Structural and Functional Analysis of SHPS-1, a Receptor-type Membrane Protein

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Src homology 2 domain-containing protein tyrosine phosphatase [SHP] substrate 1 (SHPS-1), a receptor-type transmembrane glycoprotein whose cytoplasmic region binds and activates the protein tyrosine phosphatases SHP-1 and SHP-2, and thereby modulates multiple cellular functions. Its extracellular region regulates intercellular communication in the neural and immune systems through its association with CD47 on adjacent cells. Interactions between CD47 and SHPS-1 are implicated in multiple cellular processes, including cell motility [1], neutrophil transmigration, phagocytosis of red blood cells by splenic macrophages [2], and T cell activation. Although the roles of the CD47-SHPS-1 system has been presented, little is known about the cell surface organization of these ligand/receptor complexes and the structural basis for signal transduction. To gain new insights into the physiological and biological roles of the CD47-SHPS-1 system, we determined the crystal structure of the SHPS-1 extracellular domain. The domain adopts a classical immunoglobulin (Ig) fold that was observed to form an antiparallel dimer. A dimeric form of SHPS-1 was observed *in vivo*, and our structural and biophysical data shows that the extracellular domain of SHPS-1 is dimeric in solution, compatible with the view of SHPS-1 acting as a *cis*-dimeric adhesion receptor. Previous investigations showed native CD47 formed *cis*-dimers. These features suggest that both CD47 and SHPS-1 *trans*-interact each other by the formation of *cis*-dimers and offer perceptions into interactions of related Ig superfamily receptors.

[1] Motegi S., et al., *EMBO J*., 2003, **22**, 2634. [2] Oldenborg P.A., et al., *Science*, 2000, **288**, 2051.

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