Adaptive Immune System

Akkerman, JW., Barrow, AD., Bluestone, JA., Elliott, T., Esensten, J., Garapati, P V., Heemskerk, JW., Jupe, S., May, B., Neefjes, J., Reith, W., Rhodes, DA., Rudd, C.E., Trowsdale, J., Wienands, J., de Bono, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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.

19/12/2022

https://reactome.org
**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 9 pathways (see Table of Contents)
Adaptive immunity refers to antigen-specific immune response efficiently involved in clearing the pathogens. The adaptive immune system is comprised of B and T lymphocytes that express receptors with remarkable diversity tailored to recognize aspects of particular pathogens or antigens. During infection, dendritic cells (DC) which act as sentinels in the peripheral tissues recognize and pick up the pathogen in the form of antigenic determinants and then process these antigens and present them to T cells. These T cells of appropriate specificity respond to the antigen, and either kill the pathogen directly or secrete cytokines that will stimulate B lymphocyte response. B cells provide humoral immunity by secreting antibodies specific for the pathogen or antigen.

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TCR signaling

Location: Adaptive Immune System

Stable identifier: R-HSA-202403

The TCR is a multisubunit complex that consists of clonotypic alpha/beta chains noncovalently associated with the invariant CD3 delta/epsilon/gamma and TCR zeta chains. T cell activation by antigen presenting cells (APCs) results in the activation of protein tyrosine kinases (PTKs) that associate with CD3 and TCR zeta subunits and the co-receptor CD4. Members of the Src kinases (Lck), Syk kinases (ZAP-70), Tec (Itk) and Csk families of nonreceptor PTKs play a crucial role in T cell activation. Activation of PTKs following TCR engagement results in the recruitment and tyrosine phosphorylation of enzymes such as phospholipase C gamma1 and Vav as well as critical adaptor proteins such as LAT, SLP-76 and Gads. These proximal activation leads to reorganization of the cytoskeleton as well as transcription activation of multiple genes leading to T lymphocyte proliferation, differentiation and/or effector function.

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https://reactome.org
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.
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Activated SYK and other kinases phosphorylate BLNK (SLP-65), BCAP, and CD19 which serve as scaffolds for the assembly of large complexes, the signalosomes, by recruiting phosphoinositol 3-kinase (PI3K), phospholipase C gamma (predominantly PLC-gamma2 in B cells, Coggeshall et al. 1992), NCK, BAM32, BTK, VAV1, and SHC. The effectors are phosphorylated by SYK and other kinases.

PLC-gamma associated with BLNK hydrolyzes phosphatidylinositol-4,5-bisphosphate to yield inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (Carter et al. 1991, Kim et al. 2004). IP3 binds receptors on the endoplasmic reticulum and causes release of calcium ions from the ER into the cytosol. The deple-

Second messengers (calcium, diacylglycerol, inositol 1,4,5-trisphosphate, and phosphatidylinositol 3,4,5-trisphosphate) trigger signaling pathways: NF-kappaB is activated via protein kinase C beta, RAS is activated via RasGRP proteins, NF-AT is activated via calcineurin, and AKT (PKB) is activated via PDK1 (reviewed in Shinohara and Kurosaki 2009, Stone 2006).

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Major histocompatibility complex (MHC) class I molecules play an important role in cell mediated immunity by reporting on intracellular events such as viral infection, the presence of intracellular bacteria or tumor-associated antigens. They bind peptide fragments of these proteins and presenting them to CD8+ T cells at the cell surface. This enables cytotoxic T cells to identify and eliminate cells that are synthesizing abnormal or foreign proteins. MHC class I is a trimeric complex composed of a polymorphic heavy chain (HC or alpha chain) and an invariable light chain, known as beta2-microglobulin (B2M) plus an 8-10 residue peptide ligand. Represented here are the events in the biosynthesis of MHC class I molecules, including generation of antigenic peptides by the ubiquitin/26S-proteasome system, delivery of these peptides to the endoplasmic reticulum (ER), loading of peptides to MHC class I molecules and display of MHC class I complexes on the cell surface.

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Antigen presenting cells (APCs) such as B cells, dendritic cells (DCs) and monocytes/macrophages express major histocompatibility complex class II molecules (MHC II) at their surface and present exogenous antigenic peptides to CD4+ T helper cells. CD4+ T cells play a central role in immune protection. On their activation they stimulate differentiation of B cells into antibody-producing B-cell blasts and initiate adaptive immune responses. MHC class II molecules are transmembrane glycoprotein heterodimers of alpha and beta subunits. Newly synthesized MHC II molecules present in the endoplasmic reticulum bind to a chaperone protein called invariant (Ii) chain. The binding of Ii prevents the premature binding of self antigens to the nascent MHC molecules in the ER and also guides MHC molecules to endocytic compartments. In the acidic endosomal environment, Ii is degraded in a stepwise manner, ultimately to free the class II peptide-binding groove for loading of antigenic peptides. Exogenous antigens are internalized by the APC by receptor mediated endocytosis, phagocytosis or pinocytosis into endocytic compartments of MHC class II positive cells, where engulfed antigens are degraded in a low pH environment by multiple acidic proteases, generating MHC class II epitopes. Antigenic peptides are then loaded into the class II ligand-binding groove. The resulting class II peptide complexes then move to the cell surface, where they are scanned by CD4+ T cells for specific recognition (Berger & Roche 2009, Zhou & Blum 2004, Watts 2004, Landsverk et al. 2009).

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A number of receptors and cell adhesion molecules play a key role in modifying the response of cells of lymphoid origin (such as B-, T- and NK cells) to self and tumor antigens, as well as to pathogenic organisms.

Molecules such as KIRs and LILRs form part of a crucial surveillance system that looks out for any derangement, usually caused by cancer or viral infection, in MHC Class I presentation. Somatic cells are also able to report internal functional impairment by displaying surface stress markers such as MICA. The presence of these molecules on somatic cells is picked up by C-lectin NK immune receptors.

Lymphoid cells are able to regulate their location and movement in accordance to their state of activation, and home in on tissues expressing the appropriate complementary ligands. For example, lymphoid cells may fine tune the presence and concentration of adhesion molecules belonging to the IgSF, Selectin and Integrin class that interact with a number of vascular markers of inflammation.

Furthermore, there are a number of avenues through which lymphoid cells may interact with antigen. This may be presented directly to a specific T-cell receptor in the context of an MHC molecule. Antigen-antibody complexes may anchor to the cell via a small number of lymphoid-specific Fc receptors that may, in turn, influence cell function further. Activated complement factor C3d binds to both antigen and to cell surface receptor CD21. In such cases, the far-reaching influence of CD19 on B-lymphocyte function is tempered by its interaction with CD21.

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Rap1 signalling

**Location:** Adaptive Immune System

**Stable identifier:** R-HSA-392517

**Compartments:** plasma membrane

Rap1 (Ras-proximate-1) is a small G protein in the Ras superfamily. Like all G proteins, Rap1 is activated when bound GDP is exchanged for GTP. Rap1 is targeted to lipid membranes by the covalent attachment of lipid moieties to its carboxyl terminus. Movement of Rap1 from endosomal membranes to the plasma membrane upon activation has been reported in several cell types including Jurkat T cells and megakaryocytes. On activation, Rap1 undergoes conformational changes that facilitate recruitment of a variety of effectors, triggering its participation in integrin signaling, ERK activation, and others.

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Butyrophilin (BTN) family interactions

Location: Adaptive Immune System

Stable identifier: R-HSA-8851680

Butyrophilins (BTNs) and butyrophilin like (BTNL) molecules are regulators of immune responses that belong to the immunoglobulin (Ig) superfamily of transmembrane proteins. They are structurally related to the B7 family of co-stimulatory molecules and have similar immunomodulatory functions (Afrache et al. 2012, Arnett & Viney 2014). BTNs are implicated in T cell development, activation and inhibition, as well as in the modulation of the interactions of T cells with antigen presenting cells and epithelial cells. Certain BTNs are genetically associated with autoimmune and inflammatory diseases (Abeler Domer et al. 2014).

The human butyrophilin family includes seven members that are subdivided into three subfamilies: BTN1, BTN2 and BTN3. The BTN1 subfamily contains only the prototypic single copy BTN1A1 gene, whereas the BTN2 and BTN3 subfamilies each contain three genes BTN2A1, BTN2A2 and BTN2A3, and BTN3A1, BTN3A2 and BTN3A3, respectively (note that BTN2A3 is a pseudogene). BTN1A1 has a crucial function in the secretion of lipids into milk (Ogg et al. 2004) and collectively, BTN2 and BTN3 proteins are cell surface transmembrane glycoproteins, that act as regulators of immune responses. BTNL proteins share considerable homology to the BTN family members. The human genome contains four BTNL genes: BTNL2, 3, 8 and 9 (Abeler Domer et al. 2014).

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