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Review Article

SHP-2 tyrosine phosphatase in human diseases

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Abstract: SHP-2, a ubiquitously expressed Src homology 2 (SH2) domain-containing protein tyrosine phosphatase (PTP), plays a critical role in physiology and disease. SHP-2 has been clearly demonstrated to be an important molecule in various cytoplasmic signal transduction pathways. In addition, emerging evidence indicates that SHP-2 may function in the nucleus and in the mitochondria. However, the signaling mechanisms of SHP-2 are not completely understood. Interestingly, genetic mutations in SHP-2 that either enhance or inactivate its catalytic activity have been identified in human diseases with overlapping phenotypes. In light of this hint given by nature, new cell and animal models now provide the opportunity to uncover how this molecule functions in multiple cellular processes, and more importantly, how its known mutations induce human diseases.

Key Words: SHP-2, tyrosine phosphatase, Src homology 2 domain

Role of SHP-2 in physiology

SHP-2 tyrosine phosphatase plays an essential role in cellular function and physiology. A homozygous deletion of either Exon 2 [1] or Exon 3 [2] of the SHP-2 gene (PTPN11) generates truncated SHP-2 which lacks the amino-terminal SH2 (N-SH2) domain and leads to early embryonic lethality in mice prior to or at midgestation, respectively. SHP-2 null mutant mice die much earlier — at peri-implantation [3]. An Exon 3 deletion mutation of SHP-2 blocks hematopoietic potential of embryonic stem cells both in vitro and in vivo [4-6], whereas SHP-2 null mutation causes inner cell mass death and diminished trophoblast stem cell survival [3]. Recent studies on a SHP-2 conditional knockout or tissue-specific knockout mice have further revealed an array of important functions of this phosphatase in various physiological processes. For example, deletion of SHP-2 in the brain leads to defective proliferation and differentiation in neural stem cells and early postnatal lethality in mice [7]. SHP-2 deficiency in cardiomyocytes causes dilated cardiomyopathy, leading to heart failure and premature mortality [8]. Mice with skeletal muscle-specific deletion of SHP-2 exhibit a reduction in both myofiber size and type I slow myofiber number [9]. Also, deletion of SHP-2 impairs lobulo-alveolar outgrowth in mammary glands [10]. The phenotypes demonstrated by loss of SHP-2 protein/function are largely attributed to the role of SHP-2 in the cell signaling pathways induced by environmental cues.

Molecular mechanisms of SHP-2 function

Structural basis

SHP-2 activity is tightly controlled by its structural conformation. SHP-2 contains two tandem SH2 domains, a PTP domain, and potentially other functional motifs throughout the molecule. In its basal state, SHP-2 is self-inhibited; the backside of the N-SH2 domain forms a loop and is wedged into the PTP domain, thus blocking the catalytic site, resulting in low activity [11, 12]. Numerous inter-domain hydrogen bonds exist in this conformation, either directly or bridged by water molecules. The SH2 domains,

particularly the N-SH2 domain, mediate the binding of SHP-2 to other signaling proteins via phosphorylated tyrosine residues in a sequence-specific fashion, directing SHP-2 to the appropriate subcellular location and helping to determine the specificity of substrate-enzyme interactions. When a phosphotyrosyl peptide binds the N-SH2 domain, SHP-2 undergoes a conformational change. This disrupts the interdomain binding, thus enhancing catalytic activity. The critical role of the N-SH2 domain of SHP-2 in cell signaling and function is well supported by SHP-2 structure/function studies [13] and by the severe phenotypes demonstrated by N-SH2 deletion mutant mice [1, 2]. By contrast, the carboxy-terminal SH2 (C-SH2) domain plays a minimal role in the catalytic activation of SHP-2, although a ligand with two phosphotyrosyl residues may bind both SH2 domains stimulating even greater catalytic activity [12]. Thus, both substrate targeting and activation of phosphatase capability of SHP-2 are tightly regulated by the SH2 domains.

Cytoplasmic function

SHP-2 appears to play complex roles in intracellular signal transduction. SHP-2 is primarily localized in the cytoplasm and has been implicated in diverse cytoplasmic signaling pathways that are activated by growth factors, hormones, cytokines, and extracellular matrix proteins [14, 15]. It is an important player in the regulation of cellular growth, survival, differentiation, and migration. Despite its direct function in protein dephosphorylation, SHP-2 generally plays an overall positive role in transducing signals initiated from receptor and cytosolic tyrosine kinases. The mechanisms of SHP-2 action and the significance of its catalytic activity in cell signaling, however, are not well understood. SHP-2 is involved in a variety of signal transduction cascades, including the Ras-Raf-MAP kinase, JAK/STAT, PI3K/Akt, NF-κB, and NFAT pathways [14, 15]. Furthermore, SHP-2 acts at multiple sites in individual pathways. It directly interacts with many growth factor and cytokine receptors, such as PDGFR, EGFR, IGF-1R, and the IL-3, GM-CSF, and EPO receptors. It also binds to various intermediaries of signal transduction pathways, such as SHPS-1, PZR, Gab1, Gab2, FRS-2, JAK2, IRS, and the P85 subunit of PI3 kinase. Of these interacting proteins, some are the targets of SHP-2 enzymatic activity. Nevertheless, none of the putative substrates identified to date can fully account for the overall positive signaling effects of SHP-2 on the many biological processes in which it has been implicated. SHP-2 appears to function in cell signaling in both catalytically dependent and independent manners. This notion is strongly supported by the substantial difference in the phenotypes displayed by SHP-2 knockout mice and dominant negative mutant SHP-2 transgenic mice. Mutant mice overexpressing mutant SHP-2 lacking the PTP domain only show mild phenotypes [16], in contrast to the severe consequences observed in SHP-2 null mutant mice [3]. Accumulating evidence suggests that SHP-2 may function as an adaptor protein coupling downstream signaling pathways to the proximity of the cell surface receptors/adhesion molecules. While the overexpresison of mutanted SHP-2 with a truncated PTP domain inhibits the catalytic activity of endogenous SHP-2, it increases its scaffolding functions, thus generating compound effects. By contrast, SHP-2 deficiency in knockout or knockdown cells blocks both SHP-2 adaptor function and its catalytic activity, leading to more severe phenotypes. It is important to note that in SHP-2 null cells, SHP-2 deficiency decreases cell signaling at a very early stage due to loss of the SHP-2 adaptor function. Consequently, tyrosyl phosphorylation of downstream signaling proteins, including SHP-2 substrates, is decreased, rather than increased. This provides an explanation for why the hyperphosphorylation of SHP-2 substrates is rarely observed in SHP-2 knockout or knockdown cells.

Nuclear function

Emerging evidence shows that a fraction of SHP-2 is localized in the nucleus and that nuclear SHP-2 functions in some nuclear events. In mouse embryonic fibroblasts, this fraction is about 30-40% [17]. Nuclear SHP-2 appears to promote DNA damage-induced apoptosis. Cisplatin or γ-irradiation-induced apoptosis is diminished by SHP-2 truncation lacking the N-SH2 domain [17]. SHP-2 functions in DNA damage-induced cell death in a p53-independent manner since DNA damage-induced p53 induction in SHP-2 mutant cells (embryonic stem cells) is not affected. Alternatively, the SHP-2 function in DNA damage-induced cell death is mediated

by p73, another important member of the p53 family and the effector of the c-Abl apoptosis pathway. DNA damage activation of c-Abl kinase and p73 induction are impaired in SHP-2 N-SH2 deletion mutant cells [17]. In addition, SHP-2 is required for DNA damage-induced translocation of Cdc25C from the nucleus to the cytoplasm [18]. As a result, DNA damage-induced cell cycle arrest (G2/M) is diminished in the SHP-2 deletion mutant cells. Further evidence suggests that SHP-2 functions in DNA damage-induced c-Abl activation, and therefore apoptosis, in a catalytic-dependent manner, in contrast to its role in the DNA damage-induced G2/M checkpoint response in which it does not require catalytic activity [19]. Wild type, but not catalytically-inactive mutant SHP-2 C459S, rescues the apoptotic response of SHP-2 mutant cells to DNA damage while both wild type and SHP-2 C459S efficiently restores the G2/M arrest response. It is important to mention that these experiments were conducted on PTPN11 Exon 3 deleted mutant cells. The mutant PTPN11 allele most likely is hypomorphic since the deletion mutation generates a SHP-2 mutant lacking the important N-SH2 domain. Moreover, the expression level of this mutant is greatly decreased — about 25% of that of WT SHP-2 [2, 5]. However, the N-SH2 deletion also results in the elevated PTP activity of SHP-2 [5]. Thus, the possibility that an Exon 3 deletion possesses neomorphic effects cannot be excluded. Clearly, further studies are needed to define the detailed molecular mechanisms of SHP-2 function in genotoxic stress-induced signaling. More recently, a study has shown that nuclear SHP-2 inhibits nuclear export of telomerase reverse transcriptase (TERT), the catalytic subunit of telomerase, in the nucleus by dephosphorylating tyrosine 707 of TERT, thereby enhancing nuclear telomerase activity [20]. Since telomerase plays an important role in maintaining telomere length and the shortening of telomeres has been linked to chromosomal instability and cell aging, SHP-2 may thus be involved in the regulation of aging processes.

Mitochondrial function

SHP-2 has recently been shown to be present in the mitochondria, a multifunctional organelle involved in a wide range of cellular processes. Mitochondrial SHP-2 is mainly localized inside the mitochondria and seems to be associated with cristae and/or the intercristal space [21]. The role of SHP-2 in the mitochondria remains completely unclear. Because transgenic mice specifically overexpressing catalytically deficient SHP-2 (SHP-2 C459S) in neurons are more susceptible than controls to ischemia-induced brain damage and neuronal death [22] and mitochondria play an important role in ischemia-induced cell death, it seems likely that SHP-2 functions in the maintenance of mitochondrial functional integrity. Mitochondria are the primary energy-generating system in most eukaryotic cells. During oxidative phosphorylation, highly reactive compounds known as reactive oxygen species that participate in many cellular processes are produced as by-products. In addition, mitochondria participate in intermediary metabolism, calcium signaling, and apoptosis. Given this wide range of well-established functions of mitochondria, SHP-2's physiological roles can conceivably be mediated in part by its influence in mitochondrial function. Accordingly, identification of SHP-2 mitochondrial substrate(s) will shed light on the molecular mechanisms by which SHP-2 regulates mitochondrial and cellular activities. Also, it would be interesting to test how disease-associated SHP-2 mutations impact mitochondrial functions.

Association of SHP-2 with human diseases

Activating mutation-associated diseases

Germline missense mutations in PTPN11 (encoding SHP-2) have been identified in a developmental disorder called Noonan syndrome (NS) [23]. NS is a relatively common multiple malformation syndrome characterized by facial dysmorphia, short stature, congenital heart defects, and increased risk of leukemia [24]. Mutations in PTPN11 are present in about 50% of patients with NS. Somatic missense mutations in PTPN11 have also been identified in a significant portion (~35%) of juvenile myelomonocytic leukemia (JMML) [25, 26] that is characterized by cytokine hypersensitivity of myeloid progenitor cells. In addition, PTPN11 mutations have been identified in other pediatric leukemias, such as myelodysplastic syndrome, B cell acute lymphoblastic leukemia, and acute myeloid leukemia at low frequencies [27, 28]. The vast

majority of NS mutations are found in Exons 3 and 8, which encode segments of the N-SH2 and PTP domains, respectively. These SHP-2 mutations alter critical amino acid residues that lie on the interface of the N-SH2 domain with the PTP domain. Molecular modeling and biochemical data infer that these mutations disrupt the N-SH2 and PTP interdomain binding network, leading to hyperactivation of the phosphatase activity [23, 26]. Similarly, the somatic mutations associated with leukemias also affect the N-SH2/PTP interface, leading to a gain of function for SHP-2 [29, 30]. However, leukemia mutations (Exon 3) are clustered primarily in the N-SH2 domain and tend to result in different amino acid substitutions than NS mutations. Notably, the SHP-2 mutations appear to play a causal role in the development of the related diseases. SHP-2 mutations and other well-known NS or JMML-associated Ras or Nf1 mutations are mutually exclusive in the patients [25, 26, 28]. Moreover, single SHP-2 activating mutations are sufficient to induce cytokine hypersensitivity in myeloid progenitor cells, and NS and JMML-like myeloproliferative disease in mice [31-35].

Activating mutations in PTPN11 have also been found in sporadic solid tumors, such as lung cancer, liver cancer, colon cancer, neuroblastoma, and melanoma [28]. Similar to NS and leukemia mutations, SHP-2 mutations identified in solid tumors also result in increased SHP-2 activity. Whether the SHP-2 activating mutations play a causal role in the tumorigenesis remains to be determined. It is interesting to note that the T507K mutation identified in hepatocellular carcinoma and neuroblastoma shows a distinct function from the E76K and D61G mutations that are found in leukemias/tumors and NS. The SHP-2 T507K mutant directly induces transformation in NIH3T3 cells [36]. These T507K transformed cells display foci formation and anchorage-independent growth, and develop into tumors in nude mice, whereas SHP-2 E76K or SHP-2 D61G mutants do not possess these capabilities. So far, no more than a dozen SHP-2 mutations have been identified in solid tumors; the T50K mutation is one of the few SHP-2 T507K mutations that are seen only in solid tumors but not in NS/JMML. This mutation has been identified twice from solid tumors — a neuroblastoma [28] and a hepatocellular carcinoma [36]. The molecular mechanisms responsible for the difference between T507K mutation and E76K or D61G mutations in cell transformation remain completely obscure. It would be very interesting to investigate why the SHP-2 T507K mutation induces cell transformation and how this mutation disturbs cell development and function in mice.

Inactivating mutation-associated disease

Genetic mutations in PTPN11 (mostly in Exons 7 and 12) have also been identified in nearly 90% of patients with LEOPARD syndrome (LS) [37, 38], which is clinically similar to NS. Unlike NS mutations that are distributed throughout both N-SH2 and PTP domains of SHP-2, LS mutations are primarily located in the PTP domain. LS is a rare congenital developmental disorder characterized by multiple lentigines, cardiac abnormalities, facial dysmorphism, retardation of growth, and deafness. Surprisingly, in marked contrast to NS mutations which are gain-of-function mutations, all SHP-2 mutations seen in LS are inactivating mutations, resulting in catalytically defective SHP-2 [39]. How then, do inactivating mutations in SHP-2 result in LS? It is not likely that LS is induced by PTPN11 haploinsufficiency: in several models of SHP-2 knockout mice, loss of one allele is well tolerated [1-3] and fails to produce any developmental defects resembling LS. In fact, LS SHP-2 mutants act as dominant negative molecules that interfere with SHP-2-mediated signaling. Consequently, LS inactivating mutations greatly decrease growth factor-induced activation of the Erk pathway [39]. Moreover, LS mutations also enhance the interaction between SHP-2 and its tyrosyl phosphorylated signaling partners (see below for details).

Other diseases

In addition to the directly associated diseases described above, SHP-2 has been shown to be involved in the pathogenesis of many other diseases, in particular, the oncogene-induced tumorigenesis/leukemogenesis due to its pleotropic role in multiple signaling processes. One prominent example is the discovery of SHP-2 as a critical intracellular target of the Helicobacter pylori CagA protein [40, 41]. CagA, the product of the cagA gene carried in virulent type I strains of Helicobacter pylori, is highly associated with severe gastritis and gastric carcinoma. CagA, once injected into the

host cells, is tyrosine phosphorylated and forms a physical complex with SHP-2 via its SH2 domain(s), leading to the activation of SHP-2's catalytic activity. Disruption of the CagA/SHP-2 interaction, or loss of SHP-2 protein/function, abolishes the CagA-dependent cellular responses. Thus, CagA disturbs cellular function by deregulating SHP-2. Other examples include, but are not limited to, SHP-2 mediating pathogenic effects of oncogenic tyrosine kinases BCR-ABL [42], Flt3-ITD [43], EGFRVIII [44], and NPM-ALK [45]. The mechanisms of SHP-2 in mediating oncogenic kinases induced tumorigenesis have been extensively discussed in other review articles [14, 46].

Possible mechanisms of SHP-2 associated diseases

SHP-2 activating mutations are currently thought to induce diseases through deregulating Ras, given the well established positive role of SHP-2 catalytic activity in the Ras/Erk pathway and that other components of the same Ras pathway are also mutated in the same diseases [47, 48]. However, this paradigm is challenged by the fact that SHP-2 mutations that oppositely influence its catalytic activity result in clinically similar syndromes, i.e. NS and LS with overlapping symptoms. What has nature told us? Although it is possible that a narrow window of the SHP-2 mediated Erk signaling is required for proper development and that both excessive and reduced Erk activities could result in similar developmental defects, it also seems likely that common consequences shared by the activating mutations and the inactivating mutations of SHP-2 mediate the similar phenotypes. SHP-2 activating mutations result in hyperactivation of catalytic activity, but merely enhancing catalytic activity alone may not be sufficient for the mutant SHP-2 to induce disease. SHP-2 functions in cell signaling in both catalytic-dependent and –independent manners [49-51]. The catalytic-independent SHP-2 function also promotes cell signaling. Furthermore, overexpression of wild type SHP-2 in several cell types does not generate similar phenotypes to those induced by SHP-2 activating mutations [32, 34, 35]. Recent studies have shown that activating mutations in the N-SH2 domain also enhance physical interactions of SHP-2 with tyrosine phosphorylated signaling partners Gab1 and Gab2, leading to enhanced downstream signaling, particularly the PI3K/Akt pathway [31, 34, 52]. The elevated catalytic activity may not be required for NS/leukemia mutant SHP-2 to enhance certain downstream signaling. Indeed, catalytically inactive double mutant SHP-2 E76K C459S still retains the capability to increase SHP-2 interaction with Gab2 and to enhance the PI3K/Akt pathway, in a manner similar to SHP-2 E76K [34]. LS inactivating mutations contort the SHP-2 catalytic domain and result in open, inactive forms of SHP-2. Intriguingly, LS mutations also enhance the interaction of mutant SHP-2 with its signaling partners, such as Gab1 [39]. In this regard, the LS SHP-2 mutations can also be considered as gain-of-function mutations, similar to those in NS. The increased interactions between mutant SHP-2 and Gab1 or Gab2 may thus be the aforementioned common consequences of SHP-2 mutations found in both NS and LS. The enhanced interactions between NS or LS mutant SHP-2 and tyrosine phosphorylated partners are likely due to the SHP-2 conformational change induced by the mutations. Both NS and LS mutations disrupt intramolecular binding between the N-SH2 and the PTP domains, making SHP-2 bind more effectively to tyrosine phosphorylated proteins since there is no longer any free-energy cost to disrupting the N-SH2/PTP interface and opening the N-SH2 phosphotyrosine binding pocket. In addition, SHP-2 disease mutations may alter functional interactions with its substrates by decreasing localization/accessibility to the substrates, leading to changes in the functions of its substrates. For example, JMML associated E76K mutation drastically decreases its efficiency of dephosphorylating STAT5, one of the putative downstream targets of SHP-2 [53-56], resulting in hyperactivation of STAT5 in hematopoietic cells [34, 35], which may also contribute to pathogenesis. It remains to be determined whether and how LS mutations may also change the substrate specificity of the SHP-2 enzyme.

A tumor/leukemia originates from uncontrolled cell growth. Signal transduction disorders associated with cell growth and differentiation play key roles in tumorigenesis and leukemogenesis. It is not surprising that SHP-2 promotes oncogenic tyrosine kinase-initiated tumorigenesis/leukemogenesis. This is because the general positive role of SHP-2 in receptor and cytosolic kinases initiated signal transduction has been well established, albeit

detailed molecular mechanisms remain unclear. What is surprising is that LS patients carrying SHP-2 inactivating mutations also have an increased risk of developing hematological malignancies, similar to NS patients who harbor SHP-2 activating mutations. Three cases of leukemia (acute myeloid leukemia and acute lymphoblastic leukemia) have been reported in children with LS, including one with a genetically confirmed SHP-2 mutation [57]. Since LS mutations decrease Ras activities, the Ras pathway is not likely be responsible for the development of the malignancies. This view is also supported by the different transforming capabilities of SHP-2 activating mutations that have comparable activating effects on Ras. The E76K mutation is the most potent activating mutation [26, 29]. However, neither SHP-2 E76K nor SHP-2 D61Y can directly transform NIH 3T3 cells. By contrast, the T507K mutation, which slightly elevates basal phosphatase activity and has similar activating effects on Ras to those of E76K or D61Y mutations, directly induces foci formation and anchorage-independent colony formation [36]. Together, these observations raise the possibility that SHP-2 mutations may contribute to diseases through multiple mechanisms, both Ras-dependent and –independent. More recently, Raf-1 [58, 59], K-Ras [60, 61] and SOS1 [62, 63] activating mutations have also been identified in NS. However, SOS1 mutations in solid tumors are very rare [64], unlike K-Ras and Raf1 mutations which are found in NS and a variety of sporadic neoplasms. Even the most highly activated SOS1 allele is not a potent enough transforming gene to induce human tumors, again implying that mutations of the components of the same Ras pathway may not contribute to tumorigenesis through the same mechanisms.

Perspective

In the past decade, tremendous progress has been made in the identification of the role of SHP-2 phosphatase in physiology and its clinical relevance to human diseases. SHP-2 is an important molecule that integrates signals along various cytoplasmic pathways and may also function in the nucleus and in the mitochondria. However it still remains unclear how exactly SHP-2 functions in the cell. The discovery of the SHP-2 mutations in human diseases and the availability of the cell and mouse models of the related human diseases now provide a new opportunity to uncover the molecular mechanisms of SHP-2 function. Identification of novel substrates and interacting proteins is essential for achieving this goal and remains the major focus of effort in the field. In addition to elucidating its cytoplasmic functions, an understanding of the novel functions of SHP-2 in the nucleus and mitochondria may shed light on the mechanisms by which SHP-2 mutations contribute to leukemogenesis and oncogenesis.

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