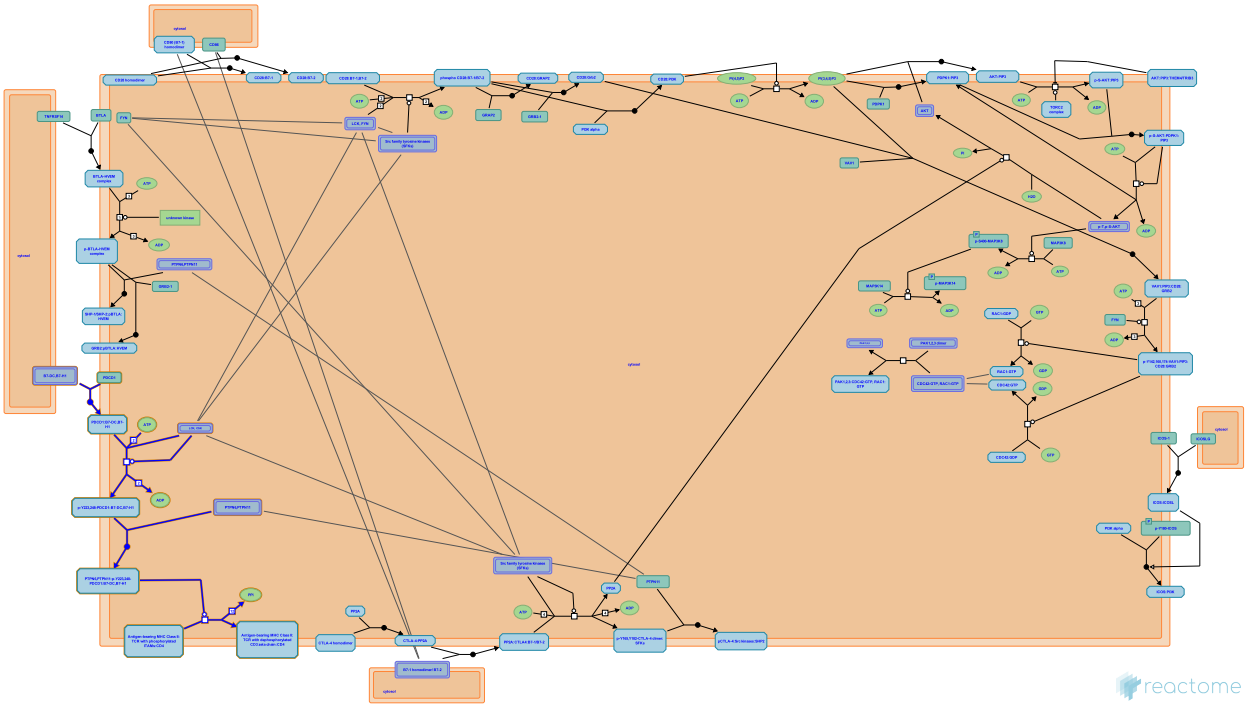
PD-1 signaling



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16/11/2019

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. ↗

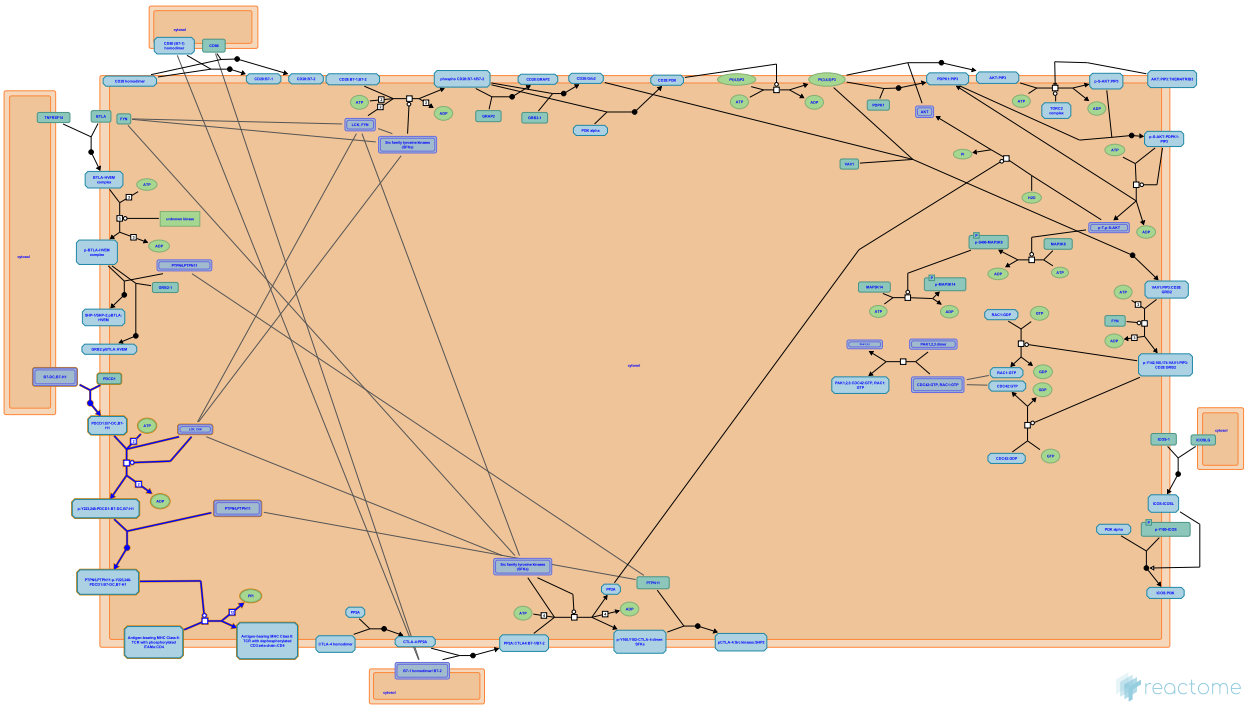
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

PD-1 signaling ↗

Stable identifier: R-HSA-389948

Compartments: plasma membrane



The Programmed cell death protein 1 (PD-1) is one of the negative regulators of TCR signaling. PD-1 may exert its effects on cell differentiation and survival directly by inhibiting early activation events that are positively regulated by CD28 or indirectly through IL-2. PD-1 ligation inhibits the induction of the cell survival factor Bcl-xL and the expression of transcription factors associated with effector cell function, including GATA-3, Tbet, and Eomes. PD-1 exerts its inhibitory effects by bringing phosphatases SHP-1 and SHP-2 into the immune synapse, leading to dephosphorylation of CD3-zeta chain, PI3K and AKT.

Literature references

Fife, BT., Bluestone, JA. (2008). Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev, 224*, 166-82. ↗

Keir, ME., Butte, MJ., Freeman, GJ., Sharpe, AH. (2008). PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol, 26*, 677-704. ↗

Editions

2008-12-16	Authored, Edited	Garapati, P V.
2009-06-01	Reviewed	Bluestone, JA., Esensten, J.

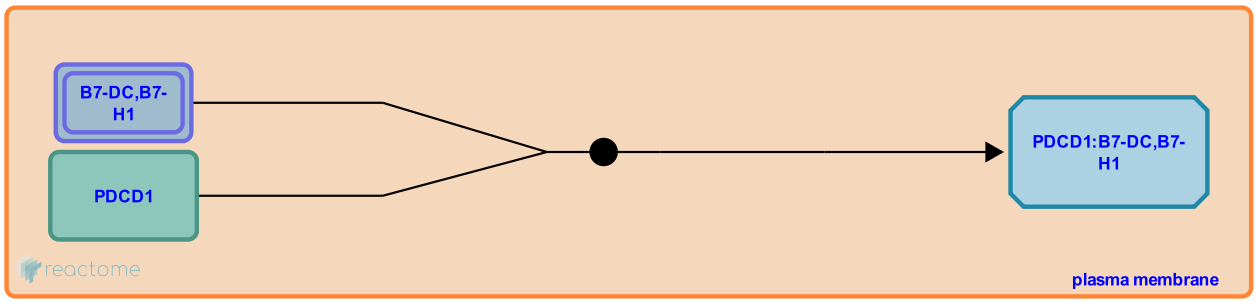
PD-1 binds B7DC and B7H1 ↗

Location: PD-1 signaling

Stable identifier: R-HSA-388828

Type: binding

Compartments: plasma membrane



The Programmed cell death protein 1 (PD-1) is functionally similar to CTLA4 and exerts an inhibitory signal on T cell activation. PD-1 binds the ligands B7H1 and B7DC but with different affinities. Interaction of PD-1/B7DC exhibited a 2-6-fold higher affinity and had different association/dissociation kinetics compared with the interaction of PD-1/B7H1.

Followed by: Phosphorylation of PD-1

Literature references

Youngnak, P., Kozono, Y., Kozono, H., Iwai, H., Otsuki, N., Jin, H. et al. (2003). Differential binding properties of B7-H1 and B7-DC to programmed death-1. *Biochem Biophys Res Commun, 307*, 672-7. ↗

Editions

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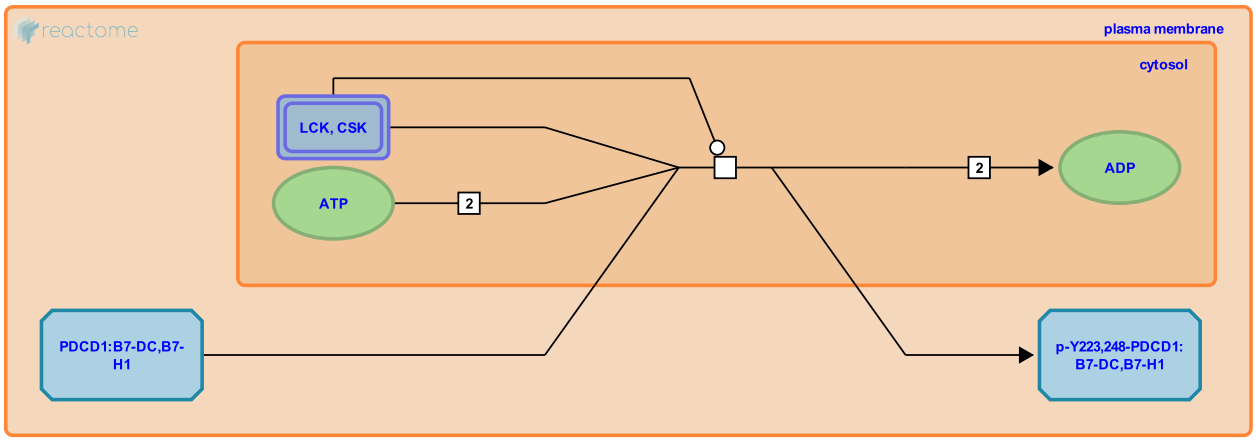
Phosphorylation of PD-1 ↗

Location: PD-1 signaling

Stable identifier: R-HSA-389762

Type: transition

Compartments: cytosol, plasma membrane



The cytoplasmic domain of PD-1 has two tyrosine motifs, ITIM and ITSM. On engagement with B7 ligands B7DC and B7H1, PD-1 is phosphorylated on tyrosine residues 223 and 248 within these motifs. Kinases Lck and Csk also bind to these motifs and these kinases may be involved in the phosphorylation of PD-1.

Preceded by: PD-1 binds B7DC and B7H1

Followed by: Interaction of SHP-1 or SHP-2 with phospho PD-1

Literature references

Fife, BT., Bluestone, JA. (2008). Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev, 224*, 166-82. ↗

Carter, LL., Carreno, BM. (2003). Cytotoxic T-lymphocyte antigen-4 and programmed death-1 function as negative regulators of lymphocyte activation. *Immunol Res, 28*, 49-59. ↗

Keir, ME., Butte, MJ., Freeman, GJ., Sharpe, AH. (2008). PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol, 26*, 677-704. ↗

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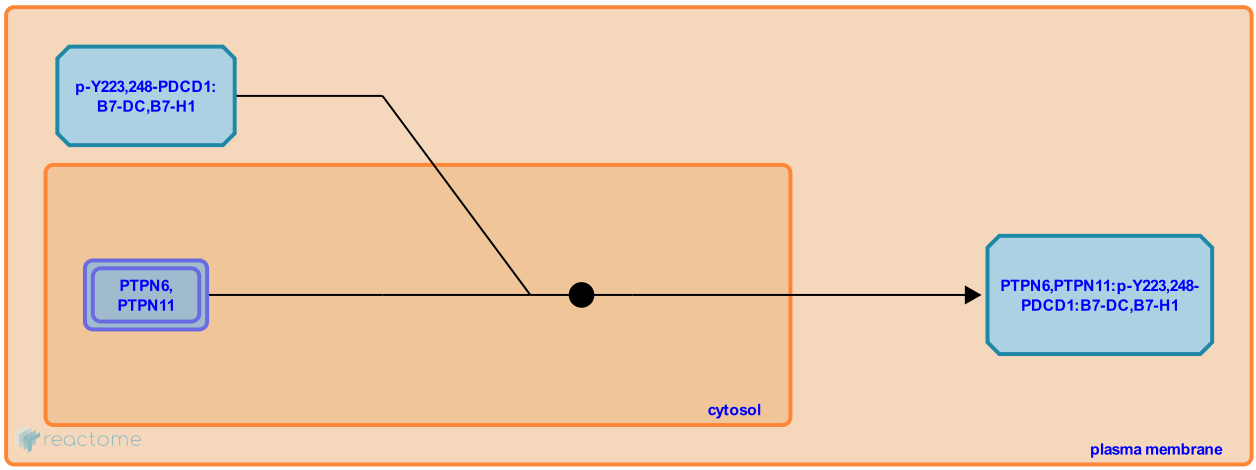
Interaction of SHP-1 or SHP-2 with phospho PD-1 ↗

Location: PD-1 signaling

Stable identifier: R-HSA-389759

Type: binding

Compartments: cytosol, plasma membrane



Once phosphorylated, SH2-domain containing tyrosine phosphatases SHP-1 and SHP-2 bind to the ITIM and ITSM motifs of PD-1. The association between SHP-1 and PD-1 appears to be weaker than the interaction of PD-1 with SHP-2.

Preceded by: Phosphorylation of PD-1

Followed by: Dephosphorylation of CD3-zeta by PD-1 bound phosphatases

Literature references

Fife, BT., Bluestone, JA. (2008). Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev, 224*, 166-82. ↗

Keir, ME., Butte, MJ., Freeman, GJ., Sharpe, AH. (2008). PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol, 26*, 677-704. ↗

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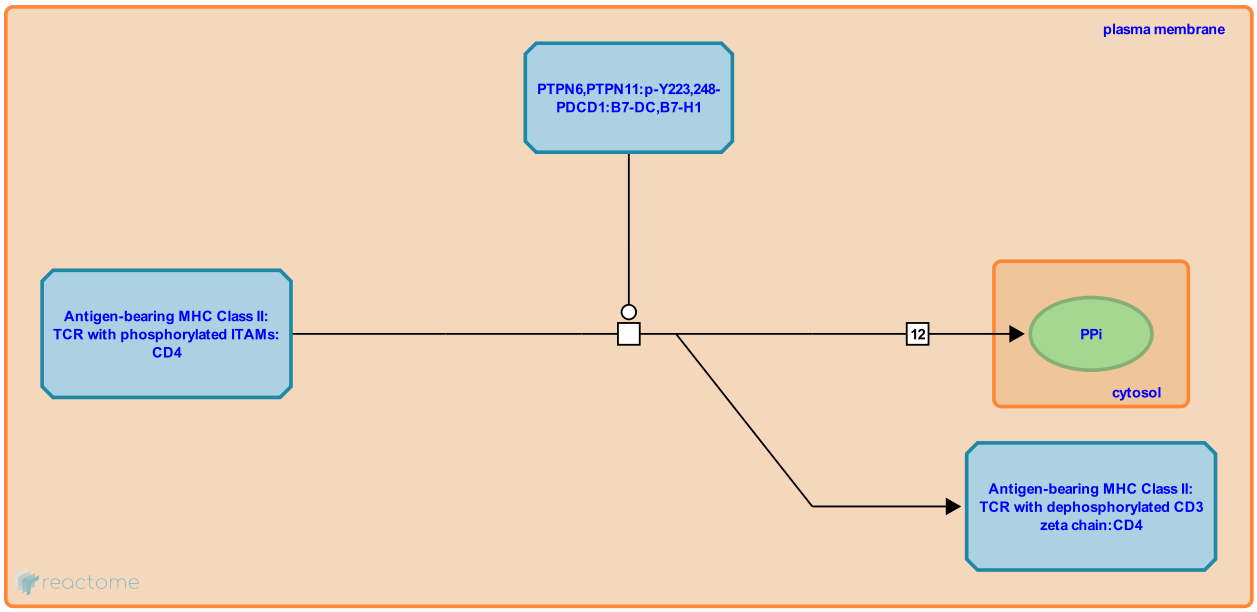
Dephosphorylation of CD3-zeta by PD-1 bound phosphatases ↗

Location: PD-1 signaling

Stable identifier: R-HSA-389758

Type: transition

Compartments: plasma membrane, cytosol



PD-1 delivers inhibitory signals and downregulates antigen receptor signaling through direct dephosphorylation of signaling intermediates. The phosphatases SHP-1 and SHP-2 dephosphorylate CD3 zeta and inhibit the phosphorylation of ZAP-70 and PKC theta.

Preceded by: Interaction of SHP-1 or SHP-2 with phospho PD-1

Literature references

Fife, BT., Bluestone, JA. (2008). Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev, 224*, 166-82. ↗

Carter, LL., Carreno, BM. (2003). Cytotoxic T-lymphocyte antigen-4 and programmed death-1 function as negative regulators of lymphocyte activation. *Immunol Res, 28*, 49-59. ↗

Keir, ME., Butte, MJ., Freeman, GJ., Sharpe, AH. (2008). PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol, 26*, 677-704. ↗

Sheppard, KA., Fitz, LJ., Lee, JM., Benander, C., George, JA., Wooters, J. et al. (2004). PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett, 574* , 37-41. ↗

Editions

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