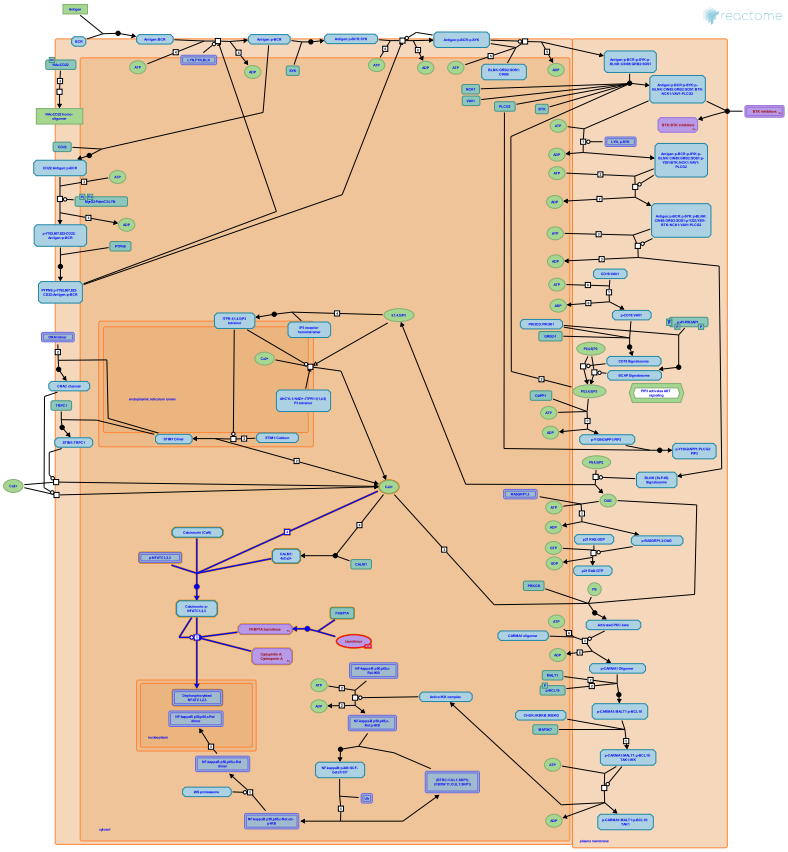
Calcineurin activates NFAT



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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.

04/05/2024

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. ↗

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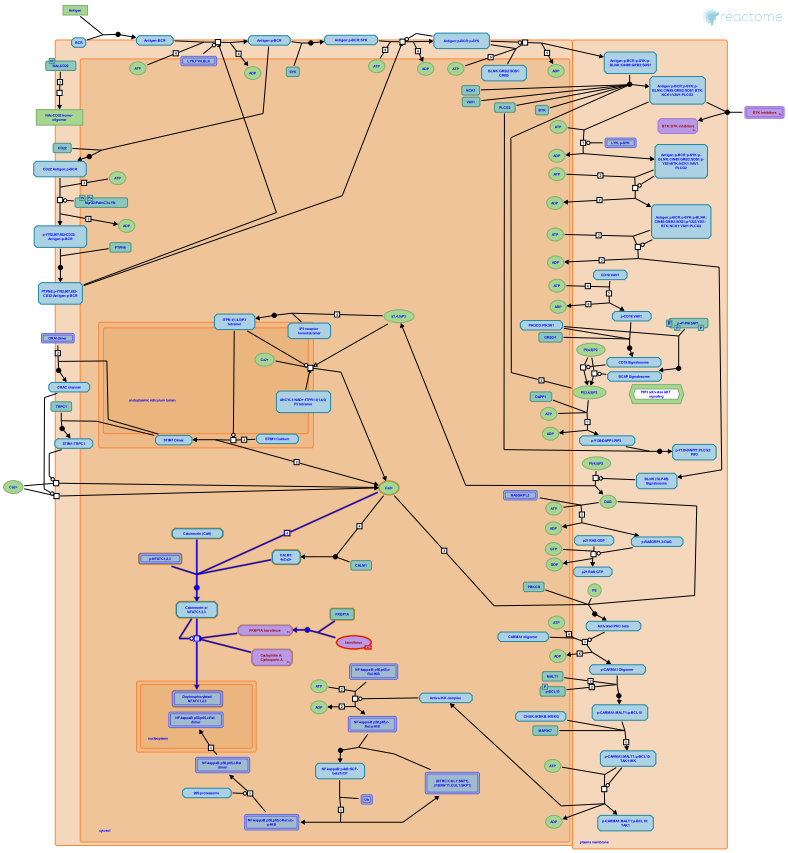
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Calcineurin activates NFAT ↗

Stable identifier: R-HSA-2025928

Compartments: cytosol, nucleoplasm



Signaling by the B cell receptor and the T cell receptor stimulate transcription by NFAT factors via calcium (reviewed in Gwack et al. 2007). Cytosolic calcium from intracellular stores and extracellular sources binds calmodulin and activates the protein phosphatase calcineurin. Activated calcineurin dephosphorylates NFATs in the cytosol, exposing nuclear localization sequences on the NFATs and causing the NFATs to be imported into the nucleus where they regulate transcription of target genes in complexes with other transcription factors such as AP-1 and JUN. Calcineurin in the target of the immunosuppressive drugs cyclosporin A and FK-506 (reviewed in Lee and Park 2006).

Literature references

Gwack, Y., Rao, A., Hogan, PG., Srikanth, S., Feske, S. (2007). Signalling to transcription: store-operated Ca2+ entry and NFAT activation in lymphocytes. *Cell Calcium, 42*, 145-56. ↗

Lee, M., Park, J. (2006). Regulation of NFAT activation: a potential therapeutic target for immunosuppression. *Mol Cells, 22*, 1-7. ↗

Editions

2011-12-11	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

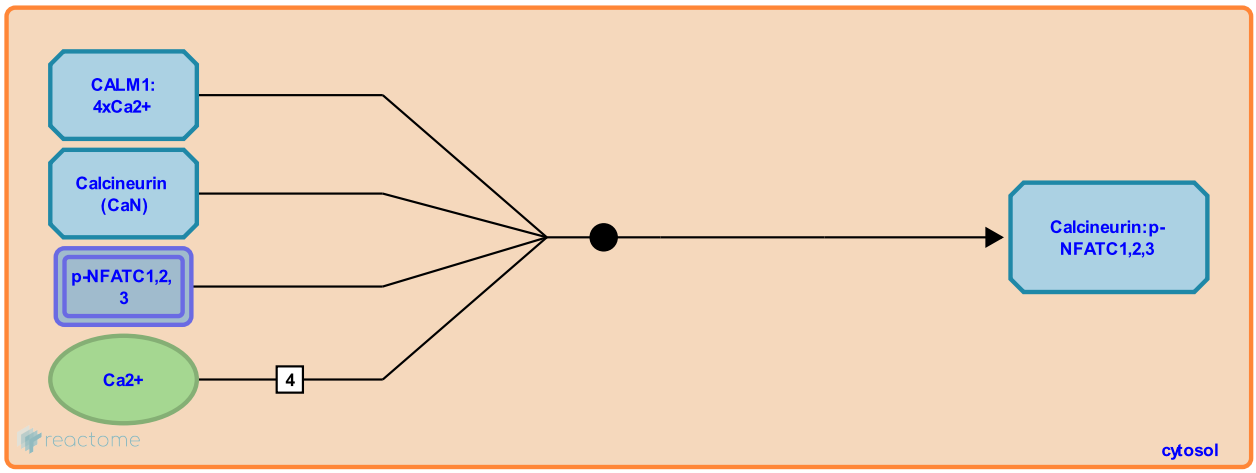
Calcineurin binds NFATC1,2,3 ↗

Location: Calcineurin activates NFAT

Stable identifier: R-HSA-2025890

Type: binding

Compartments: cytosol



Calcium activates calcineurin in two ways: binding the regulatory subunit of calcineurin directly and binding calmodulin which then interacts with the catalytic subunit of calcineurin. As inferred from mouse, B lymphocytes contain the R1 regulatory subunit (PPP3R1) and the beta catalytic subunit (PPP3CB).
In the presence of calcium and calcium:calmodulin calcineurin binds phosphorylated and unphosphorylated NFATs at 2 regions in the N-terminus (Luo et al. 1996, Garcia-Cozar et al. 1998, Park et al. 2000, evidence from mouse in Loh et al. 1996 and Wesselborg et al. 1996). Calcineurin also weakly interacts with NFATs in the absence of calcium (Garcia-Cozar et al. 1998).

Followed by: Calcineurin dephosphorylates NFATC1,2,3

Literature references

Loh, C., Carew, J., Rao, A., Viola, JP., Perrino, BA., Shaw, KT. et al. (1996). Calcineurin binds the transcription factor NFAT1 and reversibly regulates its activity. *J Biol Chem, 271*, 10884-91. ↗

Wesselborg, S., Sagoo, JK., Fruman, DA., Bierer, BE., Burakoff, SJ. (1996). Identification of a physical interaction between calcineurin and nuclear factor of activated T cells (NFATp). *J Biol Chem, 271*, 1274-7. ↗

Uesugi, M., Park, S., Verdine, GL. (2000). A second calcineurin binding site on the NFAT regulatory domain. *Proc Natl Acad Sci U S A, 97*, 7130-5. ↗

Rao, A., Perrino, BA., Hogan, PG., Garcia-Cozar, F., Shaw, KT., Aramburu, J. et al. (1996). Interaction of calcineurin with a domain of the transcription factor NFAT1 that controls nuclear import. *Proc Natl Acad Sci U S A, 93*, 8907-12. ↗

Villafranca, E., Rao, A., Pelletier, L., Aramburu, JF., Okamura, H., Shaw, KT. et al. (1998). Two-site interaction of nuclear factor of activated T cells with activated calcineurin. *J Biol Chem, 273*, 23877-83. ↗

Editions

2011-12-11	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

Calcineurin dephosphorylates NFATC1,2,3

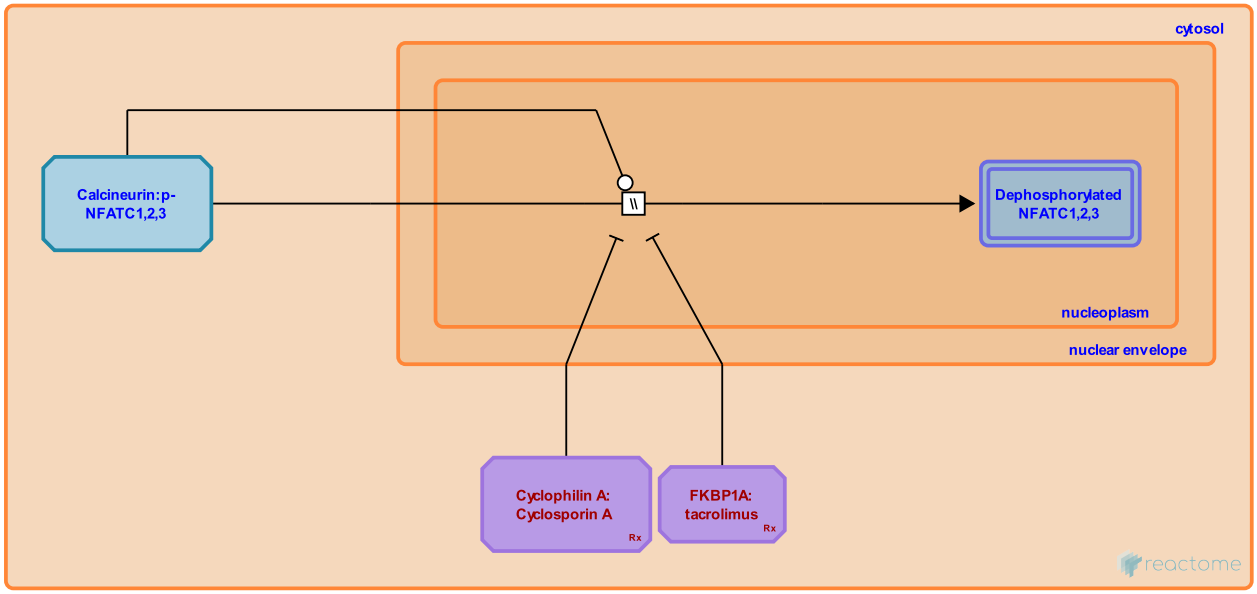
Location: Calcineurin activates NFAT

Stable identifier: R-HSA-2025882

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Calcineurin Dephosphorylates Nfatc2 (Mus musculus)



As inferred from mouse (Okamura et al. 2000), calcineurin dephosphorylates NFATC2 at 13 serine residues (Batiuk et al. 1997, Kim et al. 2000). B lymphocytes also contain NFATC2 and NFATC3 which are inferred to undergo dephosphorylation at homologous serines. Dephosphorylation of NFATs exposes a nuclear localization signal which cause NFATs to be imported into the nucleus (Kim et al. 2000). In mouse, Calcineurin is observed to also transit into the nucleus in a complex with NFATs and may remain associated (Shibasaki et al. 1996).

Preceded by: Calcineurin binds NFATC1,2,3

Literature references

Clipstone, NA., Ho, SN., Crabtree, GR., Beals, CR. (1997). Nuclear localization of NF-ATc by a calcineurin-dependent, cyclosporin-sensitive intramolecular interaction. *Genes Dev, 11*, 824-34.

Zhang, X., Rao, A., Viola, JP., Okamura, H., Hogan, PG., Tahiliani, M. et al. (2000). Concerted dephosphorylation of the transcription factor NFAT1 induces a conformational switch that regulates transcriptional activity. *Mol Cell, 6* , 539-50.

Price, ER., Shibasaki, F., Milan, D., McKeon, F. (1996). Role of kinases and the phosphatase calcineurin in the nuclear shuttling of transcription factor NF-AT4. *Nature, 382*, 370-3.

Rao, A., Sharma, S., Hogan, PG., Yaseen, NR., Park, J. (1995). Phosphorylation of the transcription factor NFATp inhibits its DNA binding activity in cyclosporin A-treated human B and T cells. *J Biol Chem, 270*, 20653-9.

Batiuk, TD., Kung, L., Halloran, PF. (1997). Evidence that calcineurin is rate-limiting for primary human lymphocyte activation. *J Clin Invest, 100*, 1894-901.

Editions

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2012-02-12	Reviewed	Wienands, J.

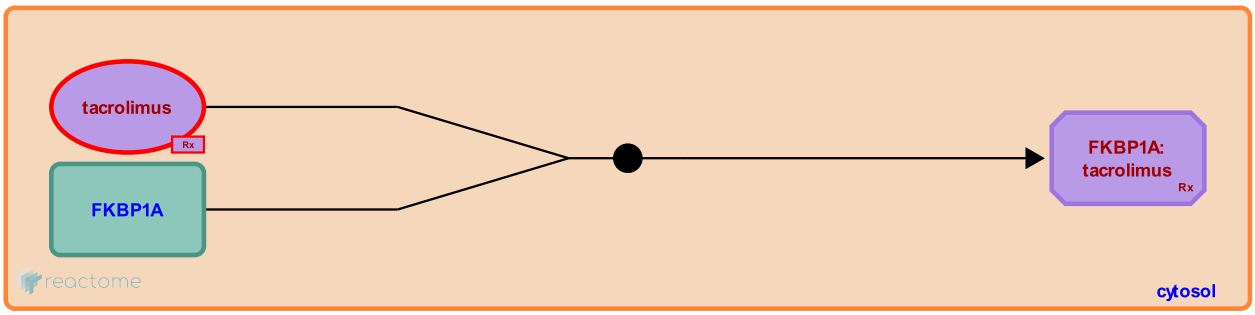
FKBP1A binds tacrolimus ↗

Location: Calcineurin activates NFAT

Stable identifier: R-HSA-9690461

Type: binding

Compartments: cytosol



Tacrolimus (also FK-506 or Fujimycin) is a macrolide compound obtained from Streptomyces hygroscopicus that acts by selectively blocking the transcriptional activation of cytokines thereby inhibiting cytokine production. It is bioactive only when bound to immunophilins. Tacrolimus is an immunosuppressive drug whose main use is after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It reduces peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP1A, creating a new complex. This complex inhibits calcineurin (Bierer et al. 1991) which inhibits T-lymphocyte signal transduction and IL-2 transcription (Kino et al. 1987, Ding et al. 2019).

Literature references

Hashimoto, M., Hatanaka, H., Imanaka, H., Okuhara, M., Nishiyama, M., Aoki, H. et al. (1987). FK-506, a novel immunosuppressant isolated from a Streptomyces. I. Fermentation, isolation, and physico-chemical and biological characteristics. *J. Antibiot., 40*, 1249-55. ↗

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Editions

2020-03-23	Authored	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

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