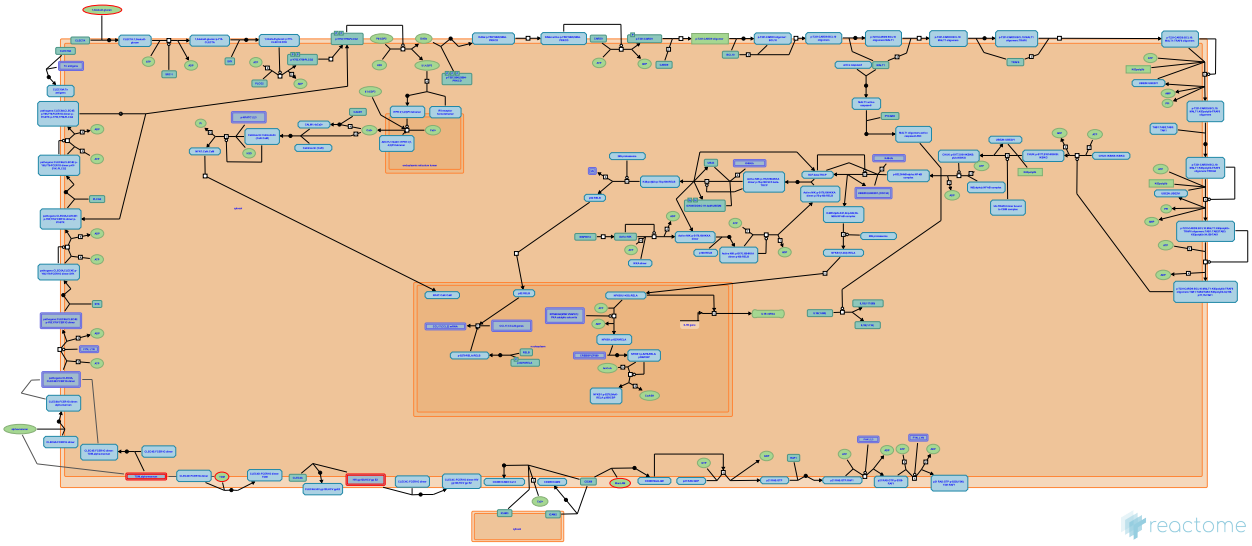
C-type lectin receptors (CLRs)



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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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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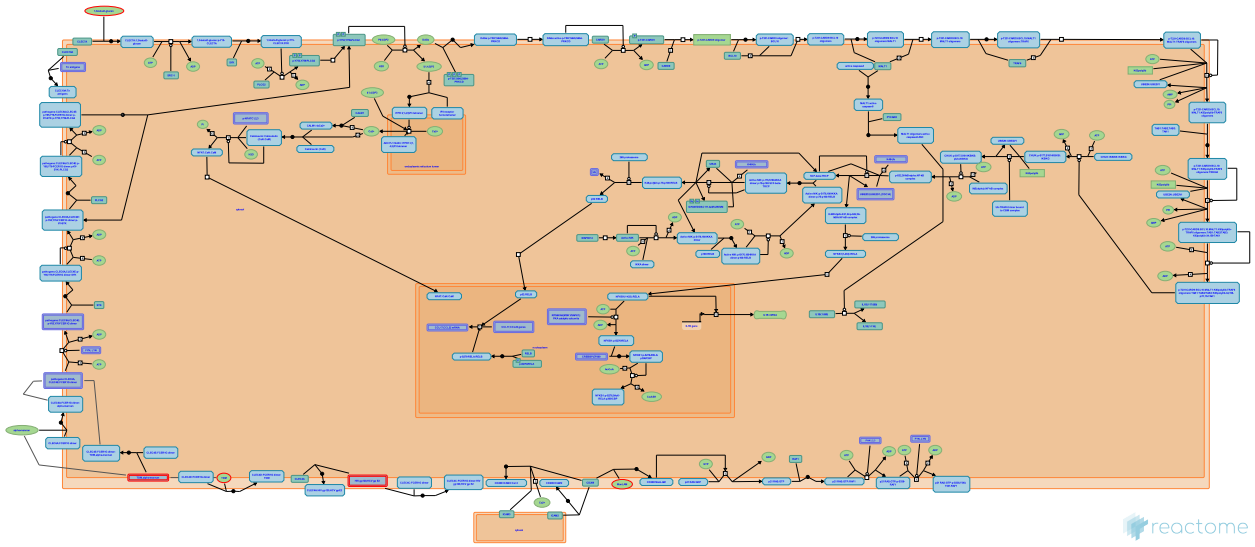
Reactome database release: 89

This document contains 4 pathways (see Table of Contents)

C-type lectin receptors (CLRs) ↗

Stable identifier: R-HSA-5621481

Compartments: cytosol, nucleoplasm, plasma membrane



Pathogen recognition is central to the induction of T cell differentiation. Groups of pathogens share similar structures known as pathogen-associated molecular patterns (PAMPs), which are recognised by pattern recognition receptors (PRRs) expressed on dendritic cells (DCs) to induce cytokine expression. PRRs include archetypical Toll-like receptors (TLRs) and non-TLRs such as retinoic acid-inducible gene I (RIG-I)-like receptors, C-type lectin receptors (CLRs) and intracellular nucleotide-binding domain and leucine-rich-repeat-containing family (NLRs). PRR recognition of PAMPs can lead to the activation of intracellular signalling pathways that elicit innate responses against pathogens and direct the development of adaptive immunity.
CLRs comprises a large family of receptors which bind carbohydrates, through one or more carbohydrate recognition domains (CRDs), or which possess structurally similar C-type lectin-like domains (CTLDs) which do not necessarily recognise carbohydrate ligands. Some CLRs can induce signalling pathways that directly activate nuclear factor-kB (NF-kB), whereas other CLRs affect signalling by Toll-like receptors. These signalling pathways trigger cellular responses, including phagocytosis, DC maturation, chemotaxis, the respiratory burst, inflammasome activation, and cytokine production.

Literature references

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Editions

2014-08-29	Authored, Edited	Garapati, P V.
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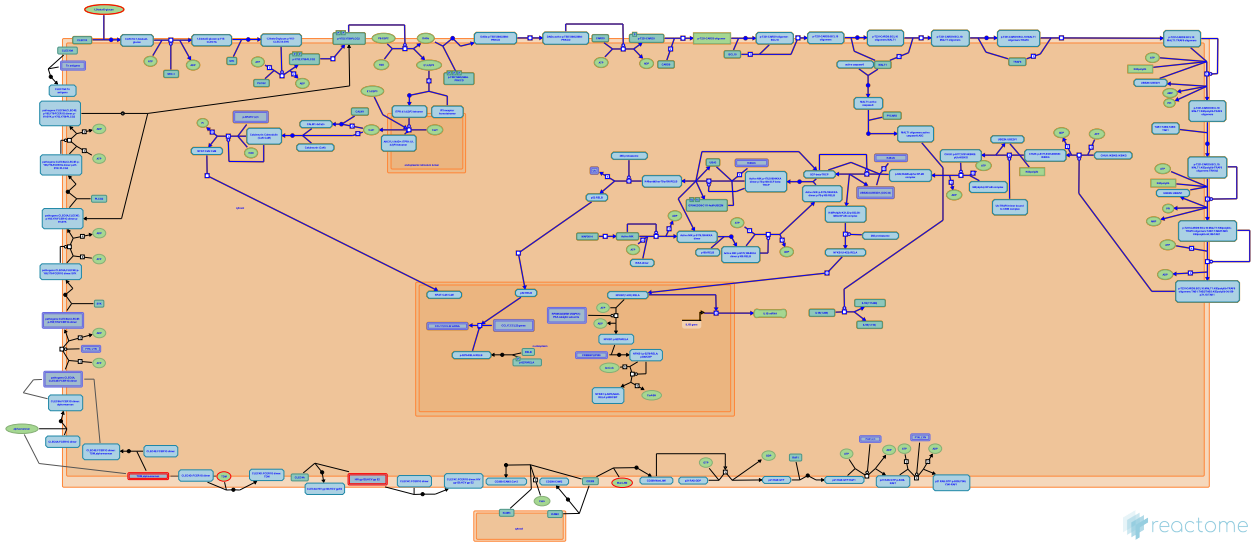
CLEC7A (Dectin-1) signaling ↗

Location: C-type lectin receptors (CLRs)

Stable identifier: R-HSA-5607764

Compartments: plasma membrane



CLEC7A (also known as Dectin-1) is a pattern-recognition receptor (PRR) expressed by myeloid cells (macrophages, dendritic cells and neutrophils) that detects pathogens by binding to beta-1,3-glucans in fungal cell walls and triggers direct innate immune responses to fungal and bacterial infections. CLEC7A belongs to thetype-II C-type lectin receptor (CLR) family that can mediate its own intracellular signaling. Upon binding particulate beta-1,3-glucans, CLEC7A mediates intracellular signalling through its cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM)-like motif (Brown 2006). CLEC7A signaling can induce the production of various cytokines and chemokines, including tumour-necrosis factor (TNF), CXC-chemokine ligand 2 (CXCL2, also known as MIP2), interleukin-1beta (IL-1b), IL-2, IL-10 and IL-12 (Brown et al. 2003), it also triggers phagocytosis and stimulates the production of reactive oxygen species (ROS), thus contributing to microbial killing (Gantner et al. 2003, Herre et al. 2004, Underhill et al. 2005, Goodridge at al. 2011, Reid et al. 2009). These cellular responses mediated by CLEC7A rely on both Syk-dependent and Syk-independent signaling cascades. The pathways leading to the Syk-dependent activation of NF-kB can be categorised into both canonical and non-canonical routes (Gringhuis et al. 2009). Activation of the canonical NF-kB pathway is essential for innate immunity, whereas activation of the non-canonical pathway is involved in lymphoid organ development and adaptive immunity (Plato et al. 2013).

Literature references

Gordon, S., Williams, DL., Willment, JA., Marshall, AS., Brown, GD., Herre, J. (2003). Dectin-1 mediates the biological effects of beta-glucans. *J. Exp. Med., 197,* 1119-24. ↗

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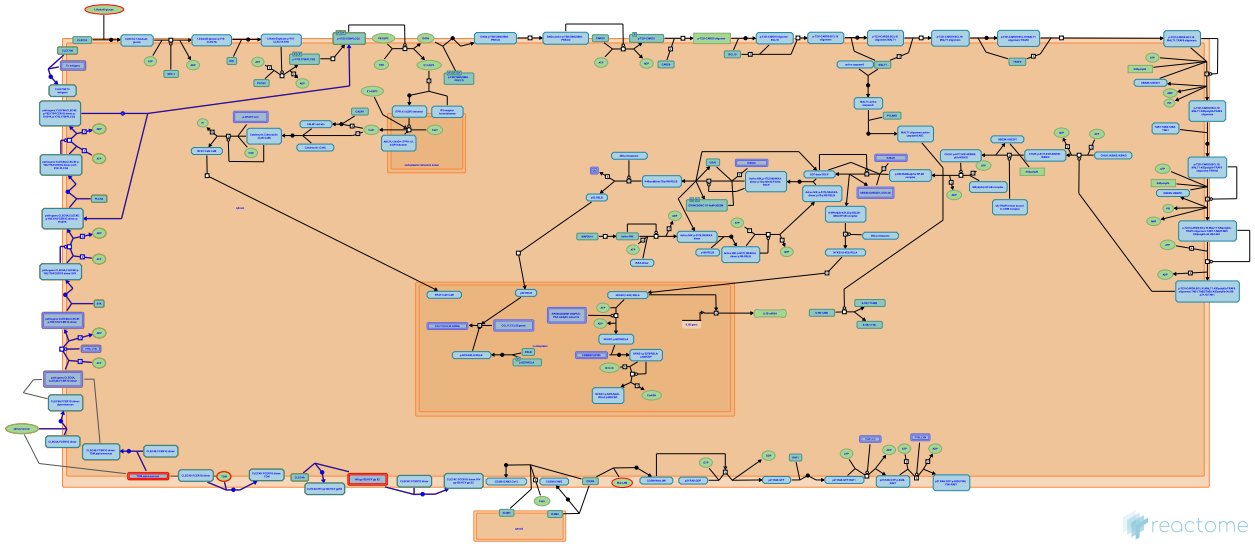
Dectin-2 family ↗

Location: C-type lectin receptors (CLRs)

Stable identifier: R-HSA-5621480

Compartments: plasma membrane



Dendritic cell-associated C-type lectin-2 (Dectin-2) family of C-type lectin receptors (CLRs) includes Dectin-2 (CLEC6A), blood dendritic antigen 2 (BDCA2/CLEC4C), macrophage C-type lectin (MCL/CLEC4D), Dendritic cell immunoreceptor (DCIR/CLEC4A) and macrophage inducible C-type lectin (Mincle/CLEC4E). These receptors possesses a single extracellular conserved C-type lectin domain (CTLD) with a short cytoplasmic tail that induces intracellular signalling indirectly by binding with the FCERG (High affinity immunoglobulin epsilon receptor subunit gamma) except for DCIR that has a longer cytoplasmic tail with an integral inhibitory signalling motif (Graham & Brown. 2009, Kerschera et al. 2013). CLEC6A (Dectin-2) binds to high mannose containing pathogen-associated molecular patterns (PAMPs) expressed by fungal hyphae, and CLEC4E (mincle) binds to alpha-mannaosyl PAMPs on fungal, mycobacterial and necrotic cell ligands. Both signaling pathways lead to Toll-like receptor (TLR)-independent production of cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL6). Similarities with Dectin-1 (CLC7A) signaling pathway suggests that both these CLRs couple SYK activation to NF-kB activation using a complex involving CARD9, BCL10 and MALT1 (Geijtenbeek & Gringhuis 2009).

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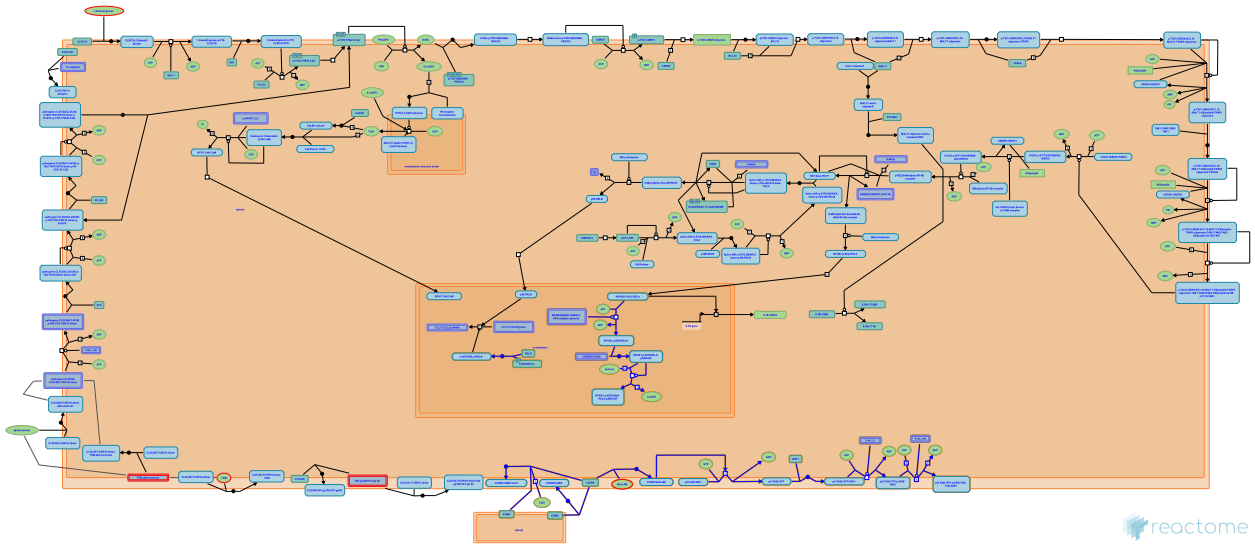
CD209 (DC-SIGN) signaling ↗

Location: C-type lectin receptors (CLRs)

Stable identifier: R-HSA-5621575



CD209 (also called as DC-SIGN (DC-specific intracellular adhesion molecule-3-grabbing non-integrin)) is a type II transmembrane C-type lectin receptor preferentially expressed on dendritic cells (DCs). CD209 functions as a pattern recognition receptor (PRR) that recognises several microorganisms and pathogens, contributing to generation of pathogen-tailored immune responses (Gringhuis & Geijtenbeek 2010, den Dunnen et al. 2009, Svajger et al. 2010). CD209 interacts with different mannose-expressing pathogens such as Mycobacterium tuberculosis and HIV-1 (Gringhuis et al. 2007, Geijtenbeek et al. 2000a). It also acts as an adhesion receptor that interacts with ICAM2 (intracellular adhesion molecule-2) on endothelial cells and ICAM3 on T cells (Geijtenbeek et al. 2000b,c). CD209 functions not only as an independent PRR, but is also implicated in the modulation of Toll-like receptor (TLR) signaling at the level of the transcription factor NF-kB (Gringhuis et al. 2009). CLEC7A (Dectin-1) and CD209 (DC-SIGN) signalling modulates Toll-like receptor (TLR) signalling through the kinase RAF1 that is independent of the SYK pathway but integrated with it at the level of NF-kB activation. The activation of RAF1 by CLEC7A or CD209 does not lead to activation of extracellular signal-regulated kinase 1 (ERK1)/2 or Mitogen-activated protein kinase kinase 1 (MEK1)/2 but leads to the phosphorylation and subsequent acetylation of RELA (p65). RELA phosphorylated on S276 not only positively regulates the activity of p65 through acetylation of p65, but also represses RELB activity by sequestering active RELB into inactive p65-RELB dimers that do not bind DNA (Gringhuis et al. 2007, Svajger et al. 2010, Jacque et al. 2005). RAF1-dependent signaling pathway is crucial in dectin-1 mediated immunity as it modulates both the canonical (promoting p65 phosphorylation and acetylation) and non-canonical (forming inactive p65-RELB dimers) NK-kB activation.

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Editions

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