cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

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

Geneviève Coulombe and Nathalie Rivard

Department of Anatomy and Cell Biology, Cancer Research Pavilion, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Quebec, Canada

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)*

Keywords: PTPN11; inflammation; gastrointestinal cancer; epithelium.

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.

Most current article

© 2016 The Authors. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2015.11.001

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

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
	Parafibromin	SH2 domain of SHP-2 and parafibromin	AGS cells	Dephosphorylation of parafibromin on Y290, Y293, and Y315 by SHP-2 ↓ Interaction between dephosphorylated parafibromin and β-catenin ↓ Nuclear accumulation of β-catenin and transcription of Wnt/β-catenin target genes	30
	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 parafibromin ↓ 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	Mouse hepatic cells Mouse pancreatic cells	FASN ubiquitination and degradation ↓ Impact on lipid metabolism and glucose homeostasis	101

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.[56–58] In addition, *cagA* may interact directly with STAT3 by binding or recruitment to gp130, thereby promoting hyperactivation and increased transcriptional activity.[59] 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. Continued

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

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; FRS2α, fibroblast growth factor receptor substrate 2 α; 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.

compared with their *cagA*− counterparts.[60] 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.[56]

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.[61] 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.[62]

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*,[63] 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.[64]

Of note, single-nucleotide polymorphisms in the *PTPN11* gene have been associated with gastric atrophy in both Japanese (rs2301756)[65,66] and Chinese (rs12229892 and rs12423190)[67,68] 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.[69–71] 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.

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$^{\text{intestinal epithelial cell (IEC)-knockout (KO)}}$ 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.[72] Importantly, these mice rapidly develop severe inflammation 1 month after birth, with clinical and histopathologic features similar to ulcerative colitis.[73] Two further studies also have reported that mice featuring a *villin*^{Cre}-mediated SHP-2 deletion rapidly develop colitis.[74,75] 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.[73] Furthermore, SHP-2$^{\text{IEC-KO}}$ mice feature reduced Goblet cell numbers associated with expansion of Paneth cells and increased lysozyme expression in their small intestine.[74] These data hence suggest that SHP-2–dependent signaling directs cells to the Goblet cell fate while preventing Paneth cell expansion.[74] Dysregulation of epithelial cell fate or differentiation, particularly in the colon, may have deleterious

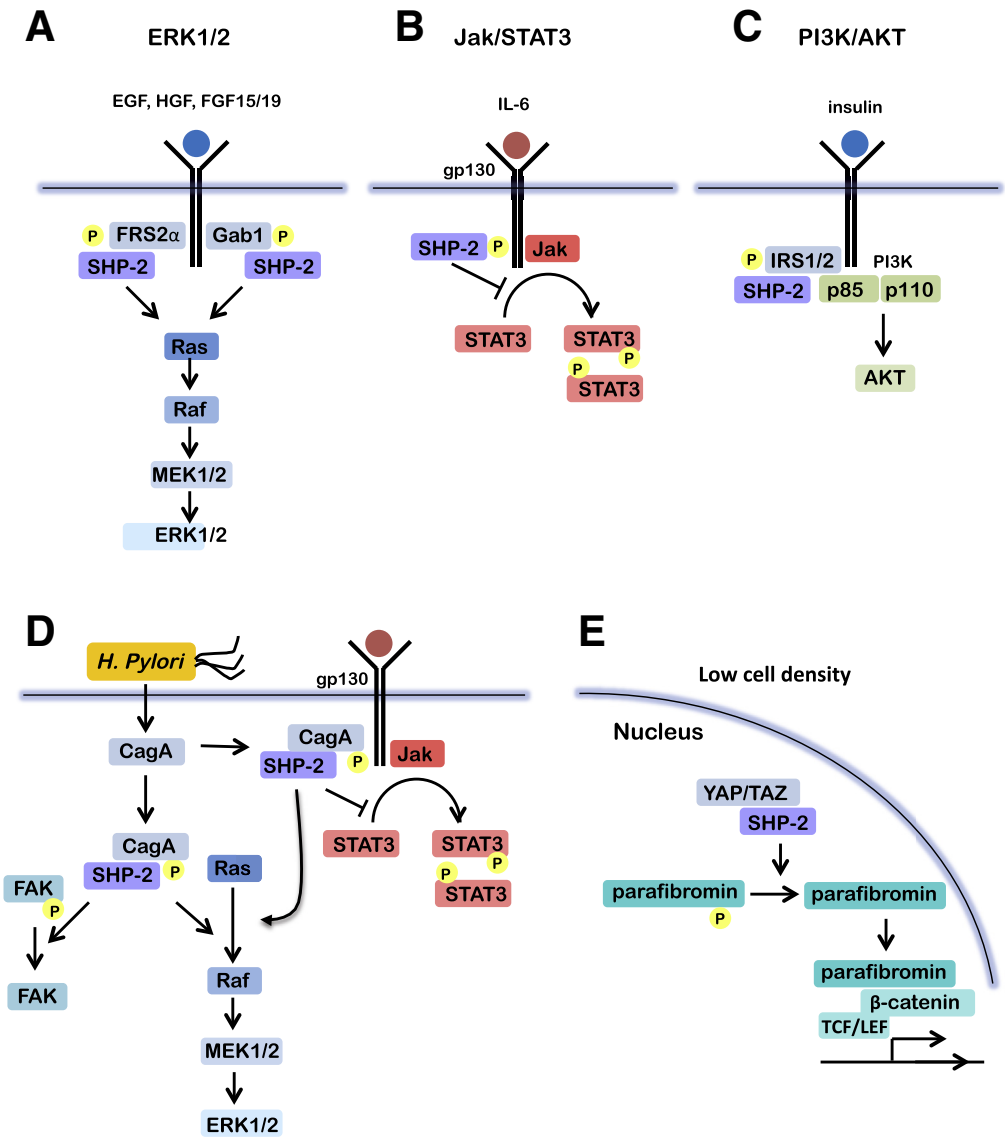

Figure 2. Signaling pathways regulated by SHP-2 in the gastrointestinal tract. (*A*) In response to growth factors, SHP-2 binds via its SH2 domains either to autophosphorylated receptors (such as that for platelet-derived growth factor, not shown) or to docking proteins (such as the Grb2-associated proteins Gabs 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.

consequences for the host as exemplified by mucin 2–deficient mice that rapidly develop severe colitis.[76] Conversely, Paneth cells that produce antimicrobial peptides such as α- and β-defensins and lysozyme also may participate in the development of colitis in SHP-2$^{IEC\text{-}KO}$ mice. Indeed, antimicrobial proteins shape the composition and abundance of microbiota, and segregate intestinal commensals from the mucosa.[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$^{IEC\text{-}KO}$ mouse model[73] suggest a role

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).[73] 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[75] or MEK1[74] markedly promotes Goblet cell differentiation in the colon of SHP-2$^{IEC\text{-}KO}$ mice and prevents the development of colitis. In fact, Heuberger et al[74] 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.[79] 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.[80] 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.[73] 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,[81] 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,[82] 2015). For instance, chronic intestinal inflammation has been shown to support tumor initiation through oxidative stress–induced mutations.[83] 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.84 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.[84,85] In keeping with this, higher expression of SHP-2 in colorectal cancer patients has been related to better survival.[86] 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.[44] 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.[44] Mutations of this residue commonly are found in JMML.[43,44] In addition, in JMML, *SHP-2* mutations are mutually exclusive with *RAS* or *NF1* (a negative regulator of Ras), and several findings indicate that SHP-2 contributes to leukemia carcinogenesis through Ras activation.[87] 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.[88,89] 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.[90] 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.[81] In keeping with these results, decreased SHP-2 expression has been detected in some human hepatocellular carcinoma (HCC) patient samples.[81,91,92] 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.[93] 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.[93]

Altogether, these data suggest that SHP-2 displays dual facets in liver cancer, either suppressing or promoting HCC development.[93,94] Such a dual signaling role shown by a single protein in tumorigenesis is not without precedent. NF-κB,[95] STAT3,[96] JNK,[97] and parafibromin[30] 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.[98] In effect, *Shp-2* deficiency impairs the expression of *Pdx1* and *insulin* genes, leading to reduced insulin production by β-cells.[98] 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-$2^{flox/flox}$ mice yields comparable results.[99] 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.[99] 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.[100] 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.[101]

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.[102,103] 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.[104] These phenotypic alterations can be explained by the fact that SHP-2 is required for FGF15/19 activation of FGFR4 and its downstream signaling pathways that repress bile acid biosynthesis in hepatocytes.[105]

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,[67] gastric cancer,[66] colitis, and serum lipid levels.[106,107] 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.[44] 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 antitumoral actions of SHP-2 furthermore have been shown with the generation of hepatocyte and intestinal epithelial cell–specific SHP-2– deficient mice.[73,81] 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[73] and hepatocytes[81] 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.[108–110] Previous studies furthermore have documented a negative regulatory role of SHP-2 in the Janus kinase/signal transducers and activators of transcription[23,81] and NF-κB signaling.[26] 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.[81] 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.[111–115] Further study in this area nonetheless is needed to elucidate whether SHP-2 limits the innate immune response in gastrointestinal tract epithelia.

Lastly, nothing is known regarding the regulation of SHP-2 phosphatase activity in IBD or other gastrointestinal

diseases. SHP-2 is inactivated during oxidative stress and in the presence of nitric oxide by-products.[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.[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.

References

1. Feng GS, Hui CC, Pawson T. SH2-containing phosphotyrosine phosphatase as a target of protein-tyrosine kinases. Science 1993;259:1607–1611.
2. Freeman RM Jr, Plutzky J, Neel BG. Identification of a human src homology 2-containing protein-tyrosine-phosphatase: a putative homolog of Drosophila corkscrew. Proc Natl Acad Sci U S A 1992;89:11239–11243.
3. Ahmad S, Banville D, Zhao Z, et al. A widely expressed human protein-tyrosine phosphatase containing src homology 2 domains. Proc Natl Acad Sci U S A 1993;90:2197–2201.
4. Vogel W, Lammers R, Huang J, et al. Activation of a phosphotyrosine phosphatase by tyrosine phosphorylation. Science 1993;259:1611–1614.
5. Adachi M, Sekiya M, Miyachi T, et al. Molecular cloning of a novel protein-tyrosine phosphatase SH-PTP3 with sequence similarity to the src-homology region 2. FEBS Lett 1992;314:335–339.
6. Yi T, Cleveland JL, Ihle JN. Identification of novel protein tyrosine phosphatases of hematopoietic cells by polymerase chain reaction amplification. Blood 1991;78:2222–2228.
7. Koch CA, Anderson D, Moran MF, et al. SH2 and SH3 domains: elements that control interactions of cytoplasmic signaling proteins. Science 1991;252:668–674.
8. Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. Trends Biochem Sci 2003;28:284–293.
9. Hof P, Pluskey S, Dhe-Paganon S, et al. Crystal structure of the tyrosine phosphatase SHP-2. Cell 1998;92:441–450.
10. Nardozza AP, D'Orazio M, Trapannone R, et al. Reactive oxygen species and epidermal growth factor are antagonistic cues controlling SHP-2 dimerization. Mol Cell Biol 2012;32:1998–2009.
11. Tang TL, Freeman RM Jr, O'Reilly AM, et al. The SH2-containing protein-tyrosine phosphatase SH-PTP2 is required upstream of MAP kinase for early Xenopus development. Cell 1995;80:473–483.
12. Rivard N, McKenzie FR, Brondello JM, et al. The phosphotyrosine phosphatase PTP1D, but not PTP1C, is an essential mediator of fibroblast proliferation induced by tyrosine kinase and G protein-coupled receptors. J Biol Chem 1995;270:11017–11024.
13. Yamauchi K, Ribon V, Saltiel AR, et al. Identification of the major SHPTP2-binding protein that is tyrosine-phosphorylated in response to insulin. J Biol Chem 1995;270:17716–17722.
14. Noguchi T, Matozaki T, Horita K, et al. Role of SH-PTP2, a protein-tyrosine phosphatase with Src homology 2 domains, in insulin-stimulated Ras activation. Mol Cell Biol 1994;14:6674–6682.
15. Qu CK. The SHP-2 tyrosine phosphatase: signaling mechanisms and biological functions. Cell Res 2000;10:279–288.
16. Milarski KL, Saltiel AR. Expression of catalytically inactive Syp phosphatase in 3T3 cells blocks stimulation of mitogen-activated protein kinase by insulin. J Biol Chem 1994;269:21239–21243.
17. Bennett AM, Hausdorff SF, O'Reilly AM, et al. Multiple requirements for SHPTP2 in epidermal growth factor-mediated cell cycle progression. Mol Cell Biol 1996;16:1189–1202.
18. Manes S, Mira E, Gomez-Mouton C, et al. Concerted activity of tyrosine phosphatase SHP-2 and focal adhesion kinase in regulation of cell motility. Mol Cell Biol 1999;19:3125–3135.
19. Maegawa H, Hasegawa M, Sugai S, et al. Expression of a dominant negative SHP-2 in transgenic mice induces insulin resistance. J Biol Chem 1999;274:30236–30243.
20. Inagaki K, Noguchi T, Matozaki T, et al. Roles for the protein tyrosine phosphatase SHP-2 in cytoskeletal organization, cell adhesion and cell migration revealed by overexpression of a dominant negative mutant. Oncogene 2000;19:75–84.
21. Qu CK, Yu WM, Azzarelli B, et al. Genetic evidence that Shp-2 tyrosine phosphatase is a signal enhancer of the epidermal growth factor receptor in mammals. Proc Natl Acad Sci U S A 1999;96:8528–8533.
22. Shi ZQ, Yu DH, Park M, et al. Molecular mechanism for the Shp-2 tyrosine phosphatase function in promoting growth factor stimulation of Erk activity. Mol Cell Biol 2000;20:1526–1536.
23. Xu D, Qu CK. Protein tyrosine phosphatases in the JAK/STAT pathway. Front Biosci 2008;13:4925–4932.
24. Yu CL, Jin YJ, Burakoff SJ. Cytosolic tyrosine dephosphorylation of STAT5. Potential role of SHP-2 in STAT5 regulation. J Biol Chem 2000;275:599–604.
25. You M, Yu DH, Feng GS. Shp-2 tyrosine phosphatase functions as a negative regulator of the interferon-stimulated Jak/STAT pathway. Mol Cell Biol 1999;19:2416–2424.
26. Xu S, Liu X, Bao Y, et al. Constitutive MHC class I molecules negatively regulate TLR-triggered inflammatory responses via the Fps-SHP-2 pathway. Nat Immunol 2012;13:551–559.
27. Ivins Zito C, Kontaridis MI, Fornaro M, et al. SHP-2 regulates the phosphatidylinositide 3'-kinase/Akt pathway and suppresses caspase 3-mediated apoptosis. J Cell Physiol 2004;199:227–236.
28. Kwon M, Ling Y, Maile LA, et al. Recruitment of the tyrosine phosphatase Src homology 2 domain tyrosine phosphatase-2 to the p85 subunit of phosphatidylinositol-3 (PI-3) kinase is required for insulin-like growth factor-I-dependent PI-3 kinase activation in smooth muscle cells. Endocrinology 2006;147:1458–1465.
29. Zhang SQ, Tsiaras WG, Araki T, et al. Receptor-specific regulation of phosphatidylinositol 3′-kinase activation by

the protein tyrosine phosphatase Shp2. Mol Cell Biol 2002;22:4062–4072.
30. Takahashi A, Tsutsumi R, Kikuchi I, et al. SHP2 tyrosine phosphatase converts parafibromin/Cdc73 from a tumor suppressor to an oncogenic driver. Mol Cell 2011; 43:45–56.
31. Tsutsumi R, Masoudi M, Takahashi A, et al. YAP and TAZ, Hippo signaling targets, act as a rheostat for nuclear SHP2 function. Dev Cell 2013;26:658–665.
32. Kontaridis MI, Eminaga S, Fornaro M, et al. SHP-2 positively regulates myogenesis by coupling to the Rho GTPase signaling pathway. Mol Cell Biol 2004; 24:5340–5352.
33. Schoenwaelder SM, Petch LA, Williamson D, et al. The protein tyrosine phosphatase Shp-2 regulates RhoA activity. Curr Biol 2000;10:1523–1526.
34. Qu CK, Shi ZQ, Shen R, et al. A deletion mutation in the SH2-N domain of Shp-2 severely suppresses hematopoietic cell development. Mol Cell Biol 1997; 17:5499–5507.
35. Aceto N, Sausgruber N, Brinkhaus H, et al. Tyrosine phosphatase SHP2 promotes breast cancer progression and maintains tumor-initiating cells via activation of key transcription factors and a positive feedback signaling loop. Nat Med 2012;18:529–537.
36. He Z, Zhu HH, Bauler TJ, et al. Nonreceptor tyrosine phosphatase Shp2 promotes adipogenesis through inhibition of p38 MAP kinase. Proc Natl Acad Sci U S A 2013;110:E79–E88.
37. Yu DH, Qu CK, Henegariu O, et al. Protein-tyrosine phosphatase Shp-2 regulates cell spreading, migration, and focal adhesion. J Biol Chem 1998;273:21125–21131.
38. Hartman ZR, Schaller MD, Agazie YM. The tyrosine phosphatase SHP2 regulates focal adhesion kinase to promote EGF-induced lamellipodia persistence and cell migration. Mol Cancer Res 2013;11:651–664.
39. Saxton TM, Henkemeyer M, Gasca S, et al. Abnormal mesoderm patterning in mouse embryos mutant for the SH2 tyrosine phosphatase Shp-2. EMBO J 1997; 16:2352–2364.
40. Tartaglia M, Mehler EL, Goldberg R, et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 2001; 29:465–468.
41. Shah N, Rodriguez M, Louis DS, et al. Feeding difficulties and foregut dysmotility in Noonan's syndrome. Arch Dis Child 1999;81:28–31.
42. Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics 2010;126:746–759.
43. Tartaglia M, Niemeyer CM, Fragale A, et al. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nat Genet 2003;34:148–150.
44. Bentires-Alj M, Paez JG, David FS, et al. Activating mutations of the noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. Cancer Res 2004;64:8816–8820.
45. Xu D, Liu X, Yu WM, et al. Non-lineage/stage-restricted effects of a gain-of-function mutation in tyrosine phosphatase Ptpn11 (Shp2) on malignant transformation of hematopoietic cells. J Exp Med 2011;208:1977–1988.
46. Chan RJ, Feng GS. PTPN11 is the first identified proto-oncogene that encodes a tyrosine phosphatase. Blood 2007;109:862–867.
47. Higashi H, Tsutsumi R, Muto S, et al. SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori CagA protein. Science 2002;295:683–686.
48. De Falco M, Lucariello A, Iaquinto S, et al. Molecular mechanisms of Helicobacter pylori pathogenesis. J Cell Physiol 2015;230:1702–1707.
49. Blaser MJ, Perez-Perez GI, Kleanthous H, et al. Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res 1995; 55:2111–2115.
50. Selbach M, Moese S, Hauck CR, et al. Src is the kinase of the Helicobacter pylori CagA protein in vitro and in vivo. J Biol Chem 2002;277:6775–6778.
51. Stein M, Bagnoli F, Halenbeck R, et al. c-Src/Lyn kinases activate Helicobacter pylori CagA through tyrosine phosphorylation of the EPIYA motifs. Mol Microbiol 2002; 43:971–980.
52. Higashi H, Nakaya A, Tsutsumi R, et al. Helicobacter pylori CagA induces Ras-independent morphogenetic response through SHP-2 recruitment and activation. J Biol Chem 2004;279:17205–17216.
53. Zhang W, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. Cell Res 2002;12:9–18.
54. Chambard JC, Lefloch R, Pouyssegur J, et al. ERK implication in cell cycle regulation. Biochim Biophys Acta 2007;1773:1299–1310.
55. Cagnol S, Chambard JC. ERK and cell death: mechanisms of ERK-induced cell death–apoptosis, autophagy and senescence. FEBS J 2010;277:2–21.
56. Jackson CB, Judd LM, Menheniott TR, et al. Augmented gp130-mediated cytokine signalling accompanies human gastric cancer progression. J Pathol 2007; 213:140–151.
57. Kamimura D, Ishihara K, Hirano T. IL-6 signal transduction and its physiological roles: the signal orchestration model. Rev Physiol Biochem Pharmacol 2003; 149:1–38.
58. Ihle JN. STATs: signal transducers and activators of transcription. Cell 1996;84:331–334.
59. Lee IO, Kim JH, Choi YJ, et al. Helicobacter pylori CagA phosphorylation status determines the gp130-activated SHP2/ERK and JAK/STAT signal transduction pathways in gastric epithelial cells. J Biol Chem 2010; 285:16042–16050.
60. Huang JQ, Zheng GF, Sumanac K, et al. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 2003;125:1636–1644.
61. Ohnishi N, Yuasa H, Tanaka S, et al. Transgenic expression of Helicobacter pylori CagA induces gastrointestinal and hematopoietic neoplasms in mouse. Proc Natl Acad Sci U S A 2008;105:1003–1008.
62. Yamazaki S, Yamakawa A, Ito Y, et al. The CagA protein of Helicobacter pylori is translocated into epithelial cells

and binds to SHP-2 in human gastric mucosa. J Infect Dis 2003;187:334–337.
63. Yamaoka Y, Kodama T, Kashima K, et al. Variants of the 3' region of the cagA gene in Helicobacter pylori isolates from patients with different H. pylori-associated diseases. J Clin Microbiol 1998;36:2258–2263.
64. Azuma T, Yamazaki S, Yamakawa A, et al. Association between diversity in the Src homology 2 domain–containing tyrosine phosphatase binding site of Helicobacter pylori CagA protein and gastric atrophy and cancer. J Infect Dis 2004;189:820–827.
65. Goto Y, Ando T, Yamamoto K, et al. Association between serum pepsinogens and polymorphism of PTPN11 encoding SHP-2 among Helicobacter pylori seropositive Japanese. Int J Cancer 2006;118:203–208.
66. Hishida A, Matsuo K, Goto Y, et al. Associations of a PTPN11 G/A polymorphism at intron 3 with Helicobacter pylori seropositivity, gastric atrophy and gastric cancer in Japanese. BMC Gastroenterol 2009;9:51.
67. Jiang J, Jia ZF, Kong F, et al. Association of polymorphism of PTPN 11 encoding SHP-2 with gastric atrophy but not gastric cancer in Helicobacter pylori seropositive Chinese population. BMC Gastroenterol 2012;12:89.
68. He C, Tu H, Sun L, et al. Helicobacter pylori-related host gene polymorphisms associated with susceptibility of gastric carcinogenesis: a two-stage case-control study in Chinese. Carcinogenesis 2013;34:1450–1457.
69. Dong S, Li FQ, Zhang Q, et al. Expression and clinical significance of SHP2 in gastric cancer. J Int Med Res 2012;40:2083–2089.
70. Jiang J, Jin MS, Kong F, et al. Increased expression of tyrosine phosphatase SHP-2 in Helicobacter pylori-infected gastric cancer. World J Gastroenterol 2013; 19:575–580.
71. Kim JS, Shin OR, Kim HK, et al. Overexpression of protein phosphatase non-receptor type 11 (PTPN11) in gastric carcinomas. Dig Dis Sci 2010;55:1565–1569.
72. Madison BB, Dunbar L, Qiao XT, et al. Cis elements of the villin gene control expression in restricted domains of the vertical (crypt) and horizontal (duodenum, cecum) axes of the intestine. J Biol Chem 2002;277: 33275–33283.
73. Coulombe G, Leblanc C, Cagnol S, et al. Epithelial tyrosine phosphatase SHP-2 protects against intestinal inflammation in mice. Mol Cell Biol 2013;33:2275–2284.
74. Heuberger J, Kosel F, Qi J, et al. Shp2/MAPK signaling controls goblet/Paneth cell fate decisions in the intestine. Proc Natl Acad Sci U S A 2014;111:3472–3477.
75. Yamashita H, Kotani T, Park JH, et al. Role of the protein tyrosine phosphatase Shp2 in homeostasis of the intestinal epithelium. PLoS One 2014;9:e92904.
76. Van der Sluis M, De Koning BA, De Bruijn AC, et al. Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. Gastroenterology 2006;131:117–129.
77. Salzman NH, Hung K, Haribhai D, et al. Enteric defensins are essential regulators of intestinal microbial ecology. Nat Immunol 2010;11:76–83.
78. Vaishnava S, Yamamoto M, Severson KM, et al. The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. Science 2011;334:255–258.
79. van Es JH, Jay P, Gregorieff A, et al. Wnt signalling induces maturation of Paneth cells in intestinal crypts. Nat Cell Biol 2005;7:381–386.
80. Narumi Y, Isomoto H, Shiota M, et al. Polymorphisms of PTPN11 coding SHP-2 as biomarkers for ulcerative colitis susceptibility in the Japanese population. J Clin Immunol 2009;29:303–310.
81. Bard-Chapeau EA, Li S, Ding J, et al. Ptpn11/Shp2 acts as a tumor suppressor in hepatocellular carcinogenesis. Cancer Cell 2011;19:629–639.
82. Fichtner-Feigl S, Kesselring R, Strober W. Chronic inflammation and the development of malignancy in the GI tract. Trends Immunol 2015;36:451–459.
83. Waldner MJ, Neurath MF. Mechanisms of immune signaling in colitis-associated cancer. Cell Mol Gastroenterol Hepatol 2015;1:6–16.
84. Cai P, Guo W, Yuan H, et al. Expression and clinical significance of tyrosine phosphatase SHP-2 in colon cancer. Biomed Pharmacother 2014;68:285–290.
85. Chang W, Gao X, Han Y, et al. Gene expression profiling-derived immunohistochemistry signature with high prognostic value in colorectal carcinoma. Gut 2014; 63:1457–1467.
86. Yu SJ, Yu JK, Ge WT, et al. SPARCL1, Shp2, MSH2, E-cadherin, p53, ADCY-2 and MAPK are prognosis-related in colorectal cancer. World J Gastroenterol 2011;17:2028–2036.
87. Loh ML, Vattikuti S, Schubbert S, et al. Mutations in PTPN11 implicate the SHP-2 phosphatase in leukemogenesis. Blood 2004;103:2325–2331.
88. Rajagopalan H, Bardelli A, Lengauer C, et al. Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. Nature 2002;418:934.
89. Nagasaka T, Sasamoto H, Notohara K, et al. Colorectal cancer with mutation in BRAF, KRAS, and wild-type with respect to both oncogenes showing different patterns of DNA methylation. J Clin Oncol 2004;22:4584–4594.
90. Bard-Chapeau EA, Yuan J, Droin N, et al. Concerted functions of Gab1 and Shp2 in liver regeneration and hepatoprotection. Mol Cell Biol 2006;26:4664–4674.
91. Jiang C, Hu F, Tai Y, et al. The tumor suppressor role of Src homology phosphotyrosine phosphatase 2 in hepatocellular carcinoma. J Cancer Res Clin Oncol 2012; 138:637–646.
92. Zhao X, Hu S, Wang L, et al. Functional short tandem repeat polymorphism of PTPN11 and susceptibility to hepatocellular carcinoma in Chinese populations. PLoS One 2014;9:e106841.
93. Han T, Xiang DM, Sun W, et al. PTPN11/Shp2 overexpression enhances liver cancer progression and predicts poor prognosis of patients. J Hepatol 2015; 63:651–660.
94. Li S, Hsu DD, Wang H, et al. Dual faces of SH2-containing protein-tyrosine phosphatase Shp2/PTPN11 in tumorigenesis. Front Med 2012;6:275–279.

95. Perkins ND. NF-kappaB: tumor promoter or suppressor? Trends Cell Biol 2004;14:64–69.
96. Zhang HF, Lai R. STAT3 in cancer-friend or foe? Cancers (Basel) 2014;6:1408–1440.
97. Tournier C. The 2 faces of JNK signaling in cancer. Genes Cancer 2013;4:397–400.
98. Zhang SS, Hao E, Yu J, et al. Coordinated regulation by Shp2 tyrosine phosphatase of signaling events controlling insulin biosynthesis in pancreatic beta-cells. Proc Natl Acad Sci U S A 2009;106:7531–7536.
99. Matsuo K, Delibegovic M, Matsuo I, et al. Altered glucose homeostasis in mice with liver-specific deletion of Src homology phosphatase 2. J Biol Chem 2010;285: 39750–39758.
100. Nagata N, Matsuo K, Bettaieb A, et al. Hepatic Src homology phosphatase 2 regulates energy balance in mice. Endocrinology 2012;153:3158–3169.
101. Yu J, Deng R, Zhu HH, et al. Modulation of fatty acid synthase degradation by concerted action of p38 MAP kinase, E3 ligase COP1, and SH2-tyrosine phosphatase Shp2. J Biol Chem 2013;288:3823–3830.
102. Thomas C, Pellicciari R, Pruzanski M, et al. Targeting bile-acid signalling for metabolic diseases. Nat Rev Drug Discov 2008;7:678–693.
103. Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Annu Rev Biochem 2003;72:137–174.
104. Calkin AC, Tontonoz P. Transcriptional integration of metabolism by the nuclear sterol-activated receptors LXR and FXR. Nat Rev Mol Cell Biol 2012; 13:213–224.
105. Li S, Hsu DD, Li B, et al. Cytoplasmic tyrosine phosphatase Shp2 coordinates hepatic regulation of bile acid and FGF15/19 signaling to repress bile acid synthesis. Cell Metab 2014;20:320–332.
106. Jamshidi Y, Gooljar SB, Snieder H, et al. SHP-2 and PI3-kinase genes PTPN11 and PIK3R1 may influence serum apoB and LDL cholesterol levels in normal women. Atherosclerosis 2007;194:e26–e33.
107. Jia ZF, Cao XY, Cao DH, et al. Polymorphisms of PTPN11 gene could influence serum lipid levels in a sex-specific pattern. Lipids Health Dis 2013;12:72.
108. Bollrath J, Greten FR. IKK/NF-kappaB and STAT3 pathways: central signalling hubs in inflammation-mediated tumour promotion and metastasis. EMBO Rep 2009; 10:1314–1319.
109. Bollrath J, Phesse TJ, von Burstin VA, et al. gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell 2009; 15:91–102.
110. Greten FR, Eckmann L, Greten TF, et al. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell 2004;118:285–296.
111. Fukata M, Abreu MT. Role of Toll-like receptors in gastrointestinal malignancies. Oncogene 2008;27: 234–243.
112. Tye H, Jenkins BJ. Tying the knot between cytokine and toll-like receptor signaling in gastrointestinal tract cancers. Cancer Sci 2013;104:1139–1145.
113. Kennedy CL, Najdovska M, Tye H, et al. Differential role of MyD88 and Mal/TIRAP in TLR2-mediated gastric tumourigenesis. Oncogene 2014;33:2540–2546.
114. Szabo G, Billiar TR, Machida K, et al. Toll-like receptor signaling in liver diseases. Gastroenterol Res Pract 2010; 2010:971270.
115. Fukata M, Shang L, Santaolalla R, et al. Constitutive activation of epithelial TLR4 augments inflammatory responses to mucosal injury and drives colitis-associated tumorigenesis. Inflamm Bowel Dis 2011; 17:1464–1473.
116. Chen CY, Willard D, Rudolph J. Redox regulation of SH2-domain-containing protein tyrosine phosphatases by two backdoor cysteines. Biochemistry 2009;48:1399–1409.
117. Higashi H, Tsutsumi R, Fujita A, et al. Biological activity of the Helicobacter pylori virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. Proc Natl Acad Sci U S A 2002; 99:14428–14433.
118. Hashi K, Murata-Kamiya N, Varon C, et al. Natural variant of the Helicobacter pylori CagA oncoprotein that lost the ability to interact with PAR1. Cancer Sci 2014; 105:245–251.
119. Tsutsumi R, Takahashi A, Azuma T, et al. Focal adhesion kinase is a substrate and downstream effector of SHP-2 complexed with Helicobacter pylori CagA. Mol Cell Biol 2006;26:261–276.
120. Meng S, Gui Q, Xu Q, et al. Association of Shp2 with phosphorylated IL-22R1 is required for interleukin-22-induced MAP kinase activation. J Mol Cell Biol 2010; 2:223–230.
121. Huber M, Izzi L, Grondin P, et al. The carboxyl-terminal region of biliary glycoprotein controls its tyrosine phosphorylation and association with protein-tyrosine phosphatases SHP-1 and SHP-2 in epithelial cells. J Biol Chem 1999;274:335–344.
122. Takahashi-Tezuka M, Yoshida Y, Fukada T, et al. Gab1 acts as an adapter molecule linking the cytokine receptor gp130 to ERK mitogen-activated protein kinase. Mol Cell Biol 1998;18:4109–4117.

Received August 28, 2015. Accepted November 10, 2015.

Correspondence
Address correspondence to: Nathalie Rivard, PhD, 3201, Jean Mignault, Sherbrooke, Quebec, Canada, J1E4K8. e-mail: Nathalie.Rivard@USherbrooke.ca.

Conflicts of interest
The authors disclose no conflicts.

Funding
Geneviève Coulombe is a Natural Sciences and Engineering Research Council of Canada Alexander Graham Bell student scholar, and Nathalie Rivard is the recipient of a Canadian Research Chair in colorectal cancer and inflammatory cell signaling.