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**REGULATION OF CELL MOTILITY BY SHP-2
TYROSINE PHOSPHATASE**

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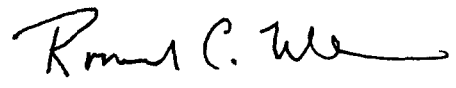


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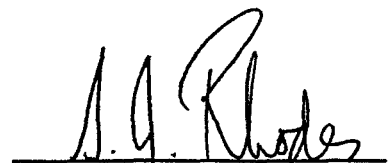


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Abstract

Shp-2 is a ubiquitously expressed SH2 domain-containing protein-tyrosine phosphatase (PTP). Accumulating experimental results suggest that this phosphatase is an important regulator in signal pathways evoked by a variety of stimuli including growth factors, cytokines and antigens. The goal of my thesis work was to define a role of Shp-2 in the control of cell motility and integrin signaling, using fibroblast cells that were derived from wild-type and Shp-2 mutant embryos with a targeted deletion of exon 3. Shp-2 mutant cells exhibited epithelial-like cell morphology, reduced cell spreading and migration on fibronectin, compared to wild-type cells. Furthermore, Shp-2 mutant cells displayed an increased number of focal adhesions and condensed F-actin aggregation at the cell periphery, properties reminiscent of focal adhesion kinase (FAK) deficient cells, suggesting that Shp-2 may work in concert with FAK to regulate focal adhesions and cell migration.

Reintroduction of wild-type, but not a catalytically inactive Shp-2, into Shp-2^{-/-} cells induced a transition from epithelia-like to fibroblastoid cell phenotype, as evidenced by increased cell migration, scattering as well as elevated expression of N-cadherin. Molecular analyses also suggest that Shp-2 acts positively to transmit biochemical signals initiated by interaction of extracellular matrix (ECM) and integrin to induce the activity of extracellular signal-regulated kinase (Erk) and the expression of c-fos in promoting fibroblastoid cell development. Evidence is also presented that SHP substrate-1 (SHPS-1) is a primary target for Shp-2 in integrin signaling.

In summary, this thesis describes a positive role for Shp-2 tyrosine phosphatase in the control of fibroblastoid cell migration and maturation, as well as in integrin signaling. Consistently, Shp-2^{-/-} embryos died at midgestation with multiple defects in the induction and patterning of mesodermal structures. Thus, I argue here that Shp-2 may participate in morphogenetic movement and differentiation of mesenchymal cells during gastrulation, and, in extension, Shp-2 may also have a role in tumor cell metastasis.

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