Cell Research (2007) 17: 295-297
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www.nature.com/cr

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COMMENTARY

Shp2, a novel oncogenic tyrosine phosphatase and potential therapeutic target for human leukemia

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Cell Research (2007) **17:**295-297. doi: 10.1038/cr.2007.18; published online 3 April 2007

Shp2, encoded by the *PTPN11* gene in human, is a ubiquitously expressed protein tyrosine phosphatase that contains two N-terminal Src homology 2 (SH2) domains (N-SH2, C-SH2, respectively), a catalytic protein-tyrosine phosphatase (PTP) domain, and a C-terminal tail with tyrosyl phosphorylation sites and a prolyl-rich motif [1]. The progress of our understanding of biological functions of Shp2 has clearly shown that Shp2 plays an important role not only in biology of normal hematopoietic cells and other mammalian cells, but also in the development of leukemia and other tumors. Most recently, *PTPN11* gene has been firmly established as the first proto-oncogene that encodes a protein tyrosine phosphatase [1-3]. In the hematopoietic system, most if not all function of Shp2 is to act as a positive component that is essential for proliferation and/or survival of hematopoietic cells through regulation of signaling pathways involving Erk, Akt and STAT5 [1-4]. Over the past few years, a number of disease-associated Shp2 mutants have been identified in human leukemia and other malignancies [1, 3, 4]. Recently, studies from our laboratories and others strongly suggest that dysregulation of wild-type Shp2 enzyme may be involved in the pathogenesis of adult leukemia [4-7]. These findings not only provide new insights into the role of Shp2 in leukemogenesis and other tumors, but also suggest new therapeutic targets for anti-leukemia drugs.

Disease-associated Shp2 mutants in human leukemia

Since Tartaglia and collegues (2003) reported somatic mutations in *PTPN11* gene in juvenile myelomonocytic leukemia (JMML), myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) [8], a number of disease-associated mutations in the *PTPN11* gene have been defined, and the hematopoietic system is the best characterized somatic tissue. Somatic mutations of *PTPN11* occur in about one-third of sporadic cases of JMML and in approximately 6% of patients with childhood acute lymphoblastic leukaemia (ALL) and in 4-5% of AML patients [3]. Expression of leukemia-associated Shp2 mutants in murine bone marrow or fetal liver cells evokes cytokine-independent myeloid colony formation, hypersensitivity to interleukin-3 (IL-3) and granulocyte-macrophage colony-stimulating factor (GM-CSF), increased myeloid colony size, altered myeloid differentiation, with a predisposition towards monocyte and/or macrophage lineage cells, and enhanced erythroid and multi-lineage colony formation [1, 3]. Consistent with this, mast cells derived from mice transplanted with Shp2-mutant-expressing bone marrow were hypersensitive to stimulation with IL-3 and GM-CSF. These cells showed increased proliferation and increased activation of ERK, AKT and STAT5 when stimulated with either IL-3 or GM-CSF. IL-3- and GM-CSF-hypersensitivity has also been found in murine fetal liver cells that are transduced with retroviruses expressing mutant Shp2 [1, 3]. GM-CSF hypersensitivity has also been reported for macrophage progenitors derived from mutant-Shp2-expressing murine bone marrow [1, 3].

Recently, Huang and colleagues proposed a novel model in which leukemia-associated Shp2 mutants dephosphorylate interferon consensus binding protein (ICSBP) in both myeloid progenitors and differentiating myeloid cells [7]. Activated Shp2 mutants thereby inhibit ICSBP-dependent NF1 transcription, impairing this negative feedback

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mechanism on cytokine-activated Ras. Therefore, these studies suggest that leukemia-associated ICSBP deficiency cooperates with leukemia-associated activating mutants of Shp2 to contribute to the proliferative phenotype in myeloid malignancies [7].

Altered Shp2 expression and localization in adult leukemia

It is noteworthy that disease-associated Shp2 mutants are mainly present in childhood leukemia, and rarely detected in adult leukemia [1, 3, 4]. Earlier studies reported that Shp2 is ubiquitously expressed in mammalian cells. However, our recent studies demonstrated that activated Shp2 enzyme (phosphorylated Shp2, p-Shp2) is low in quiescent hematopoietic cells, but abundantly expressed in proliferating cells [4]. Interestingly, p-Shp2 was significantly elevated in primary leukemia cells and a panel of human leukemia cell lines, as compared with normal hematopoietic progenitor cells. Notably, the majority of p-Shp2 was preferentially localized to the plasma membrane in leukemia cells. The p-Shp2 levels correlated well with the hyperproliferative capacity but were inversely associated with the differentiation degree of leukemia cells. The Shp2 protein expression level greatly differed in cells at different phases of the cell cycle. In non-proliferating cells, Shp2 protein is diffusively distributed in the entire cytoplasm at low level. However, once cells enter proliferating status, Shp2 protein expression level dramatically increased with cell-cycle progression, peaked in the mitotic cells at prophase, and then decreased after metaphase. In proliferating cells at S/G2 phase, membrane-associated Shp2 was detected at a high level. In addition, Shp2 was barely detectable in terminally differentiated hematopoietic cells. Consistently, the p-Shp2 protein was significantly decreased with differentiation progression of NB4 leukemia cells after treatment with all-trans retinoic acid. Similarly, down-regulation of Shp2 expression in NB4 leukemia cells also promoted cell differentiation [4].These observations suggest that the p-Shp2 protein is likely involved in both proliferation and differentiation regulation of hematopoietic cells.

It has been shown that Shp2 enzyme forms a stable protein complex with and is heavily tyrosine-phosphorylated by the oncogenic tyrosine kinase Bcr-Abl [8]. A recent study reported that Shp2 is required for hematopoietic cell transformation by Bcr-Abl [5]. *In vitro* biological effects of Bcr-Abl transduction were diminished in Shp2Delta/Delta hematopoietic cells, and the leukemic potential of Bcr-Abl-transduced Shp2Delta/Delta cells in recipient animals was compromised. Further analyses showed that the Bcr-Abl protein (p210) was degraded, and its oncogenic signaling was greatly decreased in Shp2Delta/Delta cells. Subsequent investigation revealed that Shp2 interacted with heat shock protein 90, an important chaperone protein protecting p210 from proteasome-mediated degradation [5].

Therapeutic implications

The identification of Shp2 mutants in JMML and other leukemia, as well as the requirement for Shp2 function in oncogenic signaling pathways, strongly suggests that Shp2 may harbor significant therapeutic potential for the treatment of leukemia patients. Our studies showed that overexpression and constitutive activation of Shp2 protein is a common phenotype in various types of human leukemia, and is closely associated with the proliferative capacity of leukemic blasts. Leukemia clonogenic cell growth was significantly reduced along with increased apoptosis of leukemia cells following down-regulation of Shp2 expression [4]. Scherr and co-workers demonstrated that RNAi-mediated reduction of Shp2, STAT5, and Gab2 protein expression inhibits Bcr-Abl-dependent but not cytokine-dependent proliferation in a dose-dependent manner. Similarly, colony formation of purified primary CML but not of normal CD34+ colony-forming cells is specifically reduced by inhibition of Shp2, STAT5, and Gab2 expression, respectively [6]. Chen and co-workers reported that blockade of Shp2 expression in p210-expressing cells by antisense or small-interfering RNA approaches decreased p210 level, causing cell death. Inhibition of Shp2 enzymatic activity by overexpression of catalytically inactive Shp2 mutant did not destabilize p210 but enhanced serum starvation-induced apoptosis, suggesting that Shp2 also plays an important role in downstream signaling of the p210 kinase [5]. Interestingly, 8-hydroxy-7-(6-sulfonaphthalen-2-yl) diazenyl-quinoline-5-sulfonic acid (NSC-87877) has been identified as a small molecule with a potent inhibition effect on Shp2 protein-tyrosine phosphatase [10]. NSC-87877 binds to the catalytic cleft of Shp2 and is selective for Shp2 over other protein-tyrosine phosphatases without a detectable off-target effect [10].

Acknowledgments

This work was supported by National Natural Science Foundation of China (NSFC) grant 30672381(R.Z.X).

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