Cell migration requires a highly coordinated interplay between specialized plasma membrane adhesion complexes and the cytoskeleton. Protein phosphorylation/dephosphorylation modifications regulate many aspects of the integrin-cytoskeleton interdependence, including their coupling, dynamics, and organization to support cell movement. The endoplasmic reticulum-bound protein tyrosine phosphatase PTP1B has been implicated as a regulator of cell adhesion and migration. Recent results from our laboratory shed light on potential mechanisms, such as Src/FAK signaling through Rho GTPases and integrin-cytoskeletal coupling.

Introduction

PTP1B is a non-receptor protein tyrosine phosphatase of 50 kDa, with an N-terminal catalytic domain of 240 residues, followed by a regulatory region containing SH3-binding, sumoylation, and phosphorylation motifs, and a C-terminal tail of 35 amino acids that targets the enzyme to the endoplasmic reticulum (ER). The catalytic domain of ER-bound PTP1B faces the cytosol, having the potential for substrate dephosphorylation throughout the extensive and dynamic branching network occupied by the ER. Extension of the ER toward the cell periphery allows PTP1B to dephosphorylate substrates located at the plasma membrane, for example Src, EphA3, and proteins associated to cadherin and integrin complexes. Alternatively, PTP1B can dephosphorylate the cytosolic domains of endocytosed receptors, which are brought into contact with the ER, as, for example, activated platelet-derived growth factor and epidermal growth factor receptors. Through the proline-rich motif, PTP1B has also been shown to interact directly with components of focal adhesions, such as the SH3 domain of adaptor protein p130Cas. Under specific stimulation, PTP1B is sensitive to cleavage by calpains at a site upstream from the ER-targeting sequence, producing a soluble and active 42 kDa form. This truncated form of PTP1B is required for Src-dependent formation of invadopodia and breast cancer invasion.

The identification of PTP1B substrates has been greatly benefited by the generation of efficient substrate trap mutants that lock the enzyme and substrate in stable “dead-end” complexes. This approach combined with quantitative mass spectrometry has recently been used to identify PTP1B substrates under different stimulatory conditions.

PTP1B is an important physiological modulator of insulin and leptin receptor signaling in mice and has attracted much interest as a potential drug target for diabetes and obesity. Due to its activity on several signaling proteins that promote cell growth, PTP1B has also been implicated in oncogenesis, although its exact role is complex and apparently context dependent. It is now recognized that PTP1B has multiple substrates, which, in turn, are involved in a wide range of fundamental cellular processes, such as cell adhesion, signaling, intracellular transport, motility, apoptosis, and proliferation. In this commentary we will focus on accumulating evidence implicating PTP1B in the regulation of cell adhesion and motility.
Long-Range Impact of PTP1B on Cell Adhesion and Motility

As demonstrated for the regulation of cell growth and transformation, the regulatory role of PTP1B in cell adhesion and motility is complex and apparently dependent on the cell type and context. PTP1B was shown to promote cell adhesion and motility in fibroblasts, neurons, platelets, and several tumor cell lines. An inhibitory role has been described in fibroblasts, primary aortic smooth muscle cells, ovarian cancer cells, and in glioblastoma multiforme tumor cell invasion in mice. Remarkably, the positive role of PTP1B in cell motility was frequently associated with the stimulation of integrin-dependent signaling.

In contrast, the negative effect of PTP1B on cell motility was related to antagonizing signaling from growth factor receptor tyrosine kinases. In a recent quantitative study, we analyzed the intrinsic motility and migration parameters of PTP1B-null cells (KO cells) in an isotropic 2-D fibronectin substrate. Directionality and average velocity of KO cells were significantly reduced when compared with KO cells reconstituted with wild-type PTP1B (WT cells). These effects could be partially explained by a higher tendency of KO cells to pause during migration. Visual inspection of cell morphology and kymograph analysis of the leading edge further revealed that migration of KO cells was characterized by fast extension/retraction of lamella produced in multiple directions, while WT cells persistently extended a broad lamella in the direction of movement.
and retina transfected with a dominant negative PTP1B construct, displayed axonal growth cones with similar lamellar alterations as those observed in the leading edge of KO fibroblasts. Consistently, axons also showed reduced net elongation rate and increased pause times compared with axons of control neurons. Collectively, these results strongly suggest that PTP1B promotes cell migration by mechanisms that stabilize lamellar protrusions.

**Microtubules Contribute to Position ER-Bound PTP1B at the Leading Edge**

A wide range of cell types move by extension of morphologically, functionally, and structurally different structures called lamellipodia and filopodia at the leading edge. The lamellipodium contains a polarized and dynamic F-actin array that grows and pushes the leading edge in the direction of movement. During this process, nascent adhesions assemble within the lamellipodium. Microtubules are required for protrusion and dynamics of the leading edge in fibroblasts and epithelial cells, affecting F-actin assembly and organization, as well as adhesion stability. Cortical microtubules interact with and pull ER tubules toward the cell periphery, partially by their association with the microtubule plus end directed kinesin-1. Kinesin binds to the ER transmembrane protein kinesin and interfering this binding produces the collapse of the peripheral ER.

In neurons, microtubule-dependent localization of ER-bound PTP1B at the peripheral region of axonal growth cones is critical for Src activation and filopodia stability. In migrating fibroblasts, the ER network extends toward the leading edge, positioning GFP-PTP1B over new adhesions assembled at the advancing lamella (Fig. 1A and B). Remarkably, the substrate trap mutant PTP1B D181A, which considerably increases the steady-state substrate trap, is not activated by ER-bound PTP1B. Instead, the enzyme-substrate complex is catalytically inactive mutant GFP-PTP1B (C215S). In addition, short-lived adhesions, which are more abundant in KO cells, displayed higher paxillin disassembly rates than those in WT cells. These results establish that by modulating adhesion lifetimes, ER-bound PTP1B promotes persistent lamellar protrusion and directional migration (Fig. 1F). These findings explain why the ER extension in lamellar extensions contributes to cell spreading, migration, and focal adhesion growth.

**PTP1B Regulation of Cell-Matrix Coupling to the Cytoskeleton**

Cell-matrix interactions activate signaling pathways that regulate different aspects of cell migration, such as adhesion and cytoskeletal organization and dynamics. The focal adhesion kinase FAK is a key signaling component of cell-matrix adhesions which regulates directional cell movement and adhesion dynamics. FAK is required for vinculin and talin recruitment to cell-matrix complexes, enhancing integrin-cytoskeletal coupling. FAK may also decrease integrin-cytoskeleton linkages through α-actinin phosphorylation, which reduces its affinity for actin. Biochemical experiments performed in COS and PTP1B-null cells suggested that PTP1B could dephosphorylate α-actinin and promote chemotaxis to fibronectin. We postulated that

| Substrate and targeted Tyr (Y) | Function | Localization (A) adhesions (L) Lamellipodium | References |
|-------------------------------|----------|---------------------------------------------|------------|
| Caveolin-1 (Y14)              | Scaffold protein | L | 14,53–55 |
| Cortactin (Y446)              | Scaffold protein | L | 14,56–58 |
| Alpha-actinin (Y12)           | Scaffold protein | L | 28,43 |
| CrkII (Y221)                  | Adaptor protein | A | 22,59,60 |
| Cas-L (Y189)                  | Adaptor protein | A | 14,50 |
| PI20 catenin (257)            | Scaffold protein | L | 14,61,62 |
| Src (Y529)                    | Non receptor PTK | A | 4,8,17,28,45 |
| EphA3 (Y595,603,779)          | Eph receptor tyrosine kinase | ND | 6,14,63 |
| Paxillin (Y118)               | Adaptor protein | A | 14,22 |

Listed proteins and candidate tyrosine residues (between brackets) identified as PTP1B substrates and as regulators of adhesion and migration. Localization was based on spatial co-localization and/or co-immunoprecipitation analysis. ND, not determined. Many of the listed proteins were isolated in a phosphoproteomic screen using PTP1B wild-type and null cells, as well as in vitro pull down with wild-type and substrate trap D181A PTP1B.
PTP1B dephosphorylates α-actinin in adhesions facilitating its binding to actin (Fig. 1G). This process could reinforce integrin-cytoskeleton linkages, contributing to extend the lifetimes of adhesions. In support to this notion, Bimolecular Fluorescence Complementation (BiFC) analysis revealed the presence of catalytic PTP1B/α-actinin complexes overlapping with paxillin adhesions at lamellar extensions. In addition, we observed that small paxillin adhesions assembled during lamellar protrusion in KO cells did not incorporate α-actinin efficiently and were quickly disassembled. In contrast, most adhesions assembled during lamellar protrusion in WT cells incorporated α-actinin and grew in size. These results strongly support the assumption that α-actinin is a substrate of PTP1B in adhesions, and that its dephosphorylation enhances adhesion/cytoskeleton coupling and lamellipodium growth (Fig. 1G). Our results also suggest that PTP1B function is relevant during the phase of lamellar protrusion, since PTP1B-null cells had the capacity to incorporate α-actinin in paxillin adhesions, which grew in size during lamellar retractions. Two candidate protein tyrosine phosphatases that could be involved in adhesion growth and maturation during lamellar retractions are SHP2 and RPTPα, both of which were implied in matrix force transduction. However, only SHP2 was demonstrated to modulate α-actinin dephosphorylation via the regulation of FAK activity.

**PTP1B Regulation of Cell-Matrix-Dependent Signaling to Rho GTPases**

In an early study, we found that the expression of a dominant-negative mutant of PTP1B in fibroblasts impaired integrin-dependent signaling, including FAK and Src activation, and paxillin phosphorylation. Src activation by PTP1B was further demonstrated in several different cell models. Using a combination of time lapse, total internal reflection fluorescence microscopy, and BiFC we were able to visualize ER-bound PTP1B/Src complexes as small fluorescent puncta distributed uniformly at the plasma membrane in contact with the substrate. The substrate trap mutation (D181A) in PTP1B and the tyrosine 529 at the C-tail of Src were both required for BiFC to occur, as well as the plasma membrane targeting motif of Src. This study also shows dynamic projections of ER tubules toward the plasma membrane, suggesting the assembly of catalytic PTP1B/Src BiFC complexes at random point locations in the plasma membrane/substrate interface. Nevertheless, the possibility that Src could also be targeted by PTP1B at typical adhesion structures cannot be excluded (Fig. 1E and F). We propose that PTP1B dephosphorylates the tyrosine 529 (in mouse Src) at the C-terminal region of Src, unlocking the negative regulation imposed by the phosphorylation of this residue, and releasing the Src SH2 domain. The latter event could promote the intermolecular interaction of Src with partners localized at cell-matrix adhesions. For example, the clustering and autophosphorylation of FAK in integrin adhesions could recruit Src via an SH2-pY interaction, assembling an active Src/FAK signaling complex. This complex promotes Rac1 activation through the phosphorylation of two major adaptor proteins, paxillin and p130Cas. Rac1 activity drives actin polymerization and adhesion formation at the extending lamellipodium. PTP1B may also reinforce this pathway by dephosphorylation of the adaptor protein CrkII, which promotes its binding to the adaptor proteins p130Cas and paxillin. CrkII dephosphorylated by PTP1B preferentially binds to and protects tyrosine phosphorylated p130Cas from dephosphorylation, event which could promote cell migration by facilitating the activation of Rac1 at the membrane. It has been shown that PTP1B is able to directly dephosphorylate p130Cas and promote spreading, although the relevant tyrosine substrates were not identified. A more recent phosphoproteomic study identified Cas-L/HEF-1/NEDD9, a member of the p130Cas family, as a potential PTP1B substrate. Interestingly, the phosphorylated state of one of the target tyrosines, Tyr-189, was shown to be important for adhesion stability and cell migration. The role of PTP1B in these processes involving Cas-L remains to be determined.

The Src/FAK signaling axis also promotes RhoA inactivation/activation through the temporally regulated phosphorylation and activation of p190RhoGAP and p190RhoGEF, respectively. Biochemical determinations of GTPase activity in response to integrin stimulation showed that RhoA activity was downregulated and Rac1 and Cdc42 activities were upregulated at early time points, while these activities were reversed at later time points. Consistently, Rac1 and Cdc42 activities were required for protrusion and adhesion initiation, while Rho activation was required to increase actomyosin contractility and to promote adhesion maturation. Our recent study showed that initial integrin-mediated downregulation of RhoA activity and induction of Rac1 activity were impaired in PTP1B KO cells. Thus, microtubule-dependent positioning of PTP1B at the leading edge of migrating cells may contribute to downregulate RhoA and stimulate Rac1 activities required for adhesion stability and lamellipodium protrusion (Fig. 1G). This notion agrees with results suggesting that microtubules contribute to RhoA downregulation and participate in a positive feedback loop with Rac1 that promotes leading edge protrusion in slow moving cells.

**Conclusions**

Recent studies from our laboratory illustrate how the seemingly spatial restriction imposed by the anchor of PTP1B to ER membranes, can eventually be compensated by the dynamics of the ER. ER tubules extend to the cell periphery in a microtubule-dependent manner, positioning PTP1B at a spatial range compatible with enzyme-substrate interactions. PTP1B regulates the activity of several substrates implicated in cell adhesion and motility (see Table 1). Our work has identified α-actinin and Src as two PTP1B substrates playing critical roles in adhesion dynamics and signaling. By acting on α-actinin, PTP1B contributes to adhesion/cytoskeleton coupling and adhesion stability. By promoting the activation of Src, PTP1B stimulates signaling pathways that promote Rac1 activation and inhibit RhoA. Both molecular mechanisms
regulated by PTP1B may explain its long-range effects on lamellar dynamics and directional cell migration.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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