SH2 Containing Inositol 5-Phosphatase: A View into an Immunohomeostatic Polypeptide

Sean Lastorka, Issys Salazar, and Joseph Zundell
Audrey Shor, Ph.D., M.P.H.
Department of Mathematics and Science, Saint Leo University, Saint Leo, Florida 33574
Tomar Ghansah, Ph.D., Assistant Professor
Department of Molecular Medicine, The University of South Florida, College of Medicine, Tampa, FL 33612

Abstract

SH2 containing Inositol 5-Phosphatase (SHIP-1) is a serine/tyrosine protein phosphatase expressed in blood cells that negatively regulates the Phosphoinositide-3-Kinase (PI3K) pathway. SHIP-1 plays an essential role in immune system maintenance by regulating proliferation, differentiation, cell survival/apoptosis, and B-cell antigen receptor signaling. Recent evidence has suggests that SHIP-1 may even act as a tumor suppressor, while other data suggests it promotes tumor progression. Most recently, SHIP-1 expression has been demonstrated to be down regulated in a mouse model of pancreatic cancer. The structure of SHIP-1 contains a Src homology 2 (SH2) domain, a proline rich SH3 domain (involved in recruitment to the plasma membrane), and a catalytic domain (C2, observed in many protein kinases). The SH2 domain provides essential scaffolding for anchoring to protein complexes necessary for transducing SHIP-1 initiated signals via phosphotyrosine recognition. The serine residues 30 and 36 are essential for anchoring SHIP-1 to signaling partners. When mutated, SHIP-1 was unable to dephosphorylate phosphatidylinositol (3,4,5) triphosphate and inhibit the PI3K pathway. Two arginine residues (34 and 41) are also essential for the inflammatory response mediated by SHIP-1. When mutated at Arg41, oxidative stress induced responses in leukemic cells are inhibited. SHIP-1 with mutated Arg34 exhibits diminished interaction with molecules essential for red blood cell production. Further evaluation of SHIP-1 regulation of the pro-survival PI3K pathway will provide insight for better understanding the phenotype observed in SHIP-1 mutational and knockout studies. In examining SHIP-1, medicinal compounds can be produced to stimulate activity.

Introduction

The protein SH2 containing Inositol 5' Phosphatase (SHIP-1) is an allosteric enzyme involved in the process of hematopoiesis and inflammatory response. Hematopoiesis involves the maturation and activation of B, T, and NK cells within our lymphatic system. The function of the SH2 domain of SHIP-1 in regulating immune system balance is currently in question. This has led many biochemists to conduct mutational studies of this enzyme. Mutational analysis has shown that SHIP-1 is unable to bind to essential signaling molecules[5] in immune regulation and even reduced inflammatory response utilizing the same mutational analysis conducted in other experiments.[3] It has also revealed that SHIP-1 deficient cells lead to splenomegaly (spleen enlargement) and B-cell lymphoma[1]. Other research suggests SHIP-1 (and its isoforms) play a role in a numerous diseases such as graft vs. host disease and diabetes.[1]

Story

SHIP-1, a 145kD protein,[1] is scrutinized for its role in immune system regulation and its absence in adenocarcinoma, B-cell lymphoma, and splenomegaly (enlargement of the spleen).[6]

Research performed by Dr. Ghansah's team at USF has focused on the function of SHIP-1 in murine (C57BL6/c mice) pancreatic adenocarcinoma. She has noted, as seen in the Western blot image (Figure 2), that SHIP-1 is barely present in pancreatic cancer. SHIP-1 is almost completely devoid in extract of a cell lysate of an enlarged spleen, (splenomegaly).[6] This data suggests the importance of SHIP-1 as a regulatory protein in lymphocytic derived cancers, which are often seen once cells have metastasized from late cancer stages. Further research has indicated proposed mechanisms of SHIP-1 regulation as seen in the B-cell activation image (Figure 5), and has even been shown to be involved With common pathways such as the PI3K, phosphoinositide, and Btk (Akt) signaling cascades. These cascades aid in producing cytokines for cell growth and survival.

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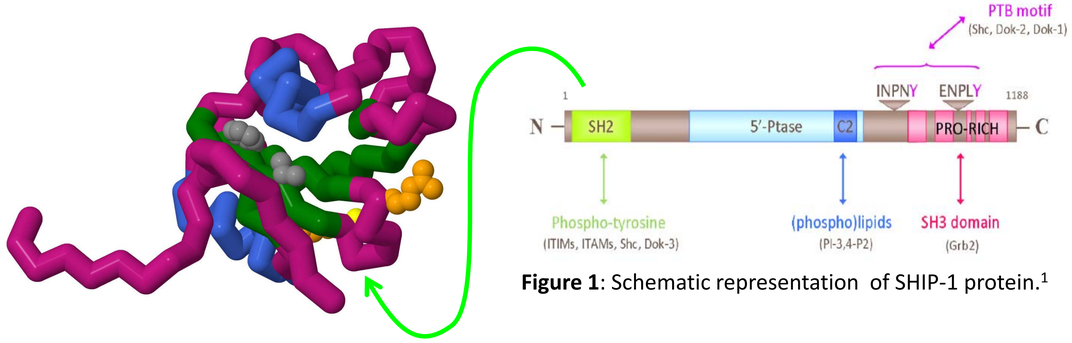


Figure 1: Schematic representation of SHIP-1 protein.[1]

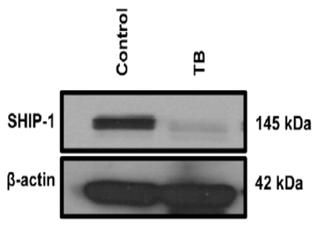


Figure 2: SHIP-1 is dampened in tumor bearing mice.[6]

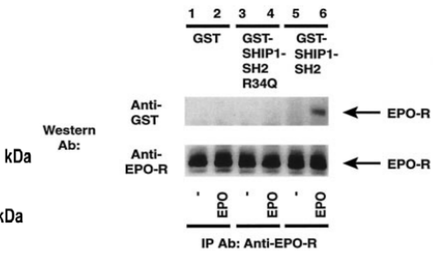


Figure 3: Arg34 is essential for complex formation at receptors[5] upon mutational analysis.

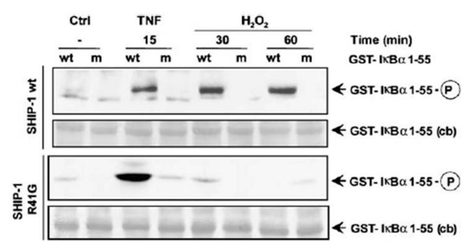
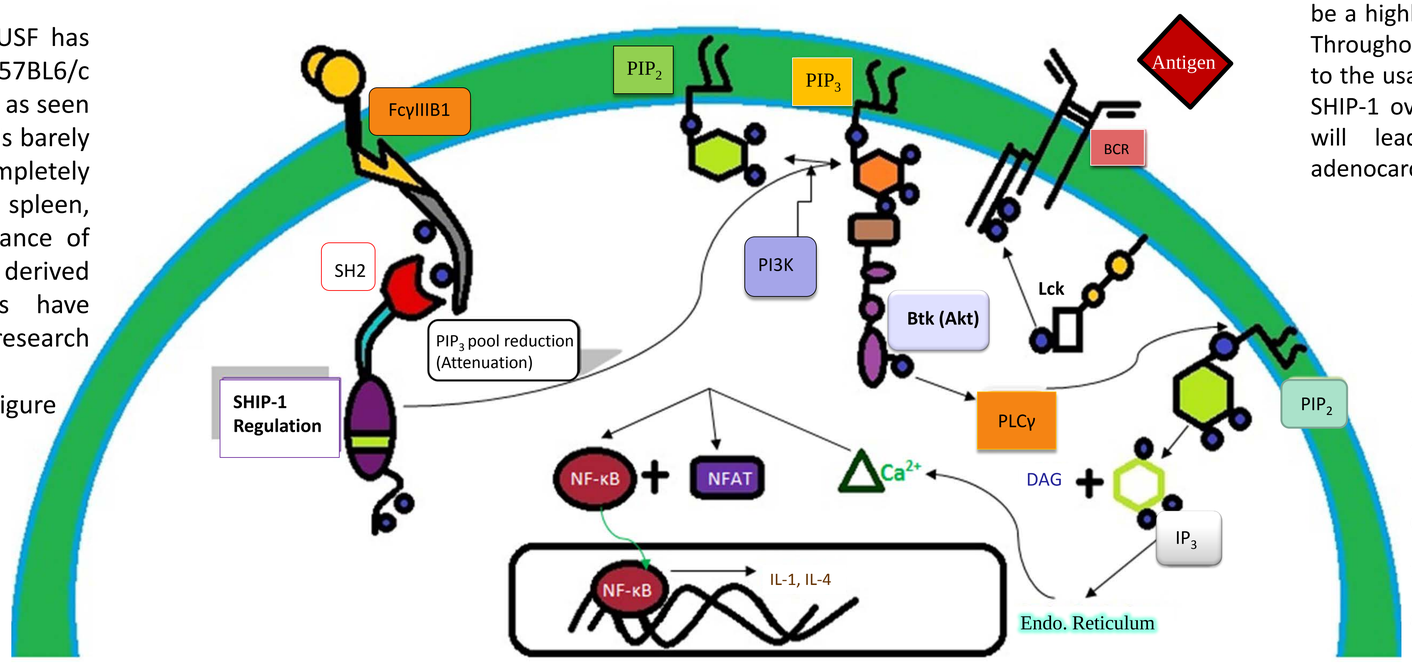


Figure 4: Arg41 is essential for inflammatory responses to oxidative stress[3] upon mutational analysis.

Figure 5: SHIP-1 regulation of B-cell activation[7]



How Do We Know?

Substituting SHIP-1 Ser30 and Ser36 with alanine depleted activity due to its inability to anchor essential protein complexes such as the Grb2-SOS[8] in the PI3K pathway. Similar mutational experiments substituted Arg34 with glutamate[5] and Arg41 with glycine.[3] These mutations were evaluated using Western blotting, immunoprecipitation, and immunodetection assays. The last notable aspect about the SHIP-1 SH2 domain is the FLVRXS sequence (residues 31-36 in our model) conserved throughout evolution in the domain.[4] This implies that this sequence has been passed on from generation to generation unchanged from the protein's origin.

What's the Next Question?

- Designing SHIP-1 regulators to further explore SHIP-1's role in the cancer phenotype.
- Characterizing the precise role of Ser30 and Ser36 in SHIP-1 activity and regulation as well as other mutational analyses that affect its function.
- SHIP-1 and PKCδ cooperation in lymphocyte regulation

Summary

SHIP-1 has been shown through varying experimentation to be a highly regulatory protein involved within hematopoiesis. Throughout the CREST program much has been learned due to the usage of modeling in understanding the relationship of SHIP-1 overall function. Continuing research on this protein will lead to a better understanding in pancreatic adenocarcinoma, B-cell lymphoma and many other diseases.

References

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