recent evidence points to a prominent role for the enzyme phosphatidylinositol phosphate kinase type Iγ (PIPKIγ), which forms complexes with both Src and talin at focal adhesions (7–9). PIPKIγ synthesizes the lipid phosphatidylinositol 4,5 bisphosphate, a key activator of proteins involved in focal adhesion assembly, including talin. For example, phosphatidylinositol 4,5 bisphosphate binding to talin relieves an autoinhibitory head-tail association that allows the talin FERM domain to bind and activate integrin (10). In an example of positive feedback, the binding of talin to PIPKIγ also activates the kinase. However, the binding sites on talin for integrin and PIPKIγ overlap, which may limit this feedback loop (11). It has recently been shown that Src activates PIPKIγ by phosphorylating its C-terminal tail, enhancing its binding to talin (9). By contrast, Src phosphorylation of the integrin tail reduces its affinity for talin, and it has been proposed that Src triggers a switch between talin binding to integrin and PIPKIγ that may also control focal adhesion assembly (9).

We showed previously by crystallographic and NMR analysis that the F3 subdomain of talin engages integrin in a variant of a canonical PTB-peptide interaction (3). The integrin sequence differs from typical PTB-NPXY interactions in that one or two extra residues are inserted between the NPXY “reverse turn” and the

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upstream β-strand, and a critical tryptophan residue located four residues upstream of the NPXY motif inserts into a deep pocket on the talin surface. The talin F3 subdomain also engages a C-terminal extension of PIPKIγ that is unique to this isoform and involves a VWSPLHY motif (7, 8). Based on comparison of the sequences of F3-binding motifs, we proposed that PIPKIγ would engage the talin F3 domain in a similar fashion to that of integrin β3 (9, 11). Here we show by direct crystallographic studies, solution-based NMR spectroscopy, and calorimetry that the binding of PIPKIγ to talin does indeed conform to a canonical PTB-peptide interaction. However, this interaction involves a novel reverse-turn SPLH motif that is immune to the Src regulation observed to talin does indeed conform to a canonical PTB-peptide interaction. However, this interaction involves a novel reverse-turn SPLH motif that is immune to the Src regulation observed to talin does indeed conform to a canonical PTB-peptide interaction. However, this interaction involves a novel reverse-turn "molecule looping" between talin and PIPKIγ.

**EXPERIMENTAL PROCEDURES**

Protein Purification and Crystallization—The cDNA sequence corresponding to residues 638–651 of murine PIPKIγ fused to residues 209–410 of mouse talin was amplified by PCR and cloned into the pET15b bacterial expression vector using NdeI and BamHI restriction sites. The absence of errors in the sequence was corroborated by DNA sequencing. The plasmid was transformed into an E. coli strain BL-21 (DE3) for protein expression. Cells were grown in "terrific broth" medium at 37 °C, and protein expression was carried out at 30 °C. The harvested cells were resuspended in a solution of the peptide at a concentration 18 times that of the protein. Solutions were degassed at 15 °C for 20 min prior to the experiment. Experiments were conducted at 25 °C and consisted of a preliminary 2-ml injection of the peptide solution, followed by 20–24 injections of 5 µl with intervals of 210 s. Solutions were injected at a rate of 0.5 µl/min. Stirring of the cell solution was carried out at 310 rpm. The heat of dilution values were calculated by injecting peptide solutions into the buffer alone. The average heat of dilution was then subtracted from the main experiment. Data analysis was carried out with MicroCal Origin software using a single binding site model.

**NMR Spectroscopy**—All NMR experiments were carried out at 25 °C on spectrometers built in-house at the Oxford Centre for Molecular Sciences. Spectrometers were equipped with Oxford Instruments superconducting magnets (500, 600, and 750 MHz 1H operating frequencies) and 20/200 MHz 13C/15N frequencies. Data were collected at 100 K at the Stanford Synchrotron Radiation Laboratory beamline 1.5 using a Quantum-4R charge-coupled device detector. Data were indexed with DENOZ and reduced with SCALEPACK (13) (Table I). The structure was solved by molecular replacement using the algorithm PHASER (14), which found six copies of the molecule in the asymmetric unit arranged in three pairs of two molecules related by 2-fold non-crystallographic rotation axes nearly parallel to the crystallographic symmetry axes. This quasi-symmetric arrangement of molecules gave rise to an intensity distribution that confirmed the presence of noncrystallographic twinning. Refinement was performed by simulated annealing and energy minimization in CNS (15) with model building in TURBOFRODO (16). Given the unusual non-crystallographic symmetry (NCS), the Rwork set was chosen to obey P622 symmetry in order to minimize the risk of bias. Electron density corresponding to the PIPKIγ sequence was evident in the first maps, and a model was built for all six copies. The six amino acid differences between chicken and mouse sequences (all in the F2 domain) were also incorporated. Initially, strong (weight of 300 kcal/mol Å2 for positional NCS and σ<sub>A</sub> of 5 for B-factors) 6-fold NCS restraints were applied to three separate groups as follows: (i) residues 642–648 of PIPKIγ; (ii) residues 649–651 of PIPKIγ and 209–309 of talin; and (iii) residues 310–389 and 379–400 of talin. The weight for positional NCS restraints was gradually relaxed to only 5 kcal/mol Å2 in the last cycle of refinement. The final R<sub>work</sub> (25.3; R<sub>free</sub> = 28.6) consists of residues 642–651 of PIPKIγ and 209–400 of talin. The positional root mean square deviation between Ca atoms in different molecules ranged from 0.2 to 0.8 Å. Residues 209–400 of chain A superpose with the corresponding residues in the talin/integrin β3 (Protein Data Bank code 1M1Z) with root mean square deviation (Ca) of 1 Å. All stereochemical parameters are excellent as analyzed with PROCHECK (17). The crystal structure and structure factors have been deposited with the Protein Data Bank (deposition code 1Y19).

**Protein Expression and Purification for NMR**—For NMR experiments, the F3 domain (residues 309–405) of C338S mutant mouse talin was subcloned into a pGEX-6P-2 vector (Amersham Biosciences) between the BamHI and EcoRI restriction sites. The C338S substitution in talin has no effect on integrin β-talin binding (18). Protein was expressed in E. coli strain BL-21. 15N-Labeled protein was expressed in M9 minimal media. Cells were harvested by centrifugation and resuspended in phosphate-buffered saline containing lysosome (1 mg/ml), MgSO<sub>4</sub> (10 mM), and DNase I from Sigma (20 µg/ml). Cells were lysed by freeze/thaw cycles before adding Triton X-100 (Roche Applied Science) to a final concentration of 0.1% (v/v) and centrifuging. The supernatant was loaded onto a phenyl-Sepharose column (Amersham Biosciences) and purified according to the product manual. Glutathione S-transferase fusion proteases 3C<sup>me</sup> was added to cleave the fusion protein overnight at 4 °C (19), and the talin F3 domain was purified away from the glutathione S-transferase and protease by using glutathione-Sepharose 4B. The identity and purity of the final protein was confirmed by electrospray mass spectrometry and SDSPAGE. The PIPKIγ peptides PTEDRWYPSLYHYSAR and PTEDRWYPSLYHYSAR (phosphotyrosine is in boldfaced type) and the β-integrin peptide RAKWDTANNPLYKE were purchased from Alta Bioscience (Birminghanm, UK) and further purified by reverse phase high performance liquid chromatography.
Two-dimensional spectra that were acquired on the D$_2$O sample were a $^1$H-$^1$H-TOCSY with a 70-ms mixing time (21), $^1$H-$^1$H double quantum-filtered correlated spectroscopy (DQF-COSY) (22), and a $^1$H-$^1$H NOESY with a 100-ms mixing time (23). Data processing was achieved using the FELIX 2.3 software package (Biosym Technologies Inc.), and spectra were assigned using the program SPARKY (www.cgl.ucsf.edu/home/sparky). Spectra were referenced to an external DSS sample at 0 ppm ($^1$H), with indirect referencing in the $^{15}$N dimension using a $^{15}$N-$^1$H frequency ratio of 0.101329118 (24).

For the peptide binding studies two samples were used per titration, each containing 100 $\mu$M U-$^{15}$N-labeled F3, with the second sample also containing the maximal concentration of the peptide under study. Intermediate peptide concentrations were then obtained by adding the appropriate volume of the peptide/protein stock solution to the sample of talin F3 alone. Two-dimensional gradient-enhanced $^1$H-$^{15}$N HSQC spectra (25) with water flip-back (26) were acquired at each titration point. The concentrations of the PIPKI$\gamma$ peptides, which bound in slow exchange, were 0, 0.05, 0.1, 0.2, 0.4, 0.8, 1.2, 1.6, 3, 4.5, 6.5, 9, and 14 mM, and in this case saturation was not achieved.

RESULTS

Deletion analysis defined a minimal binding motif on the PIPKI$\gamma$ tail to the heptapeptide, WVYSPLH, which binds to the F3 subdomain of talin (7, 11). For crystallographic studies we engineered a chimeric molecule that takes advantage of a fortuitous intermolecular contact as described previously for the talin-integrin complex (3). The chimera comprises residues 638–651 (DERSWVYSPLHYSA) of PIPKI$\gamma$ fused to residues 209–410 of murine talin (the F2 and F3 FERM subdomains). The chimeric protein yielded crystals that diffract to a 2.6-Å resolution, and the structure was solved by molecular replacement. The asymmetric unit contains six molecules arranged as

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**Fig. 1. Crystal structure of the talin FERM F3-PIPKI$\gamma$ interaction.**

A, surface representation of talin FERM F3 domain colored by electrostatic potential (red for $-6$ kT/e and blue for 6 kT/e) with the PIPKI$\gamma$ ligand, residues 641–649, shown as sticks. Trp-642 (W642) in the PIPKI$\gamma$ sequence (which is critical for binding) binds into a deep pocket on the surface of F3. The SPLH sequence adopts the same reverse-turn conformation as the classic NPXY motif. Thus, serine plays a similar role as that of asparagine, forming an N-cap to the reverse turn; the proline promotes the reverse turn, the leucine packs against the hydrophobic surface of F3, and the histidine takes the place of the tyrosine or phenylalanine found in the integrins, packing against a flat somewhat acidic surface. B, comparison of PIPKI$\gamma$ (yellow) and integrin $\beta$3 (light green) sequences bound to talin FERM F3 (ribbon representation in blue). The $\beta$3 structure was superposed by aligning the conserved C atoms of the talin FERM F3 domain of the talin-PIPKI$\gamma$ and talin-$\beta$3 complexes. PIPKI$\gamma$ and $\beta$3 residues are labeled in red and green respectively. C, detailed stereo view of the talin-PIPKI$\gamma$ interaction. Talin residues involved in the interaction are shown in gray, and the PIPKI$\gamma$ ligand is shown in yellow. Intramolecular and intermolecular H-bonds are shown as dotted lines. Surface electrostatic potential was calculated with the program APBS (30). Molecular representation figures were generated with the programs MOLSCRIPT (31, 32), RASTER3D (32), and PyMol (http://www.pymol.org). Single letter amino acid abbreviations are used with position numbers.
three dimers in which the PIPKIγ arms are exchanged pairwise. The talin-PIPKIγ interaction is essentially identical in the six crystallographically independent copies.

Talin F3 contains two antiparallel β-sheets that form a β-sandwich with a single helix at the C terminus packing at the edge of the sandwich (Fig. 1). PIPKIγ residues 642–644 (WVY) augment the β5-β6-β7 sheet by creating an additional strand at the β5 end of the sheet, where it packs against the α-helix. The main chain conformation and location of the tripeptide closely correspond to those of integrin (Fig. 1). As expected, strand β6 makes a 3,10 helix H-bond to the main chain N of Leu-647, whereas its C Y turn in which Ser-645 plays the same role as the asparagine, forming an N-cap to the turn by making an N-cap to the turn by making a H-bond to the main chain N of Leu-647, where its C=O group makes a 3,10 helix H-bond to His-648. The side chain of Leu-647 makes a leucine zipper-like contact by inserting its side chain into a pocket created by three aliphatic residues at the end of the C-terminal helix; in the talin-integrin complex no such contact is possible because of a 60° tilt of the NPLY motif. The His side chain sits in the pocket occupied by the NPLY tyrosine in the talin-integrin complex, lying flat against the protein surface and forming an H-bond between its side chain Ne2 and Thr-364 C=O. The tyrosine downstream of the SPLH motif, Tyr-649, lies flat against the outside of the reverse turn.

We assigned the backbone resonances of the isolated F3 domain in solution by NMR (see “Experimental Procedures”) and studied the chemical shift perturbations upon binding the PIPKIγ peptide PTDERSWVYSPHYSAR (B), as well as the β3 integrin binding peptide RAKWDANNPLYKE (Fig. 2). The NMR perturbation data are consistent with the crystallographic data, showing that the chimeric crystal structure is a reliable model for the complex in solution. The residues perturbed by PIPKIγ binding are the same as those perturbed by β-integrin peptide binding. The NMR data indicate that the PIPKIγ peptide binds tighter than the integrin peptide, as evidenced by generally larger shift perturbations and a slow (separate signals) exchange regime for the PIPKIγ peptide as compared with the fast exchange regime observed for the integrin peptide (Fig. 2D).

The NMR data provide further insights into the conformational changes induced by ligand binding. The major perturbations are to the β5-β6-β7 sheet and the C-terminal helix (Fig. 2E). As expected, strand β5, which forms the main chain β-sheet contacts, is the region most affected by binding. Surprisingly, the whole of the β6-β7 loop is strongly perturbed; at its tip, this loop contacts the Tyr/His of the NPLY/SPLH motif. In previously determined crystal structures of talin lacking a ligand with a reverse turn motif, the β6-β7 loop
adopts a conformation in which a tyrosine from this loop (Tyr-373) packs against the body of the domain. In the talin-integrin complex, the loop changes its conformation such that the Phe-370 phenyl ring packs more deeply into its hydrophobic pocket and the Tyr-373 Ca shifts 7 Å as its phenol ring flips by 180° to become exposed on the protein surface. This switch appears to be driven by the packing of the NPYX tyrosine into its pocket. In the talin-PIPKIγ crystal structure, the histidine projects less far into its pocket, and both conformations are observed in different copies of the asymmetric unit. The biological significance of this conformational switch remains to be defined; although Tyr-373 is not part of a known kinase recognition motif, it is predicted with high confidence to be a phosphorylation site according to the NetPhos method (www.cbs.dtu.dk/services/NetPhos/).

We next studied the NMR chemical shift perturbations of a phosphorylated PIPKIγ peptide, PTDERSWYVSPLHYSSAR (phosphotyrosine is boldfaced), corresponding to the site identified as a site of Src kinase modification (Tyr-644). The NMR perturbations are very similar to those for the non-phosphorylated peptide, indicating that the binding mode and strength are very similar (Fig. 2, B and C). In general, the shifts are a little higher for the phosphorylated peptide, suggesting either somewhat stronger binding or a direct effect of the phosphate group on the amide resonances. We measured the binding of these two peptides to talin F3 in solution using isothermal titration calorimetry. We found that the dissociation constant for the phosphorylated peptide (pH 7.4) was lower than that for the unphosphorylated peptide ($K_d = 170 \pm 5 \text{ nm} \text{ versus } 271 \pm 0.6 \text{ nm}$) (see the supplementary data in the on-line version of this article), but the difference is less than that observed in previous studies using fluorescein-labeled peptide (9). Some of the observed differences may result from the use here of isolated F3 rather than the intact FERM domain used by Ling et al. (9). Modeling (not shown) of the phosphotyrosine onto the crystal structure shows that rotation of the tyrosine about its Ca-Cβ bond generates favorable ionic contacts between the phosphate group and the side chain of both Arg-358 and Lys-357 without disrupting the main chain contacts with the β5 strand. Modeling of the second tyrosine (Tyr-649) in its phosphorylated form also shows that a favorable contact with the Lys-357 side chain can be made.

**DISCUSSION**

Our structural model of the talin-PIPKIγ interaction reveals a novel variant of the PTB-peptide interaction in which an SPLH motif replaces the classical NPYX motif. We show directly that the binding sites for integrin and PIPKIγ on talin are essentially identical and, thus, mutually exclusive. The stronger binding of PIPKIγ may be explained by the tighter packing of the SPLH motif against the hydrophobic core of the F3 domain than that observed for integrin, where a two-residue insertion between the β-strand and reverse turn creates a bulge filled by a water molecule. A 60° tilt of the integrin NPLY motif allows the tyrosine to fit into its pocket, but this prevents the leucine from packing against the hydrophobic core of F3. The binding mode for PIPKIγ demonstrates that the talin F3 domain can indeed bind peptides in the “canonical” mode, and increases the likelihood that the protein layilin (27), which has two talin binding sequences (VVENEIY and FVTNDIY), will bind talin in the same fashion.

Previous studies have indicated that phosphorylation of the tyrosine preceding the SPLH motif by Src enhances binding to talin (9). Using fluorescein-labeled peptides, Ling et al. (9) showed by fluorescein anisotropy that phosphorylation at either or both of the tyrosines in the WWVSYPLHY motif increased binding to the talin FERM domain by ~10-fold. Our NMR and calorimetric data, generated with unmodified peptide and the F3 domain, also indicate a positive, although more modest (~2-fold), effect on binding to talin. Our structural model is consistent with these results, because the use of the SPLH motif places the two flanking tyrosine side chains (Tyr-644 and Tyr-649) in surface-exposed locations appropriately placed to make favorable ionic interactions with exposed basic residues.

Surface-exposed salt bridges generally have a much smaller energetic consequence than buried charge-charge interactions (such as those found in classic PTB-phosphopeptide interactions), because exposed groups must compete with water of solvation (28). By contrast, it has been shown that phosphorylation of the NPYX motif on integrin leads to loss of talin binding (9, 29); this finding is consistent with our model of the talin-integrin complex, because the tyrosine side chain fits into a hydrophobic and acidic pocket on the protein surface. Thus, our data support the proposal by Ling et al. (9) that Src phosphorylation of integrin and PIPKIγ promotes a switch from integrin binding to PIPKIγ binding by talin. That is, by substituting an SPLH motif for an NPYX motif, PIPKIγ avoids modification by the Src kinase that would inhibit talin binding.

The observation that talin binding to PIPKIγ activates the latter suggests that the talin binding motif is involved in autoinhibitory interactions in unactivated PIPKIγ, which could plausibly be relieved by phosphorylation and provide an alternative rationale for the strong activating effect of Src. Recent data have indicated that the SPLH serine is a target of MEK phosphorylation, which abolishes the PIPKIγ-talin interaction. Because this serine is buried in our complex and forms an H-bond that stabilizes the SPLH reverse turn, phosphorylation at this site is strongly predicted to disrupt binding.

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Structural Basis for Phosphatidylinositol Phosphate Kinase Type Iγ Binding to Talin at Focal Adhesions

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