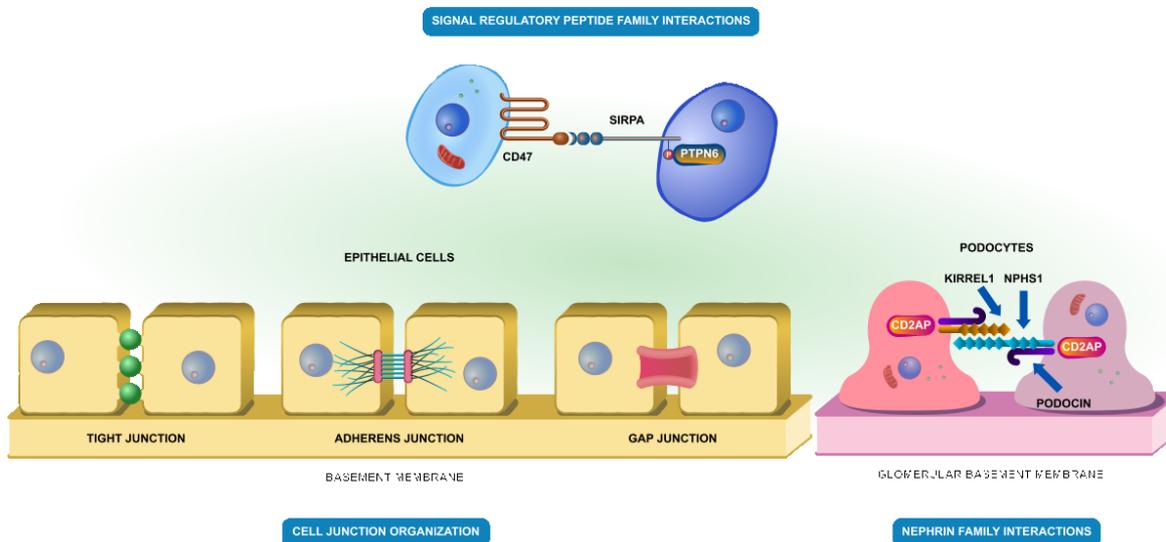


Cell-Cell communication



Barclay, AN., Garapati, P V., Grahammer, Florian., Huber, TB., Matthews, L., de Bono, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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

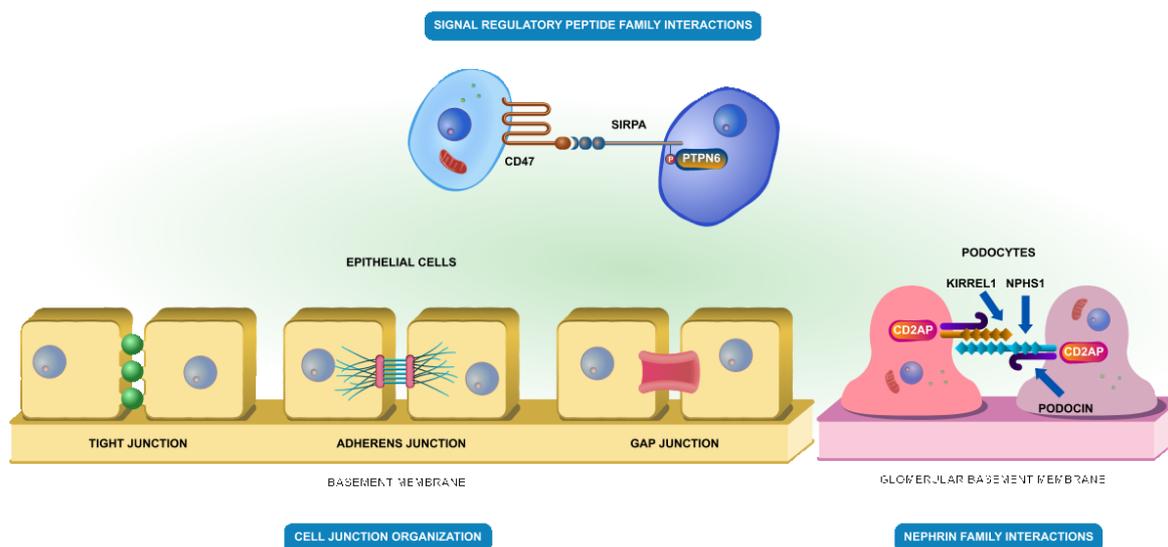
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 70

This document contains 4 pathways ([see Table of Contents](#))

Cell-Cell communication ↗

Stable identifier: R-HSA-1500931



Cell-to-Cell communication is crucial for multicellular organisms because it allows organisms to coordinate the activity of their cells. Some cell-to-cell communication requires direct cell-cell contacts mediated by receptors on their cell surfaces. Members of the immunoglobulin superfamily (IgSF) proteins are some of the cell surface receptors involved in cell-cell recognition, communication and many aspects of the axon guidance and synapse formation-the crucial processes during embryonal development (Rougon & Hobert 2003).

Processes annotated here as aspects of **cell junction organization** mediate the formation and maintenance of adherens junctions, tight junctions, and gap junctions, as well as aspects of cellular interactions with extracellular matrix and hemidesmosome assembly. **Nephrin protein family interactions** are central to the formation of the slit diaphragm, a modified adherens junction. Interactions among members of the **signal regulatory protein family** are important for the regulation of migration and phagocytosis by myeloid cells.

Literature references

- Rougon, G., Hobert, O. (2003). New insights into the diversity and function of neuronal immunoglobulin superfamily molecules. *Annu Rev Neurosci*, 26, 207-38. ↗
- Hattori, D., Millard, SS., Wojtowicz, WM., Zipursky, SL. (2008). Dscam-mediated cell recognition regulates neural circuit formation. *Annu Rev Cell Dev Biol*, 24, 597-620. ↗
- Kurihara, H., Harita, Y., Ichimura, K., Hattori, S., Sakai, T. (2010). SIRP-alpha-CD47 system functions as an intercellular signal in the renal glomerulus. *Am J Physiol Renal Physiol*, 299, F517-27. ↗
- Patrakka, J., Tryggvason, K. (2007). Nephrin--a unique structural and signaling protein of the kidney filter. *Trends Mol Med*, 13, 396-403. ↗
- Schneeberger, EE., Lynch, RD. (1992). Structure, function, and regulation of cellular tight junctions. *Am J Physiol*, 262, L647-61. ↗

Editions

2011-08-23

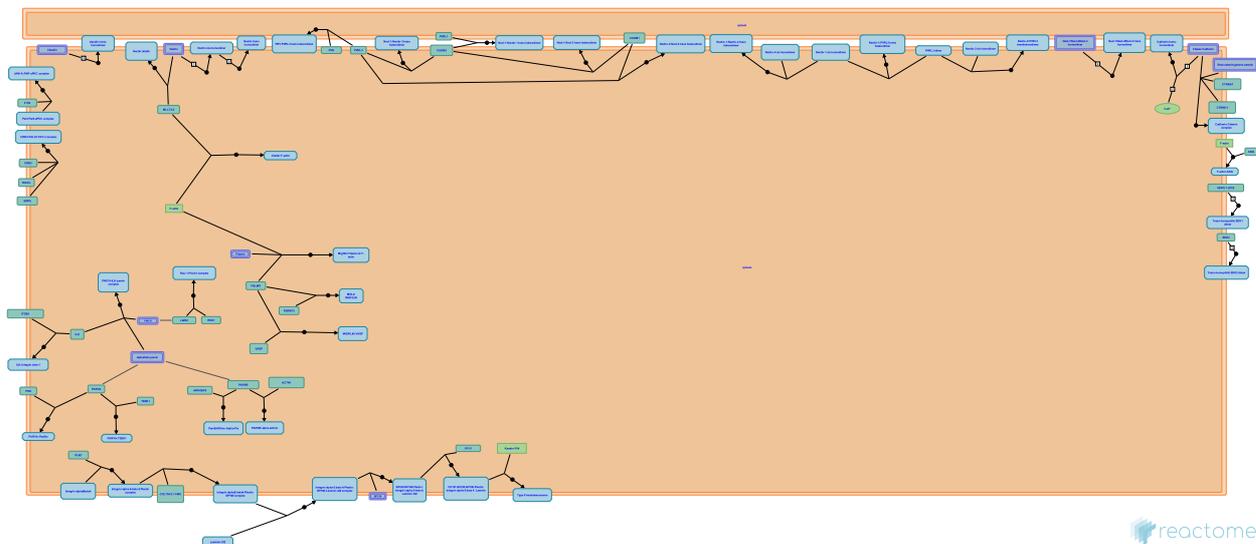
Authored, Edited

Garapati, P V.

Cell junction organization ↗

Location: Cell-Cell communication

Stable identifier: R-HSA-446728



Cell junction organization in Reactome currently covers aspects of cell-cell junction organization, cell-extracellular matrix interactions, and Type I hemidesmosome assembly.

Editions

2009-11-17

Edited

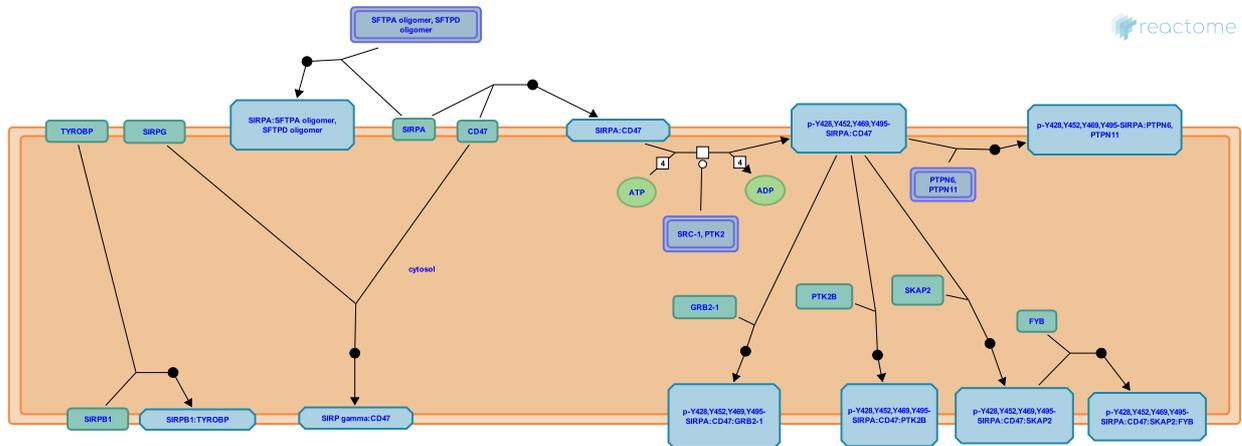
Matthews, L.

Signal regulatory protein family interactions ↗

Location: Cell-Cell communication

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

- Barclay, AN., Brown, MH. (2006). The SIRP family of receptors and immune regulation. *Nat Rev Immunol*, 6, 457-64. ↗
- Oshima, K., Ruhul Amin, AR., Suzuki, A., Hamaguchi, M., Matsuda, S. (2002). SHPS-1, a multifunctional transmembrane glycoprotein. *FEBS Lett*, 519, 1-7. ↗
- Matozaki, T., Murata, Y., Okazawa, H., Ohnishi, H. (2009). Functions and molecular mechanisms of the CD47-SIRPalpha signalling pathway. *Trends Cell Biol*, 19, 72-80. ↗
- Liu, Y., Buhring, HJ., Zen, K., Burst, SL., Schnell, FJ., Williams, IR. et al. (2002). Signal regulatory protein (SIRPalpha), a cellular ligand for CD47, regulates neutrophil transmigration. *J Biol Chem*, 277, 10028-36. ↗
- van den Berg, TK., van Beek, EM., Buhring, HJ., Colonna, M., Hamaguchi, M., Howard, CJ. et al. (2005). A nomenclature for signal regulatory protein family members. *J Immunol*, 175, 7788-9. ↗

Editions

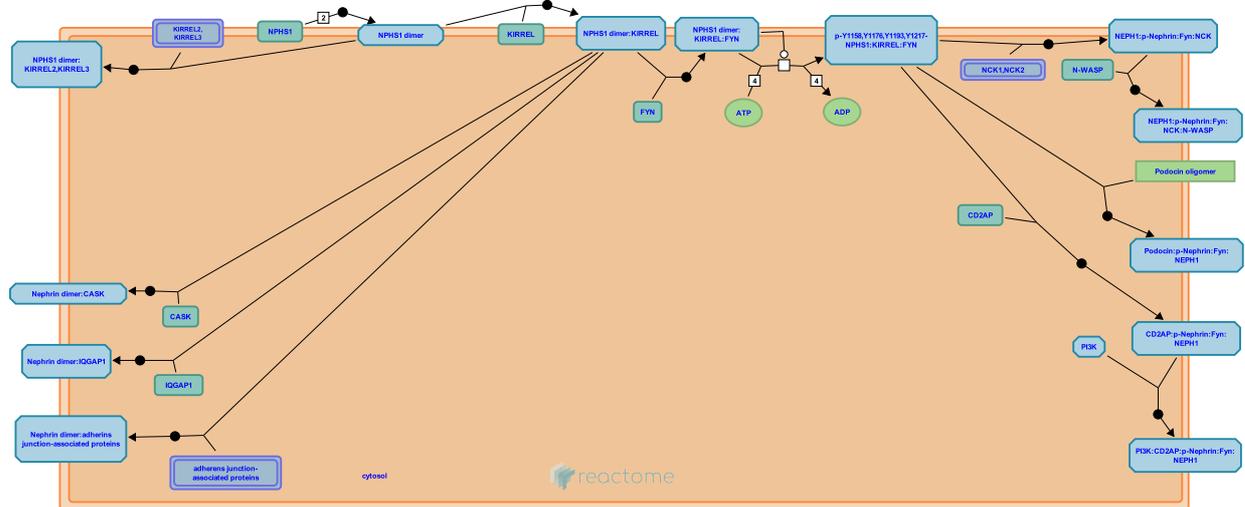
2009-02-12	Authored, Edited	Garapati, P V.
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Nephrin family interactions ↗

Location: Cell-Cell communication

Stable identifier: R-HSA-373753

Compartments: plasma membrane



Nephrin (NPHS1) is a member of the Super-IgG-Molecule family and is most prominently expressed in kidney podocytes. It is a major if not the most important structural component of the slit diaphragm, a modified adherens junction inbetween these cells. NPHS1 has an extracellular domain that contains eight distal IgG like domains and one proximal fibronectin type III domain, a transmembrane domain and a short intracellular domain. NPHS1 molecules show both homophilic and heterophilic interactions. Among heterophilic interaction partners, slit diaphragm proteins such as Kin of IRRE-like protein 1 (KIRREL, Nephrin-like protein 1, NEPH1), KIRREL3 (NEPH2) and KIRREL2 (NEPH3) were shown to stabilize the slit diaphragm structure. Intracellularly Podocin (NPHS2), CD2 associated protein (CD2AP) and adherens junction associated proteins like IQGAP, MAGI, CASK and spectrins all interact with NPHS1. Hence it seems to play a major role in organizing the molecular structure of the slit diaphragm itself and via its binding partners links it to the actin cytoskeleton. NPHS1 tyrosine phosphorylation by the Src kinase FYN initiates the PI3K-AKT signaling cascade, which seems to promote antiapoptotic signals.

Literature references

- Patrakka, J., Tryggvason, K. (2007). Nephrin--a unique structural and signaling protein of the kidney filter. *Trends Mol Med*, 13, 396-403. ↗
- Ruotsalainen, V., Ljungberg, P., Wartiovaara, J., Lenkkeri, U., Kestilä, M., Jalanko, H. et al. (1999). Nephrin is specifically located at the slit diaphragm of glomerular podocytes. *Proc Natl Acad Sci U S A*, 96, 7962-7. ↗
- Tryggvason, K. (1999). Unraveling the mechanisms of glomerular ultrafiltration: nephrin, a key component of the slit diaphragm. *J Am Soc Nephrol*, 10, 2440-5. ↗
- Tryggvason, K., Patrakka, J., Wartiovaara, J. (2006). Hereditary proteinuria syndromes and mechanisms of proteinuria. *N Engl J Med*, 354, 1387-401. ↗
- Huber, TB., Hartleben, B., Kim, J., Schmidts, M., Schermer, B., Keil, A. et al. (2003). Nephrin and CD2AP associate with phosphoinositide 3-OH kinase and stimulate AKT-dependent signaling. *Mol Cell Biol*, 23, 4917-28. ↗

Editions

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