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REVIEW

# The SHP-2 tyrosine phosphatase: Signaling mechanisms and biological functions

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## ABSTRACT

Cellular biological activities are tightly controlled by intracellular signaling processes initiated by extracellular signals. Protein tyrosine phosphatases, which remove phosphate groups from tyrosine phosphorylated signaling molecules, play equally important tyrosine roles as protein kinases in signal transduction. SHP-2, a cytoplasmic SH2 domain containing protein tyrosine phosphatase, is involved in the signaling pathways of a variety of growth factors and cytokines. Recent studies have clearly demonstrated that this phosphatase plays an important role in transducing signal relay from the cell surface to the nucleus, and is a critical intracellular regulator in mediating cell proliferation and differentiation.

**Key words:** *SHP-2, SHP-1, Signal transduction.*

## INTRODUCTION

Cells can not survive without environmental factors. Cellular responses to a variety of extracellular cues are mediated by intracellular signaling pathways. A great deal of evidence has demonstrated that dysregulation of such signaling pathways initiated from extracellular factors causes malfunctioning of the targeted cells, and eventually

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leads to diseases. Many important cellular activities, such as cell proliferation, differentiation, and death, are highly controlled by the cellular signal transduction processes in which protein phosphorylation and dephosphorylation are central events[1-3]. It is increasingly clear that these biochemical processes are carried out by protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Protein phosphorylation and dephosphorylation are closely related to the activities of the signaling proteins and directly mediate protein-protein interaction. Thus, PTPs, which dephosphorylate tyrosine phosphorylated signaling molecules, play an equally important role as PTKs in transducing signal flow and controlling cellular behavior. However, studies regarding PTPs are lagging behind. SHP-2, a Src homology 2 (SH2) domain containing non-transmembrane PTP, has been demonstrated to be involved in a variety of cytokine and growth factor initiated signal transduction processes[4-8]. Increasing evidence has indicated that this phosphatase plays an important role in diverse signaling pathways to regulate cellular biological processes. Even though significant progress has been made in the last several years, many aspects of the activities of this phosphatase still remain unaddressed. This review will focus on the signaling mechanisms and the biological functions of this enzyme. Particular attention will be paid to its role in hematopoietic cell regulation.

## Signaling mechanisms

SHP-2, previously called SH-PTP2, PTP1D, SH-PTP3, and Syp, was identified independently by several groups as a cytosolic SH2 domain containing protein tyrosine phosphatase[4-8]. It is ubiquitously expressed in various tissues and cell types. It has a similar overall structure and high homology with the hematopoietic cell specific-SHP-1 phosphatase[9],[10]. Both of these phosphatases contain two tandem SH2 domains at the N-terminus and one phosphatase domain at the C-terminus. The SH2 domain is a 100 amino acid motif which mediates the binding of SHP-2 and SHP-1 to the phosphorylated tyrosine residues on other molecules, thus directing the specific protein-protein interaction for these two phosphatases[11]. Normally, the auto-inhibitory influence of their SH2 domains renders these two enzymes catalytically inefficient. Occupancy of the SH2 domains by phosphotyrosine residues leads to an increase in the catalytic activity of the SHP-2 and SHP-1 phosphatases, possibly by inducing conformational changes in the enzymes[12,13]. Accumulated biochemical data have shown that both SHP-2 and SHP-1 act downstream of receptor and cytoplasmic tyrosine kinases to propagate the signal relay from the cell surface to the nucleus. Despit high homology between SHP-2 and SHP-1, their functions might be distinct. Genetic analyses on Xenopus revealed that both the SH2 domains and the phosphatase domains contribute to signaling, and thus functional specificity of these two PTPs[14,15].

SHP-2 is expressed in various tissues and cell types, and has been implicated in diverse signaling pathways including those initiated by growth factors such as PDGF,

EGF, and IGF-1, cytokines such as IL-3, GM-CSF, and EPO, as well as insulin and interferon[16,17]. SHP-2 has compound signaling functions. It appears to be involved in a variety of signal transduction processes, such as the Ras-Raf-MAP kinase, Jak-Stat, and PI3 kinase pathways. Within a single signaling pathway, SHP-2 may act at multiple sites to participate in the signal relay. For instance, SHP-2 directly interacts with cytokine and growth factor receptors, such as PDGF, EGF, SCF, and EPO receptors. It has also been demonstrated to bind with a variety of signaling intermediates such as Grb2, FRS-2, Jak2, p85 subunit of PI3 kinase, IRS-1, and Gab1 and 2. As a protein tyrosine phosphatase, SHP-2 is believed to function by dephosphorylating its associated signaling molecules, thus diminishing the local signaling flow. However, the ultimate effect of SHP-2 action in most signaling pathways is to enhance the signal transduction. The precise mechanism remains to be defined.

In most circumstances, SHP-2 plays a positive role in transducing the signal relay from receptor PTKs[14], [18-21]. Previous biochemical evidence has demonstrated that the SHP-2 enzymatic activity is required for its function in signal transduction[21], [22]. Cysteine (Cys) at amino acid residue 459 has been identified as critical for its phosphatase activity. While the replacement of cysteine with serine (Ser) at this site completely abolishes its enzymatic activity, the capacity for this mutant molecule to bind to other signaling intermediates via its SH2 domains remains unaltered. This mutant functions thus as a dominant negative molecule over the endogenous wild type SHP-2. Using the dominant negative approach, SHP-2 has been reported, in a number of studies, to positively regulate the signaling pathways of insulin, EGF, PDGF, and FGF. Overexpression of this mutant protein has been shown to block the signaling functions of endogenous SHP-2 in both in vitro and in vivo models. For example, the introduction of a catalytically inert SHP-2 molecule markedly inhibited the activation of MAP kinase in response to EGF, insulin, and fibronectin stimulation[19], [21],[23-26]. The precise biochemical basis for such positive regulation for this phosphatase still remains unclear. Biochemical studies on the Drosophila homologue of SHP-2, csw, revealed that SHP-2 may function at a parallel level or upstream of Ras in the MAP kinase pathway[27].

In some cases, SHP-2 does play a negative role in intracellular signaling processes, thus it may have dual functions in cytokine and growth factor signal transduction. For instance, SHP-2 negatively regulates the Jak-Stat signaling pathway initiated by interferon -$\alpha$ and - $\gamma$. As a consequence, SHP-2 mutant cells are more sensitive to the cytotoxicity of interferons, and the activation of downstream Stat2 and Stat1 is elevated[28]. Another prominent example is that SHP-2 was found to function to diminish the signal relay from gp130[29-31]. For instance, the recent knockin mouse model, in which the endogenous gp130 has been replaced with a human gp130 Y759F (equivalent to residue 757 in mouse) mutant, displayed lymphoadenopathy, splenomegaly, and an enhanced acute-phase response. However, the data supporting the negative regulatory role for SHP-2 is based on observed increases in gp130-dependent signaling when

Y757 on gp130, a pivotal binding site for SHP-2, is mutated to phenylalanine. The question remaining to be resolved is whether these phenotypes are really mediated by SHP-2, because a more recent finding demonstrated that the Y757 is also the recognition site for SOCS-3, a putative SH2 domain containing cytokine signaling suppressor [32]. SOCS-3 and SHP-2 may compete to bind to this site, and SHP-2 functions to block the effects of SOCS-3 in gp 130 pathway.

SHP-2 is also highly expressed in hematopoietic cells, and has been indicated to be involved in hematopoietic growth factor signal transduction[33-35]. It has been shown to participate in the signal transduction from IL-3, EPO, SCF, GM-CSF, and IL-5. However, compared to SHP-1 phosphatase, understanding of the physiological and biochemical functions of SHP-2 in hematopoietic cells lags far behind. A potential role of SHP-2 phosphatase in hematopoietic cell signaling is indicated by indirect evidence based on receptor-mediated changes in SHP-2 tyrosine phosphorylation and/or its association with receptors or other signaling intermediates. Unfortunately, the cellular significance of SHP-2 involvement in these pathways remains to be elucidated. This could be achieved through the signal transduction studies on the hematopoietic cell lines lacking this phosphotase. Thus, direct evidence showing the biological function and the cellular significance of the enzymatic activity of this signaling protein may be obtained.

Identification of the down-stream targets or substrates of SHP-2 will help to elucidate the biochemical basis of SHP-2 activity in signal transduction. To date, several such molecules have been identified, for instance, SHPS-1[36], PZR[37], and the newly characterized pleckstrin homology domain-containing scaffolding or docking proteins, Gab1[38] and Gab2[39-41]. In fact, Gab2 was originally identified in IL-3 stimulated hematopoietic cells[42], and was shown to be a major SHP-2-binding protein. Subsequently, this strong interaction was further demonstrated to be induced by TPO and EPO stimulation as well as TCR engagement[41]. In addition, the SHP-2/Gab2 complex is also assembled in hematopoietic cells after b1 integrin cross-linking (Qu et al., unpublished data). Our recent studies showed that SHP-1 also associates with Gab2. However, unlike the SHP-2/Gab2 association, SHP-1 and Gab2 are associated in a constitutive manner. Thus both the SHP-2 and SHP-1 phosphatases anchor to the same docking protein Gab2, which may serve as a linker for the functional interaction between these two phosphatases.

## Biological functions

An extensive distribution of SHP-2 phosphatase indicates that it might have a wide range of physiological functions. Recent data from SHP-2 gene knockout mice have clearly suggested this notion. Mice homozygous for a SHP-2 mutation are embryonic lethal. Homozygous mutants die at midgestation with multiple developmental defects in the mesodermal pattering and body organization[43],[44]. A similar requirement for

SHP-2 in Xenopus development was found to be attributed to its positive role in basic fibroblast growth factor signaling[15]. Chimeric mice generated from homozygous mutant ES cells die at different stages, depending on the contribution from the mutant cells [45]. This strategy has proven to be an alternative approach for further defining the physiological functions that are masked due to the early embryonic lethality of mutant mice. Some interesting phenotypes were observed in chimeric mice containing SHP-2 mutant cells, such as abnormal development of the skeleton and limbs[45],[46]. Another striking observation was that 50 % of the chimeric mice had an open eyelid phenotype, which is a typical phenotype of EGF receptor knockout mice, suggesting that SHP-2 is required for in vivo action of EGF. Further genetic analyses showed that a SHP-2 heterozygous mutation dominantly enhanced the phenotypes of EGF receptor weak allele ( wa-2/ wa-2). Reducing SHP-2 protein levels by half further significantly diminished the EGF signaling on the background of EGF receptor mutation[47]. Additionally, subsequent studies showed that the penetrance and severity of the defective cardiac semilunar valvulogenesis was enhanced in wa-2/wa-2 mice with a heterozygous mutation of SHP-2, indicating a functional requirement for SHP-2 in heart development[48].

In vitro studies have revealed that SHP-2 plays critical roles in regulating a number of cellular activities. ES cells are totipotent embryonic stem cells, that can be induced to differentiate into a variety of cell lineages, including hematopoietic cells, cardiomyocytes, and even neuronocytes. SHP-2 mutation in these stem cells severely decreased erythroid lineage differentiation. Myeloid lineage development was completely blocked[49]. Consistently, in vivo hematopoietic progenitor development of mutant ES cell origin in the bone marrow and fetal liver from the chimeric mice generated from homozygous mutant ES cells was undetectable[45]. Hematopoietic progenitor analyses demonstrated that hematopoietic activity in the yolk sac from homozygous mutant embryos was dramatically decreased, suggesting that the SHP-2 mutation blocks hematopoietic development at the primitive hematopoiesis stage. Moreover, SHP-2 is also required for lymphoid lineage development, as SHP-2 mutation completely blocked the T and B lymphocyte development in SHP-2-/-/RAG-2-/- chimeric mice. No Thy+ T cells and B220+ B cells derived from mutant ES cells were detected, suggesting T and B lymphocyte development was blocked at the Pro-T and Pro-B stages (Qu et al., unpublished data). It seems that these developmental defects occur at very early stages in the differentiation process of ES cells. Indeed, SHP-2 mutation significantly reduced ES cell differentiation potential[30],[50], the differentiation of other lineages, including cardiomyocytes and fibroblasts from mutant ES cells was also decreased.

In contrast with SHP-2 phosphatase, the hematopoietic cell specific-SHP-1 phosphatase negatively regulates hematopoietic cell regulation[51-54]. Functional studies on SHP-1 phosphatase have been considerably aided by analyses of motheaten ( me/me) and viable motheaten ( $mev^{v}/mev^{v}$) mice which have spontaneous mutations in the coding region for the N-terminal SH2 domain and the catalytic domain of SHP-1 respectively

[55]. Homozygous mutants have obvious hematological abnormalities. Both me/me and $mev^{v}/mev^{v}$ mice develop systemic autoimmune disease and die after approximately 3 and 9 w, respectively[56]. High levels of immunoglobulins-particularly autoantibodies-in peripheral blood and excessive erythropoiesis in spleen suggest a primarily negative regulatory role for this phosphatase in hematopoietic development and function. Consistent with this, it has been found that SHP-1 attenuates signals emanating from receptors for EPO, IL-3, GM-CSF, and M- CSF, and mediates inhibitory signals triggered by immunoglobulin $\gamma$ Fc domains (Fc $\gamma$RIIB1), NK cell inhibitory receptor, TCR, BCR, CD22, and CD72[52-54], [57-60].

Taken together, these findings suggest that SHP-2 and the homologous SHP-1 phosphatase have opposite functions in regulating hematopoietic cell development, despite sharing high homology. Indeed, recent data from SHP-2/SHP-1 double mutant mice strongly support this notion. Defective primitive hematopoiesis caused by the SHP-2 mutation was partially rescued by an additional SHP-1 mutation (Qu et al., unpublished data). A profound biochemical basis for the distinct functions of these phosphatases remains to be elucidated.

In addition, SHP-2 appears to positively regulate fibroblast cell adhesion and migration[23],[24], [61],[62]. SHP-2 homozygous mutant fibroblast cells have reduced cell spreading and migration. Further biochemical studies have indicated that SHP-2 participates in focal adhesion kinase-mediated integrin signaling. Moreover, SHP-2 is required for in vivo insulin action. Transgenic mice expressing dominant negative SHP-2 displayed insulin resistance[25]. Plasma insulin levels in transgenic mice after 4 h fasting were 3 times greater than none-transgenic controls with comparable blood glucose levels. In the presence of physiological concentration of insulin, the insulin-stimulated glucose uptake in muscle and adipocytes from transgenic mice was impaired.

## Perspectives

It is clear that SHP-2 tyrosine phosphatase plays critical roles in regulating signal transduction, and mediating a variety of cellular biological processes. However, many questions regarding the biochemical basis for its signaling functions still remain unaddressed. Prominent questions are: why does a protein tyrosine phosphatase play a positive role in transducing signal relay from cell surface receptors, and what is the biochemical significance of the phosphatase activity of this enzyme? Importantly, several recent reports have indicated a clinical relevance of SHP-2 phosphatase to some diseases such as neutropenia (Kostmann's syndrome)[63] and diabetes[64],[65], which further emphasizes the importance of studies on the signaling regulation of this PTP. Understanding the profound mechanisms of SHP-2 action will provide novel insights into the regulation of intracellular signaling processes, and may lead to novel molecular therapeutic approaches for certain diseases.

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