REGULATION OF CELL MOTILITY BY SHP-2 TYROSINE PHOSPHATASE

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Submitted to the faculty of the University Graduate School

in partial fulfillment of the requirements

for the degree

Doctor of Philosophy

In the Department of Biochemistry and Molecular Biology

Indiana University

September 2002

Acceptance page

Accepted by the Graduate Faculty, Indiana University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Defense Date: July 23, 2002

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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