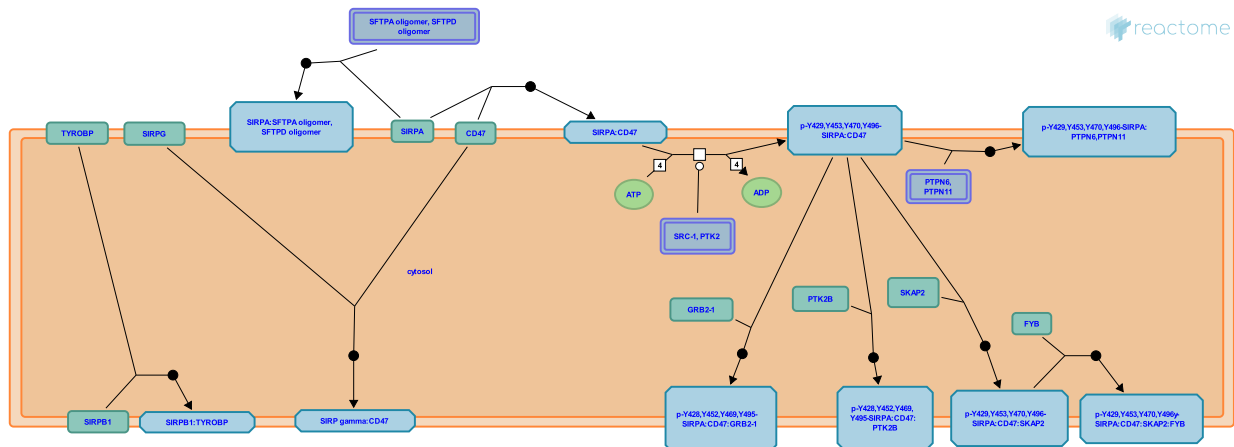


Signal regulatory protein family interactions



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook).

16/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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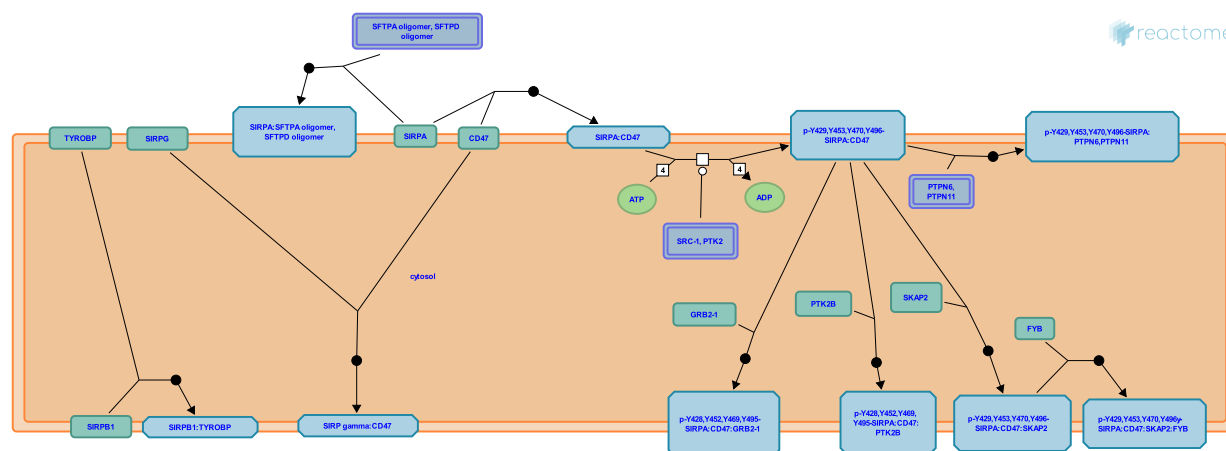
Reactome database release: 88

This document contains 1 pathway and 10 reactions ([see Table of Contents](#))

Signal regulatory protein family interactions ↗

Stable identifier: R-HSA-391160

Compartments: plasma membrane



Signal regulatory protein alpha (SIRPA, SHPS1, CD172a) is a transmembrane protein expressed mostly on myeloid cells. CD47, a widely expressed transmembrane protein, is a ligand for SIRP alpha, with the two proteins constituting a cell-cell communication system. The interaction of SIRPA with CD47 is important for the regulation of migration and phagocytosis. SIRPA functions as a docking protein to recruit and activate PTPN6 (SHP-1) or PTPN11 (SHP-2) at the cell membrane in response to extracellular stimuli. SIRPA also binds other intracellular proteins including the adaptor molecules Src kinase-associated protein (SKAP2 SKAP55hom/R), Fyn-binding protein/SLP-76-associated phosphoprotein (FYB/SLAP-130) and the tyrosine kinase PYK2. SIRPA also binds the extracellular proteins, surfactant-A (SP-A) and surfactant-D (SP-D).

The SIRP family members SIRPB and SIRPG show high sequence similarity and similar extracellular structural topology, including three Ig domains, but their ligand binding topology might differ. SIRPB is expressed on myeloid cells, including monocytes, granulocytes and DCs. It has no known natural ligand. SIRPG can bind CD47 but with lower affinity than SIRPA.

Literature references

- Liu, Y., Howard, CJ., Parkos, CA., van den Berg, TK., van Beek, EM., Vignery, A. et al. (2005). A nomenclature for signal regulatory protein family members. *J Immunol*, 175, 7788-9. ↗
- Barclay, AN., Brown, MH. (2006). The SIRP family of receptors and immune regulation. *Nat Rev Immunol*, 6, 457-64. ↗
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- Ohnishi, H., Okazawa, H., Matozaki, T., Murata, Y. (2009). Functions and molecular mechanisms of the CD47-SIRPalpha signalling pathway. *Trends Cell Biol*, 19, 72-80. ↗
- Parkos, CA., Liu, Y., Buhring, HJ., Zen, K., Schnell, FJ., Burst, SL. et al. (2002). Signal regulatory protein (SIRPalpha), a cellular ligand for CD47, regulates neutrophil transmigration. *J Biol Chem*, 277, 10028-36. ↗

Editions

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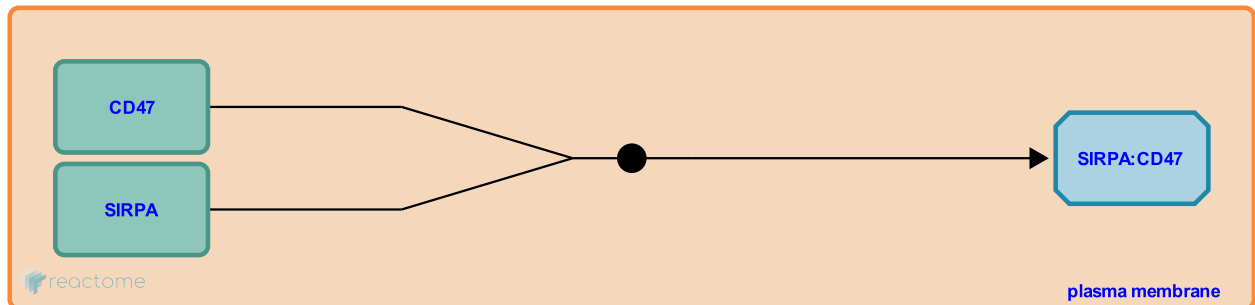
SIRP alpha binds CD47 [↗](#)

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391158

Type: binding

Compartments: plasma membrane



CD47 is an extracellular ligand for SIRP alpha. SIRP alpha directly binds to the loops of the Ig variable like domain of CD47 in an end-to-end fashion. The SIRP alpha/CD47 interaction is unusual in that it can lead to bidirectional signaling through SIRP alpha and CD47. The major function of this interaction is prevention of phagocytosis of RBC and platelets by macrophages.

Followed by: [Phosphorylation of ITIM motif in SIRP alpha](#)

Literature references

- Harlos, K., Barclay, AN., Graham, SC., Stuart, DI., Turner, J., Hatherley, D. (2008). Paired receptor specificity explained by structures of signal regulatory proteins alone and complexed with CD47. *Mol Cell*, 31, 266-77. [↗](#)
- Zhou, Y., Tong, Q., Liu, Y., Chen, Y-T., Buhning, HJ., Zen, K. et al. (2007). Functional elements on SIRPalph IgV domain mediate cell surface binding to CD47. *J Mol Biol*, 365, 680-93. [↗](#)
- Harlos, K., Barclay, AN., Graham, SC., Stuart, DI., Hatherley, D. (2009). Structure of signal-regulatory protein alpha: a link to antigen receptor evolution. *J Biol Chem*, 284, 26613-9. [↗](#)
- Harlos, K., Dunlop, DC., Barclay, AN., Stuart, DI., Hatherley, D. (2007). The structure of the macrophage signal regulatory protein alpha (SIRPalph) inhibitory receptor reveals a binding face reminiscent of that used by T cell receptors. *J Biol Chem*, 282, 14567-75. [↗](#)
- Chen, Z., Cant, C., Brown, EJ., Brugger, W., Buhning, HJ., Kanz, L. et al. (1999). Human signal-regulatory protein is expressed on normal, but not on subsets of leukemic myeloid cells and mediates cellular adhesion involving its counterreceptor CD47. *Blood*, 94, 3633-43. [↗](#)

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Phosphorylation of ITIM motif in SIRP alpha ↗

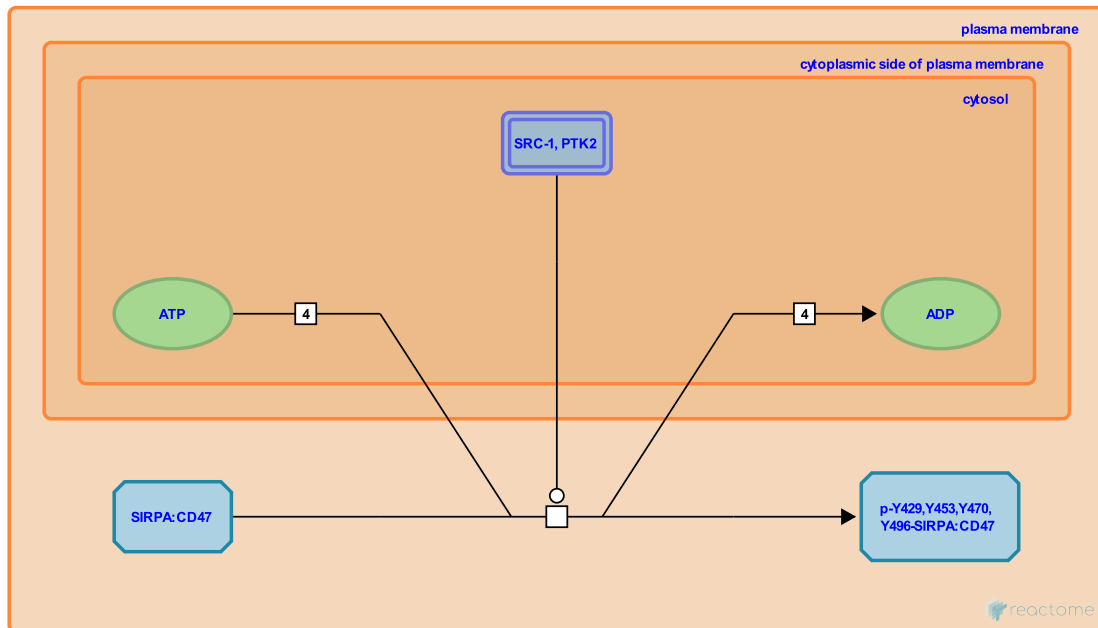
Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391156

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: [Phosphorylation of ITIM in SIRP alpha \(Rattus norvegicus\)](#), [Phosphorylation of ITIM in SIRP alpha \(Mus musculus\)](#)



Various growth factors and events such as integrin-mediated cell adhesion to extracellular matrix (ECM) proteins induce the tyrosine phosphorylation of SIRP alpha. The cytoplasmic tail of SIRP alpha has two ITIMs with four tyrosine residues that are potential sites for phosphorylation. Phosphorylation is not dependent on CD47 engagement but the presence of CD47 may enhance the effect. Src family kinases may be involved in the phosphorylation.

Preceded by: [SIRP alpha binds CD47](#)

Followed by: [p-4Y-SIRP alpha:CD47 binds PTPN6, PTPN11](#), [p-4Y-SIRP alpha:CD47:SKAP2 binds FYB](#), [p-4Y-SIRP alpha:CD47 binds PTK2B](#), [p-4Y-SIRP alpha:CD47 binds GRB2-1](#), [p-4Y-SIRP alpha:CD47 binds SKAP2](#)

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p-4Y-SIRPA:CD47 binds PTPN6,PTPN11 ↗

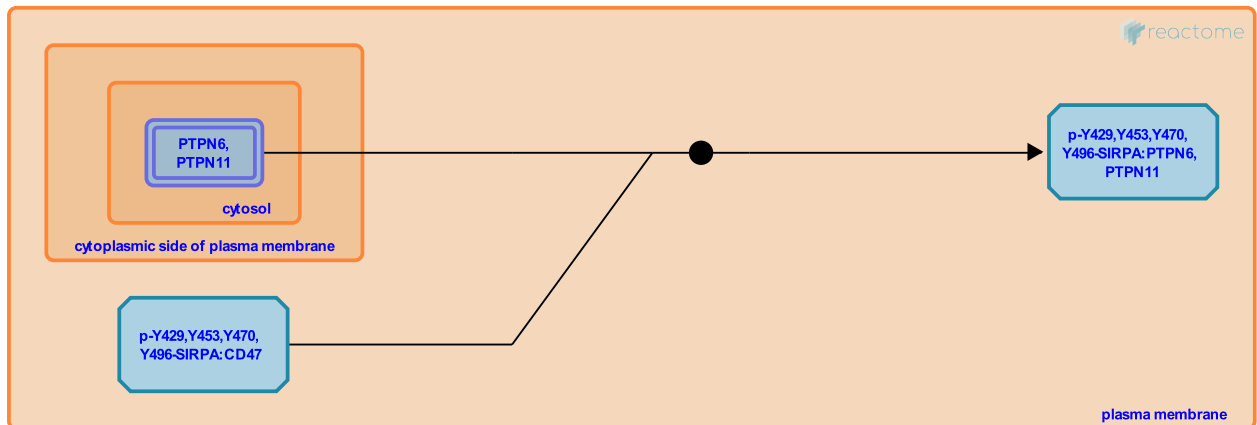
Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391150

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: [Recruitment of Shp-2 to pSIRP alpha \(Rattus norvegicus\)](#), [Recruitment of Shp-1 to pSIRP alpha \(Mus musculus\)](#)



SIRP alpha functions as a docking protein. The tyrosine-phosphorylated residues of SIRP alpha trigger the binding and activation of tyrosine phosphatases SHP-1 and SHP-2. All four phosphotyrosines of SIRP alpha may serve as substrates for SHP-1 and SHP-2. SIRP alpha binds mostly to SHP-1 in hematopoietic cells and with SHP-2 in non-hematopoietic cells. These phosphatases mediate the specific functions of SIRP alpha.

Preceded by: [Phosphorylation of ITIM motif in SIRP alpha](#)

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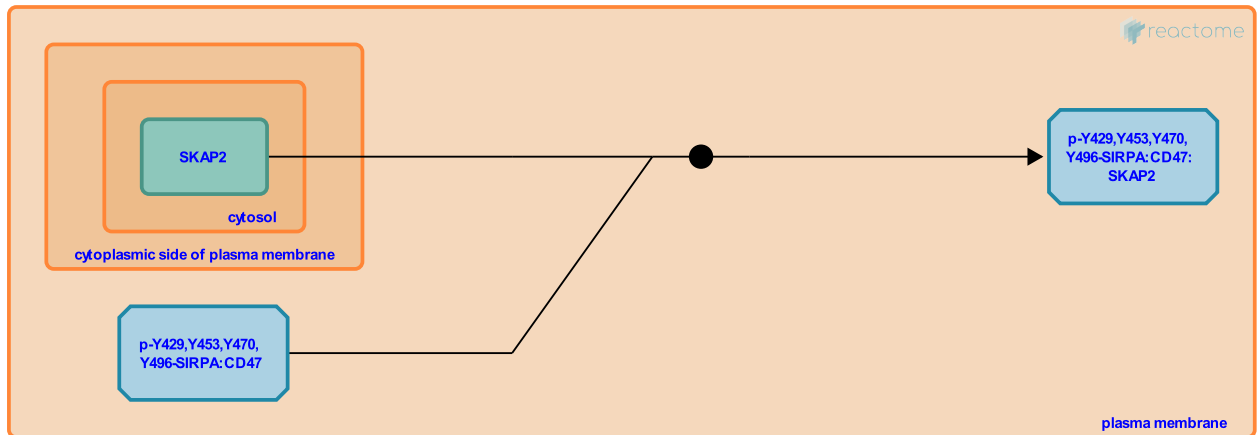
p-4Y-SIRPA:CD47 binds SKAP2 ↗

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391157

Type: binding

Compartments: plasma membrane, cytosol



SRC-family-associated phosphoprotein 2 (SCAP2) has been shown to bind to SIRP alpha. Evidence from immunoprecipitation experiments performed in COS-7 lysates suggests that the SH3 domain of SCAP2 is involved in the interaction.

Preceded by: [Phosphorylation of ITIM motif in SIRP alpha](#)

Literature references

Timms, JF., Raab, M., Neel, BG., Marie-Cardine, A., Swanson, KD., Schraven, B. et al. (1999). SHPS-1 is a scaffold for assembling distinct adhesion-regulated multi-protein complexes in macrophages. *Curr Biol*, 9, 927-30. ↗

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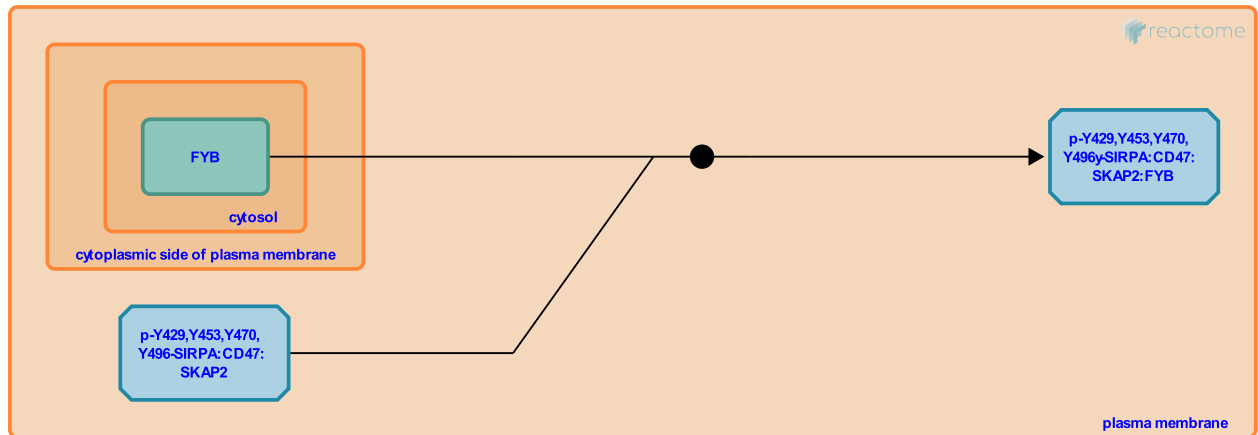
p-4Y-SIRPA:CD47:SKAP2 binds FYB ↗

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391151

Type: binding

Compartments: plasma membrane, cytosol



The Fyn binding protein FYB (SLAP130, ADAP) has been found to associate with SIRP alpha (SIRPA). Recruitment of FYB to SIRPA requires SKAP2.

Preceded by: [Phosphorylation of ITIM motif in SIRP alpha](#)

Literature references

Timms, JF., Raab, M., Neel, BG., Marie-Cardine, A., Swanson, KD., Schraven, B. et al. (1999). SHPS-1 is a scaffold for assembling distinct adhesion-regulated multi-protein complexes in macrophages. *Curr Biol*, 9, 927-30. ↗

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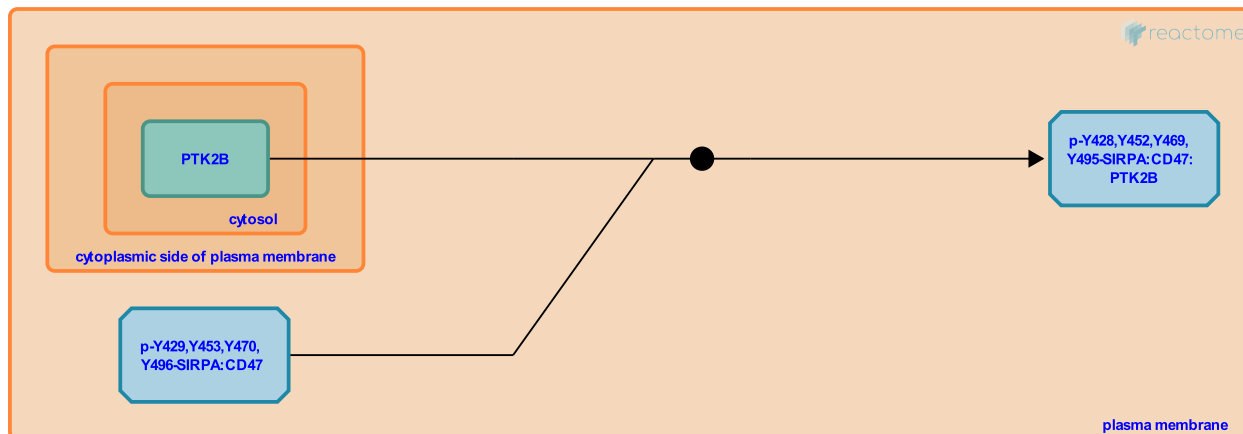
p-4Y-SIRPA:CD47 binds PTK2B ↗

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391152

Type: binding

Compartments: plasma membrane, cytosol



Protein-tyrosine kinase 2-beta (PTK2B, PYK2, FADK2), a cytosolic tyrosine kinase related to FAK, has been shown to complex with SIRP alpha.

Preceded by: [Phosphorylation of ITIM motif in SIRP alpha](#)

Literature references

Timms, JF., Raab, M., Neel, BG., Marie-Cardine, A., Swanson, KD., Schraven, B. et al. (1999). SHPS-1 is a scaffold for assembling distinct adhesion-regulated multi-protein complexes in macrophages. *Curr Biol*, 9, 927-30. ↗

Ruhul Amin, AR., Matsuda, S., Oshima, K., Hamaguchi, M., Suzuki, A. (2002). SHPS-1, a multifunctional transmembrane glycoprotein. *FEBS Lett*, 519, 1-7. ↗

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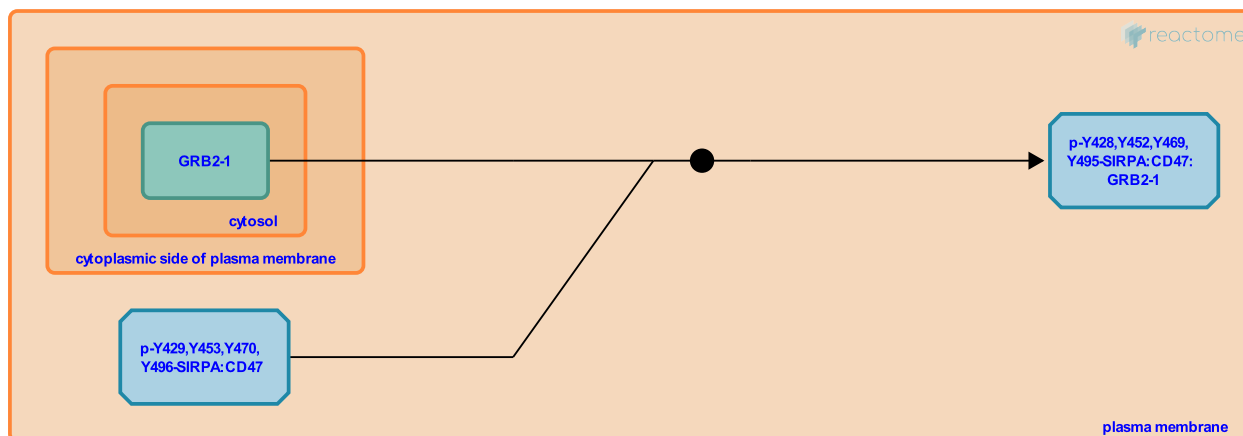
p-4Y-SIRPA:CD47 binds GRB2-1 [↗](#)

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391153

Type: binding

Compartments: plasma membrane, cytosol



GRB2 binds to phosphorylated tyrosine residues in SIRP alpha (SIRPA) in vitro; this interaction has negative regulatory effects on cellular responses induced by growth factors, oncogenes or insulin.

Preceded by: [Phosphorylation of ITIM motif in SIRP alpha](#)

Literature references

Chen, Z., Ullrich, A., Wang, H., Kharitonov, A., Schilling, J., Sures, I. (1997). A family of proteins that inhibit signalling through tyrosine kinase receptors. *Nature*, 386, 181-6. [↗](#)

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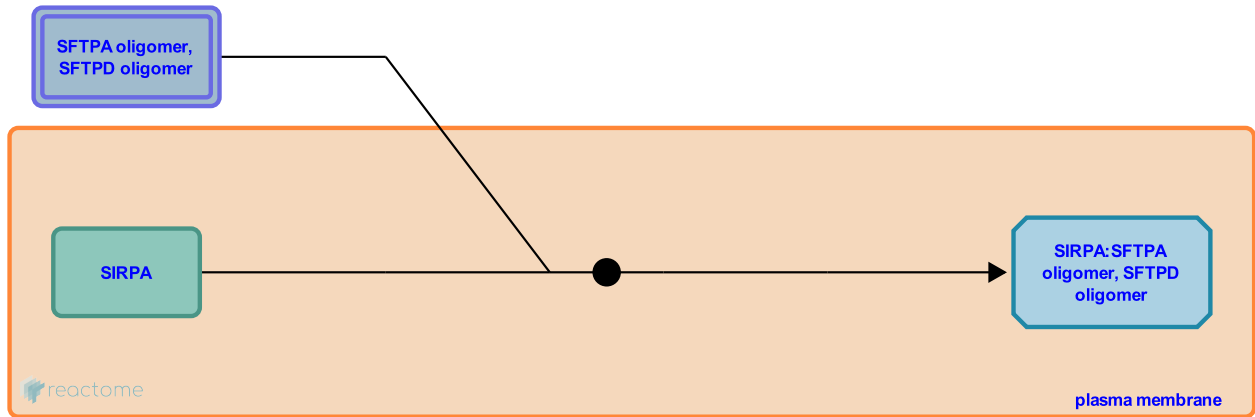
SIRPA binds SFTPA oligomer, SFTPD oligomer [↗](#)

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391155

Type: binding

Compartments: plasma membrane, extracellular region



Pulmonary surfactant-associated proteins A1, A2 and D (SFTPA1, SFTPA2 and SFTPD) are soluble multivalent ligands shown to bind SIRP alpha (SIRPA) on resident alveolar cells and macrophages via their lectin domain (globular head). SFTPA and SFTPD bind to the same region of SIRPA as CD47, blocking subsequent binding of CD47.

Literature references

Xiao, YQ., Gardai, SJ., Voelker, DR., Dickinson, M., Henson, PM., Nick, JA. et al. (2003). By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. *Cell*, 115, 13-23. [↗](#)

Kishore, U., Madan, T., Shrive, AK., Greenhough, TJ., Waters, P., Chakraborty, T. et al. (2006). Surfactant proteins SP-A and SP-D: structure, function and receptors. *Mol Immunol*, 43, 1293-315. [↗](#)

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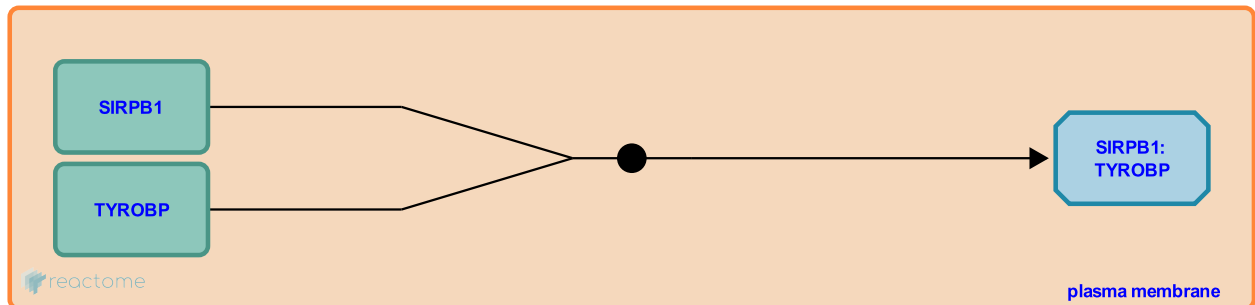
SIRP beta binds TYROBP ↗

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-210274

Type: binding

Compartments: plasma membrane



SIRP beta (SIRPB, CD172b) is expressed mainly on myeloid cells and has a very short cytoplasmic region of only six amino acids, lacking the signaling motifs required for association with phosphatases that are found in SIRPA. Instead, SIRPB associates with a dimeric protein TYROBP (DAP12) to transmit activating signals via its ITAM motif. A positively charged amino acid in the transmembrane domain of TYROBP associates with a basic amino acid in the transmembrane region of SIRPB.

Literature references

Buhring, HJ., Colonna, M., Dietrich, J., Seiffert, M., Cella, M. (2000). Cutting edge: signal-regulatory protein beta 1 is a DAP12-associated activating receptor expressed in myeloid cells. *J Immunol*, 164, 9-12. ↗

Vivier, E., Cant, C., Vely, F., Ullrich, A., Buhring, HJ., Andre, P. et al. (2000). Association of signal-regulatory proteins beta with KARAP/DAP-12. *Eur J Immunol*, 30, 2147-56. ↗

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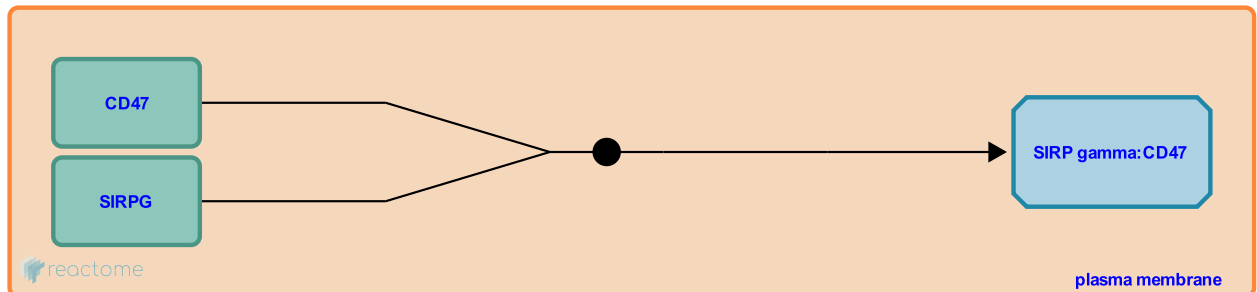
SIRP gamma binds CD47 [↗](#)

Location: [Signal regulatory protein family interactions](#)

Stable identifier: R-HSA-391168

Type: binding

Compartments: plasma membrane



SIRP gamma (SIRPG) is expressed by T cells and has been shown to engage with CD47, albeit with lower affinity than SIRP alpha. The engagement of SIRPG on the surface of T cells increased cell-cell adhesion.

Literature references

Brooke, G., Barclay, AN., Brown, MH., Holbrook, JD. (2004). Human lymphocytes interact directly with CD47 through a novel member of the signal regulatory protein (SIRP) family. *J Immunol*, 173, 2562-70. [↗](#)

Strader, CA., Facchetti, F., Boles, KS., Piccio, L., Colonna, M., Cella, M. et al. (2005). Adhesion of human T cells to antigen-presenting cells through SIRPbeta2-CD47 interaction costimulates T-cell proliferation. *Blood*, 105, 2421-7. [↗](#)

Chen, Z., Cant, C., Brown, EJ., Brugger, W., Buhring, HJ., Kanz, L. et al. (1999). Human signal-regulatory protein is expressed on normal, but not on subsets of leukemic myeloid cells and mediates cellular adhesion involving its counterreceptor CD47. *Blood*, 94, 3633-43. [↗](#)

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