Minireview

SHPS-1, a multifunctional transmembrane glycoprotein

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Abstract Src homology 2 (SH2) domain-containing protein tyrosine phosphatase substrate 1 (SHPS-1) is a member of the signal regulatory protein (SIRP) family. The amino-terminal immunoglobulin-like domain of SHPS-1 is necessary for interaction with CD47, a ligand for SHPS-1, which plays an important role in cell–cell interaction. The intracellular region of SHPS-1, on the other hand, may act as a scaffold protein, binding to various adapter proteins. Interestingly, increasing evidence has shown that SHPS-1 is involved in various biological phenomena, including suppression of anchorage-independent cell growth, negative regulation of immune cells, self-recognition of red blood cells, mediation of macrophage multinucleation, skeletal muscle differentiation, entrainment of circadian clock, neuronal survival and synaptogenesis. Recent progress has been made in attributing these novel exciting functions. Here we discuss how this interesting molecule works and consider its true role in biology.

Key words: SHPS-1; SIRP; CD47; Adaptor protein; SH2; SH3; Tyrosine phosphorylation

1. Introduction

Rapid and dynamic regulation of cell surface adhesion receptors is important for cell migration, growth, extravasation and invasion. One group of proteins involved in cell adhesion is the integrins, a family of heterodimeric adhesion receptors fundamentally important to mediating cell–cell and cell–extracellular matrix (ECM) interactions, communication and recognition [1]. Clustering of integrins triggers a cascade of intracellular signaling pathways leading to the phosphorylation of cytoplasmic and cytoskeletal substrates such as focal adhesion kinase (FAK) and paxillin. Furthermore, modifying integrin signaling pathways may contribute to cell migration, tumor invasion and metastasis [2,3]. However, the mechanism by which cells modulate integrin adhesiveness is not fully understood. It has been shown that several kinds of proteins, including immunoglobulin (Ig) superfamily proteins that bind to integrins, may generally function in concert to mediate both cell–cell and cell–ECM interactions, which in turn stimulate cytoskeletal reorganization, migration and invasion. For example, the interaction between the Ig superfamily and integrins such as PECAM-1/αvβ3 integrins, VCAM-1/α4 integrins, MadCAM-1/α4 integrins, ICAM/β2 integrins and junctional adhesion molecule 1/β2 integrin lymphocyte function-associated antigen 1, mediate leukocyte endothelial/epithelial/fibroblast adhesion governing inflammatory responses and tumor metastases [4–7]. Signal regulatory proteins (SIRPs) belong to the Ig superfamily and relate to integrin signaling cascades. One of the SIRPs [8,9], Src homology 2 domain-containing protein tyrosine phosphatase substrate 1 (SHPS-1), is also known as SIRP α1 [10], BIT (brain Ig-like molecule with tyrosine-based activation motifs) [11], P84 [12], MFR (macrophage fusion receptor) [13] and MyD-1 [14]. SIRPs appear ubiquitously expressed as Ig-like transmembrane glycoproteins composed of two subgroups, SIRP α and SIRP β (Fig. 1), that overall constitute a subfamily within the Ig superfamily. There are several arguments against using the term 'family' for SIRP genes; however, we use the word 'family' for the sake of convenience in this review. Among SIRPs, SHPS-1 was first identified as a novel tyrosine phosphorylated protein that binds to Src homology 2 (SH2)-containing protein tyrosine phosphatases, SHP-1 and SHP-2, in v-Src-transformed fibroblasts (SR-3Y1 cells) [8]. Various mitogens such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) induce the tyrosine phosphorylation of SHPS-1 to recruit the tyrosine phosphatases and several SH2-containing adapters to the plasma membrane [10]. In addition, SHPS-1 exerts its effects by means of its ligand, CD47, which is also a transmembrane glycoprotein, to regulate cell–cell interaction through bi-directional signaling. Up to the present, it has been shown that SHPS-1 is involved in various biological functions.

2. Expression and structures of SHPS-1 and SIRP family

A protein of the SIRP family consists of three domains: the extracellular domain, the transmembrane domain and the intracellular domain (Fig. 1). The extracellular domain is further divided into three Ig-like regions, an amino-terminal Ig variable (V) region and two Ig constant (C) regions. The second and third IgC can be removed by alternative splicing. At least 15 human members [10], varying in the form of subtle amino acid differences in the IgV region, have been identified in the SIRP family. Two subfamilies termed SIRP α and SIRP β are distinguished by the length of the cytoplasmic region. The SIRP is generally considered a colleague of the Ig-like receptor superfamily proteins, such as killer cell Ig-like inhibitory receptors (KIRs), Ig-like transcripts (ILTs), leuko-

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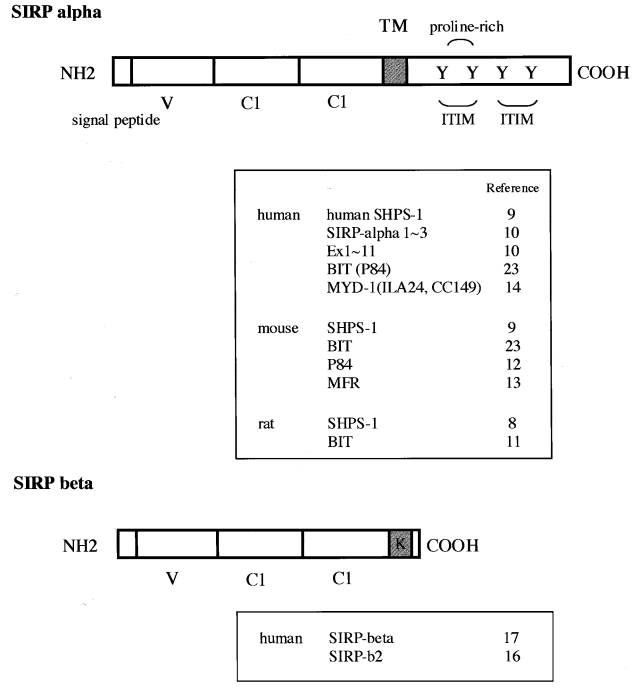

Fig. 1. Structure of the SIRP family. The SIRP family consists of two subfamilies, SIRP α and SIRP β, which differ in their cytoplasmic domains. The SIRP α contains two ITIMs, which bind to a SH2 domain-containing protein tyrosine phosphatase and a proline-rich region in the cytoplasmic domain. The SIRP β has a short cytoplasmic domain and a transmembrane domain with a positively charged lysine residue which associates with DAP12.

cyte Ig-like receptors (LIRs), monocyte/macrophage Ig-like receptors and paired Ig-like receptors (PIRs) [15], that modulates signals transduced by the distinct receptors involved in the function of the cells.

The cytoplasmic region of the SIRP α subfamily proteins contains two immunoreceptor tyrosine-based inhibitory motifs (ITIMs) and a proline-rich region near the carboxy-terminus, which represent a binding site for Src homology 3 (SH3) domain-containing molecules [10,13]. The ITIM is characterized by a consensus amino acid sequence of 'I/VxYxxL'. Phosphorylation of the ITIM-associated tyrosine residues enables recruitment of SHP-1, SHP-2 and SH2 domain-containing inositol phosphatase, which in turn dephosphorylates specific protein substrates involved in mediating various physiological effects. It has been shown that ITIMs are present in a large group of molecules which negatively regulate cell functions mediated by certain receptors including KIR, PIR-B, ILT/LIR-1, leukocyte-associated Ig-like receptor-1, gp49, C-type lectin inhibitory receptors, Fcγ RIIB and CD22.

The SIRP β subfamily, which consists of SIRP β and SIRP-b2 [16], has a short cytoplasmic region with a positively charged lysine residue at the juxta-transmembrane domain, which associates with DAP12 via an ionic transmembrane domain interaction [17,18]. DAP12, also known as KARAP [19], has one immunoreceptor tyrosine-based activating motif (ITAM). Phosphorylation of two tyrosine residues within the ITAM leads to association with Syk, an SH2 containing cytosolic tyrosine kinase important for receptor signaling. The SIRP β–DAP12 complex formation leads to tyrosine phosphorylation of DAP12, then induces activation of the mitogen-activated protein kinase (MAPK) pathway as shown in myeloid cells [18].

SHPS-1 has a relative molecular weight of 90–120 kDa and is differentially glycosylated in a species- and tissue-specific manner [10]. SHPS-1 contains potential *N*-glycosylation sites and a large number of serines and threonines that can serve as *O*-glycosylation sites [8,9,13,20]. Because the rat SHPS-1 carries no O-linked glycans, the species-specific difference of molecular weight may be due to the number of potential *N*-glycosylation sites (NXS/T) that are found: 15 times in rats [8], 17 times in mice [9,12] and five times in humans [9]. The tissue-specific difference of glycosylation may be due to the galactosylation capacity. It has been shown that the differential galactosylation of SHPS-1 determines its cellular binding specificity [21].

The localization of the SHPS-1 gene is identified on the human chromosome 20p13 and the mouse chromosome 2 [9,22,23]. Genes of the SIRP family members are also localized on the same chromosome. The open reading frame region of SHPS-1 is composed of eight exons, corresponding to a signal peptide, one V-type domain, two C-type domains, a transmembrane segment and three parts of one cytoplasmic domain. There are splicing variants of SHPS-1, the cytoplasmic VQSL insertion sequence from exon 7, a signal peptide and a V-type domain in the extracellular part (absence of exon 3 and 4) and no Ig-like domain in the extracellular part (absence of exons 2, 3 and 4) [24]. The SHPS-1 mRNA is ubiquitously expressed in all tissues examined (heart, brain, spleen, lung, liver, muscles, kidney and testis), being most abundant in the brain and the spleen [10]. Using immunohistochemistry with a specific anti-SHPS-1 antibody, it has been shown that SHPS-1 is strongly expressed in myeloid cells (macrophages, monocytes, granulocytes, dendritic cells) and neurons [20].

3. Biochemical approach to SHPS-1 function

3.1. A ligand of SHPS-1

CD47, also known as IAP (integrin-associated protein), Rh-related protein [25] and OA3 (ovarian cancer antigen) [26], is a highly glycosylated ~50 kDa transmembrane glycoprotein with a broad tissue distribution [27] and is reported to bind to SHPS-1 as a ligand [28–31]. CD47 was first identified as a copurified protein with the integrin αvβ3 protein from the placenta and platelets [32]. CD47 also belongs to the Ig receptor superfamily. The protein consists of an IgV-like domain at the amino-terminus and a highly hydrophobic stretch with five membrane-spanning segments (also called a multiple membrane-spanning domain). The carboxy-terminal cytoplasmic region can be spliced to several forms ranging in length from 3 to 36 amino acids [33]. In addition to the SHPS-1, CD47 has been found to associate physically with several families of integrins (β1, β2 and β3) and may regulate the functions of these integrins [33,34]. The Ig domain of CD47 and the amino-terminal Ig domain of SHPS-1 can bind directly to each other and the binding is sufficient to mediate the following transcellular bi-directional signaling via the respective cytoplasmic regions [35–40]. Most of the sequence variation among SIRP α members lies in their IgV domain and this difference may account for the varied binding affinity of SIRP α proteins to CD47 [41]. However, there may be additional

ligands for a single receptor or group of receptors of SIRP α [41]. SIRP β does not bind to CD47 [41].

3.2. Intracellular signaling of SHPS-1

The cytoplasmic region of SHPS-1 contains two ITIMs with four tyrosine residues of which phosphorylation can be induced by various mitogen stimuli such as serum, insulin [8], lysophosphatidic acid [8], growth hormones (GH) [42], EGF [10], PDGF [10] and neurotrophic factors [43] as well as integrin-mediated cell adhesions to laminin or fibronectin (FN) [8,10]. After 1–2 min, mitogenic stimulation leads to tyrosine phosphorylation of SHPS-1 via the receptor tyrosine kinases; however, stimulation of integrins by the adhesion of cells to laminin or FN leads within 15 min to tyrosine phosphorylation that may be catalyzed by non-receptor tyrosine kinases such as c-Src [44]. Reduced tyrosine phosphorylation of SHPS-1 is found in cell lines overexpressing CSK that inhibit Src family kinases. Furthermore, CSK associates with SHPS-1 endogenously in macrophage, although the physiological role is not clear [45]. The other Src family kinase, Fgr, has been reported to potentiate the binding between SHPS-1 and SHP-1, but does not phosphorylate SHPS-1 directly. In this case, Fgr seems act as an adapter molecule rather than a kinase to transduce signals [46]. A cytosolic tyrosine kinase involved in the STAT pathway, Janus kinase 2 (JAK2), associates with SHPS-1 when both molecules are overexpressed in cells [42]. The JAK2 phosphorylates SHPS-1 in vitro [47]. The GH-induced tyrosine phosphorylation of SHPS-1 thus seems to be mediated by JAK2. A cytosolic tyrosine kinase related to FAK, PYK2, has also been shown to form complexes with SHPS-1 [48]. Two tyrosines of SHPS-1, Tyr449 and Tyr473, are phosphorylated after insulin stimulation on RAT1-IR cells, suggesting that an insulin receptor kinase may phosphorylate them [49]. Site directed mutation of either of the tyrosines abolishes almost all binding to SHP-2 via the SH2 domain. So tyrosine phosphorylation is necessary for the recruitment of SHP-2. In particular, the phosphorylated Tyr449 has a specific affinity to the amino-terminal SH2 domain of SHP-2, while Tyr473 prefers the carboxy-terminal SH2 domain [49]. By a crystal structure analysis, it has been revealed that the amino-terminal SH2 domain of SHP-2 regulates the catalytic activity while the carboxy-terminal domain plays an accessory role [50]. All four phosphotyrosines of SHPS-1 may serve as substrates for the SHP-2, stimulating the catalytic activity of the phosphatases [8,49,51]. Recently, the two adapter proteins FyB/SLAP-130 and SKAP55hom have been found to associate with SHPS-1 [48]. Furthermore, SHPS-1 has also been shown to be able to associate with Grb2 in vitro [10]. The intracellular domain of SHPS-1 may be important in recruiting these signaling molecules at the site of transmembrane receptors.

4. Involvement of SHPS-1 in various cell functions

Because SHPS-1 has been shown to bind to various adapter proteins such as FyB/SLAP 130, SKAP55hom and Grb2

Table 1

Biological function	Effect	Cell or tissue type	Stimulation	Signalling	Reference
(1) Immunology					
Mast cell activation	downregulation	mast cell		SHP-1, SHP-2	[35]
NO production	upregulation	rat alveolar macrophage	anti-SIRP		[20]
Phagocytosis	inhibition	mouse splenic red pulp macrophage	$CD47^{+/+}$RBC	CD47	[36]
Phagocytosis	inhibition	mouse splenic red pulp macrophage	$CD47^{+/+}$RBC	CD47, SHP-1	[53]
T cell proliferation	downregulation	memory T cell	anti-SHPS-1 Ab	CD47	[14]
T cell activation	downregulation	T cell	anti-SHPS-1 Ab	CD47	[41]
Cytokine production	downregulation	dendritic cell	T cell	CD47	[40]
(2) Hematology					
Macrophage fusion		murine macrophage		CD47	[13,37,38]
Cell aggregation	inducible	Ba/F3		CD47	[39]
(3) Neurology					
Synaptogenesis		rat brain	?	CD47	[28]
Neural survival		rat cerebral cortical neuron primary culture	BDNF	P13K-Akt	[56]
Circadian clock	phosphorylation of SHPS-1	hypothalamic suprachiasmatic nucleus	light	SHP-2	[57]
(4) Oncology					
Colony formation (soft agar)	suppression	SR3Y1	?		[58]
MAPK activation	upregulation	CHO-IR, Rat1-IR, NIH3T3	insulin	SHP-2	[49]
MAPK activation	downregulation	v-Fms-transformed NIH3T3		SHP-2	[10]
Motility	downregulation	glioma cell (U87MG)	EGF	P13K-Akt	[61]
Focus formation	downregulation	glioma cell (U87MG)	EGF	P13K-Akt	[61]
Apoptosis	enhancement	glioma cell (U87MG)	irradiation	P13K-Akt	[61]
Focus formation	upregulation	SHPS-1 mutant fibroblast	cytoplasmic deletion	Rho	[62]
Migration	downregulation	SHPS-1 mutant fibroblast	cytoplasmic deletion	Rho	[62]
MAPK activation	no change	SHPS-1 mutant fibroblast	EGF	SHP-2	[62]
MAPK activation	upregulation	SHPS-1 mutant fibroblast	IGF-1	SHP-2	[62]
JNK activation	upregulation	SHPS-1 mutant fibroblast	IGF-1, EGF	SHP-2	[62]
(5) Others					
Myogenesis	inducible	myoblast (C2C12)	?	SHP-2	[42]
Scaffold protein		macrophage	FN	SKAP55hom, FYB/SLAP	[48]

[10,48], SHPS-1 may work as a scaffold protein to recruit these signaling molecules to the close site of the plasma membrane. Recently, SHPS-1 has been identified as a tyrosine phosphorylated protein associating with the SHP-2 in myoblasts, suggesting that SHPS-1 functions in skeletal muscle differentiation [52]. Likewise, it has been shown that SHPS-1 is involved in various cell functions (Table 1). According to the claim of the referenced paper, the roles of SHPS-1 could be annotated briefly as follows.

4.1. In immunology

SHPS-1 works as an inhibitory Ig receptor superfamily and at times works in cooperation with them. The inhibitory receptors, which can affect activation signals via ITAM-containing molecules including BCR Igα and Igβ, CD3ε, CD3γ, TCRζ, FcεRIγ, and DAP12, have a suppressive effect on the cell function of several hematopoietic lineage cells. A truncated form of SHPS-1 can inhibit IgE-induced cytokine synthesis in mast cells. This inhibition requires SHPS-1 coaggregation with ITAM-bearing high affinity IgE receptors (FcεRI) [35]. An anti-SHPS-1 antibody induces the activation of NO synthesis in macrophages, suggesting that SHPS-1 generally inhibits the synthesis [20]. One of the Src kinases, Fgr, associates with SHPS-1 and augments the binding between SHPS-1 and SHP-1 in macrophages, which is responsible at least in part for decreasing activity of the phagocytosis [46].

It has been shown that CD47 functions as a marker of self-recognition of red blood cells [36]. CD47-deficient cells are rapidly cleared from the bloodstream by splenic red pulp macrophages. On the other hand, CD47 on normal red blood cells prevents this elimination by binding to SHPS-1. The binding complex between CD47 and SHPS-1 causes tyrosine phosphorylation of SHPS-1, which is sufficient to inhibit macrophage functions such as phagocytosis [36]. It is also reported that inhibition of red blood cell phagocytosis mediated by Fcγ and complement receptors is caused by CD47–SHPS-1 interaction [53]. In this way, the inhibitory signal via the CD47–SHPS-1 complex appears important in preventing excess red blood cell clearance or autoimmune hemolytic anemia.

The proliferation of resting memory T cells is significantly reduced when the extracellular domain of SHPS-1 is stimulated by an anti-SHPS-1 antibody [14]. However, the binding of the extracellular domain of SHPS-1 to the CD47 on a lymphocyte is not sufficient for the signaling [41]. The intracellular signaling of SHPS-1 mediated by cell–cell interaction might be required in certain conditions. CD47–SHPS-1 binding prevents the phenotypic and functional maturation of immature dendritic cells (DCs) and suppresses interleukin-12 (IL-12) production by mature DCs. The binding also inhibits IL-12 responsiveness of T cells, which is caused by decreased IL-12 receptor expression on T cells [40].

Thus, the role of SHPS-1 in the immune system lies mainly in the negative regulation of phagocytosis, mast cell activation and dendritic cell activation through CD47 and/or SHP-1 functions. In particular, CD47–SHPS-1 interaction plays novel regulatory roles on immune cells, which may be involved in the maintenance of immune homeostasis, preventing the escalation of the immune response.

4.2. In hematology

SHPS-1 is also abundantly expressed in myeloid cells including monocytes and granulocytes. SHPS-1 expression is increased at the onset of macrophage fusion, which in turn results in giant cells or osteoclasts. Interestingly, an anti-SHPS-1 antibody can inhibit macrophage fusion [13]. The CD47 may also be involved in this process, because inhibition of SHPS-1–CD47 complex formation using an anti-CD47 antibody inhibits macrophage multinucleation [37,38]. In an IL-3-dependent pro-B cell that lacks endogenous SHPS-1, a Ba/F3 cell, forced expression of SHPS-1 results in a rapid formation of macroscopic Ba/F3 cell aggregates. The aggregation is mediated by the interaction between the CD47 and the amino-terminal IgV domain of SHPS-1. Either CD47-null cells or cells expressing mutant SHPS-1 lacking the IgV cannot form the aggregation [39]. SHPS-1 is expressed on immature $CD34^{+}CD38^{-}CD133^{+}$ hematopoietic progenitor cells and may play an important role in the regulation of early hematopoiesis [41]. Overall, the function of SHPS-1 on myeloid cells seems to overlap with that on immune cells.

4.3. In neurology

In neuronal cells, SHPS-1 is documented as an adhesion molecule and implicated in neuronal outgrowth and axon guidance [54]. The SHPS-1 and CD47 form a heterophilic binding pair that may be involved in bi-directional signaling at the synapse [28]. The binding functions to modify synaptic activity or possibly trophic interactions between central neurons [55]. Cerebral cortical neurons can extend their neurites on SHPS-1-coated substrate. Anti-SHPS-1 antibodies specifically inhibit this effect [11]. The heterophilic adhesive properties and the localization at the synapse suggest that SHPS-1 may also be involved in the regulation of synapse formation or maintenance [12]. Brain-derived neurotrophic factor (BDNF)-promoted survival of cultured cerebral cortical neurons was enhanced by the wild-type SHPS-1 and a specific PI3K inhibitor blocked this enhancement, indicating that its effect depends on the PI3K–Akt pathway. However, the tyrosine phosphorylation of SHPS-1 is not involved in this survival [56]. SHPS-1 at the rat suprachiasmatic nucleus is highly tyrosine phosphorylated in the light period compared to the dark period according to the light cycles [57]. The tyrosine phosphorylation of SHPS-1 may be involved in light-induced entrainment of the circadian clock.

4.4. In oncology

It has been reported that v-Src suppresses SHPS-1 expression and that overexpression of SHPS-1 onto v-Src-transformed fibroblasts abrogates anchorage-independent cell growth [58]. Activation of the Ras-MAP-kinase signaling cascade may be critical for the suppression of SHPS-1 expression. Accordingly, the expression level of SHPS-1 in cancerous tissues of breast carcinomas frequently seems lower than that of paired normal tissues [59]. SHPS-1 expression is also absent or significantly reduced on the majority of myeloid blasts from patients with acute myeloid leukemia or chronic myeloid leukemia [29]. Moreover, a low level of SHPS-1 expression is observed in tissues of hepatocellular carcinomas [60]. SHPS-1 may function as a suppressor against tumorigenesis. However, it is confusing as to whether SHPS-1 has an effect on MAPK activation. It has been reported that overexpression of wild-type SHPS-1 significantly increased MAPK activity in response to insulin [49]. In contrast, overexpression of human SHPS-1 in v-Fms-transformed NIH3T3 cells was reported to

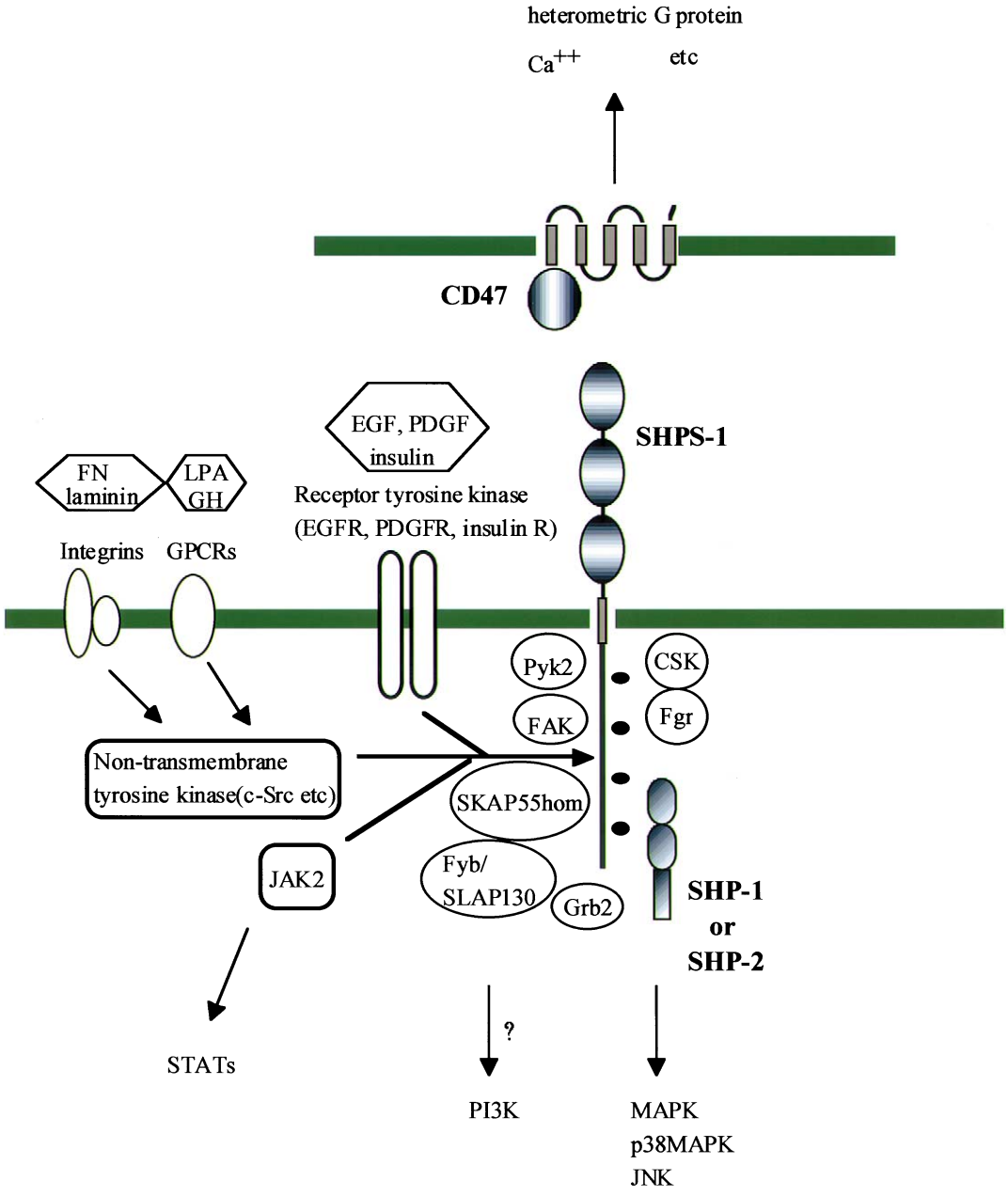

Fig. 2. Schematic representation of the SHPS-1 signaling pathways. Stimulation of a variety of receptors results in tyrosine phosphorylation of SHPS-1. Receptor kinases and some non-receptor tyrosine kinases can directly phosphorylate SHPS-1. However, other non-receptor tyrosine kinases such as PyK2, FAK, CSK and Fgr only bind to SHPS-1 but cannot phosphorylate it. Tyrosine phosphatases, SHP-1 and/or SHP-2, bind to and dephosphorylate SHPS-1. Adapter molecules such as Grb2, Fyb/SLAP-130 and SKAP55hom/R also bind to SHPS-1. The signaling components involve a family of molecules in some cases. The extracellular region of SHPS-1 accept the CD47 as a ligand, which also transduces a signal through the cytoplasmic domain, that is to say, 'bi-directional signaling'. SHPS-1 relates with a variety of signal transduction pathways.

inhibit MAPK activation [10]. SHPS-1 overexpression caused reduced cell migration and cell spreading in U87MG glioblastoma cells; however, no MAPK activation was found in the cells [61]. Likewise, fibroblasts expressing an SHPS-1 mutant lacking most of the cytoplasmic region exhibit several effects on stress fiber formation, cell spreading and migration [62] that is often related to MAPK activation. In fibroblasts, growth factor-induced c-Jun *N*-terminal kinase activation is enhanced by the SHPS-1 mutant lacking most of the cytoplasmic region, although the activation of Ras extracellular signal-regulated kinase (ERK) is dependent on the kind of growth factor. Though EGF-induced ERK activation in the SHPS-1 mutant cells is similar to that in wild-type cells, IGF-1-induced ERK activation in the mutant cells is enhanced [62]. Thus, the effects of SHPS-1 on MAPK activation have been controversially reported. Further studies are needed to establish the mechanism by which SHPS-1 regulates MAPK signaling.

5. Discussion

The mechanisms by which SHPS-1 exerts these different

effects on the cell have not yet been made clear. In most cases, probably, SHPS-1 acts as a scaffold molecule for the SH2-containing protein tyrosine phosphatases SHP-1 and/or SHP-2 to activate them (Fig. 2) and the nature of the SHPS-1 function depends on the function of the phosphatases. The roles of the phosphatases in cell signaling also have not been conclusive. SHP-2 is a cytoplasmic phosphatase and its membrane localization is important for its activation. Stimulation of cells with various growth factors and mitogens activate tyrosine phosphorylation of SHPS-1 and subsequent binding of SHPS-1 with SHP-2, thereby recruiting SHP-2 at the vicinity of the cell membrane. In some instances, SHPS-1 negatively regulates MAPK and Akt pathways, although in such cases SHP-2 may be a mediator. However, there are several other proteins (Gab-1/2, IRS-1/2, etc.) which act as potential adapter molecules for SHP-2, or these proteins may compete with SHPS-1 for SHP-2 binding. In such cases, activation of SHP-2 is performed by some other protein and overexpression of SHPS-1 competitively binds SHP-2, making it less available for the particular adapter. Careful biochemical studies for the SHPS-1 complex may bring us novel findings that are useful for understanding SHPS-1.

There are 17 trinucleotide (CCA) repeats in the 3′ untranslated region of the human SHPS-1 gene. It has been suggested that expansion of trinucleotide repeats is responsible for several hereditary pathological disorders, including myotonic dystrophy, fragile X syndrome, spinal and bulbar atrophy, Huntington's disease, spinocerebellar ataxia, Machado–Joseph disease and dentatorubral–pallidoluysian atrophy. So, genetic alteration of the SHPS-1 gene might cause a disease. In particular, it seems likely that SHPS-1 is deeply involved in immunological and hematological disorders, as mentioned above. Recently, SHPS-1 mutant mice lacking most of the cytoplasmic region of this protein were generated. The SHPS-1 mutant fibroblasts exhibit increased formation of actin stress fibers and focal adhesion, quick-spreading and impaired polarized extension and cell migration, which demonstrates that SHPS-1 plays crucial roles in integrin-mediated cytoskeletal reorganization and cell motility. In addition, growth factor-induced activation of MAPK is reduced in the mutant cells. Taken together, SHPS-1 has a pivotal role in various important signaling pathways. Further analyses using gene targeting should unravel the involvement of SHPS-1 in disorders.

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