**Association of Tyrosine Phosphatase SHP-2 with F-actin at Low Cell Densities**

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SHP-2 is an intracellular SH2 domain-containing protein-tyrosine phosphatase with an essential role in cell signaling. Here we demonstrate that localization of SHP-2 is regulated by cell density in a cell adhesion-dependent manner. When cells were plated at low densities, SHP-2 was distributed in Triton X-100-insoluble fractions, whereas it was totally soluble when cells were plated at high densities or when low density cells approached confluence. In all cases, the total protein level of SHP-2 was not changed. Fluorescent cell staining revealed that SHP-2 was co-localized with actin stress fibers to the cell peripheral at low cell densities but was diffused in the entire cytoplasm at high cell densities. Transient transfection of cells with truncated forms of SHP-2 demonstrated that the catalytic domain of the enzyme was responsible for the density-regulated distribution of SHP-2, but the catalytic activity was not required. An in vitro co-sedimentation study demonstrated direct binding of full-length and SH2 domain-truncated forms of SHP-2 to F-actin. The data indicate that SHP-2 is regulated by cell density and that it may have a role in assembling and disassembling of the actin network.

SHP-2 is a widely distributed protein-tyrosine phosphatase (PTP) that contains tandem SH2 domains (1–4). By structural nature, SHP-2 is an intracellular enzyme. However, it is recruited to the plasma membrane by binding to tyrosine phosphorylated molecules, including growth and cytokine receptors, the T and B cell receptors (1–4), and other cell surface anchor proteins including SHPS-1 (5, 6), PECAM-1 (7, 8), and PZR (9).

Overwhelming studies have shown that SHP-2 is most often a component of tyrosine-phosphorylated signaling complexes, SHP-2 appears to be the major phosphotyrosine phosphatase associated with growth factor receptors, cytokine receptors, and most probably cell adhesion molecules (10). SHP-2 is primarily a cytoplasmic enzyme, but it is also present at the plasma membrane (11). The presence of SHP-2 at the membrane is believed to contribute to the regulation of cell adhesion and migration (12, 13). SHP-2 is known to associate with the actin cytoskeleton and the formation of podosomes (14). The association of SHP-2 with the actin cytoskeleton is essential for cell motility (15). SHP-2 is recruited to focal contacts by integrin engagement (16). Overexpression of an SHP-2 mutant that lacks the catalytic domain increased the formation of stress fibers and focal adhesions and inhibited spreading of the cells (17). SHP-2 also plays a role in integrin-mediated cell signaling (18). Overexpression of a catalytically inactive mutant form of SHP-2 in Chinese hamster ovary cells or Rat-1 fibroblasts induced a marked change in cell morphology accompanied by substantial increases in the numbers of actin stress fibers and focal adhesion contacts (19). SHP-2 is also necessary for morphological transformation by v-Src because v-Src-induced reorganization of the actin cytoskeleton and the formation of podosomes were compromised in SHP-2-deficient cells (20).

Cell density has major effects on cell activities including cell morphology, motility, and cytokinesis. In this study, we have investigated the effects of cell density on intracellular distribution of SHP-2. We found that cell density regulates localization of SHP-2. At low cell densities, SHP-2 was co-localized with F-actin. To our knowledge, this is the first example that a tyrosine phosphatase constitutes a part of actin stress fibers.

**EXPERIMENTAL PROCEDURES**

Materials—Polyclonal anti-SHP-2 antibody (C-18) was purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA). Rhodamine-conjugated phalloidin, fluorescein isothiocyanate-labeled goat anti-rabbit IgG, and cytochalasin D were from Sigma. Horseradish peroxidase-conjugated anti-rabbit immunoglobulin was from Amersham Pharmacia Biotech. 

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**Fig. 1.** The protein level of SHP-2 in the Triton X-100-soluble cell extract is regulated by cell density. HeLa, HepG2, NIH 3T3, and HT-1080 cells were plated at the indicated densities (0.2–6×10^6/cm² plates) and cultured overnight (top and middle panels). HeLa cells were plated at a low density (0.2×10^6/cm² plate) for 1–6 days as indicated or at the indicated densities and cultured for 0, 3, 6, and 24 h (bottom panel). The Cells were lysed at 0 °C on the plates with Buffer A. Cell extracts containing 10 μg of total proteins were separated on 10% SDS gel and then transferred to polyvinylidene difluoride membranes. Western blotting was performed with the anti-SHP-2 and anti-FAK antibodies.

**RESULTS**

**Cell Density Regulates the Level of Triton X-100-soluble SHP-2**—As an important transducer of cell signaling, SHP-2 has a major implication in cell migration (3). Because cell migration is regulated by cell density, SHP-2 may play a role in density-dependent cellular processes. We plated four different cell lines, including HeLa, HepG2, NIH 3T3, and HT-1080 in plastic cell culture dishes at densities of 0.2–6×10^6/cm² plate. After overnight culturing, cells were lysed on the plate with a solution containing 0.25% Triton X-100. The protein level of SHP-2 was determined by Western blotting with an anti-SHP-2 polyclonal antibody. As shown in the top panel of Fig. 1, cell density had a profound effect on the protein level of SHP-2 in the Triton X-100-soluble cell fraction with all the cell lines tested. At low cell densities, SHP-2 was hardly detected. As the cell density increased, a marked elevation of SHP-2 level was observed. As a control, the protein level of focal adhesion kinase FAK was not affected by the change in cell density (Fig. 1, middle panel). In fact, our recent studies showed that tyrosine phosphorylation of FAK decreased as the cell density increased (29). We used HeLa cells to investigate further the effects of cell density on the SHP-2 protein level. The cells were plated at a low density and cultured for 6 days. As shown in the bottom panel of Fig. 1, the level of SHP-2 was lower at day 1 but gradually increased as the cells approached confluency. We also investigated the change of SHP-2 level during a shorter time course (Fig. 1, bottom panel, right). Trypsinized HeLa cells were plated at low, medium, and high densities (0.2, 1, and 6×10^6/plate) and cultured cells for 3, 6, and 24 h. Before plating, the trypsinized suspension cells displayed a high level of soluble SHP-2. A near total depletion of soluble SHP-2 was seen after 3 h of plating at the low cell density (0.2×10^6/plate), and a slight gradual increase was observed by 24 h. When cells were plated at higher densities (and 6×10^6/plate), the level of soluble SHP-2 was constantly high. These data thus suggest that cell density modulated SHP-2 protein level in the Triton X-100-soluble fraction.

**In Vitro Binding of SHP-2 with F-actin**—G-actin was purified from rabbit skeletal muscle following the procedure of Pardee and Spudich (28). The purified G-actin showed a homogenous band on SDS gels. G-actin was diluted to 2 mg/ml in the polymerization buffer containing 2 mM Tris-HCl (pH 8.0), 0.2 mM ATP, 1 mM MgCl₂, and 0.2 mM CaCl₂.GST-SHP-2, GST, SHP-2, and ΔSHP-2 were diluted to 0.1 mg/ml in a buffer containing 20 mM Tris-HCl (pH 8.0), 1 mM glutathione, 1 mM dithiothreitol, and 1.0 mM bovine serum albumin. The solutions were centrifuged at 100,000 × g for 45 min to remove any possible precipitation, and the supernatants were used for binding assays. Equal volumes of G-actin and GST-SHP-2, GST, SHP-2, or ΔSHP-2 were mixed. Polymerization of actin was triggered by addition of 2 mM KCl, 20 mM ATP, 1 mM MgCl₂, and 0.1 mM EGTA to final concentrations of 0.1 mM KCl, 1 mM ATP, 5 mM MgCl₂, and 0.5 mM EGTA. The samples were incubated on ice for 2 h and then centrifuged at 100,000 × g for 45 min. The pellets were washed with the same polymerization buffer and centrifuged as above. The final pellets were dissolved in 1× SDS sample buffer. GST and GST-SHP-2 were analyzed by Western blotting with an anti-GST antibody, whereas SHP-2 and ΔSHP-2 were detected by using anti-SHP-2 antibody.

**Regulation of Soluble SHP-2 Level by Cell Density Is Dependent on Cell Adhesion**—As noted above, the level of soluble SHP-2 in tryptsinized suspension cells was high, and thus the decrease must be related to cell attachment to the plate. To further investigate the effects of cell adhesion on SHP-2 solubility, we cultured HeLa cells in suspension as described under “Experimental Procedures.” HeLa cells grew in suspension medium at a rate similar to that observed with adherent cell culture. Western blot analyses demonstrated a constantly high level of SHP-2 in HeLa cells cultured in suspension despite cell...
densities and the time the cells were cultured in suspension (Fig. 2, upper panel). However, once the cells were transferred to cell culture plates and allowed to attach to the plates at a low density, the level of soluble SHP-2 decreased dramatically. As expected, when the attached cells approached confluence on the plates, the level of soluble SHP-2 was recovered. To further the study, we detached the cells plated at the low density (0.2 × 10^6/plate) by incubating them in PBS at 37 °C for 0.5 h. Interestingly, this caused a total recovery of SHP-2 in the soluble fraction (Fig. 2, lower panel). PBS treatment of the cells plated at higher densities exhibited no effects on SHP-2, which remained in the soluble fraction. These results indicate that the protein level of SHP-2 in the Triton X-100-soluble fraction is associated with both cell density and cell attachment.

**SHP-2 Is Partitioned in the Triton X-100-insoluble Fraction at Low Cell Densities**—The protein level of SHP-2 in the Triton X-100-soluble fraction may not necessarily reflect the total protein level of SHP-2 in the cells. To clarify this, we extracted cells first with Buffer A and then re-extracted the pellets with the SDS sample buffer containing 1% SDS. As shown in Fig. 3, a significant portion of SHP-2 was found in the Triton X-100-insoluble pellets when cells were grown at a low density. As the density increased, the SHP-2 level in the Triton X-100-soluble fraction increased, but that in the Triton X-100-insoluble fraction displayed a concurrent decrease. As expected, when the cells were directly extracted with SDS gel sample buffer containing 1% SDS, the total level of SHP-2 showed no change at different cell densities. Similar results were obtained with HT-1080 cells (Fig. 3, bottom panel). In this case, a nonspecific band below SHP-2 served as an internal control to show a protein whose protein level was not affected by cell density. Taken together, the data suggest that cell density regulates cellular distribution of SHP-2.

**SHP-2 Is Co-localized with Actin Stress Fibers at Low Cell Densities**—Cytoskeletal proteins constitute a major part of the Triton X-100-insoluble cell pellets. Partition of SHP-2 in the Triton X-100-insoluble fraction implies that it may be associated with cytoskeleton. To find the exact intracellular localization of SHP-2, we performed immunofluorescent cell staining with anti-SHP-2 antibody. The results are shown in Fig. 4. At low cell densities, SHP-2 was condensed at the periphery of cells with a fiber-like structure. At high densities, however, SHP-2 was diffused in the entire cytosol. We then co-stained the cells with rhodamine-conjugated phallolidin that detects F-actin. In low density cells, F-actin staining essentially super-imposed the SHP-2 staining, indicating that SHP-2 is co-localized with the actin stress fibers formed by F-actin. At high cell densities, SHP-2 was dissociated from the actin stress fibers. It should be noted that the distribution of the actin stress fibers at low cell densities was different from that at high cell densities. At low cell densities, actin stress fibers are distributed around the periphery of cells, whereas they were dispersed over the ventral surface in high-density cells. In addition, at lower density, the cells appeared larger because of extensive spreading. To further verify the co-localization of SHP-2 with F-actin, we treated cells with cytochalasin D to break actin stress fibers. As shown in Fig. 4, cytochalasin D caused total disruption of the fiber-like structure of SHP-2 together with the actin stress fibers. Interestingly, SHP-2 remained co-localized with F-actin with a punctuated pattern in the cytochalasin D-treated cells.

**The Catalytic Domain of SHP-2 Is Responsible for Its Density-regulated Cellular Distribution, but the Catalytic Activity Is Not Required**—To dissect which part of the SHP-2 molecule is responsible for the distribution of SHP-2 at low cell density and whether catalytic activity is required, we expressed an SH2 domain-truncated form of the enzyme and the correspondent catalytically inactive mutant. We chose HT-1080 cells for transient expression of the truncated enzymes. As shown in Fig. 5, both ΔSHP-2 and ΔSHP-2M displayed a density-regulated distribution pattern similar to that of the endogenous full-length SHP-2. These results suggest that neither the SH2 domains nor the catalytic activity of SHP-2 is required for the binding of SHP-2 to actin fibers. Therefore, the interaction may be independent of tyrosine phosphorylation.

**SHP-2 Binds F-actin Directly in Vitro**—Co-localization of SHP-2 with actin fiber suggests an interaction of SHP-2 with F-actin. The interaction can be direct or can be mediated by other proteins. To examine possible direct interaction, we performed in vitro binding assays by using purified GST-SHP-2, SHP-2, and ΔSHP-2. GST was used as a control. The data shown in Fig. 6 indicate co-sedimentation of SHP-2, SHP-2, and ΔSHP-2 with F-actin. As a negative control, no co-sedimentation of GST with F-actin was observed. These
results suggest that SHP-2 directly bind F-actin and that the interaction is mediated by the catalytic domain. However, considering the relative amounts of actin and SHP-2 used in the binding assays and the fraction of SHP-2 co-sedimented with F-actin, the binding is far from stoichiometric. There might be other factors facilitating a stronger binding in vivo.

**DISCUSSION**

In the present study, we have demonstrated that cell density regulates intracellular distribution of SHP-2 and that SHP-2 is co-localized with the entire actin stress fibers at low cell densities. To our knowledge, this is the first example that a tyrosine phosphatase is co-localized with F-actin fibers. By supporting the plasma membrane of eukaryotic cells, the actin cytoskeleton plays a critical role in a number of cellular processes including cell shape, motility, chemotaxis, endocytosis, exocytosis, and cell division. Change in the rigidity of the cortical actin network constitutes an important process in the cellular response to receptor activation. Being a major component of the actin fibers when cells are at low densities and are poised to expand, SHP-2 must have a crucial role. Our data thus provided a novel mechanism by which SHP-2 regulates cell signaling and controls cell activities. The data also provided an explanation for the changes in morphology and cytoskeletal organization of cells with defective SHP-2 expression (23–25).

The actin network is regulated by a variety of actin-binding proteins. The important role of the small molecular weight...
GTases of the Rho family has been well accepted (30, 31). Involvement of tyrosine kinases in cytoskeletal control has also been well documented. Src family members regulate actin assembly and cell shape by inducing the tyrosine phosphorylation of a diversity of cytoskeletal-associated proteins including cortactin, talin, paxillin, p130cas, WASP, and FAK (32, 33). In particular, actin cross-linking activity of cortactin and its catalytic-mediated proteolysis are regulated by tyrosine phosphorylation (34, 35). FAK is another major tyrosine kinase involved in cytoskeletal regulation (36). It regulates cell adhesion that mediates cell and extracellular matrix interactions. FAK phosphorylates p130cas and paxillin in response to integrin-mediated adhesion, and the phosphorylation is also regulated by Rho (37). The third major tyrosine kinase that regulates cytoskeletal organization is Abl (38). Abl has a C-terminal actin binding motif, and it induces cytoskeletal abnormalities when expressed as an oncogenic BCR-Abl (38–41). As counterparts of tyrosine kinases, PTPs have also been implicated in cytoskeletal regulation. Treatment of cells with PTP inhibitors such as phenylarsine oxide are added in combination with cytochalasin D, reorganization inside cells.

This may be due to the transient nature of tyrosine phosphorylation that turns over rapidly. After all, protein tyrosine phosphorylation and dephosphorylation exist in a dynamic balance, and likewise, the cytoskeletal structure is under constant reorganization inside cells.

Our study not only revealed co-localization of SHP-2 with actin stress fibers but also demonstrated that this is regulated by cell density. Cell density has a major role in regulation of cellular activities such as cell migration and proliferation. Translocation of SHP-2 is one way that the regulation is carried out. Regulation of PTPs by cell density has been extensively studied. It has been shown that PTP activity in the membrane fractions of contact-inhibited Swiss 3T3 cells was much higher compared with proliferating cells and that cells overcome density-dependent growth inhibition in the presence of vanadate, a nonspecific PTP inhibitor (59). DEP-1, a receptor PTP, is dramatically induced when cells reach high densities (60). RPTPL and RPTPM, which are localized to cell-cell contacts, are also up-regulated by increasing cell density (61–64).

Both enzymes can mediate homophilic interaction that results in accumulation of the enzymes at cell-cell contacts. In addition, RPTPM is associated with β-catenin and γ-catenin/plakoglobin (62), whereas RPTPG binds directly to the intracellular domain of E-cadherin and regulates its tyrosine phosphorylation (63, 64). This contact-induced clustering of RPTPs presumably causes dephosphorylation of intracellular substrates at cell-cell contact regions. Up-regulated by increase in cell density, all of these PTPs may play a negative role in cell proliferation.

In contrast, as an intracellular enzyme, SHP-2 is unique by interacting with the entire actin stress fibers inside of the cells when cells are at low densities poised to proliferate. Association of SHP-2 with F-actin may regulate its enzymatic activity, thereby afecting cell growth. When cells reach a high density, SHP-2 becomes diffused in the cytosol where it stays at the inactive state as defined by the purified enzyme (27).

In vitro binding of SHP-2 to F-actin suggests that co-localization of SHP-2 with actin stress fiber may be mediated by direct interaction of these proteins. Because the association is found in vivo only when cells are at low densities, other proteins and factors may be involved. The presence of SHP-2 on the entire actin fiber suggests the general importance of the enzyme in regulating the actin network. The physiological substrates of SHP-2 are still to be defined. Some of the possible targets include c-Src, cortactin, and c-Abl, which are associated with actin fibers. In addition, actin itself may also be a target of SHP-2. In fact, actin is phosphorylated on tyrosine in Dictyostelium, and the phosphorylation is associated with changes of cell shapes (65).

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