14 The Shp-2 tyrosine phosphatase

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Abstract

Shp-2 functions as a cytoplasmic protein tyrosine phosphatase in multiple fundamental cellular signaling pathways, to regulate basic mechanisms such as proliferation, differentiation, apoptosis, and motility. Notably, one genetic disorder in humans, Noonan Syndrome, has been linked to gain-of-function mutations in the Shp-2/PTPN11 gene, and this phosphatase also appears to be a cellular target of the Helicobacter pylori virulence factor CagA protein implicated in pathogenesis of gastric carcinoma. The requirement for Shp-2 activity in development has been demonstrated in vertebrate as well as in invertebrate models. While Shp-2 activity has been implicated in numerous signaling pathways, including the Ras/MAPK and JAK/STAT pathways, its physiological substrates remain elusive to investigators. This chapter provides a general background for Shp-2 signaling and discusses its contribution to a number of diverse biological functions in humans and other organisms.

14.1 Introduction

The Src homology 2 containing protein tyrosine phosphatase, Shp-2 (previously known as SH-PTP2, Syp, PTPN11, PTP1D, and PTP2C), is a cytoplasmic enzyme. It belongs to a subfamily of protein tyrosine phosphatases, consisting of itself and Shp-1, both of which share a similar overall protein structure. Shp-1 and Shp-2 phosphatases possess at their N-terminus two tandem SH2 domains—conserved sequence motifs of approximately 100 amino acids which regulate interactions between signaling molecules through binding to phosphotyrosine (pTyr) residues—and a catalytic phosphatase domain at the C-terminus. Despite their similar architecture, their expression pattern is unique. Whereas Shp-1 expression is limited to hematopoietic cells, Shp-2 is ubiquitously expressed. Also apparent from the phenotypes in mutant mice is that these phosphatases are functionally distinct, since neither Shp-1 nor Shp-2 can compensate for loss of the other. Whereas Shp-1 functions primarily in negative regulation of signaling pathways, Shp-2 can act either positively or negatively in regulation.

Corkscrew (CSW) is the Drosophila homologue of mammalian Shp-2. CSW was identified as a positive regulator of the Torso signaling pathway, acting downstream of Torso and in concert with D-raf (Perkins et al. 1992). The absence of CSW suppressed a torso gain-of-function phenotype. CSW functions in other
RTK signaling as well, including Drosophila EGF receptor DER, FGFR Breathless and Sevenless (Herbst et al. 1996; Perkins et al. 1996; Raabe et al. 1996).

The crystal structure of Shp-2 (Hof et al. 1998) reveals that the N-terminal SH2 domain (SH2-N) folds in on itself to auto-inhibit the phosphatase domain, until which time it binds to a pTyr residue, when the inhibition is relieved. The most commonly used Shp-2 mutant is a dominant negative form in which active site residue Cysteine 459 has been substituted with Serine (C459S). This mutant functions as a dominant negative since the phosphatase domain can still bind phosphorylated residues, but is unable to remove the phosphate group. In addition, mutants within the SH2 domains, such as R32K or R138K, which disrupt SH2 interactions, have also been used to analyze Shp-2 activity (Pluskey et al. 1995). Mutations such as D61A or E76A result in constitutively active mutants—exhibiting 20-100 fold increases in phosphatase activity--due to loss of auto-inhibition (O'Reilly et al. 2000; Takai et al. 2002). Recently, a substrate trapping mutant that combined the D to A and C to S mutations was used in a screen to identify new Shp-2 interacting proteins (Agazie and Hayman 2003).

In this chapter, we will discuss how Shp-2 contributes to various cellular functions and how de-regulation of this phosphatase results in cellular apoptosis and disease states. We will then include an analysis of the various signaling pathways in which Shp-2 function has been implicated.

14.2 Shp-2 function in development

Shp-2 function has been shown to be required for gastrulation and in early vertebrate development. Homozygous deletion of the SH2-N domain of Shp-2 (Shp-2\textsuperscript{Δ46-110}) resulted in early embryonic lethality of mice at midgestation, at day E8.5-E10.5, with severe defects in posterior structures, and failure to complete gastrulation (Saxton et al. 1997). Analysis of chimeric mice revealed a requirement for Shp-2 to properly respond to fibroblast growth factor (FGF) signaling; defects in migration of mesodermal cells from the primitive streak were observed in these mice (Saxton and Pawson 1999). Studies of chimeric mice also demonstrated a functional requirement for Shp-2 in limb bud formation (Saxton et al. 2000). Previous experiments using microinjections also implicated Shp-2 function in the regulation of mesoderm formation in Xenopus (Tang et al. 1995; O'Reilly and Neel 1998), and more recent studies suggested a functional interaction between Shp-2 and the Src family kinase protein Laloo in this process (Weinstein and Hemmati-Brivanlou 2001).

Phenotypic analyses of chimeric animals and compound mutant animals have also provided clues about Shp-2 function in postnatal development and in adults. Although this phosphatase is widely expressed, Shp-2 appears to play a critical role in hematopoietic cell development as compared to other cell types (Qu et al. 1998). Genetic evidence for a signal-enhancing effect by Shp-2 on EGF signaling was obtained in compound mutant mice defective in both Shp-2 (Shp-2\textsuperscript{Δ46-110}) and EGFR (waved-2, wa-2) (Qu et al. 1999). A heterozygous Shp-2 mutation dramati-