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, phosphatidylinositol 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 cytokinesis-associated antigen A (CagA), the major virulence factor of Helicobacter pylori, and is associated with increased risks of gastric cancer. Further complications of 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; P38, phosphatidylinositol 3-kinase; PTP, protein tyrosine phosphatase; RAS, rat sarcoma viral oncogene.
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.12,14,15–20 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-214 or Ptpn11 gene exon 3-deleted mouse embryonic fibroblasts22 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 RhoA32,33 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, Sprotty, 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.

**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).

**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.33 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 gastrointestinal diseases ranging from peptic ulcer diseases to gastric adenocarcinoma.40,49 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.40,47 Tyrosine-phosphorylated cagA then specifically binds to the SH2 domains of SHP-2, relieving the autoinhibition mechanism and thereby increasing its phosphatase activity,40 resulting in activation of the downstream ERK/MAPK pathway.12,24 Activated ERK1/2 MAPK then promotes proliferation and survival gene programs.23–55 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.37,52 These studies hence provide a molecular basis for the pathogenic actions of cagA on gastric epithelial cells.

**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.16

Accumulating evidence now is emerging whereby dysfunction in this PTP also represents a key factor in the pathogenesis of gastrointestinal 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.
this brake on STAT3 activation and resulting in increased transcription of STAT3 target genes, many of which promote proliferation, inflammation, angiogenesis, and inhibition of apoptosis. In addition, *cagA* may interact directly with STAT3 by binding or recruitment to gp130, thereby promoting hyperactivation and increased transcriptional activity. Of note, the STAT3, but not the ERK1/2, pathway can be activated to a lesser extent by *cagA*-negative *H pylori* strains, suggesting that STAT3 may be driven by other bacterial factors. The differential activation of these 2 signaling proteins may explain in part the increased predisposition of gastric epithelium to gastric cancer when infected with *cagA*+ *H pylori* strains.

### Table 1. Binding Partners of SHP-2 in Gastrointestinal Cells

| Organs | Proteins | Interactions | Cell types | Cell outcomes | References |
|--------|----------|--------------|------------|---------------|------------|
| Stomach | CagA | SH2 domain of SHP-2 and phosphorylated tyrosine in the EPIYA motif of CagA | AGS cells Human gastric epithelial cells | Increased phosphatase activity of SHP-2 ↓ Induction of the hummingbird phenotype | 47, 59, 62, 117, 118 |
| FAK | SHP-2 in complex with CagA and FAK | AGS cells | Dephosphorylation of FAK on Y397, Y576, and Y577 by SHP-2 ↓ Induction of the hummingbird phenotype | 119 |
| gp130 | SHP-2 in complex with gp130 | AGS cells | Activation of ERK1/2 by gp130 ↓ Inhibition of the Jak2/STAT3 pathway by SHP-2 | 59 |
| Parafibron | SH2 domain of SHP-2 and parafibron | AGS cells | Dephosphorylation of parafibron on Y290, Y293, and Y315 by SHP-2 ↓ Interaction between dephosphorylated parafibron and β-catenin ↓ Nuclear accumulation of β-catenin and transcription of Wnt/β-catenin target genes | |
| YAP and TAZ | C-terminal tail of SHP-2 and WW domain and C-terminus PDZ-binding motif of TAZ | AGS cells | Dephosphorylation of YAP/TAZ by SHP-2 ↓ Nuclear accumulation of SHP-2 ↓ Interaction between dephosphorylated parafibron ↓ Transcription of TEAD-regulated genes | 31 |
| Intestine | IL22R1 | SHP-2 and phosphorylated IL22R1 (Y251, Y301) | SW480 cells | Activation of the ERK1/2 and Jak/STAT3 signaling pathways by IL22 | 120 |
| Bgp1 | N-SH2 domain of SHP-2 and phosphorylated Y in the ITIM motif of Bgp1 | CT51 cells | ND | 121 |
| Liver | FRS2α | SH2 domain of SHP-2 and phosphorylated Y of FRS2α | Hep3B cells Mouse hepatic cells | Activation of the ERK1/2 pathway by FGFR4 | 105 |
| Gab1 | SH2 domain of SHP-2 and phosphorylated Y of Gab1 | Hep3B cells Hep2G cells Mouse hepatic cells | Activation of the ERK1/2 pathway | 90, 105, 122 |
| Liver and pancreas | COP1 | FASN | N-SH2 domain of SHP-2 in a complex, association with FASN and COP1 | FASN ubiquitination and degradation ↓ Impact on lipid metabolism and glucose homeostasis | 101 |
compared with their cagA− counterparts. Nevertheless, because SHP-2, STAT3, and ERK1/2 MAPK are components of intracellular signaling of both growth factors and cytokines, it is likely that inappropriate activation of these proteins also may occur in gastric tumors, independently of infection.

Of particular interest, transgenic mice expressing wild-type cagA show gastric epithelial hyperplasia, with some of the mice developing gastric polyps and adenocarcinoma. By contrast, these pathologic abnormalities are not observed in transgenic mice expressing the phosphorylation-resistant cagA, which is unable to bind SHP-2. These findings thus highlight the importance of cagA tyrosine phosphorylation, which enables cagA to deregulate SHP-2 in the development of H pylori-associated neoplasms. Of note, in vivo interaction between cagA and SHP-2 has been observed in patients with atrophic gastritis, but not in patients with intestinal metaplasia or cancer, suggesting that this mechanism is critical in the early phases of human gastric carcinogenesis.

Different cagA types have been studied in relation to gastric cancer incidence. CagA-positive strains can be divided into East Asian and Western types based on differences in the sequences in the 3′ region of cagA, which contains a different number of copies of the Glu-Pro-Ile-Tyr-Ala tyrosine phosphorylation site motif. In particular, patients infected with the East Asian cagA-positive strains present higher disease severity compared with patients infected with the Western cagA-positive strains, the former being correlated with stronger SHP-2-binding activity.

Of note, single-nucleotide polymorphisms in the PTPN11 gene have been associated with gastric atrophy in both Japanese (rs2301756) and Chinese (rs12229892 and rs12423190) populations. Although the impact of these polymorphisms currently is unknown, one could speculate that they may affect SHP-2 expression or activity or the interaction between cagA and SHP-2. Further studies in human specimens are needed to verify this hypothesis.

Interestingly, SHP-2 is overexpressed in gastric carcinomas but independently of H pylori infection. This suggests that SHP-2 could be modulated by different oncogenic pathways, emphasizing that this phosphatase may be crucial for gastric tumorigenesis. Although the precise mechanisms underlying the effect of SHP-2 on gastric carcinogenesis remain to be investigated further, targeting SHP-2 may represent a novel therapeutic approach for gastric cancer.

**Table 1. Continued**

| Organs | Proteins | Interactions | Cell types | Cell outcomes | References |
|--------|----------|--------------|------------|--------------|------------|
| Pancreas | p85/PI3K | SHP-2 in a complex with p85 and IRS2 | INS-1 832/13 pancreatic cells | Glucose-induced activation of the Akt/FoxO1 pathway | 98 |
| | IRS2 | | | Insulin production | 98 |
| | | Sprouty 1 | ND | | |
| | | | INS-1 832/13 cells | Dephosphorylation of Sprouty 1 on Y by SHP-2 | 98 |
| | | | | Glucose-induced activation of the ERK1/2 pathway | |
| | | | | | Insulin production |

AGS, human gastric carcinoma cells; Bgp1, biliary glycoprotein 1; COP1, constitutive photomorphogenesis protein 1; CT51, mouse colonic carcinoma cells; EPIYA, Glu-Pro-Ile-Tyr-Ala; FAK, focal adhesion kinase; FASN, fatty acid synthase; FRS2a, fibroblast growth factor receptor substrate 2; Gab1, Grb2-associated binding protein; Hep, human hepatocellular carcinoma cells; IL22R1, interleukin-22 receptor 1; INS-1 832/13 cells, insulin-producing β-cells; IRS2, insulin receptor substrate 2; ITIM, immunoreceptor tyrosine-based inhibitor motif; ND, not determined; SW480, human colonic adenocarcinoma cells; TAZ, transcriptional coactivator with PDZ-binding motif; Y, tyrosine; gp130, glycoprotein 130; YAP, yes-associated protein.

**SHP-2 in Intestinal Inflammatory Bowel Diseases**

A major advancement in understanding some of the in vivo functions of SHP-2 in the intestine recently was achieved by using conditional tissue-specific disruption of SHP-2 in mice (SHP-2 intestinal epithelial cell [IEC]-knockout [KO] mice). Our group generated a mouse model with impaired SHP-2 expression by using the villin promoter villin-Cre, which ablates the floxed gene from all epithelial cells (including stem cells) of the small intestine and colon, but not in the mesenchymal compartment. Importantly, these mice rapidly develop severe inflammation 1 month after birth, with clinical and histopathologic features similar to ulcerative colitis. Two further studies also have reported that mice featuring a villin-Cre-mediated SHP-2 deletion rapidly develop colitis. These findings thus clearly establish intestinal epithelial SHP-2 as a critical determinant for prevention of inflammation in the colon.

Of particular interest, intestinal permeability is increased markedly in mice with IEC-specific deletion of SHP-2. Furthermore, SHP-2IEC-KO mice feature reduced Goblet cell numbers associated with expansion of Paneth cells and increased lysozyme expression in their small intestine. These data hence suggest that SHP-2-dependent signaling directs cells to the Goblet cell fate while preventing Paneth cell expansion. Dysregulation of epithelial cell fate or differentiation, particularly in the colon, may have deleterious effects.
consequences for the host as exemplified by mucin 2–deficient mice that rapidly develop severe colitis.\(^\text{76}\) Conversely, Paneth cells that produce antimicrobial peptides such as \(\alpha\)- and \(\beta\)-defensins and lysozyme also may participate in the development of colitis in SHP-2\(^{\text{IEC-KO}}\) mice. Indeed, antimicrobial proteins shape the composition and abundance of microbiota, and segregate intestinal commensals from the mucosa.\(^{\text{77,78}}\) Hence, one could speculate that loss of epithelial SHP-2 expression has a significant effect on key gut microbial groups that are important for homeostasis. Of note, the beneficial effect of antibiotics observed in the SHP-2\(^{\text{IEC-KO}}\) mouse model\(^{\text{73}}\) suggest a role

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**Figure 2.** Signaling pathways regulated by SHP-2 in the gastrointestinal tract. (A) In response to growth factors, SHP-2 binds via its SH2 domains either to autophosphorylated receptors (such as that for platelet-derived growth factor, not shown) or to docking proteins (such as the Grb2-associated proteins Gab and fibroblast growth factor receptor substrate [FRS2]), which are tyrosine-phosphorylated by activated receptor tyrosine kinases or by Src family kinases. Such interactions result in the activation of SHP-2 and its consequent promotion of Ras activation, leading to cell growth. (B) In response to cytokines, the Janus kinases become phosphorylated and then phosphorylate STAT transcription factors, which dimerize and enter the nucleus. SHP-2 can inhibit this process by directly dephosphorylating either the Janus kinases or STAT proteins. (C) In response to insulin, SHP-2 assembles in a complex with insulin-receptor substrate (IRS)1/2 and the p85 subunit of PI3K, leading to Akt activation, leading to cell survival. (D) During \(H\) pylori infection, cagA is injected into the gastric epithelial cells and is phosphorylated by Src family kinases. SHP-2 then interacts with phosphorylated cagA, leading to the activation of the ERK1/2 MAPK pathway in a Ras-independent manner and to focal adhesion kinase (FAK) dephosphorylation and inactivation. CagA also can interact directly with STAT3 by binding or recruitment to gp130, thereby promoting hyperactivation and increased transcriptional activity. (E) At low cell density, nonphosphorylated YAP/TAZ promotes nuclear translocation of SHP-2, which in turn stimulates T-cell factor/lymphoid enhancer factor– and TEA domain family members–regulated genes via parafibromin dephosphorylation.
for microflora in the initiation of inflammation. In this respect, both clinical observations and animal studies support the involvement of intestinal microflora in the pathogenesis of inflammatory bowel diseases (IBDs). It therefore is tempting to speculate that a distinctive microbiota composition and a reduced functionality of the mucus barrier observed early in SHP-2-deficient mice are at the source of this inflammation.

Exactly how SHP-2 impacts cell fate is not totally clear but may rely on its ability to activate the Raf/MAPK pathway. Indeed, concomitant expression of activated KRas or MEK1 markedly promotes Goblet cell differentiation in the colon of SHP-2IEC-KO mice and prevents the development of colitis. In fact, Heuberger et al recently reported that SHP-2-dependent ERK signaling controls the choice between Goblet and Paneth cell fate in the small intestine. These investigators showed that inhibition of ERK signaling in small intestinal organoids and cultured cells promotes β-catenin transcriptional activity, which in turn induces a Paneth-cell maturation program. Taken together, these studies suggest that SHP-2-dependent ERK signaling directs Goblet cell differentiation after secretory progenitor specification, at the expense of Paneth cell differentiation in the intestine.

Importantly, intronic polymorphisms in the PTPN11 gene encoding for SHP-2 have notably been described in Japanese patients with ulcerative colitis. However, the impact of these polymorphisms on SHP-2 function was not elucidated. These investigators speculated that PTPN11 polymorphisms may affect the expression, activity, or affinity of SHP-2 to immunoreceptors in T and B cells. Accordingly, we found reduced SHP-2 gene transcripts in intestinal biopsy specimens from patients with active ulcerative colitis, emphasizing the inverse relationship between SHP-2 expression and colonic inflammatory phenotype. This could suggest that PTPN11 SNPs affect SHP-2 expression. However, additional biochemical and molecular studies conducted in a large number of human specimens are needed to verify this hypothesis.

Overall, these findings show that SHP-2 is required for homeostasis of the intestinal epithelium, in particular for proper differentiation of secretory progenitors. The next step will be to elucidate the exact molecular mechanisms by which SHP-2 exerts such protective effects on intestinal barrier function. Given that IBDs are very complex diseases, the identification of the specific SHP-2 targets may be one additional step in understanding the heterogeneity of these diseases.

**SHP-2 in Colorectal Cancer**

Recent data from our laboratory have shown that IEC-specific deletion of SHP-2 promotes chronic inflammation in the colon that results in regenerative hyperplasia and development of adenocarcinomas in aged mice (Gagné-Sansfaçon et al, unpublished data). These findings are reminiscent of those observed by Bard-Chapeau et al, who recently reported that hepatocyte-specific deletion of SHP-2 also promoted inflammation and tumorigenesis in the liver of aged mice. Over the past decade, many studies have linked chronic inflammation to cancer development, particularly in the GI tract (recently reviewed by Fichtner-Feigl et al, 2015). For instance, chronic intestinal inflammation has been shown to support tumor initiation through oxidative stress–induced mutations. Therefore, these results suggest that by suppressing inflammation, SHP-2 prevents the development of tumors in the colon and the liver (see later for further discussion regarding the liver). Accordingly, SHP-2 levels are decreased significantly in colitis-associated tumors in mice. Likewise, in colorectal carcinomas, SHP-2 has been reported to be down-regulated at both the messenger RNA and protein levels, with lower SHP-2 expression being correlated with advanced stages. In keeping with this, higher expression of SHP-2 in colorectal cancer patients has been related to better survival. Thus, these findings support the concept that, under specific contexts (such as inflammation), SHP-2 can act as a tumor suppressor.

Paradoxically, however, in human beings, gain-of-function mutations in the PTPN11 gene (SHP-2 gene) previously associated with certain forms of leukemias have been found in certain solid carcinomas including colorectal cancers. The somatic mutation specifically found in colorectal cancer specimens, the E76G mutation, disrupts the inhibitory intramolecular interaction with the PTP domain and leads to the hyperactivation of SHP-2. Mutations of this residue commonly are found in JML. In addition, in JML, SHP-2 mutations are mutually exclusive with NF1 or RAS (a negative regulator of Ras), and several findings indicate that SHP-2 contributes to leukemia carcinogenesis through Ras activation. Of note, in colorectal cancer, KRAS or NRAS are mutated in nearly 50% of colorectal tumors at a relatively early stage of the carcinogenic process. It therefore remains possible that the SHP-2 E76G mutation and/or SHP-2 overexpression/activation, by inducing the Ras/ERK signaling pathway, may be involved in early alterations leading to tumor formation in the colon in a sporadic context. It will be pertinent in future studies to determine whether gain-of-function mutations or overexpression of SHP-2 in intestinal epithelial cells also can cause or enhance colorectal tumorigenesis.

**SHP-2 in Liver Inflammation and Cancer**

A study conducted in hepatocyte-specific SHP-2 knocked-out mice has shown that SHP-2 ablation attenuates hepatocyte proliferation and liver regeneration after partial hepatectomy. However, these mice also develop hepatic inflammation and necrosis and, with age, develop hepatocellular adenomas. Moreover, hepatocyte-specific ablation of SHP-2 also drastically enhances liver tumor development in mice after injection of the chemical carcinogen diethylnitrosamine, reinforcing the tumor-suppressing function of SHP-2 in the liver. In keeping with these results, decreased SHP-2 expression has been detected in some human hepatocellular carcinoma (HCC) patient samples. However, SHP-2 expression recently was examined extensively in a large number of human HCCs and in which SHP-2...
transcripts were significantly lower in 22% of HCCs relative to the paired noncancerous tissues, although higher SHP-2 expression surprisingly was found in 78% of HCCs. Immunoblot and immunostaining analyses also showed SHP-2 up-regulation in a majority of HCCs. Of particular note, SHP-2 expression was increased significantly in metastatic foci compared with the matched primary HCCs or adjacent normal tissues, thus indicating a potential role of SHP-2 in HCC metastasis. In addition, SHP-2 silencing in hepatoma cells suppressed their proliferation as well as their tumorigenic and invasive/metastatic potential, possibly by reducing the activation of RAS/ERK and PI3K/Akt signaling.

Altogether, these data suggest that SHP-2 displays dual facets in liver cancer, either suppressing or promoting HCC development. Such a dual signaling role shown by a single protein in tumorigenesis is not without precedent. NF-κB, STAT3, JNK, and parafibromin also can function as tumor suppressors or oncoproteins in a cell context-dependent manner. One could speculate that different binding partner proteins may direct the opposing cellular responses under physiological and pathologic conditions.

SHP-2 in Lipid and Glucose Metabolism

Accumulating evidence from mouse models has indicated that SHP-2 regulates glucose and lipid metabolism. For instance, Shp-2 deletion in the pancreas in mice causes defective glucose-stimulated insulin secretion and impaired glucose tolerance. In effect, Shp-2 deficiency impairs the expression of Pdx1 and insulin genes, leading to reduced insulin production by β-cells. On the other hand, mice lacking Shp-2 in the liver show increased hepatic insulin action and glucose tolerance, as well as enhanced systemic insulin sensitivity compared with control mice, indicating that SHP-2 is a negative regulator of insulin signaling in hepatocytes. Acute SHP-2 deletion by tail-vein injection of adenovirus-carrying Ad5-Cre in Shp-2-flox/−/lox mice yields comparable results. SHP-2 has been proposed to putatively regulate liver insulin signaling by inhibiting insulin-receptor substrate 1/2 tyrosine phosphorylation, thereby attenuating PI3K association and Akt activation. Of note, SHP-2 protein expression in hepatocytes is regulated by nutritional status, increasing in mice fed a high-fat diet and decreasing during fasting. Thus, when challenged with high-fat feeding, mice with hepatic SHP-2 deficiency gain less weight and show decreased liver steatosis in comparison with control mice. In addition, hepatic SHP-2 deficiency attenuates the development of high-fat-diet-induced insulin resistance.

Lastly, in addition to the earlier-described observations, SHP-2 has been shown to regulate the degradation of fatty acid synthase, a key enzyme in fatty acid biosynthesis. Indeed, SHP-2 interacts with fatty acid synthase and induces its ubiquitination and degradation by forming a complex with ubiquitin E3 ligase COP1 and p38 MAPK. Accordingly, increased FAS protein levels have been observed in the liver and pancreas of SHP-2 conditional knocked-out mice.

Studies in the past decade have provided evidence that bile acids are not simply biological detergents facilitating lipid absorption, but also key metabolic regulators of glucose and lipid homeostasis. Interestingly, a novel function of SHP-2 in control of bile acid homeostasis has been found. Indeed, hepatocyte-specific deletion of SHP-2 results in bile acid accumulation and an enlarged bile acid pool in the liver. When fed a chow diet, these mice develop liver injury consistent with bile acid–induced damage to the hepatobiliary system. These phenotypic alterations can be explained by the fact that SHP-2 is required for FGFR5/19 activation of FGFR4 and its downstream signaling pathways that repress bile acid biosynthesis in hepatocytes.

Collectively, these studies indicate that hepatic SHP-2 is involved in the regulation of lipid and glucose metabolism, as well as in systemic energy balance.

Conclusion and Perspectives

Genome-wide association studies have associated the PTPN11 gene with gastric atrophy, gastric cancer, colitis, and serum lipid levels. The mechanisms underlying these associations are still in the hypothesis stage, which stipulates that PTPN11 SNPs may change the expression of the gene and consequently influence the SHP-2 protein, which in turn regulates proliferation, differentiation, and/or metabolism in the cells. Conversely, somatic gain-of-function mutations in PTPN11 have been detected in colorectal cancer. Hence, these genetic alterations strongly suggest that SHP-2 may play a prominent role in various functions of the GI system. Accordingly, anti-inflammatory and anti-tumoral actions of SHP-2 furthermore have been shown with the generation of hepatocyte and intestinal epithelial cell–specific SHP-2 deficient mice. The exact mechanism by which SHP-2 ablation in colonocytes and hepatocytes induces such effects is not totally clear. Notably, although the ERK pathway consistently was inhibited in colonocytes and hepatocytes of these mice, NF-κB and STAT3 conversely were hyperactivated. Importantly, both of these transcription factors have been identified as important contributors to inflammation-associated tumor development. Previous studies furthermore have documented a negative regulatory role of SHP-2 in the Janus kinase/signal transducers and activators of transcription signaling. However, the context in which these major proinflammatory pathways specifically are regulated by SHP-2 remains unknown. Interestingly, IECs and hepatocytes have been found to be hypersensitive to lipopolysaccharide challenge (increased NF-κB activation and chemokine/cytokine production) after SHP-2 silencing. Hence, one could speculate that the phosphatase SHP-2 protects epithelial cells from aberrant Toll-like receptor signaling, which can lead to uncontrolled inflammation detrimental to the host. Abundant evidence also supports the pivotal role of pattern-recognition receptors including Toll-like receptors in gastric, intestinal, and liver carcinogenesis. Further study in this area nonetheless is needed to elucidate whether SHP-2 limits the innate immune response in gastrointestinal tract epithelia.
diseases. SHP-2 is inactivated during oxidative stress and in the presence of nitric oxide by-products.\textsuperscript{116} This suggests that loss of SHP-2 activity and of the cellular pathways regulated by SHP-2 may coincide with cell injury and oxidative stress occurring during inflammation.\textsuperscript{82} Fully characterizing not only the downstream effectors but also the upstream regulators of SHP-2 phosphatase will provide further insights in explaining the mechanistic link between inflammation and GI cancers.

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