Should I stay or should I go?
Shedding of RPTPs in cancer cells switches signals from stabilizing cell-cell adhesion to driving cell migration

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Dissolution of cell-cell adhesive contacts and increased cell-extracellular matrix adhesion are hallmarks of the migratory and invasive phenotype of cancer cells. These changes are facilitated by growth factor binding to receptor protein tyrosine kinases (RTKs). In normal cells, cell-cell adhesion molecules (CAMs), including some receptor protein tyrosine phosphatases (RPTPs), antagonize RTK signaling by promoting adhesion over migration. In cancer, RTK signaling is constitutive due to mutated or amplified RTKs, which leads to growth factor independence or autonomy. An alternative route for a tumor cell to achieve autonomy is to inactivate cell-cell CAMs such as RPTPs. RPTPs directly mediate cell adhesion and regulate both cadherin-dependent adhesion and signaling. In addition, RPTPs antagonize RTK signaling by dephosphorylating molecules activated following ligand binding. Both RPTPs and cadherins are downregulated in tumor cells by cleavage at the cell surface. This results in shedding of the extracellular, adhesive segment and displacement of the intracellular segment, altering its subcellular localization and access to substrates or binding partners. In this commentary we discuss the signals that are altered following RPTP and cadherin cleavage to promote cell migration. Tumor cells both step on the gas (RTKs) and disconnect the brakes (RPTPs and cadherins) during their invasive and metastatic journey.

Introduction
Migration, invasion and metastasis of tumor cells are responsible for most cancer-related mortality. Understanding how tumor cells acquire a migratory phenotype to become invasive and metastatic is crucial to developing effective strategies to block tumor progression. The first step in tumor cell invasion is dissolution of cell-cell adhesions in favor of cell-matrix adhesions that support cell migration. Once the cell has freed itself from the original tumor mass, it reorganizes its actin cytoskeleton forming membrane protrusions stabilized by adhesions to the extracellular matrix (ECM) that facilitate directed cell movement (Fig. 1). Cells migrate in response to extracellular cues such as growth factors, which bind their cognate receptor protein tyrosine kinases (RTKs) at the cell surface. RTK activation initiates signaling cascades that contribute to the destabilization of cell-cell adhesions and promote migration by influencing the reorganization of the actin cytoskeleton. Activation of RTKs typically involves receptor dimerization and subsequent trans-autophosphorylation of a series of tyrosine residues within the cytoplasmic domain of the RTK. The phosphotyrosine residues provide docking sites for the recruitment and activation of downstream signaling molecules containing SH2 or PTB domains. Activation of RTKs initiates multiple signaling pathways, but for simplicity, we will comment only on a subset of signaling molecules downstream of RTKs that influence cell motility. These

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include phospholipase Cγ1 (PLCγ1), protein kinase Cs (PKCs), Src family kinases, Rho GTPases, catenins and IQGAP1 (Fig. 2).

At the plasma membrane, the activity of RTKs is counter-balanced by receptor protein tyrosine phosphatases (RPTPs). RPTPs serve to terminate signals generated by RTKs, maintaining appropriate spatial and temporal signaling; if RTKs are the gas pedal for migration, RPTPs are the brakes. In tumor cells, RTK activity is often constitutive due to RTK gene mutation or amplification. This gives tumor cells an advantage over non-cancerous cells because the tumor cells no longer depend on growth factors to drive cell migration. RPTPs are often inactivated in human tumors, at both the genetic and epigenetic level, suggesting they are important regulators of tumor progression. Tumor-specific methylation within the 5′ regulatory region of genes encoding RPTPs has been observed in several human cancers resulting in loss of gene expression. Furthermore, inactivating mutations in the RPTP tumor suppressor genes LAR, PTPβ, PTPδ and DEP-1 have been identified in several human cancers. Changes in RPTPs at the protein level such as cleavage of PTPμ and PTPδ have been associated with tumor progression.

For a comprehensive review of RPTPs associated with human cancers, see Julien et al. For microarray studies focused on PTPs in cancer see Tiscornia et al. and McArdle et al.

Cell adhesion molecules (CAMs) are transmembrane glycoproteins expressed on the cell surface that mediate both cell-cell and cell-ECM interactions. Cell-cell CAMs include the cadherins and immunoglobulin (Ig)-like CAMs while integrins mediate cell-ECM adhesions. In general, cadherin based cell-cell adhesions are associated with stable cell-cell adherens junctions that suppress a migratory phenotype while the integrin-mediated cell-ECM adhesions are associated with the promotion of cell motility (Fig. 1).

Tyrosine phosphorylation of the cadherin/catenin complex by activated RTKs, or by members of the Src family of tyrosine kinases (activated downstream of RTKs) destabilizes cell-cell adhesions to promote cell-matrix adhesion. RPTP activity tends to stabilize cell-cell adhesion and suppresses migration.

There is accumulating evidence in the literature that cell-cell CAMs, including RPTPs and cadherins, are downregulated in tumor cells by proteolytic cleavage at the cell surface. Proteolysis results in shedding of the extracellular, adhesive segment and displacement of the intracellular segment, altering its subcellular localization and the availability of substrates or binding partners. Cleavage of most cell-cell CAMs follows a model similar to that described for the Notch receptor. Notch is processed by three sequential proteolytic events, a process also known as regulated intramembrane proteolysis. The first cleavage event takes place in the trans-Golgi and is mediated by a furin-like convertase.
RPTPs

The structure of RPTP family members is diverse, but most possess CAM-like domains in their extracellular segments and one or two catalytic domains in their intracellular segments. Based on the structure of their extracellular segments, RPTPs have been divided into eight subfamilies. Four subtypes (type II–V) have thus far been shown to be cleaved. The type II RPTPs are members of the Immunoglobulin (Ig)-like superfamily of CAMs and include the IIa RPTPs [LAR, PTPδ and PTPσ (CRYPα)] with Ig and fibronectin III (FNIII) repeats, and the IIb RPTPs (PTPμ, PTPκ, PCP-2 and PTPρ) with a MAM domain, an Ig domain to the destabilization of cell-cell adhesions and disruption of protein-protein interactions at the plasma membrane. Meanwhile, unchecked membrane-based RTK signaling sustains the pro-migratory signals initiated by molecules such as PLCγ1. In this commentary, we discuss the intracellular consequences of RPTP and cadherin cleavage with a focus on the signaling cascades downstream of RTKs that regulate both cell-cell adhesion and migration. We propose that cleavage of RPTPs and cadherins contributes to a migratory phenotype not only through shedding of their adhesive, extracellular domains but also by shifting the subcellular localization of the new intracellular fragments to impact signaling.
and four FNIII repeats in their extracellular segments. Type III RPTPs (PTPβ/VE-PTP, DEP-1/PTPη, SAP-1, GLEPP1, PTPS31) have multiple FNIII repeats in their extracellular segments, and a single phosphatase domain in their intracellular segment. Members of the type IV RPTP subfamily (PTPκ and PTPε) have short, highly glycosylated ECDs with no known structural motifs. Members of the type V subfamily (PTPζ and PTPμ) are characterized by an extracellular carbonic anhydrase-like (CA) domain, a glycosylated unique spacer region and a single FNIII repeat. RPTPs can participate in both homophilic interactions; i.e., the RPTP binds an identical RPTP on an adjacent cell and heterophilic interactions where a distinct protein serves as the ligand for the RPTP. We recently covered the ligands for these RPTPs in another review.14 With regard to migration, several RPTPs can mediate adhesion as well as regulate both cell-cell and cell-extracellular matrix (ECM) adhesions by direct interaction with, and dephosphorylation of adhesion complex components.20,21 Therefore, any change in the activity of RPTPs that associate with adhesion complexes could alter cell adhesion to promote migration.

It is interesting to note that some of the same RPTPs inactivated at the transcriptional level in cancer,7 are known to be regulated at the post-translational level via proteolysis.14 Type IIa (LAR, PTPβ, PTPα) IIb (PTPμ, PTPκ) and V (PTPζ/β) RPTPs have been demonstrated to be cleaved by a Notch-like mechanism, to yield shed ECDs and membrane-free intracellular domains (ICDs), which localize to the cytosol and nucleus.33 The proteases responsible for the shedding of some RPTPs are known. ADAM-17/TACE activity induces the shedding of LAR.22 ADAM-17 and MMP-9 are implicated in the shedding of PTPζ/β,23 while ADAM-10 has been identified as the protease that cleaves PTPκ.24 Proteolysis of PTPκ and PTPε is not mediated by a Notch-like mechanism. Instead, these RPTPs are cleaved by calpain.25 The in vivo mechanism, to yield shed ECDs and demonstrated to be cleaved by a Notch-like proteases has been observed in many cancers and may be the cause of constitutive cleavage of CAMs in some tumors.23 Cleavage of RPTPs can have profound effects on cells due to the loss of their adhesive ECD and displacement of the enzymatically active phosphatase domain in the ICD.

**Regulation of RTK activation by RPTPs.** Several RPTPs are known to interact with and dephosphorylate RTKs. LAR has been shown to decrease the activity of multiple RTKs including the insulin receptor, the hepatocyte growth factor (HGF) receptor, the epidermal growth factor receptor (EGFR), and Ret.26-27 PTPσ dephosphorylates EGFR and Ret,27,28 while PTPα can dephosphorylate EGFR.29 Finally, PTPζ/β dephosphorylates the RTK Anaplastic lymphoma kinase (ALK).30 In these instances, RPTP dephosphorylation reduces RTK activity. Therefore, some RPTPs can regulate migration initiated by RTKs by directly affecting the activity of the RTK. RPTPs can also regulate downstream signaling of RTKs by interaction with, and in some cases dephosphorylation of, RTK activated molecules. These include PLCγ1, classical and novel PKCs, IQGAP1, β-catenin and pl20-catenin as discussed below.21,31,32

**Signals Downstream of RTKs that are Regulated by RPTPs to Control Cell Migration.**

PLCγ1. PLCγ1 is implicated in the invasion and metastasis of several tumor types in response to both RTK and integrin activation.33,34,35 Upon RTK activation, PLCγ1 is recruited to the plasma membrane via its SH2 domain and phosphorylated on several tyrosine residues including Y783, which is critical to its activation.36 Active PLCγ1 hydrolyzes phosphatidylinositol-(4,5)-bisphosphate (PIP2) to diacylglycerol (DAG) and inositol-trisphosphate (IP3), setting off a signaling cascade leading to the release of calcium (Ca2+), activation of PKC isoforms and release of PIP2-sequestered proteins such as coflin and gelsolin, which promote localized actin polymerization (Fig. 2).33,34

Several signaling pathways initiated by growth factors including PLCγ1 converge on the Rho GTPases to regulate cell migration.37 The Rho-family GTPases, including Rac, Rho and Cdc42, coordinate the assembly and organization of the actin cytoskeletal machinery.38 Activation of Rac is associated with lamellipodia formation at the leading edge of migrating cells whereas Cdc42 regulates filopodia formation and cell polarity. Rho activation induces stress fiber formation and the assembly of focal adhesions. Rho-family GTPases are molecular switches that cycle between an active GTP-bound state and an inactive GDP-bound state. The nucleotide state of the GTPases is controlled by guanine nucleotide exchange factors (GEFs) that promote GTP loading and GTPase-activating proteins (GAPs), which increase the molecule’s intrinsic GTPase activity to hydrolyze GTP to GDP.39 GAPs and GEFs are critical for the spatial and temporal coordination of Rho GTPase activity and the regulation of these molecules is key to the control of actin remodeling to promote migration.39 Several GEFs and GAPs are activated in response to growth factor stimulation via tyrosine phosphorylation. The regulation of GEF and GAP activity ultimately controls cell migration via the Rho GTPases.37 PLCγ1 activity is required for Rac1 activation and subsequent lamellipodia formation downstream of RTKs. The SH3 domain of PLCγ1 has been shown to possess GEF activity towards Rac1.40 In addition, PLCγ1 forms a complex with the β-Pix GEF and GIT1, which is required for Rac1 and Cdc42 activation and integrin-mediated cell spreading.41 Although the mechanism of Rac1 and Cdc42 activation downstream of PLCγ1 may vary depending on the stimulus, there is a clear requirement for PLCγ1 in the modulation of actin structures downstream of RTK activation.35,34

Recently, we published that PLCγ1 is a substrate for the RPTP, PTPμ.32 We predicted that dephosphorylation of PLCγ1 by PTPμ would inactivate PLCγ1 and antagonize migration. PTPμ itself is able to mediate cell-cell adhesion and regulate cadherin-dependent adhesion.42-44

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PTPμ is downregulated in human glioblastoma (GBM) tissue samples and shRNA-mediated downregulation of PTPμ in the human glioma cell line, U-87 MG, induces a migratory phenotype. Blocking PLCγ1 activity reversed the migratory phenotype induced by the downregulation of PTPμ implying PLCγ1 activity is required for migration induced by PTPμ downregulation. There is evidence that the decrease of PTPα observed in GBM is achieved by constitutive cleavage. Loss of PTPμ expression at the plasma membrane in cancer cells would reduce its ability to dephosphorylate and inactivate PLCγ1, allowing PLCγ1 to promote migration through the activation of downstream pathways that modulate the actin cytoskeleton (Fig. 2).

PKCs. Downstream of PLCγ1, the second messengers DAG and IP3 contribute to the activation of classical and novel isoforms of the PKC serine/threonine kinases. Activated PKCs are targeted to specific cellular locations based on binding to scaffolding proteins, such as the Receptor for Activated C Kinase 1 (RACK1). Src phosphorylated PKCδ (Y311) is a substrate of PTPμ, and PCKδ is likely recruited to PTPμ via the scaffolding protein RACK1. E-cadherin-mediated adhesion is regulated by PCKδ. We hypothesize that proteolysis of PTPμ would reduce its phosphatase activity at the plasma membrane, thus regulating PCKδ activity and altering E-cadherin mediated adhesion.

PKCα or PKCβ may be RPTPζ/β substrates, as stimulation of RPTPζ/β with its ligand, pleiotrophin (which activates the receptor, reviewed in ref. 50), induces PKC activation and phosphorylation of its substrate, β-adducin. This, in turn, decreases β-adducin’s ability to stabilize filamentous actin with spectrin at the plasma membrane, thereby disrupting cytoskeletal integrity and cell-cell adhesions and promoting cytoskeletal remodeling. β-adducin is also phosphorylated on tyrosine residues by the Src family kinase Fyn and is itself a substrate of RPTPζ/β. Tyrosine phosphorylation of β-adducin results in its recruitment to the plasma membrane thus decreasing the cytoplasmic pool of β-adducin available to stabilize the actin cytoskeleton, enabling cells to reorganize their actin cytoskeleton and initiate migration. We hypothesize that cleavage of the constitutively active RPTPζ/β would yield the same effect as pleiotrophin stimulation. Cleavage would reduce RPTPζ/β phosphatase activity, thereby destabilizing the actin cytoskeleton to promote migration by increasing both serine/threonine and tyrosine phosphorylation of β-adducin.

Stimulation of RPTP ectodomain cleavage often occurs in response to phorbol ester stimulation. Phorbol esters tend to activate PKCs. PKC activity has been shown to be required for the transcriptional regulation of PCP-2 expression and for the phosphorylation of PTPα, which may affect its activity. It remains to be seen whether PKC activity is also required for the cleavage of RPTPs from the plasma membrane.

Signals Downstream of RTKs and Cadherins that Would Be Altered by CAM Cleavage

Classical cadherins mediate calcium dependent homophilic cell-cell adhesion and are the primary adhesion molecules of adherens junctions. The cytoplasmic domain of cadherins is anchored to the actin cytoskeleton through binding of p120-catenin, β-catenin and α-catenin, generating stable cell-cell adhesions. RTKs and their immediate effector molecules such as Src family kinases phosphorylate components of the cadherin-catenin complex to disrupt adhesion. RPTPs help maintain cell-cell adhesions and suppress migration not only by countering the level of tyrosine phosphorylation catalyzed by RTKs, but also by sequestering scaffolding proteins that regulate the reorganization of the actin cytoskeleton. Several RPTPs, including PTPμ, LAR, RPTPβ/β and PTPκ dephosphorylate components of the cadherin-catenin complex, thereby promoting stable cell-cell adhesions. Loss of these RPTPs at the plasma membrane by proteolytic cleavage would contribute to cell migration since they would no longer be in proximity of their cadherin/catenin substrates as discussed below.

Classical cadherins are proteolytically cleaved via a mechanism similar to the Notch and RPT pathway mentioned above. Shed ECD fragments of the classical cadherins are capable of promoting epithelial-to-mesenchymal transition, invasion and cell migration. Furthermore, the ICDs generated are capable of translocating to the nucleus to alter transcription (Fig. 2).

β-catenin. Tyrosine phosphorylation of β-catenin on Y142 by Src tyrosine kinase antagonizes β-catenin function at the cell membrane and results in β-catenin binding to the BCL9-2 transcription factor, nuclear translocation and Wnt gene transcriptional activation. Tyrosine phosphorylation of β-catenin Y489 and Y654, by Abl and EGF receptor and/or Src, respectively, disrupts the interaction between β-catenin and cadherins. Both cytosolic and receptor PTPs, including PTPκ, PCP-2, PTPζ/β, LAR and PTP1B dephosphorylate β-catenin. LAR dephosphorylation of β-catenin in NBT-II cells correlates with a reduction in the levels of cytosolic β-catenin and reduced EGF-stimulated cell migration. Likewise, PCP-2 dephosphorylates β-catenin and ectopic expression of PCP-2 in BHK-21 cells reduces cell migration. PTPζ/β also dephosphorylates β-catenin, although PTPζ/β is inactivated when stimulated with pleiotrophin. Pleiotrophin stimulation, in turn, induces a morphological epithelial to mesenchymal transition in human GBM cells.

Loss of RPTP phosphatase activity from the plasma membrane would likely result in increased β-catenin tyrosine phosphorylation, thus promoting cellular migration. This is supported by studies of PTPκ cleavage, in which PTPκ cleavage has been associated with increased cell migration and translocation of the PTPκ-ICD into the nucleus results in increased β-catenin-regulated transcription. Likewise, cadherin cleavage would promote the translocation of β-catenin from the plasma membrane to the cytosol, as has been demonstrated in the case of N-cadherin cleavage. N-cadherin cleavage is correlated with increased transcription of the β-catenin-regulated gene, cyclin D1.

IQGAP1. IQGAP1 is a cellular scaffolding protein that binds several molecules including β-catenin, E-cadherin, PTPμ, APC, CLIP-170 and members
of the MAP kinase cascade. IQGAP1 modulates the actin cytoskeleton through its interaction with the Rho GTPases Rac and Cdc42 and can promote either cell migration or cell adhesion depending on its interacting partners. IQGAP1 localizes to E-cadherin mediated cell-cell adhesions. The interaction of IQGAP1 with activated Rac1 is required for stable cell-cell adhesion. In response to RTK activation, IQGAP1 localizes to the leading edge of migrating cells where it interacts in a complex with Rac1/Cdc42, APC and CLIP-170 to regulate both actin and microtubule dynamics in the migrating cell (Fig. 2). Although IQGAP1 is required for stable E-cadherin mediated cell adhesion, overexpression of IQGAP1 can disrupt cell-cell adhesion by competing for the α-catenin binding site on β-catenin. IQGAP1 binds β-catenin, un tethering E-cadherin from the actin cytoskeleton and disrupting cell-cell adhesion. This implies the amount of IQGAP1 available to bind β-catenin is tightly regulated, allowing for the precise manipulation of stable cell-cell adhesions or the promotion of migration.

IQGAP1 is present at the lamellipodia of migrating cells and becomes stabilized at nascent cell-cell contacts where it co-localizes with PTPμ. PTPμ’s interaction with IQGAP1 is enhanced when Rac1 and Cdc42 are bound to GTP. We hypothesize that PTPμ binds IQGAP1 when IQGAP1 is bound to Rac1/Cdc42-GTP at cell-cell adhesions. PTPμ binding would sequester IQGAP1 and make it unavailable to interact with β-catenin. If PTPμ is cleaved from the cell surface, it could no longer keep IQGAP1 from interacting with β-catenin, which may lead to disassembly of cadherin-mediated adhesions and promotion of migration. Cleavage of cadherins could also increase the cytoplasmic pool of IQGAP1, leading to IQGAP1 accumulation at the leading edge of migrating cells.

p120-catenin. p120-catenin is tyrosine phosphorylated on as many as eight tyrosine residues by v-Src and on at least one residue, Y228, either directly or indirectly by the EGFR. RPTPs known to dephosphorylate p120-catenin include PTPμ and DEP-1. The function of p120-catenin tyrosine phosphorylation is unclear and has been suggested to both promote and antagonize cadherin-based adhesion.

E-cadherin cleavage to yield E-cad/CTF2 results in its nuclear translocation along with p120-catenin. The presence of the E-cad/CTF2/p120-catenin complex in the nucleus blocks Kaiso-mediated gene repression, resulting in enhanced MMP-7 transcription. One effect of increased MMP-7 expression would be increased proteolysis of cell-cell CAMs, thereby reducing cell-cell adhesion and creating a positive feedback loop for continued proteolytic cleavage of cell-cell CAMs.

p120-catenin regulates the actin cytoskeleton by modulating the activity of the Rho GTPases, RhoA, Rac1 and Cdc42. In general, p120-catenin inhibits RhoA activity and promotes Cdc42 and Rac activity. Overexpression of p120-catenin results in the loss of focal adhesions and perturbation of stress fibers, leading to increased cell migration. Importantly, p120-catenin expression is necessary for anchorage independent growth downstream of Rac1 and Src.

All of these activities are attributed to the ability of p120-catenin to inhibit RhoA activity. Cytoplasmic p120-catenin is proposed to activate Rac1 and Cdc42, possibly through its interaction with the GEF Vav2. More recently, p120-catenin was shown to inhibit RhoA activity by binding to p190RhoGAP, a GTPase-activating protein. Finally, p120-catenin may itself have intrinsic guanine nucleotide dissociation inhibitor (GDI) activity, preventing GDP dissociation from RhoA and thus preventing RhoA activation.

Cytoplasmic p120-catenin is associated with inhibition of RhoA activity and activation of Rac1 and Cdc42, while p120-catenin bound to cadherins is suggested to promote RhoA activation. When considered in light of E-cadherin cleavage, p120-catenin release from the plasma membrane would lead to the inhibition of RhoA activity and the concomitant activation of Rac and Cdc42, resulting in the net effect of potentiating a migratory cell phenotype. Furthermore, cleavage of PTPμ may reduce the ability of PTPμ to dephosphorylate p120-catenin at the plasma membrane, thereby releasing p120-catenin from the cadherin/catenin complex.

Perspectives/Concluding Remarks

The studies described above demonstrate that RPTPs are important regulators of cell adhesion and migration by modulating cadherin- and RPTP-based adhesion and by counteracting RTK initiated signals. Although simplistic, the general assumption is that RTKs promote migration, while RPTPs and cadherins antagonize it (Fig. 1). The fact that RPTPs and cadherins are cleaved in cancer cells to yield a shed ECD and a plasma membrane liberated ICD suggests that all of their associated signaling machinery would also be disrupted. We hypothesize that RPTP and cadherin cleavage would promote cell migration by disrupting the CAMs’ ability to regulate signaling molecules such as PLCγ1, p120-catenin, β-catenin, PKCs and IQGAP1, all of which influence the actin cytoskeleton (Fig. 2).

There is evidence that RTKs may regulate the cleavage of RPTPs, thereby amplifying RTK activation. Cleavage of LAR by ADAM-17/TACE can be stimulated by EGFR signaling via activation of the MAPK, pathway. In addition, the microenvironment of cancer cells promotes CAM cleavage. For instance, N-acetylglucosaminyltransferase-V (GnT-V) is elevated in tumors and promotes CAM cleavage. For instance, N-acetylglucosaminyltransferase-V (GnT-V) is elevated in tumors and induces the glycosylation of PTPκ, targeting PTPκ for proteolytic cleavage.

PTPκ cleavage promotes EGF-mediated tumor cell migration likely because its membrane liberated ICD no longer dephosphorylates EGFR. These positive feedback loops emphasize the insidious means that cancer cells use to drive tumor cell migration, invasion and metastasis throughout the body.

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