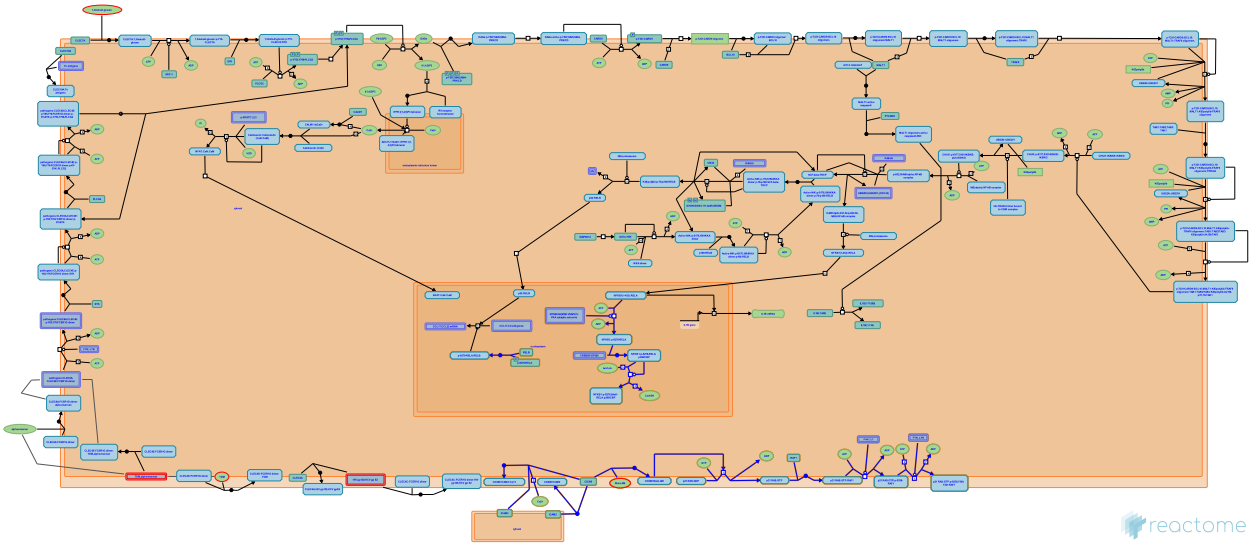
CD209 (DC-SIGN) signaling



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29/04/2024

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.

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).

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. ↗

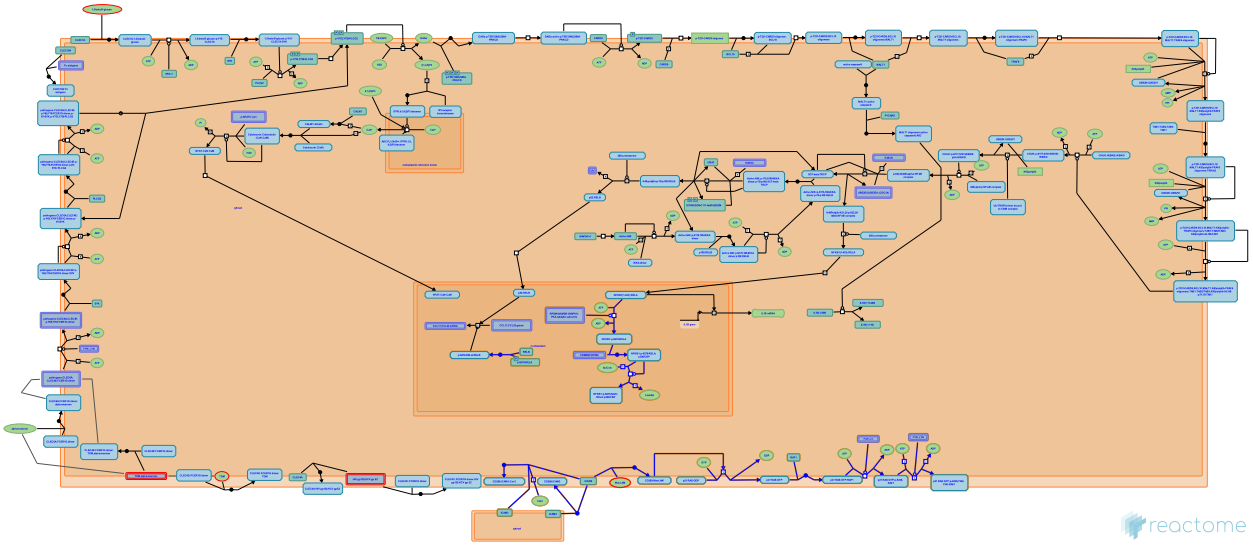
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

CD209 (DC-SIGN) signaling ↗

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.

Literature references

Geijtenbeek, TB., Gringhuis, SI. (2010). Carbohydrate signaling by C-type lectin DC-SIGN affects NF-kappaB activity. *Meth. Enzymol., 480*, 151-64. ↗

Geijtenbeek, TB., Gringhuis, SI., den Dunnen, J. (2009). Innate signaling by the C-type lectin DC-SIGN dictates immune responses. *Cancer Immunol. Immunother., 58*, 1149-57. ↗

Litjens, M., Geijtenbeek, TB., Gringhuis, SI., van Kooyk, Y., den Dunnen, J., van Het Hof, B. (2007). C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. *Immunity, 26*, 605-16. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
2015-01-05	Authored, Edited	Garapati, P V.

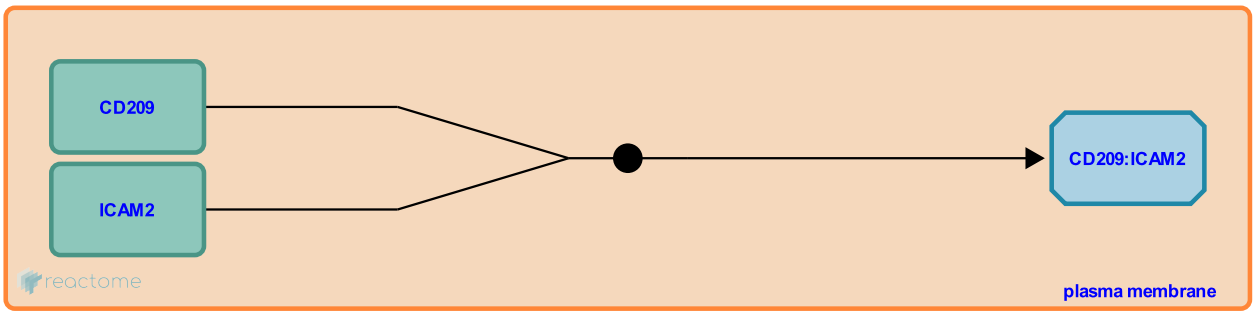
CD209 binds ICAM2 ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5621571

Type: binding

Compartments: plasma membrane



CD209 (DC-SIGN) acts as an adhesion molecule and besides foreign antigens (Ags), it binds to a number of endogenous ligands, particularly to intracellular adhesion molecule 2 (ICAM2) on endothelial cells. This CD209-ICAM2 interaction regulates chemokine-induced transmigration of dendritic cells across both resting and activated endothelium (Geijtenbeek et al. 2000).

Literature references

van Kooyk, Y., Krooshoop, DJ., van Duijnhoven, GC., Bleijs, DA., Figdor, CG., Geijtenbeek, TB. et al. (2000). DC-SIGN-ICAM-2 interaction mediates dendritic cell trafficking. *Nat. Immunol., 1*, 353-7. ↗

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2014-09-02	Reviewed	Geijtenbeek, TB.
2015-01-05	Authored, Edited	Garapati, P V.

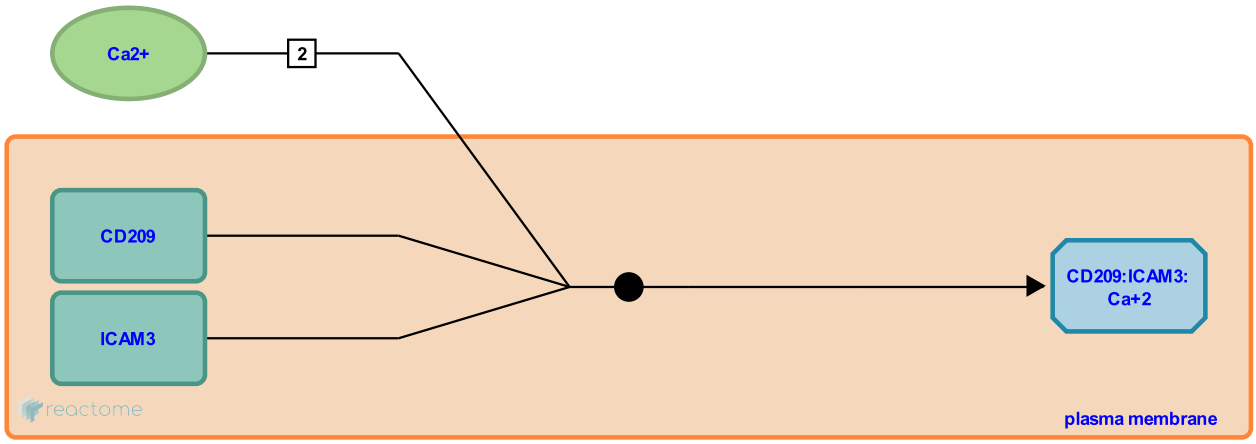
CD209 binds ICAM3 ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5621615

Type: binding

Compartments: plasma membrane, extracellular region



Contact between dendritic cells (DC) and resting T cells is essential to initiate a primary immune response. CD209 binds the intracellular adhesion molecule 3 (ICAM3) with very high affinity. CD209 interacts primarily with the immunoglobulin (Ig)-like second domain of ICAM2 and ICAM3. CD209-ICAM3 interaction mediates clustering of DCs with naive T cells forming a DC-T cell synapse (Geijtenbeek et al. 2000). CD209 binding to ICAM3 is calcium dependent, and CD209 CRD (carbohydrate recognition domain) binds two Ca2+ ions, one essential for tertiary structure and the other for coordinating ligand binding (Feinberg et al. 2001, Svajger et al. 2010).

Literature references

van Kooyk, Y., van Duijnhoven, GC., Figdor, CG., Geijtenbeek, TB., van Vliet, SJ., Torensma, R. et al. (2000). Identification of DC-SIGN, a novel dendritic cell-specific ICAM-3 receptor that supports primary immune responses. *Cell, 100*, 575-85. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
2015-01-05	Authored, Edited	Garapati, P V.

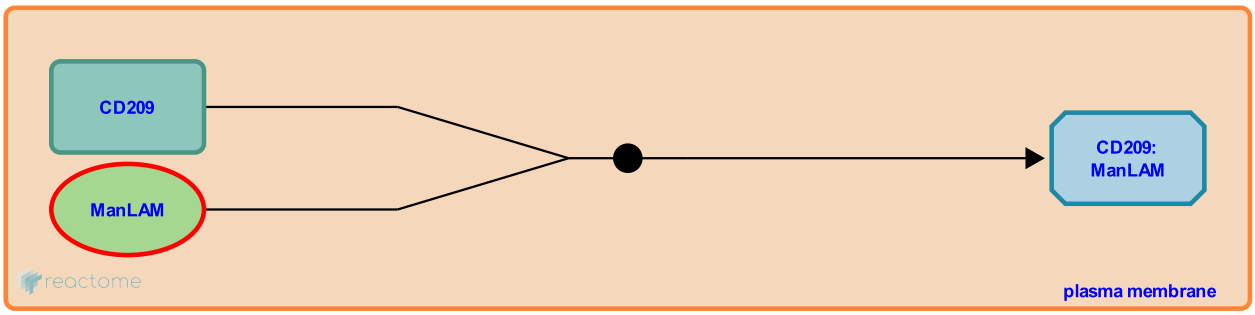
CD209 binds ManLAM ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5621606

Type: binding

Compartments: plasma membrane



CD209 (DC-SIGN) interacts with pathogens through either mannose or fucose containing glycans. It interacts with mannose capped cell-wall component of Mycobacterium tuberculosis ManLAM (lipoarabinomannan). The carbohydrate recognition domain (CRD) of CD209 recognizes Man-LAM and lipomannans and the amount of Man-LAM determines the binding strength. The interaction of ManLAM and CD209 leads to the activation of serine/threonine kinase RAF1 and increases the production of the immunosuppressive cytokine interleukin 6 (IL6), IL10 and IL12 in the presence of Toll like receptor stimulation (Geijtenbeek et al. 2003, Gringhuis et al. 2007 & 2009).

Followed by: CD209 activate GTPase RAS

Literature references

Vandenbroucke-Grauls, CM., Geijtenbeek, TB., Van Vliet, SJ., van Kooyk, Y., Appelmelk, B., Sanchez-Hernandez, M. et al. (2003). Mycobacteria target DC-SIGN to suppress dendritic cell function. *J. Exp. Med., 197*, 7-17. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
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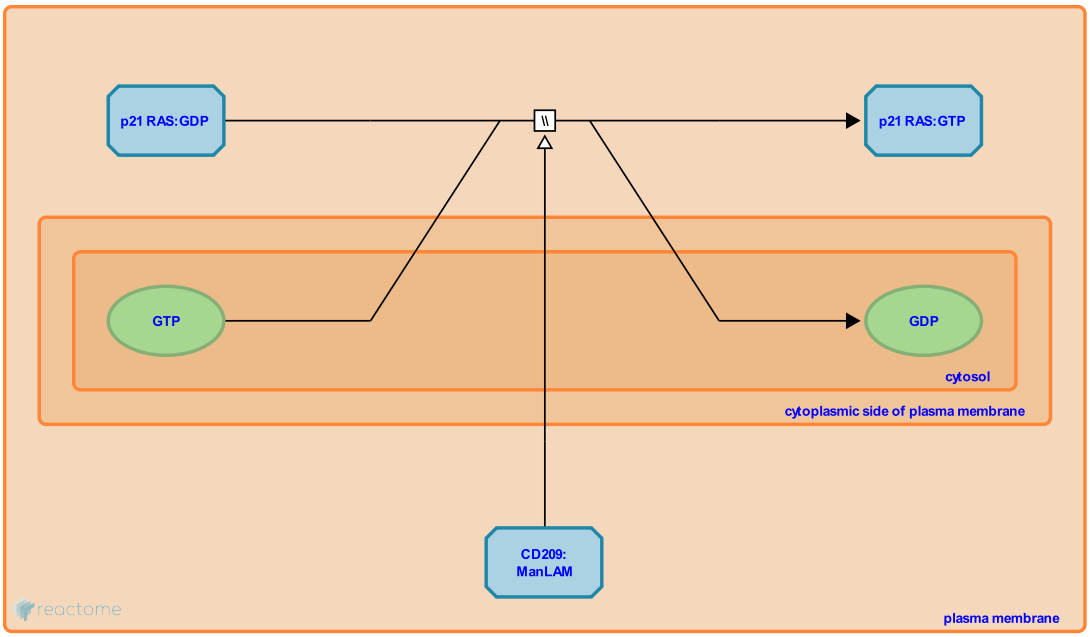
CD209 activate GTPase RAS ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5621573

Type: omitted

Compartments: plasma membrane, cytosol



Both CLEC7A (Dectin-1) and CD209 (DC-SIGN) modulates Toll-like receptor signalling by activating RAF1 which in turn induces the phosphorylation of p65 (RELA) subunit leading to the modification of p50/p65 NF-kB dimer (Gringhuis et al. 2007 & 2009). Gringhuis et al. demonstrated that CD209 (DC-SIGN) stimulated by ManLAM (lipoarabinomannan) activates the small GTPase RAS. Immunoblotting detected active RAS in dendritic cells when induced by ManLAM (Gringhuis et al. 2007). RAF1 is recruited to the membrane through an interaction with the active form of RAS.

Preceded by: CD209 binds ManLAM

Followed by: RAF1 binds p21 RAS:GTP

Literature references

Litjens, M., Geijtenbeek, TB., Gringhuis, SI., van Kooyk, Y., den Dunnen, J., van Het Hof, B. (2007). C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. *Immunity, 26*, 605-16. ↗

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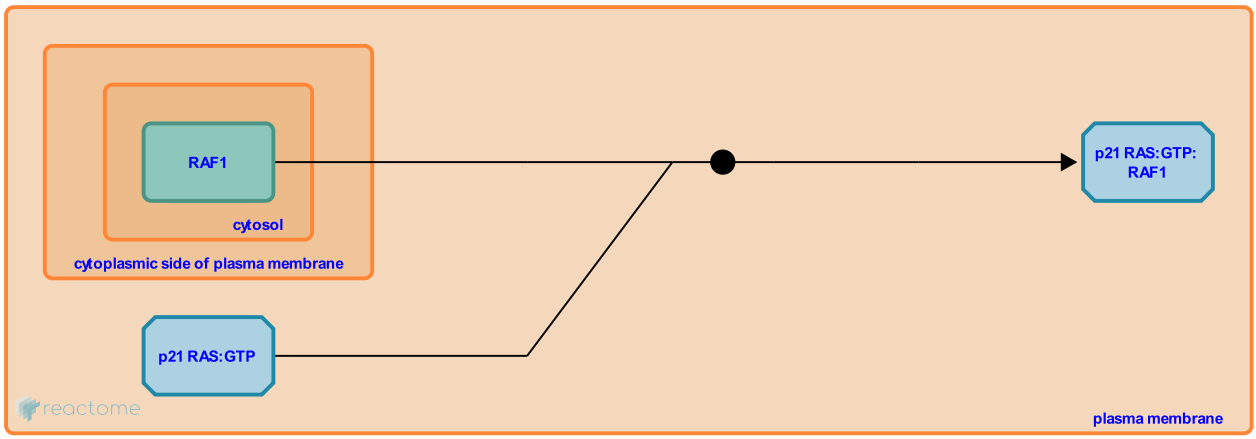
RAF1 binds p21 RAS:GTP ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5624494

Type: binding

Compartments: plasma membrane, cytosol



Upon CLEC7A (Dectin-1) and CD209 (DC-SIGN) activation, RAF1 translocates to the membrane through interaction with the active form of RAS. This interaction induces a conformational change in RAF1 and is required for RAF1 activation (Gringhuis et al. 2007, Wellbrock et al. 2004).

Preceded by: CD209 activate GTPase RAS

Followed by: PAK phosphorylates p21 RAF1 on S338

Literature references

Wellbrock, C., Karasarides, M., Marais, R. (2004). The RAF proteins take centre stage. *Nat Rev Mol Cell Biol, 5*, 875-85. ↗

Cleghon, V., Morrison, DK. (1994). Raf-1 interacts with Fyn and Src in a non-phosphotyrosine-dependent manner. *J Biol Chem, 269*, 17749-55. ↗

Litjens, M., Geijtenbeek, TB., Gringhuis, SI., van Kooyk, Y., den Dunnen, J., van Het Hof, B. (2007). C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. *Immunity, 26*, 605-16. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
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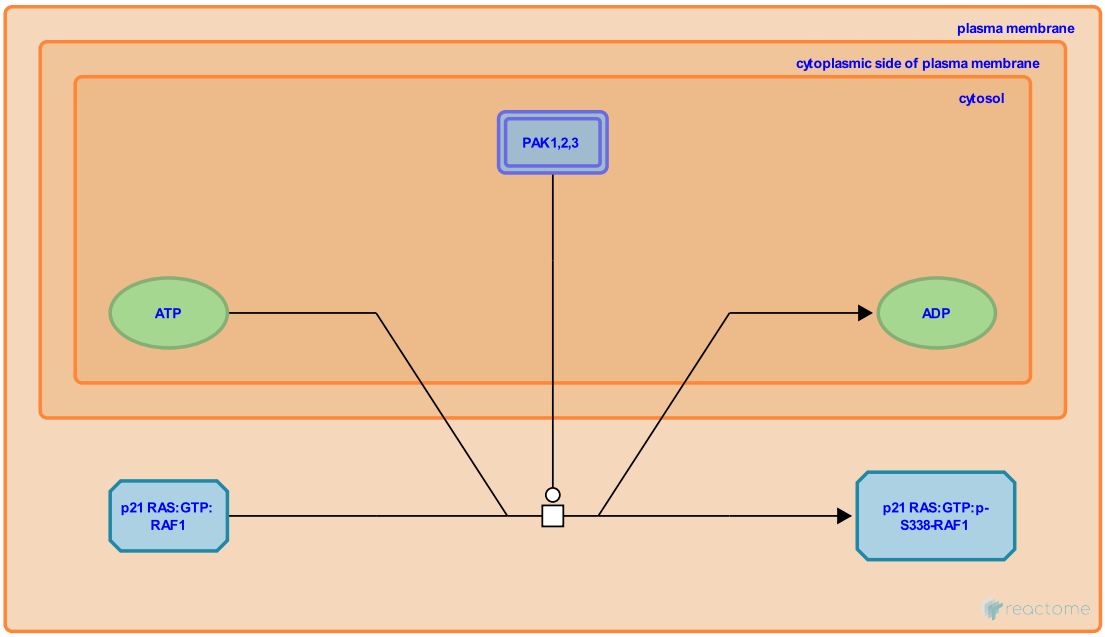
PAK phosphorylates p21 RAF1 on S338 ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5624492

Type: transition

Compartments: plasma membrane, cytosol



RAF regulation is highly complex and is not solely mediated by conformational changes but also requires phosphorylation. Several phosphorylation sites on RAF1 have been identified that are involved in its kinase activity. Two of these phosphorylation sites are serine 338 (S338) and tyrosine 340 and 341 (Y340/341). Gringhuis et al. demonstrated that ManLAM activation of CD209 (DC-SIGN) results in induced phosphorylation of RAF1 on S338 and Y340/341. The phosphorylation of S338 is mediated by p21-activated kinases (PAK). Inhibition of Rho GTPases with toxin B blocks CD209 induced phosphorylation of RAF1on S338 (Gringhuis et al. 2007, Wellbrock et al. 2004).

Preceded by: RAF1 binds p21 RAS:GTP

Followed by: SFKs phosphorylates RAF1 on Y340,Y341

Literature references

Wellbrock, C., Karasarides, M., Marais, R. (2004). The RAF proteins take centre stage. *Nat Rev Mol Cell Biol, 5,* 875-85. ↗

Obermajer, N., Svajger, U., Anderluh, M., Jeras, M. (2010). C-type lectin DC-SIGN: an adhesion, signalling and antigen-uptake molecule that guides dendritic cells in immunity. *Cell. Signal., 22,* 1397-405. ↗

Litjens, M., Geijtenbeek, TB., Gringhuis, SI., van Kooyk, Y., den Dunnen, J., van Het Hof, B. (2007). C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. *Immunity, 26,* 605-16. ↗

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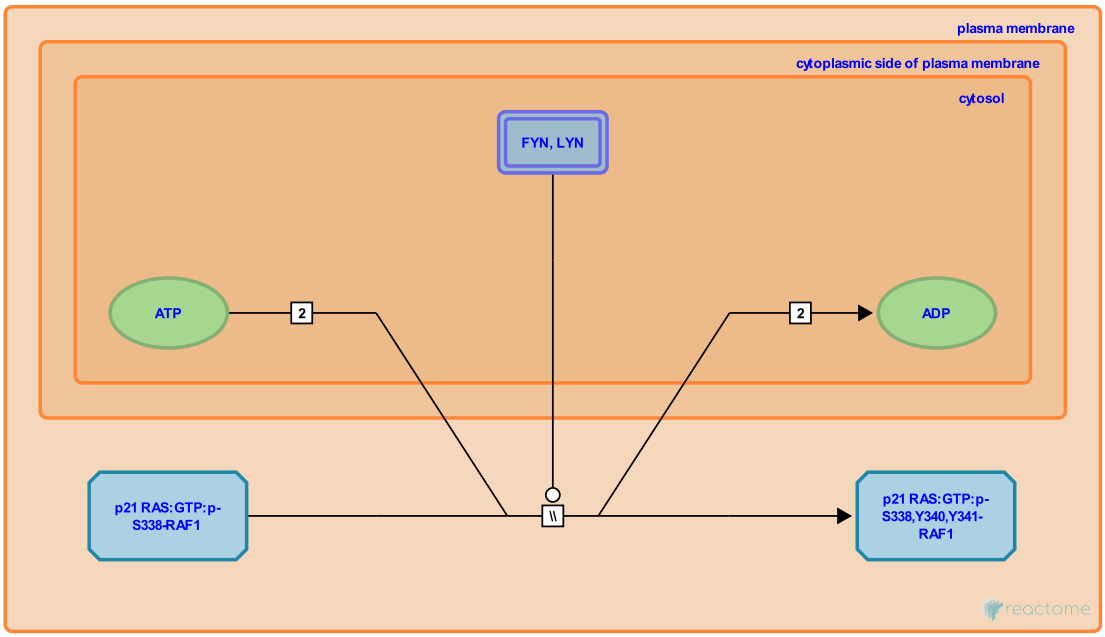
SFKs phosphorylates RAF1 on Y340,Y341 ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5624486

Type: omitted

Compartments: plasma membrane, cytosol



Phosphorylation of tyrosine 340, 341 (Y340,341) on RAF1 in response to CD209 (DC-SIGN) signalling depends on yet unidentified members of the Src family of tyrosine kinases (SFKs). In imunoprecipitation studies, CD209 from lipid rafts of dendritic cells was found to co-precipitate with LYN, a member of the SFK, as well as with SYK tyrosine kinase, indicating their possible involvement in DC-SIGN signalling (Caparros et al. 2006, Svajger et al. 2010).

Preceded by: PAK phosphorylates p21 RAF1 on S338

Followed by: Protein kinase A (PKA) and RPS6KA5 (MSK1) phosphorylates p65 (RELA) subunit

Literature references

Obermajer, N., Svajger, U., Anderluh, M., Jeras, M. (2010). C-type lectin DC-SIGN: an adhesion, signalling and antigen-uptake molecule that guides dendritic cells in immunity. *Cell. Signal., 22*, 1397-405. ↗

Munoz, P., Corbí, AL., Serrano-Gómez, D., Puig-Kröger, A., Rodríguez-Fernández, JL., Mellado, M. et al. (2006). DC-SIGN ligation on dendritic cells results in ERK and PI3K activation and modulates cytokine production. *Blood, 107* , 3950-8. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
2015-01-05	Authored, Edited	Garapati, P V.

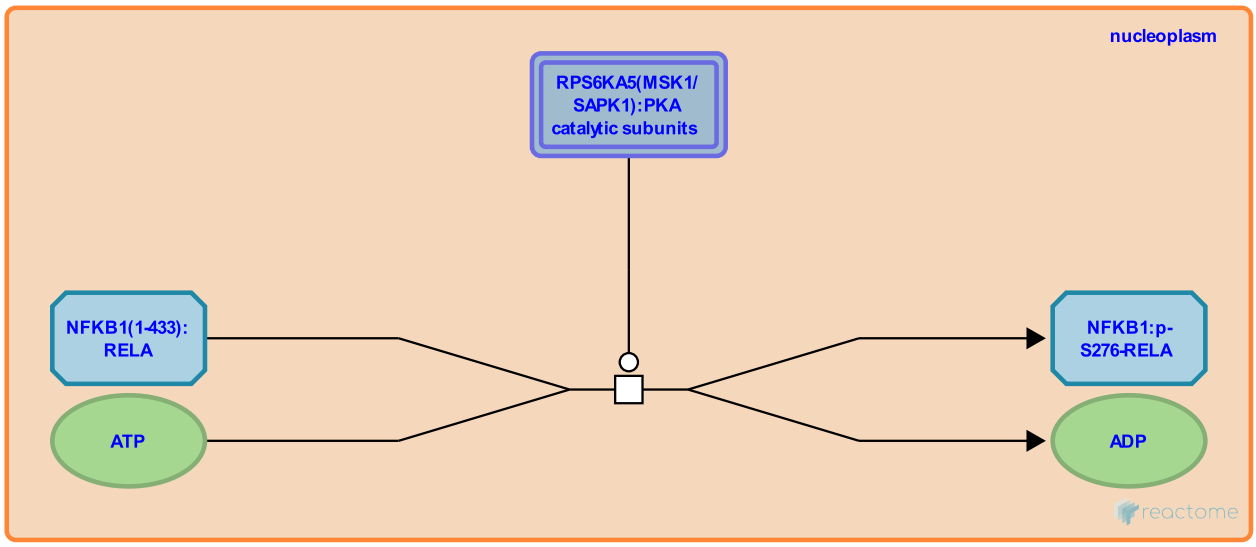
Protein kinase A (PKA) and RPS6KA5 (MSK1) phosphorylates p65 (RELA) subunit ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5624473

Type: transition

Compartments: nucleoplasm



Protein kinase A (PKA/PRKACA) and Ribosomal protein S6 kinase alpha-5 (RPS6KA5/MSK1/SAPK1) phosphorylate serine 276 (S276) in the Rel homology domain (RHD) of nuclear p65 subunit RELA (Yoon et al. 2008, Reber et al. 2009). Few other phosphorylation sites (S311, S529 and S536) have also been proposed in RELA (Duran et al. 2003) note: in this reaction we are showing only S276 phosphorylation)). Phosphorylation of RELA subunit enhances the association of RELA with p300 and this is a prerequisite for later NF-kB modification by histone acetyltransferases (HATs) p300/CBP. Phosphorylation of RELA also cross-regulates CLEC7A (dectin-1) mediated non-canonical NF-kB pathway by forming inactive p65 and RELB dimers, that cannot bind DNA.

Preceded by: SFKs phosphorylates RAF1 on Y340,Y341

Followed by: p-S276-RELA binds RELB, CBP and p300 binds NF-kB complex

Literature references

Wevers, B., Litjens, M., Geijtenbeek, TB., Bruijns, SC., Gringhuis, SI., den Dunnen, J. et al. (2009). Dectin-1 directs T helper cell differentiation by controlling noncanonical NF-kappaB activation through Raf-1 and Syk. *Nat. Immunol., 10*, 203-13. ↗

Yoon, C., Carter, BD., Korade, Z. (2008). Protein kinase A-induced phosphorylation of the p65 subunit of nuclear factor-kappaB promotes Schwann cell differentiation into a myelinating phenotype. *J. Neurosci., 28*, 3738-46. ↗

Reber, L., Frossard, N., Vermeulen, L., Haegeman, G. (2009). Ser276 phosphorylation of NF-kB p65 by MSK1 controls SCF expression in inflammation. *PLoS ONE, 4*, e4393. ↗

De Wilde, G., Vanden Berghe, W., Vermeulen, L., Haegeman, G., Van Damme, P. (2003). Transcriptional activation of the NF-kappaB p65 subunit by mitogen- and stress-activated protein kinase-1 (MSK1). *EMBO J., 22*, 1313-24. ↗

Litjens, M., Geijtenbeek, TB., Gringhuis, SI., van Kooyk, Y., den Dunnen, J., van Het Hof, B. (2007). C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. *Immunity, 26*, 605-16. ↗

Editions

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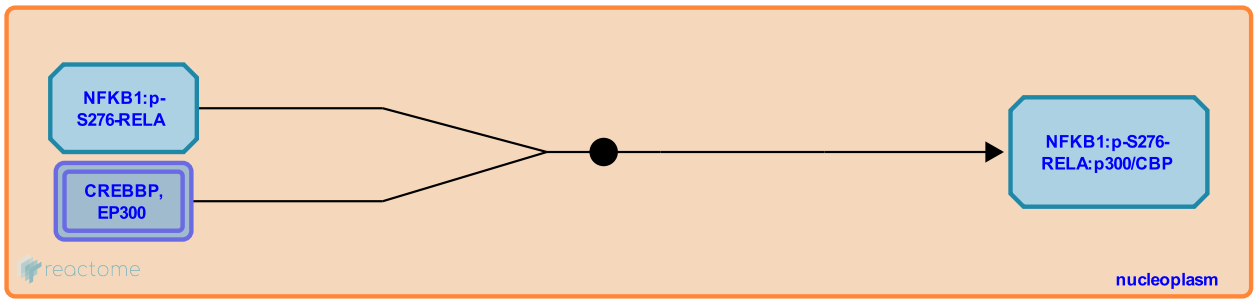
CBP and p300 binds NF-kB complex ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5660666

Type: binding

Compartments: nucleoplasm



The phosphorylation of p65 subunit has been shown to be important for RELA transcriptional activity. Once phosphorylated RELA/p65 has been shown to recruit transcriptional coactivators CREB binding protein (CBP) and p300 (Chen at al. 2002). The association between CBP/p300 and NF-kB p65 occurs through RHD (Rel homology domain) and C-terminal transactivation domain (Zong et al. 1998). Both p300 and CBP contain a histone acetyltransferase (HAT) enzymatic activity that regulates gene expression through acetylation of RELA, and promoter proximal nucleosomal histones, resulting in increased accessibility of the DNA for other essential regulators (Kalkhoven 2004).

Preceded by: Protein kinase A (PKA) and RPS6KA5 (MSK1) phosphorylates p65 (RELA) subunit

Followed by: p300 acetylates RELA subunit

Literature references

Voll, RE., Ghosh, S., Zhong, H. (1998). Phosphorylation of NF-kappa B p65 by PKA stimulates transcriptional activity by promoting a novel bivalent interaction with the coactivator CBP/p300. *Mol. Cell, 1*, 661-71. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
2015-01-05	Authored, Edited	Garapati, P V.

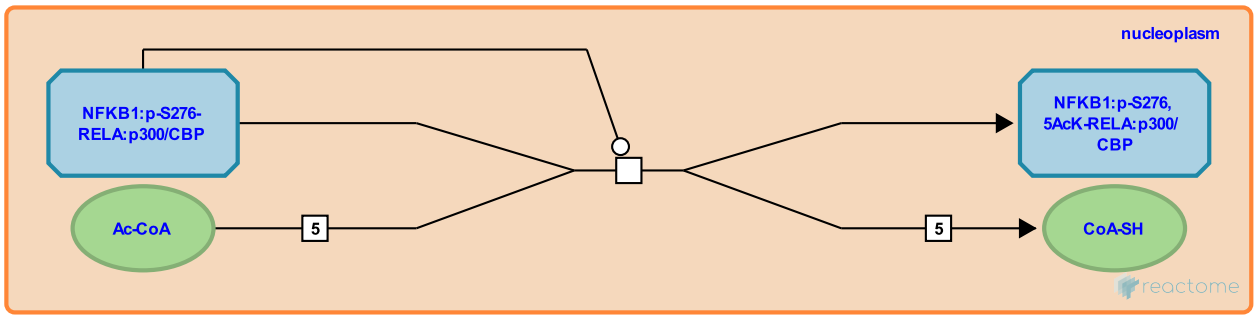
p300 acetylates RELA subunit ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5660660

Type: transition

Compartments: nucleoplasm



Acetylation of RELA/p65 subunit differentially regulates distinct biological activities of the NF-kB transcription factor complex. The acetylation enables increased DNA binding and transcriptional activity by NF-kB, leading to up-regulated IL6 (interleukin 6), IL10, IL12p35, IL12p40 and IL23p19 production (Geijtenbeek and Gringhuis 2009). Acetyltransferases p300 and CBP are involved in the acetylation of RELA on multiple sites including lysines 122, 123, 218, 221 and 310. Acetylation of lysine 221 by p300/CBP increases the DNA binding affinity of RELA for the IkB enhancer and, together with acetylation of lysine 218, impairs assembly of RELA with newly synthesized IkBalpha, which shuttles in and out of the nucleus. Acetylation of lysine 310 does not modulate DNA binding or IkBalpha assembly but markedly enhances the transcriptional activity of NF-kB (Chen et al. 2002, 2005).

Preceded by: CBP and p300 binds NF-kB complex

Literature references

Greene, WC., Mu, Y., Chen, LF. (2002). Acetylation of RelA at discrete sites regulates distinct nuclear functions of NF-kappaB. *EMBO J., 21*, 6539-48. ↗

Williams, SA., Chen, LF., Greene, WC., Mu, Y., Duerr, JM., Nakano, H. et al. (2005). NF-kappaB RelA phosphorylation regulates RelA acetylation. *Mol. Cell. Biol., 25*, 7966-75. ↗

Editions

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2015-01-05	Authored, Edited	Garapati, P V.

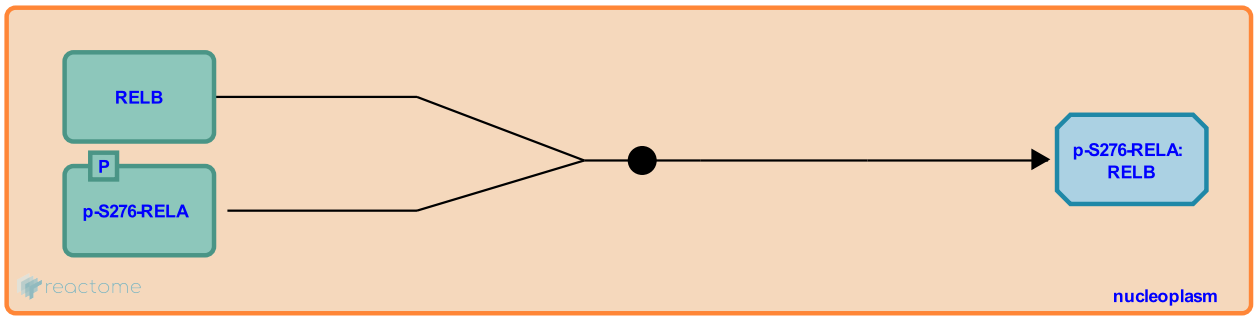
p-S276-RELA binds RELB ↗

Location: CD209 (DC-SIGN) signaling

Stable identifier: R-HSA-5660980

Type: binding

Compartments: nucleoplasm



Phosphorylated RELA besides undergoing further acetylation by the histone acetyltransferases (HATs) CBP and p300 also forms a complex with RELB to form inactive RELA-RELB dimers that cannot bind DNA. Because RELB requires p50 or p52 as a dimerization partner to bind DNA, it is possible that sequestration of RELB from its complex partners p50 and p52 by RELA might account for the lack of RELB DNA binding. RELA-RELB dimers have important regulatory consequences on dectin-1 mediated non-canonical NF-kB pathway. Inactive p65-RELB dimers blocks binding of RELB-p52 to the promoters of the chemokine genes CCL17 (CC-chemokine ligand 17) and CCL22, thereby blocking chemokine expression (Gringhuis et al. 2009).

Preceded by: Protein kinase A (PKA) and RPS6KA5 (MSK1) phosphorylates p65 (RELA) subunit

Literature references

Wevers, B., Litjens, M., Geijtenbeek, TB., Bruijns, SC., Gringhuis, SI., den Dunnen, J. et al. (2009). Dectin-1 directs T helper cell differentiation by controlling noncanonical NF-kappaB activation through Raf-1 and Syk. *Nat. Immunol., 10*, 203-13. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
2015-01-05	Authored, Edited	Garapati, P V.

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