ABSTRACT

The integrin signaling network involves over 180 components to regulate a wide range of biological activities including cell adhesion, survival and migration. However, the details of the molecular mechanisms that govern these cellular processes remain unclear. Since aberrant integrin signaling is often associated with diseases such as cancer, a precise understanding of the molecular mechanisms underlying integrin-mediated processes may provide insights for therapeutic development against cancer.

Protein tyrosine phosphatase alpha (PTPα) is an oncogenic receptor PTP that activates Src family kinases (SFKs) upon integrin stimulation. In addition, its C-terminal tail Tyr789 phosphorylation, mediated by an active Src-FAK complex, promotes integrin-induced cell spreading, focal adhesion (FA) formation, and migration. We hypothesized that PTPα-phosphoTyr789 serves as a binding site to recruit other focal adhesion proteins to regulate cell migration.

By re-expressing an unphosphorylable mutant (Y789F) PTPα in PTPα-null cells, we found that PTPα-Tyr789 promotes FA localization and tyrosine phosphorylation of Cas, a key player in cell migration. Furthermore, we identified BCAR3 as a novel binding partner of PTPα-phosphoTyr789 that mediates Cas association with PTPα, localizing Cas to FAs to promote downstream signaling and cell migration. In addition to BCAR3, the adaptor protein Grb2 also interacts with PTPα-phosphoTyr789 but its role in association with PTPα is unknown. Using a Grb2-silencing approach, I discovered that Grb2 regulates integrin-induced PTPα-Tyr789 phosphorylation via two distinct mechanisms: 1) Grb2 regulates FAK/Src complex activation and 2) the SH2 and C-terminal SH3 domains of Grb2 mediate the formation of a PTPα-Grb2-FAK complex to promote Src-FAK-mediated PTPα tyrosine phosphorylation.

In summary, my results reveal both the upstream molecular mechanisms that regulate PTPα-Tyr789 phosphorylation and the downstream PTPα-Tyr789-dependent events that regulate cell migration.