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REVIEW

New and Unexpected Biological Functions for the Src-Homology 2 Domain-Containing Phosphatase SHP-2 in the Gastrointestinal Tract

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SUMMARY

SHP-2 is a tyrosine phosphatase widely expressed and involved in multiple cell signaling processes. Accumulating evidence now is emerging whereby dysfunction in this protein tyrosine phosphatase also represents a key factor in the pathogenesis of gastrointestinal diseases, in particular in chronic inflammation and cancer.

SHP-2 is a tyrosine phosphatase expressed in most embryonic and adult tissues. SHP-2 regulates many cellular functions including growth, differentiation, migration, and survival. Genetic and biochemical evidence show that SHP-2 is required for rat sarcoma viral oncogene/extracellular signal-regulated kinases mitogen-activated protein kinase pathway activation by most tyrosine kinase receptors, as well as by G-protein–coupled and cytokine receptors. In addition, SHP-2 can regulate the Janus kinase/signal transducers and activators of transcription, nuclear factor-κB, phosphatidyl-inositol 3-kinase/Akt, RhoA, Hippo, and Wnt/β-catenin signaling pathways. Emerging evidence has shown that SHP-2 dysfunction represents a key factor in the pathogenesis of gastrointestinal diseases, in particular in chronic inflammation and cancer. Variations within the gene locus encoding SHP-2 have been associated with increased susceptibility to develop ulcerative colitis and gastric atrophy. Furthermore, mice with conditional deletion of SHP-2 in intestinal epithelial cells rapidly develop severe colitis. Similarly, hepatocyte-specific deletion of SHP-2 induces hepatic inflammation, resulting in regenerative hyperplasia and development of tumors in aged mice. However, the SHP-2 gene initially was suggested to be a proto-oncogene because activating mutations of this gene were found in pediatric leukemias and certain forms of liver and colon cancers. Moreover, SHP-2 expression is up-regulated in gastric and hepatocellular cancers. Notably, SHP-2 functions downstream of cytotoxin-associated antigen A (CagA), the major virulence factor of *Helicobacter pylori*, and is associated with increased risks of gastric cancer. Further compounding this complexity, most recent findings suggest that SHP-2 also coordinates carbohydrate, lipid, and bile acid synthesis in the liver and pancreas. This review aims to summarize current knowledge and recent data regarding the biological functions of SHP-2 in the gastrointestinal tract. *(Cell Mol Gastroenterol Hepatol 2016;2:11–21; http://dx.doi.org/10.1016/j.jcmgh.2015.11.001)*

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SHP-2 is a SH2 domain-containing protein tyrosine phosphatase (PTP) encoded by the *PTPN11* gene.[1–5] This PTP is expressed ubiquitously, sharing similar overall structure and high homology with SHP-1 phosphatase, which is expressed predominantly in hematopoietic cells.[6] Both phosphatases contain 2 tandem SH2 domains at the N-terminus and 1 tyrosine phosphatase domain at the C-terminus (Figure 1). The SH2 domain is a sequence-specific phosphotyrosine-binding motif that mediates substrate recruitment and regulates phosphatase activity.[7] In its inactive state, the N-terminal SH2 domain of SHP-2 binds the PTP domain, thus blocking access of substrates to the active site. Upon binding to phosphoproteins, the SH2 domain is released from the PTP domain, enabling SHP-2 to dephosphorylate its substrates.[8,9] In addition, a new regulatory mechanism based on SHP-2 dimerization recently was described. Indeed, 15% of SHP-2 in resting cells has been found to be in dimeric form, resulting in a decrease in catalytic activity of the phosphatase. Of note, the SH2 domains have no role in SHP-2 self-association.[10] Importantly however, the dimer/monomer ratio is not static and is regulated by growth factors and the cell redox state.[10] Given the significant regulatory role of SHP-2 in major signaling pathways (described later), keeping SHP-2 activity under control may be crucial for cell homeostasis.[10]

Previous biochemical evidence has shown that SHP-2 enzymatic activity is required for its function in signal transduction.[11–14] The replacement of cysteine 459 by

Abbreviations used in this paper: CagA, cytotoxin-associated gene A; ERK, extracellular signal-regulated kinases; FGF, fibroblast growth factor; GI, gastrointestinal; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; JMML, juvenile myelomonocytic leukemia; KO, knockout; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PI3K, phosphatidyl-inositol 3-kinase; PTP, protein tyrosine phosphatase; RAS, rat sarcoma viral oncogene.

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Figure 1. Structure of SHP-2. Defined domains within SHP-2 are indicated. SHP-2 contains 2 tandem SH2 domains (blue), a single PTP domain (red), and a C-terminal hydrophobic tail that includes tyrosine phosphorylation sites (green).

serine abolishes its enzymatic activity but not the capacity to bind to other signaling intermediates via its SH2 domains. This mutant thus functions as a dominant-negative molecule over the endogenous wild-type SHP-2.[15] By using this Cys459Ser mutant, SHP-2 has been shown to positively regulate the signaling pathways of insulin, epidermal growth factor, platelet-derived growth factor, and fibroblast growth factor (FGF) in a number of studies, in both in vitro and in vivo models. More specifically, the introduction of this catalytically inactive SHP-2 mutant markedly inhibits the activation of mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinases (ERK)1/2 in response to epidermal growth factor, insulin, thrombin, and fibronectin.[12,14,16–20] Further genetic and biochemical evidence also strongly shows that SHP-2 indeed is required for ERK/MAPK pathway activation by most, if not all, tyrosine kinase receptors, as well as by G-protein–coupled receptors, cytokine receptors, and integrins.[8,12,14,21,22] SHP-2 binds directly to certain tyrosine kinase receptors or, more often, to scaffolds (Table 1), leading to its activation. Cells expressing dominant-negative SHP-2[14] or Ptpn11 gene exon 3–deleted mouse embryonic fibroblasts[22] show defective rat sarcoma viral oncogene (RAS) activation, suggesting that SHP-2 acts upstream of RAS (Figure 2). However, other data have shown that a catalytically inactive mutant of SHP-2 (Cys459Ser) can perturb components of downstream signaling, even in the presence of a constitutively active RAS, suggesting that SHP-2 also may function either downstream and/or in parallel to RAS.[13] In addition, SHP-2 was shown to functionally regulate other pathways including the Janus kinase/signal transducers and activators of transcription,[23,24] nuclear factor-κB (NF-κB),[25,26] phosphatidylinositol 3-kinase (PI3K)/Akt,[27–29] Wnt/β-catenin,[30,31] Hippo,[31] and RhoA[32,33] signaling (Figure 2).

Despite extensive studies over the past decade, the mechanisms of SHP-2 action remain unclear. SHP-2 has been reported to interact with a number of diverse signaling components such as Gab1/2, fibroblast growth factor receptor substrate, insulin receptor substrate 1/2, p85, STAT1/3/5, Sprouty, and yes-associated protein/transcriptional coactivator with PSD-95, discs large, zona occludens 1-binding motif (Table 1 and Figure 2). As a result, SHP-2 has been shown to regulate numerous cellular functions, including progenitor cell development,[34] growth,[12,35] differentiation,[32,36] and migration.[37,38] Notably, homozygous mice carrying a targeted mutation in the murine *Shp2* gene, resulting in deletion of residues in the N-terminal SH2 domain, die around day 8.5–10.5 of gestation, with multiple defects in mesodermal patterning.[39]

PTPN11 Mutations and Phenotypes

In human beings, germline mutations in the *Ptpn11* gene (which encodes SHP-2) have been identified in more than 50% of children with Noonan syndrome, a developmental disorder characterized by short stature, minor facial anomalies, and congenital heart defects.[40] Of note, most children with Noonan syndrome show feeding and digestive disorders including vomiting, constipation, abdominal pain, and distension.[41,42] Noonan syndrome also frequently is associated with the development of juvenile myelomonocytic leukemia (JMML).[40,43] Conversely, somatic mutations in the *PTPN11* gene also have been identified in 34% of JMML patients. Most of these somatic mutations are clustered within the PTP or the N-SH2 domain,[44] altering the autoinhibition mechanism and resulting in hyperactivated SHP-2.[43] Accordingly, expression of the most common and most active *PTPN11* mutation (E76K) found in JMML and acute leukemias in pan hematopoietic cells in mice is sufficient to trigger the development of myeloproliferative disorder. Subsequently, these mice progress to acute leukemias.[45] SHP-2 consequently has been identified as the first proto-oncogene to encode a tyrosine phosphatase.[46]

Accumulating evidence now is emerging whereby dysfunction in this PTP also represents a key factor in the pathogenesis of gastrointestinal (GI) diseases, in particular in chronic inflammation and cancer. The following sections provide an overview of current knowledge on the functions and roles of SHP-2 in the epithelia of stomach, intestine, pancreas, and liver.

SHP-2 in Gastric Carcinogenesis

A role for SHP-2 in gastric cancer was first suggested in 2002 when it was found that this phosphatase is an intracellular target of Helicobacter pylori cytotoxin-associated gene A (CagA) protein.[47] CagA is the product of the cagA gene carried in virulent type I strains of H pylori, which infects approximately half of the world's population, causing gastric diseases ranging from peptic ulcer diseases to gastric adenocarcinoma.[48,49] *CagA* is introduced into gastric epithelial cells through a type IV secretion system and, once inside, Src family kinases phosphorylate the Glu-Pro-Ile-Tyr-Ala motif on tyrosine.[50,51] Tyrosine-phosphorylated *cagA* then specifically binds to the SH2 domains of SHP-2, relieving the autoinhibition mechanism and thereby increasing its phosphatase activity,[47] resulting in activation of the downstream ERK/MAPK pathway.[52] Activated ERK1/2 MAPK then promotes proliferation and survival gene programs.[53–55] Furthermore, infection of gastric epithelial cells with *cagA*-positive *H pylori* has been shown to induce a unique elongated cell shape termed the *hummingbird phenotype*, which is dependent on *cagA*–SHP-2 interaction.[47,52] These studies hence provide a molecular basis for the pathogenic actions of *cagA* on gastric epithelial cells.

STAT3 also is activated in patients with infection with *cagA*-positive *H pylori* strains and with gastric adenocarcinoma.[56] Because SHP-2 is a major negative regulator of STAT3 activation,[23] sequestration or preferential binding by *cagA* may reduce the intracellular pool of SHP-2, thereby depleting