Costimulation by the CD28 family

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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.

15/12/2022
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


Reactome database release: 83

This document contains 4 pathways and 6 reactions (see Table of Contents)
Optimal activation of T-lymphocytes requires at least two signals. A primary one is delivered by the T-cell receptor (TCR) complex after antigen recognition and additional costimulatory signals are delivered by the engagement of costimulatory receptors such as CD28. The best-characterized costimulatory pathways are mediated by a set of cosignaling molecules belonging to the CD28 superfamily, including CD28, CTLA4, ICOS, PD1 and BTLA receptors. These proteins deliver both positive and negative second signals to T-cells by interacting with B7 family ligands expressed on antigen presenting cells. Different subsets of T-cells have very different requirements for costimulation. CD28 family mediated costimulation is not required for all T-cell responses in vivo, and alternative costimulatory pathways also exist. Different receptors of the CD28 family and their ligands have different regulation of expression. CD28 is constitutively expressed on naive T cells whereas CTLA4 expression is dependent on CD28/B7 engagement and the other receptor members ICOS, PD1 and BTLA are induced after initial T-cell stimulation.

The positive signals induced by CD28 and ICOS molecules are counterbalanced by other members of the CD28 family, including cytotoxic T-lymphocyte associated antigen (CTLA)4, programmed cell death (PD)1, and B and T lymphocyte attenuator (BTLA), which dampen immune responses. The balance of stimulatory and inhibitory signals is crucial to maximize protective immune responses while maintaining immunological tolerance and preventing autoimmunity.

The costimulatory receptors CD28, CTLA4, ICOS and PD1 are composed of single extracellular IgV-like domains, whereas BTLA has one IgC-like domain. Receptors CTLA4, CD28 and ICOS are covalent homodimers, due to an interchain disulphide linkage. The costimulatory ligands B71, B72, B7H2, B7H1 and B7DC, have a membrane proximal IgC-like domain and a membrane distal IgV-like domain that is responsible for receptor binding and dimerization. CD28 and CTLA4 have no known intrinsic enzymatic activity. Instead, engagement by their physiologic ligands B71 and B72 leads to the physical recruitment and activation of downstream T-cell effector molecules.
Literature references


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In naive T cells, CD28 costimulation enhances cell cycle entry, potently stimulates expression of both the mitogenic lymphokine interleukin-2 (IL-2) and its receptor, and stimulates the activation of an antiapoptotic program. CD28 engages with one or both members of the B7 receptor family, B7.1 and B7.2. Upon ligand binding the tyrosines and proline-rich motifs present in the cytoplasmic tail of CD28 are phosphorylated by Lck or Fyn. Upon phosphorylation CD28 recruits and induces phosphorylation and activation of a more restricted set of intracellular signaling components that, together with those mobilized by the TCR, contribute to convert membrane-based biochemical and biophysical changes into gene activation events. Proteins like PI3K, Vav-1, Tec and Itk kinases, AKT, and the Dok-1 adaptor have been identified as elements of the CD28 signaling pathway by biochemical or genetic approaches or both.

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**CTLA4 inhibitory signaling**

**Location:** Costimulation by the CD28 family

**Stable identifier:** R-HSA-389513

CTLA4 is one of the best studied inhibitory receptors of the CD28 superfamily. CTLA4 inhibits T cell activation by reducing IL2 production and IL2 expression, and by arresting T cells at the G1 phase of the cell cycle. CTLA-4 expressed by a T cell subpopulation exerts a dominant control on the proliferation of other T cells, which limits autoreactivity. CTLA4 also blocks CD28 signals by competing for the ligands B71 and B72 in the limited space between T cells and antigen-presenting cells. Though the mechanism is obscure, CTLA4 may also propagate inhibitory signals that actively counter those produced by CD28. CTLA4 can also function in a ligand-independent manner.

CTLA-4 regulates the activation of pathogenic T cells by directly modulating T cell receptor signaling (i.e. TCR-zeta chain phosphorylation) as well as downstream biochemical signals (i.e. ERK activation). The cytoplasmic region of CTLA4 contains a tyrosine motif YVKM and a proline rich region. After TCR stimulation, it undergoes tyrosine phosphorylation by src kinases, inducing surface retention.

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Inducible T cell co-stimulatory (ICOS) protein is the third member of the CD28 family that regulates T-cell activation and function. ICOS interacts with B7H2 (ICOSL, B7RP-1), a member of the B7 family expressed on the antigen-presenting cell.

**Literature references**


The p85 unit of PI3K is the only signaling molecule identified so far that interacts with ICOS. ICOS contains several conserved motifs also found in CD28, including the YxxM motif in the cytoplasmic tail, which binds the lipid kinase phosphatidylinositol 3-kinase (PI3K) upon tyrosine phosphorylation after complex formation with ICOS. However, ICOS costimulation shows greater PI3K activity than CD28 in T cells.

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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**


BTLA interacts with HVEM

**Location:** Costimulation by the CD28 family

**Stable identifier:** R-HSA-389523

**Type:** binding

**Compartments:** plasma membrane

The B and T lymphocyte attenuator, BTLA, is one of the co-inhibitory receptors of CD28 superfamily along with CTLA-4 and PD-1. BTLA differs from other CD28 members by having an extracellular Ig C-like domain, instead of a V-like one. Herpesvirus entry mediator (HVEM) is the external ligand for BTLA, providing the first example of a functional interaction between a TNFR and an Ig superfamily member. Binding of HVEM to BTLA delivers an inhibitory signal to T cells.

**Followed by:** HVEM indues BTLA phosphorylation

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Binding of HVEM to BTLA induces tyrosine phosphorylation of BTLA on three cytoplasmic tyrosines. The phosphorylated tyrosine Y274 and 299 (Y257 and 282 in human BTLA) associate with tyrosine phosphatase SHP2 and down regulate proximal TCR signalling. Phosphorylated Y245 (Y226 in human BTLA) in BTLA associates with growth receptor bound 2 (GRB2) (Murphy et al. 2006).

Preceded by: BTLA interacts with HVEM
Followed by: Grb2 binds pBTLA, SHP-1 and SHP-2 bind pBTLA

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**SHP-1 and SHP-2 bind pBTLA**

**Location:** Costimulation by the CD28 family

**Stable identifier:** R-HSA-389941

**Type:** binding

**Compartments:** plasma membrane, cytosol

The cytoplasmic tail of BTLA contains three tyrosine residues that are conserved in most organisms. The tyrosine residues Y257 and Y282 are both present in ITIM motif sequences. These tyrosine residues are phosphorylated after BTLA cross-linking, and both ITIM motifs recruit the tyrosine phosphatases SHP1 and SHP2. The targets of SHP1 and SHP2 recruited to BTLA are not known, although it is possible that they also have a role in dephosphorylating signaling intermediates downstream of antigen receptors in lymphocytes or in specifically targeting the PI3K-AKT pathway.

**Preceded by:** HVEM induces BTLA phosphorylation

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Grb2 binds pBTLA

Location: Costimulation by the CD28 family

Stable identifier: R-HSA-389919

Type: binding

Compartments: plasma membrane, cytosol

The sequence around Y226 in the BTLA cytoplasmic domain is a predicted recruitment site for Grb2. Despite the prediction there is no direct evidence of protein recruitment to this tyrosine motif.

Preceded by: HVEM induces BTLA phosphorylation

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