1. CELL-MATRIX ADHESION

Protein tyrosine phosphatases are key regulators of protein tyrosine phosphorylation. More than merely terminating the pathways initiated by protein tyrosine kinases, phosphatases are active participants in many signaling pathways. Signals involving tyrosine phosphorylation are frequently generated in response to cell-matrix adhesion. In addition, high levels of protein tyrosine phosphorylation generally promote disassembly or turnover of adhesions. In this brief review, we will discuss the role of protein tyrosine phosphatases in cell-matrix adhesions.

Cell adhesion and migration are two tightly coupled processes critical to normal development and physiology. Two types of adhesion are usually distinguished: adhesion of cells to the underlying extracellular matrix (ECM) and adhesion between adjacent cells. This review will focus on the former. Adhesions are more than simple physical links to the matrix or to other cells; they are also sites where signals are initiated, allowing cells to monitor their immediate environment. Prominent among the signaling pathways that emanate from adhesion sites are those involving protein tyrosine phosphorylation. The differential tyrosine phosphorylation of cell adhesion molecules and their associated proteins is one means of altering the assembly and stability of adhesions. Tyrosine phosphorylation status reflects the balance between protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs).

PTPs were discovered several years after PTKs and have been studied less extensively. However, the number of genes encoding PTPs rivals that of PTKs, suggesting that the functions of PTPs may be just as complex (1). In addition, the diversity of phenotypes in knockout mice lacking various PTP genes demonstrates that many PTPs have non-redundant functions. Several families of PTPs have been identified, including classical PTPs, dual specificity PTPs, myotubularins, PTEN-related PTPs and aspartic acid-based PTPs (2). In this review, we will focus primarily on the classical PTPs and their functions in cell-matrix adhesion; the role of PTPs in cell-cell adhesions will be covered in a subsequent review (3).

Classical PTPs contain a highly conserved catalytic domain with a critical cysteine sulfhydryl in the catalytic site. They show considerable diversity in their other domains, allowing for variations in binding partners, localization, and function. In humans, 38 classical PTPs have been identified and these fall into two groups, either transmembrane receptor-type PTPs (RPTPs) or cytoplasmic PTPs (2). RPTPs contain extracellular domains often resembling adhesion receptors and either single or tandem catalytic domains in the intracellular sequence. Cytoplasmic PTPs consist of a single catalytic domain with various amino- or carboxy-terminal protein-binding motifs such as SH2 or FERM domains that serve targeting or regulatory roles.

PTPs and adhesion to extracellular matrix

Transmembrane receptors of the integrin family are responsible for adhesion to many different ECM proteins, including fibronectin, laminin and collagen (4). For cells in tissue culture, sites of strong adhesion to the ECM are known as focal adhesions and they serve to anchor bundles of...
microfilaments (stress fibers) to the plasma membrane via integrins. Focal adhesions not only play a structural role, but also act as scaffolds for numerous signaling pathways downstream from integrin-mediated adhesion. Prominent among these signals is tyrosine phosphorylation of proteins at the cytoplasmic face of focal adhesions catalyzed by PTKs such as FAK and Src family kinases (SFKs) (5). Engagement of integrins in itself is insufficient to induce the tyrosine phosphorylation and activation of FAK; integrin clustering at focal adhesions is required (6). The aggregation of integrins and resulting tyrosine phosphorylation at these sites is driven by myosin dependent cytoskeletal forces. This is, in turn, stimulated by the Rhoa/Rho kinase pathway or pathways activating myosin light chain kinase (7). During integrin-induced adhesion, in parallel with the activation of FAK and SFKs, there is a general inhibition of PTP activity (8).

In comparison with the large amount known about the role of PTKs in focal adhesions, much less is known about PTPs. Several studies have reported changes in tyrosine phosphorylation within focal adhesions in response to manipulating specific PTPs. However, the identification of PTP targets within focal adhesions has been difficult and sometimes contradictory. The problem arises because tyrosine phosphorylation is important not only as a consequence of integrin-mediated adhesion, but it is also involved in many upstream signaling pathways that affect integrin clustering and focal adhesion assembly. Consequently, it is often difficult to discern whether manipulation of a PTP is directly affecting the phosphorylation of a protein downstream from integrins, or whether it is affecting focal adhesion assembly or disassembly, and thereby indirectly affecting tyrosine phosphorylation of focal adhesion components. Strategies used for investigating the roles of specific PTPs have included over-expression of wildtype PTPs, expression of mutant or catalytically dead PTPs and elimination of specific PTPs, either by knockout or siRNA strategies. However, all of these approaches may influence upstream signaling, and can be misleading when the readout is the tyrosine phosphorylation of focal adhesion components. One of the best approaches to identify specific targets is to use catalytically dead PTPs to “trap” their substrates (9).

PTPs can affect integrin-mediated adhesion and the tyrosine phosphorylation that occurs in focal adhesions by acting at least at three different levels. They can affect signaling upstream, for example, by regulating the activities of GEFs and GAPs for Rho proteins; they can act proximal to integrin engagement, for example by regulating Src kinase activity; or they can dephosphorylate downstream targets, some of which may feedback to influence upstream signaling pathways affecting focal adhesion assembly and turnover.

1. Upstream regulation of Rho protein activity by protein tyrosine phosphatases: PTP-PEST, Shp-2 and LMW-PTP

Important upstream regulators of cell matrix adhesions are members of the Rho family of small GTPases (10). In humans, this family of regulatory proteins includes approximately 20 proteins, although most work has been focused on three ubiquitously expressed members, RhoA, Rac1 and Cdc42. Like other G proteins, these proteins are active in the GTP-bound form and are inactive when GTP is hydrolyzed to GDP. Activation of Rho proteins is catalyzed by guanine nucleotide exchange factors (GEFs) which stimulate exchange of bound GDP with GTP from the cytoplasmic pool. Most Rho proteins have intrinsic GTPase activity, which is further stimulated by GTPase activating proteins (GAPs). Many GEFs and GAPs are regulated by tyrosine phosphorylation. Consequently, PTPs can profoundly influence the cycle of Rho protein activation by regulating the state of phosphorylation of GEFs and GAPs (Figure 1). Examples of PTPs that have been reported to regulate Rho protein activity are given in Table 1. PTP-PEST is one PTP that affects adhesion and migration, in part by regulating the activity of Rho proteins. Over-expression of PTP-PEST depresses membrane ruffling at the leading edge of cells due to decreased Rac1 activity (11). Conversely, in PTP-PEST-/- cells Rac1 activity is elevated and sustained in cells plated on fibronectin (Sastry and Burridge, unpublished observation). Several pathways by which PTP-PEST might regulate Rac activity are suggested from published studies. PTP-PEST has been shown to bind and act on both p130Cals and

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paxillin (12,13) (Table 2). Both of these proteins, when tyrosine phosphorylated, interact with Rac GEFs. Tyrosine phosphorylated p130Cas and paxillin bind the adapter Crk (14-16), which in turn recruits the Rac GEF DOCK180 (17,18). In addition, paxillin binds the Rac GEF PIX via the adapter protein Pkl/Git (19). Therefore, a loss of PTP-PEST may increase Rac activity by increasing the pool of phosphorylated p130Cas and paxillin, thus preserving their interactions with and regulation of their GEF binding partners. Recent work has revealed that trapping mutants of PTP-PEST also bind Vav2 (Sastry and Burridge, unpublished results), a ubiquitously expressed GEF regulated by tyrosine phosphorylation (20). This observation raises the possibility that PTP-PEST may directly regulate Rac activity by controlling the phosphorylation state of this GEF without the need for adaptor proteins such as p130Cas/paxillin.

The increased Rac1 activity found in PTP-PEST-/- fibroblasts would be predicted to increase migration, but these cells actually have reduced migration rates (21). Examination of cell morphology reveals prominent ruffling membranes/lamellipodia (hallmarks of active Rac1), but the cells develop elongated tails, indicative of problems in detaching from the substrate (Sastry and Burridge, unpublished observation). Elongated tails are often associated with low RhoA activity (22). Through interactions with both a Rac GEF and an as yet unidentified Rho GAP, PTP-PEST may regulate the activities of both GTPases, thereby influencing migration by controlling membrane ruffling and tail retraction. However, an inability to disassemble focal adhesions in the rear would also account for the phenotype of the PTP-PEST null cells. Focal adhesion disassembly is regulated by tyrosine phosphorylation as well and will be discussed below. These results point to the complexity of phenotypes generated by PTP knockouts due to the actions of PTPs on multiple targets.

Another PTP implicated in regulating Rho protein activity is Shp-2. Here, conflicting results have been obtained, with some groups reporting that Shp-2 inhibits RhoA activity (23,24), while other groups find that Shp-2 stimulates RhoA activity (25,26), and still others suggest that Shp-2 can exert both positive and negative regulatory effects on RhoA activity (27). One target for Shp-2 is p190RhoGAP, a widely expressed GAP for RhoA (28) (Table 2). The activity of p190RhoGAP is stimulated by tyrosine phosphorylation (28,29). By dephosphorylating p190RhoGAP and so suppressing its GAP activity, Shp-2 can elevate RhoA GTP levels (i.e. activate RhoA). Paradoxically, Shp-2 is one of the PTPs that stimulates Src activity (see below), and Src is responsible for phosphorylation and activation of p190RhoGAP (30). Consequently, Shp-2 can act on both sides of the phosphorylation equation regulating p190RhoGAP activity. In addition, Shp-2 may be one of the PTPs that inactivates Rho GEFs that are regulated by tyrosine phosphorylation (23,24). Thus, the apparently conflicting role of Shp-2 with regards to RhoA activity could be reconciled by the differential action of the PTP on targets that can either positively or negatively regulate RhoA activity.

One non-classical PTP that warrants mentioning in the context of RhoA activity is LMW-PTP. It has been reported to act downstream of Src to regulate the phosphorylation state of p190RhoGAP, thereby controlling Rho-mediated cytoskeletal rearrangement (31). LMW-PTP has also been implicated in the crosstalk between Rac1 and RhoA, in which Rac1 mediated generation of reactive oxygen species was observed to inhibit LMW-PTP. This elevated p190RhoGAP tyrosine phosphorylation and activity, suppressing RhoA activity (32).

2. PTPs acting proximal to integrins: Shp-2, PTPα, and PTP1B

What is the initiating signal downstream from integrin-mediated adhesion? Several studies have implicated Src family kinases (SFKs) in some of the earliest steps downstream from integrins and preceding the activation of FAK (30,33,34). SFKs have been shown to bind β-integrin cytoplasmic domains (35,36), which has prompted investigation into how these kinases are regulated in response to interaction of the integrins with their ligands. SFKs are held in an inhibitory state by two intramolecular interactions. One interaction involves the SH3 domain binding to the linker region between the kinase and SH2 domains. This constraint may be removed by association of the SFK with integrin cytoplasmic domains (37). The second intramolecular
constraint to SFK activity involves binding of the SH2 domain to the phosphorylated C-terminal tyrosine residue (Y527 in avian, Y529 in mammalian cells). This inhibitory phosphorylation of Src is catalyzed by C-terminal Src kinase (Csk). Csk complexes with Src and inactive integrin αIIb/β3 (36). A PTP must dephosphorylate the C-terminal tyrosine in order for SFK activation. In addition, for full activity, phosphorylation of Y416 must occur in the activation loop within the kinase domain. Activation by removal of the C-terminal phosphate raises the possibility that PTPs may be involved in the initiation of the signaling downstream from integrin engagement or clustering. Several PTPs are capable of activating SFKs and, in the context of integrins, three have been studied, Shp-2, PTPα, and PTP1B (37-41).

Cells expressing a truncated form of Shp-2 (lacking the N-terminal SH2 domain), reveal diminished activation of Src and elevated phosphorylation of the inhibitory site, Y529, in response to adhesion to ECM (41,42). These cells spread more slowly and display reduced tyrosine phosphorylation of FAK, paxillin and p130Cas (40,41). In addition, Shp-2 may indirectly regulate Src activity by regulating the recruitment of Csk to the membrane. Csk is recruited to the membrane via association with tyrosine phosphorylated PAG (phosphoprotein associated with glycosphingolipid-enriched microdomains), a transmembrane glycoprotein. Shp-2 dephosphorylates PAG and abolishes the Csk binding site, resulting in a reduction in membrane associated Csk and a reduction of Csk-mediated Src inhibition (42). Thus Shp-2 may activate Src both by directly acting on its C-terminal phosphorylation site and by alleviating inhibitory constraints on Src recruitment. A protein that may act in parallel to PAG is SHPS-1 (SIRPα1). Like PAG, SHPS-1 recruits Shp-2 to the membrane and is a target for its activity (41,43).

PTPα is a receptor type, transmembrane PTP involved in the activation of SFKs and in integrin signaling pathways. Ectopic expression of PTPα enhances the dephosphorylation of the c-terminal Y529, strongly activating src and fyn kinases (39). Cells lacking PTPα spread more slowly and contain decreased tyrosine phosphorylation of focal adhesion components (44,45). The decrease in tyrosine phosphorylation of FAK, especially at autophosphorylation site Y397, in PTPα/-/- cells suggests that this phosphatase lies between integrins and the activation of FAK (46). PTPα and the integrin αvβ3 co-immunoprecipitate from cells spreading on ECM substrates (47). This association has been shown to be involved in the activation of SFKs following integrin engagement, which, in turn, is involved in the reinforcement of integrin-cytoskeletal forces in response to tension (47). In this study, the SFK involved was Fyn rather than Src. No evidence for an interaction between β1 integrins and PTPα was seen, but because similar downstream responses are observed for β1 and β3 integrins, it seems likely that parallel pathways may operate, possibly involving different PTPs and different SFKs.

In platelets, activation of Src occurs rapidly in response to integrin engagement, whereas FAK activation is a relatively late event (33). The association of Src with the β3 cytoplasmic domain involves binding via its SH3 domain, relieving one of the inhibitory constraints on Src (37). With platelet αIIb/β3, the activation involves release of associated Csk from the integrin/SFK complex and the subsequent recruitment of PTP1B. Interestingly, the recruitment of PTP1B requires tyrosine phosphorylation of PTP1B and is blocked by Src inhibitors (37). This implies that some level of Src activation must precede the recruitment of PTP1B. Shattil and colleagues propose a model in which binding of αIIb/β3 to fibrinogen induces micro-clustering of αIIb/β3, juxtaposing Src molecules so that these cross-phosphorylate on Y416. It is suggested that this results in initial activation sufficient to phosphorylate and recruit PTP1B, which, by removing the C-terminal phosphorylation of Src results in full activity. In this model, many of the subsequent tyrosine phosphorylations, including FAK activation, are triggered downstream from these initial events (37).

3. Differential PTP1B signaling in various cell types

With regard to its role in ECM adhesion, conflicting results have been reported for PTP1B. The finding that PTP1B binds and acts on p130Cas (48) led to experiments investigating the
effects of expressing wildtype or mutant forms of PTP1B unable to bind to p130Cas in cell adhesion situations. Expression of wildtype but not mutant PTP1B slowed fibroblast spreading and depressed tyrosine phosphorylation of p130Cas and other proteins in response to adhesion (49). In addition, the expression of wildtype PTP1B enhanced the assembly of focal adhesions with short thick stress fibers, and decreased cell migration. Consistent with these findings, depressing PTP1B expression in vascular smooth muscle enhanced tyrosine phosphorylation of p130Cas and stimulated migration (50). Seemingly contradictory results, however, were obtained in another study in which wildtype or catalytically dead PTP1B were expressed in L cells (51). In these experiments, expression of the wildtype PTP1B did not depress tyrosine phosphorylation in response to adhesion to fibronectin, whereas expression of a catalytically dead mutant did. Expression of the inactive mutant also suppressed Src activity and depressed cell attachment to a fibronectin substratum. Additionally, the cells expressing the mutant PTP1B displayed an elongated morphology, with focal adhesions that were reduced in size and number. A third study examined the behavior of fibroblasts derived from PTP1B null mice (52). In this work, the cells lacking PTP1B exhibited delayed spreading on a fibronectin-coated surface, but surprisingly little effect was found in terms of tyrosine phosphorylation in response to adhesion to fibronectin. However, when wildtype and PTP1B null cells were transformed with SV40Tag, effects on tyrosine phosphorylation were seen. Now the transformed null cells exhibited decreased tyrosine phosphorylation of p130Cas relative to transformed wildtype cells following short periods (20 min) of adhesion to fibronectin. These null cells also showed hyperphosphorylation of the inhibitory site in Src (Y527) in some situations. Notably, the SV40Tag-transformed fibroblasts revealed an increased expression of PTP1B relative to primary mouse embryo fibroblasts, possibly accounting for the differences between the transformed and primary cells.

Can these apparently conflicting observations with PTP1B be reconciled? As the authors have suggested, cell type differences may be critical, especially given that SV40Tag-transformed cells elevate expression of PTP1B (52). Cell types may also diverge both as to where PTP1B is acting in adhesion signaling pathways and in the degree of compensation by other PTPs. For example, in some cell types PTP1B may have a major role regulating the C-terminal inhibitory phosphorylation site of SFKs, whereas in other cell types different PTPs (e.g. PTPα or Shp-2) may be more important. P130cas is a major substrate for Src and so in cells in which PTP1B is regulating Src activity, one would predict lower phosphorylation of p130Cas when PTP1B is absent or inactive (51,52). However, in other cell types where different PTPs may be more critical in regulating SFK activity, the effect of depressing PTP1B activity would be predicted to be less significant in terms of p130Cas phosphorylation. Since PTP1B can also dephosphorylate p130Cas, it would not be surprising in these cells to observe that over-expression of wildtype PTP1B decreases the phosphorylation of this target protein (49).

One of the striking observations from Chernoff’s group is that the cells over-expressing PTP1B revealed enhanced focal adhesions and stress fibers (49). This is suggestive of increased RhoA activity and could arise because of dephosphorylation and inactivation of a regulatory protein such as p190RhoGAP. However, this phenotype could also result from defective focal adhesion disassembly (see below).

4. Focal adhesion disassembly: Downstream regulation by PTPs

With the discovery of FAK activation in response to integrin-mediated adhesion, it was widely interpreted that tyrosine phosphorylation promoted focal adhesion assembly. However, the phenotype of FAK knockout cells, as well as cells in which FAK was displaced from focal adhesions, revealed robust and stable focal adhesions in the absence of FAK and tyrosine phosphorylation detectable by immunofluorescence (53,54). Rather than assembly of focal adhesions, FAK activity correlated with focal adhesion turnover and disassembly (5). While several pathways downstream of FAK could contribute to focal adhesion disassembly (5,19,55-59), a novel, endocytic pathway (60) suggests a potentially important role for an as yet unidentified PTP. In this work, tyrosine phosphorylated FAK was found to recruit dynamin to focal adhesions (60).
Dynamin is a protein involved in endocytosis and expression of a dominant negative form of dynamin that inhibits endocytosis blocked focal adhesion disassembly. The association of FAK with dynamin is mediated by the adaptor protein Grb2, which binds to phosphorylated Y925 in FAK and to the proline rich region of dynamin. Expression of the non-phosphorylatable FAK mutant, Y925F, failed to rescue focal adhesion disassembly in FAK null fibroblasts (60).

Identification of the PTP that removes the phosphate from Y925 in FAK will be important. Based on the above information, it would be predicted that this PTP would have a key role in regulating focal adhesion disassembly and, by extension, in regulating cell migration. In order for cells to migrate, focal adhesions must be disassembled so that strong adhesions to the underlying ECM can be released. The PTP that mediates dephosphorylation of Y925 in FAK would be anticipated to increase focal adhesion stability and decrease migration when it is overexpressed, but to increase migration rates and the turnover of focal adhesions when it is inhibited or knocked out. This phenotype matches that described by Liu and coworkers when they overexpressed PTP1B in fibroblasts (49) and it will be interesting to learn whether PTP1B or another PTP regulates the phosphorylation status of Y925 in FAK.

Concluding remarks

PTPs play critical roles in cell-matrix adhesion dynamics, an important component of cell migration. An exciting area is the potential involvement of PTPs in the initiation of signals following integrin engagement. It will be interesting to determine whether different integrins associate with specific PTPs and whether by activating different members of the Src family these trigger distinct signaling cascades. Downstream of adhesions to the ECM, several proteins become tyrosine phosphorylated; many of these proteins are phosphorylated on multiple residues. Different PTPs are able to target specific residues on phosphorylated proteins, and elucidating which sites are the targets for particular PTPs will contribute to understanding how different PTPs can influence the outcome of signaling pathways. Whereas most attention has been directed toward the role of PTPs in regulating tyrosine phosphorylation downstream of integrins, PTPs are also important upstream, regulating the assembly and disassembly of ECM adhesions. For instance, the action of PTPs on Rho family GEFs and GAPs is only beginning to be investigated, but promises to be crucial to understanding the dynamics of cell-matrix adhesion.

REFERENCES


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Abbreviations: PTK, protein tyrosine kinase; PTP, protein tyrosine phosphatase; RPTP, receptor protein tyrosine phosphatase; ECM, extracellular matrix; SFK, Src family kinase; GEF, guanine nucleotide exchange factor; GAP, GTPase activating protein; FAK, focal adhesion kinase; LMW-PTP, low-molecular weight protein tyrosine phosphatase; ROS, reactive oxygen species

Figure 1. PTP regulation of integrin-mediated adhesion signaling and focal adhesions. Upstream, the clustering of integrins is determined by RhoA-GTP levels (activity). PTPs can regulate the activity of Rho proteins by controlling the phosphorylation states of GEFs and GAPs. Downstream, integrin...
clustering leads to SFK and FAK activation. PTPs can both activate and inhibit SFKs by removing inhibitory or activating phosphorylations. Regulating the tyrosine phosphorylation of downstream targets such as FAK regulates the dynamics and disassembly of focal adhesions.
Table 1. Regulation of Rho-GTPase activity by PTPs

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<th>PTP</th>
<th>GTP level</th>
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* implied from phenotype, GTP levels not measured
Table 2. Binding partners and substrates for PTPs involved in regulating cell-matrix adhesion

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