Emerging role of paxillin-PKL in regulation of cell adhesion, polarity and migration

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Cell adhesion and motility is of fundamental importance during development, normal physiology and pathologic conditions such as tumor metastasis. Focal adhesion proteins and their dynamic interactions play a critical role in the regulation of directed cell migration upon exposure to extracellular guidance cues. Using a combination of pharmacological inhibitors, knockout and knockdown cells and mutant protein expression, we recently reported that following adhesion and growth factor stimulation the dynamic interaction between paxillin and PKL(GIT2) is regulated by Src/FAK-dependent phosphorylation of PKL and that this interaction is necessary for the coordination of Rho family GTPase signaling controlling front-rear cell polarity and thus directional migration. Herein, we discuss the implications of these observations.

Introduction

Cell adhesion either to adjacent cells or to the surrounding extracellular matrix (ECM), coordinately regulates cell migration towards physical and chemical cues. Coordination of cell adhesion and polarized migration is critical for numerous biological events including embryonic development, the immune response and wound repair. Disregulation of signaling cascades to the cytoskeleton results in abnormal cell morphology and migration, which are frequently observed in many disease conditions, notably cancer cell invasion and metastasis. Thus, it is of fundamental importance to understand how the cell precisely regulates cell adhesion and migration in physiological and pathological contexts. By combining protein knockdown and point mutation analysis, our recent cell culture studies position focal adhesion proteins paxillin, the ArfGAP PKL (also known as GIT2), as well as its binding partner Rac1/Cdc42 GEF PIX (p21 kinase-interacting exchange factor) and serine/threonine kinase PAK (p21-activated kinase) as important integrators of cell adhesion and receptor tyrosine kinase (RTKs) signaling crosstalk, controlling cell polarity and directed migration (Fig. 1).

A challenging question in the cell adhesion and motility field is discerning the mechanism through which cells integrate signaling to coordinate shape changes to promote a distinct front-rear morphology during directional migration. Numerous studies now indicate that the balancing of phosphorylation/dephosphorylation signals, as well as the spatiotemporal regulation of small GTPase activities of the Rho and Arf families play critical roles during this process with new details continuing to emerge. Importantly, ECM-integrin adhesion, in combination with positional growth factor signaling coordinately regulates the localized modulation of adhesion as well as cytoskeleton-membrane organization through activation of the non-receptor tyrosine kinases focal adhesion kinase (FAK) and Src family kinases (SFKs), thereby promoting phosphorylation of various key signaling adaptor and effector proteins enriched in focal adhesions including paxillin, p130Cas and p120RasGAP/p190RhoGAP. Genetic ablation of SFK or FAK results in

Key words: FAK, Src, PTP-PEST, PIX, PAK, Arf6, Rac1, cell polarity, cell migration, tyrosine phosphorylation

Abbreviations: GIT, G-protein receptor kinase interacting tyrosine phosphorylated; PKL, paxillin-kinase-linker; PIX, p21 kinase-interacting exchange factor; PAK, p21-activated kinase; SH2, Src homology 2; ECM, extracellular matrix; RTKs, receptor tyrosine kinases; FAK, focal adhesion kinase; EMT, epithelial mesenchymal transition

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PKL Phosphorylation and Rho GTPase Signaling

The phosphorylation status of focal adhesion components is counterbalanced by the action of various protein tyrosine phosphatases, for example PTP-PEST which negatively regulates FAK, p130Cas and paxillin tyrosine phosphorylation. As with Src/FAK activity, the spatio-temporal control of PTP-PEST function is also implicated in regulating asymmetric focal adhesion dynamics between the protrusive front and trailing tail, thus allowing persistent cell migration. Importantly, paxillin interacts with PTP-PEST and the paxillin recruitment of PTP-PEST results in PKL dephosphorylation as well as Rac1 activity regulation (Fig. 1). Together, these results position PKL tyrosine phosphorylation cycling as a critical component of the directional cell migration machinery. However, the causal relationship between SFK/FAK, PTP-PEST, paxillin and PKL still remains to be resolved. An interesting possibility is that the signaling feedback loop between kinase (Src/FAK), adaptor (paxillin) and phosphatase (PTP-PEST) contributes to the disruption of polarized cell shape and persistent migration. Upon asymmetric receptor activation, FAK and Src are temporally activated at specific subcellular locations thereby contributing to local activation of Rho family GTPases such as Rac1. Our studies now show that FAK and Src directly phosphorylate PKL in response to both cell adhesion and growth factor stimulation (Fig. 1). Consequently, PKL and its phosphorylation stimulates its localization to focal adhesions via interaction with paxillin and regulates front-rear polarity and directional cell migration through modulation of Rac1 and Cdc42 activities. Mutation of PKL at its primary tyrosine phosphorylation sites, or disruption of the paxillin-PKL interaction results in multiple unstable, random protrusions indicating hyperactive Rac1. These observations position paxillin-PKL as an important facilitator, bridging FAK/Src function to restrict Rac1 activity and enable polarized migration. Future experiments will be directed towards understanding the respective roles of SFKs and FAK in the differential phosphorylation of PKL and how this in turn promotes its stable association with paxillin at focal adhesions to restrict protrusive activities to the front, rather than the side and rear of migrating cells. The development of PKL phospho-specific antibodies and live-cell imaging techniques using paxillin-PKL FRET probes will help address this spatio-temporal relationship.

Figure 1. A model for the Paxillin-PKL modulated signaling network. The physical engagement of integrins and growth factor receptors results in the activation of FAK and Src kinases. The adaptor protein paxillin recruits many scaffold and signaling components into focal adhesions. FAK/Src regulated tyrosine phosphorylation of paxillin and PKL facilitates dynamic protein-protein interaction with Rho GTPase regulators and effectors, thereby coordinating cytoskeleton organization and membrane remodeling. ECM, extracellular matrix; GF, growth factor; RTK, receptor tyrosine kinase; PM, plasma membrane.
to sequential phosphorylation of specific PKL tyrosine residues, thereby allowing interactions between PKL and different SH2 domain-containing proteins contributing to focal adhesion dynamics and morphological changes during cell migration. Indeed, our recent studies demonstrated that PKL is phosphorylated at three principal tyrosine residues and that their phosphorylation contributes to PKL localization into focal adhesions.6,7 Although tyrosine phosphorylation of PKL is important for its targeting/stabilization at focal adhesions, it is still unclear how each of the individual phosphotyrosine events contributes to this localization and related cell behaviors. Although such a detailed analysis is ongoing, it has already been established that PKL tyrosine phosphorylation promotes association with the SH2 domains of Nck, Crk and Src, that in turn provide additional potential bridges between PKL and paxillin and/or p130Cas to stabilize PKL in focal adhesions.34,27 Phosphorylation-dependent PKL interaction with GTPase regulators such as Crk and p120RasGAP (our unpublished observations) may further link PKL to the spatiotemporal regulation of Rho family GTPases. Interestingly, paxillin phosphorylation also promotes a transient association with Crk and p120RasGAP to temporally regulate Rac1 and RhoA GTPase activities.28,29 Whether PKL and paxillin provide functional redundancy in this context or perhaps a mechanism to fine-tune the local signaling through Rac1 and RhoA remains to be determined. It is worth noting that FAK mediates cell polarity and directional migration partially through paxillin binding to p120RasGAP/p190RhoGAP, a complex that is also regulated by tyrosine phosphorylation.30 Thus, the paxillin-PKL complex and SFK/FAK regulated phosphorylation events might in part be responsible for the Rac1-to-RhoA phenotype conversion during nascent adhesion maturation and membrane protrusion through locally restricting GTPase activities, to thereby coordinate cell contraction and directionality during migration.

GIT1 is a closely related homologue of PKL, (GIT2).33,34 However, unlike PKL, whose tyrosine phosphorylation facilitates its localization to focal adhesions through its regulated interaction with paxillin, we previously reported that GIT1 is stably localized to focal adhesions independent of its phosphorylation.5,6 PKL phosphorylation and its interaction with paxillin are tightly coupled with the spatial regulation of PAK activity.7,6 Conversely, others have documented that PAK-dependent phosphorylation of paxillin on serine 273 within the LD4 motif is involved in regulating GIT1-paxillin interaction and subcellular localizations (Fig. 1).31,32 These somewhat conflicting data may be due to the different cell types and biological assays used. However, the analysis is incomplete as paxillin phosphorylation-dependent binding of PKL was not tested in these studies.31,32 Indeed, most studies have focused on a single GIT isoform and their respective roles. It is noted that PKL and GIT1 interact with paxillin with differential affinity.33 The phosphorylation of paxillin by PKL may play a distinct role in modulating the interaction of paxillin with PKL versus GIT1, suggesting different functional roles for PKL and GIT1 that are dependent on biological context. This hypothesis is further implicated by histochemical studies in which distinct expression patterns of PKL and GIT1 are observed in different tissues34 and loss-of-function by gene ablation also showed differential physiological roles of GIT family proteins: PKL being important for neutrophil chemotaxis,35 and GIT1 playing a critical role in vascular development36 and gonadal distal tip cell migration.37

**PKL/GIT1 and Arf GTPase Signaling**

It is important to note that PKL and GIT1 are ArfGAPs.38 Arfs are small GTPases that regulate vesicle trafficking. They have also been linked to regulation of Rho family members, particularly Rac1.39 There is accumulating evidence that PKL/GIT1-paxillin complexes are likely involved in endocytosis or exocytosis of various membrane components of the cell migration machinery including integrins.40-42 Arf1-dependent paxillin shuttling between the Golgi and focal adhesions has been described for the ArfGAP GIT2short, a truncated isoform of PKL.53 Recent studies showed that GIT1 GAP activity for Arf6 indirectly inhibits Rac1 activity, thereby regulating polarized migration of fibroblasts and endothelial cell adhesion (Fig. 1).43,44 It will be important to determine if and/or how tyrosine phosphorylation may regulate PKL/GIT1 GAP activity during cell adhesion and migration. Interestingly, PI3k, a phosphoinositide enriched at the leading edge of migrating cells also regulate the activities of ArfGAPs including PKL and GIT1.38 This, in combination with tightly regulated phosphorylation, will provide an additional level of control for modulating GAP activity for Arfs and consequently the delivery of Rac1 and integrins to the leading edge of motile cells. The emergence of refined live cell imaging techniques such as FRET analysis of Arf6 and Rho family GTPase activity45,46 will facilitate our understanding of how paxillin-PKL/GIT1 complexes may differentially contribute to the directed transport of focal adhesion components,42 as well as the precise regulation of the localized small GTPase activities and thereby cytoskeleton reorganization.

**GitTs in Cell-Cell versus Cell-ECM Adhesion Signaling**

Cell migration in vivo, for instance during epithelial-to-mesenchymal transition (EMT) or tumor cell invasion/metastasis, requires the coordination of cell-ECM adhesion signaling and dynamics along with the remodeling of cell-cell adhesion. In the case of EMT, which is essential for tissue remodeling during embryonic development, cells lose their intercellular adhesion and remodel their cell-ECM adhesions and accompanying cytoskeleton resulting in a conversion from apical-basal to a front-rear polarity (Fig. 2).48 The subsequent single cell migration is coordinately regulated by focal adhesion components such as paxillin and ILK as well as their dynamic interactions with various binding partners.48-50 Our lab previously demonstrated that TGFβ-induced EMT of breast and kidney epithelial cells was associated with the downregulation of a truncated form of paxillin, called paxillin δ9 and the coordinate upregulation of Hic-5,50 a close homologue of paxillin.
polarized cells. Therefore, a GIT protein-PIX complex (or βPIX alone) might provide a mode of local crosstalk between the Scribble polarity complex and paxillin/Hic-5 dependent ECM-cell adhesion signaling. This represents a potentially central mechanism for coordinating the regulation of cytoskeleton organization and receptor trafficking at cell-cell junctions and the leading edge of migrating cells during EMT and invasion.

Finally, in animal models, genetic deletions of SFK, FAK, paxillin, GIT or PIX lead to pronounced developmental defects involved in the disruption of cell polarity and directed cell migration. Abnormal Rho GTPase and PAK signaling, as well as paxillin phosphorylation were frequently observed in embryonic-derived null cells. Additionally, point mutations in PKL/GIT1 and paxillin have been associated with human glioblastoma multiforme and lung cancers, respectively. Given the importance of cell adhesion signaling and cell migration in development and disease, it will be essential to precisely dissect the functional role of paxillin and Hic-5 when coexpressed exhibit complimentary as well as antagonistic functions. Interestingly, they can bind the PKL/GIT1-PIX-PAK complex. It will be important to determine if PKL tyrosine phosphorylation affects its interaction with Hic-5, as it does paxillin, as well as clarifying how PKL and GIT1 are involved in Hic-5 versus paxillin signaling in focal adhesions during EMT and tumor invasion.

Neither paxillin nor Hic-5 is enriched in cell-cell adhesions. In contrast, recent studies suggest a direct functional role for the GIT1-PIX-PAK complex in modulating cell-cell junction homeostasis. The TGFβ receptor is associated with the GIT1-PIX-PAK complex and this interaction is differentially modulated during TGFβ-stimulated EMT, in agreement with the observation that PIX and PAK regulate contact inhibition between epithelial cells. Furthermore, GIT1 binds to EphA2 and EphrinB through the adaptor Nck/Grb4 in a tyrosine phosphorylation dependent manner and, although the involvement of PKL has not been determined, GIT family ArfGAP activity towards Arf6 GTPase is likely important for Eph-Ephrin dependent cell-cell contact homeostasis (Fig. 2). In view of the fact that Arf6 and Rac1 activities are important for adherens junction turnover and stability, it will be important to examine the precise role of PKL/GIT1 function as Arf6 GAPs as well as their phosphorylation dependent signaling to Rho family GTPase for adhesion receptor trafficking and cell-cell junction stabilization. In addition, the GIT1-PIX-PAK complex has also been reported to interact with the polarity component Scribble, revealing a further mechanism by which it may regulate EMT and invasion. In epithelial cells, Scribble is essential for apical-basal polarity while in migrating mesenchymal cells exhibiting front-rear polarity, Scribble changes its localization to the plasma membrane at the leading edge, where it facilitates the targeting of βPIX (Fig. 2). Interestingly, we have now demonstrated an essential role for PKL/GIT2 tyrosine phosphorylation in also regulating polarized βPIX redistribution, but in this case to paxillin-containing focal adhesions beneath the lamellipodia in front-rear polarized cells. Therefore, a GIT protein-PIX complex (or βPIX alone) might provide a mode of local crosstalk between the Scribble polarity complex and paxillin/Hic-5 dependent ECM-cell adhesion signaling. This represents a potentially central mechanism for coordinating the regulation of cytoskeleton organization and receptor trafficking at cell-cell junctions and the leading edge of migrating cells during EMT and invasion.

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paxillin-PKL/GIT1 and their phosphorylation-dependent interactions in these processes.

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