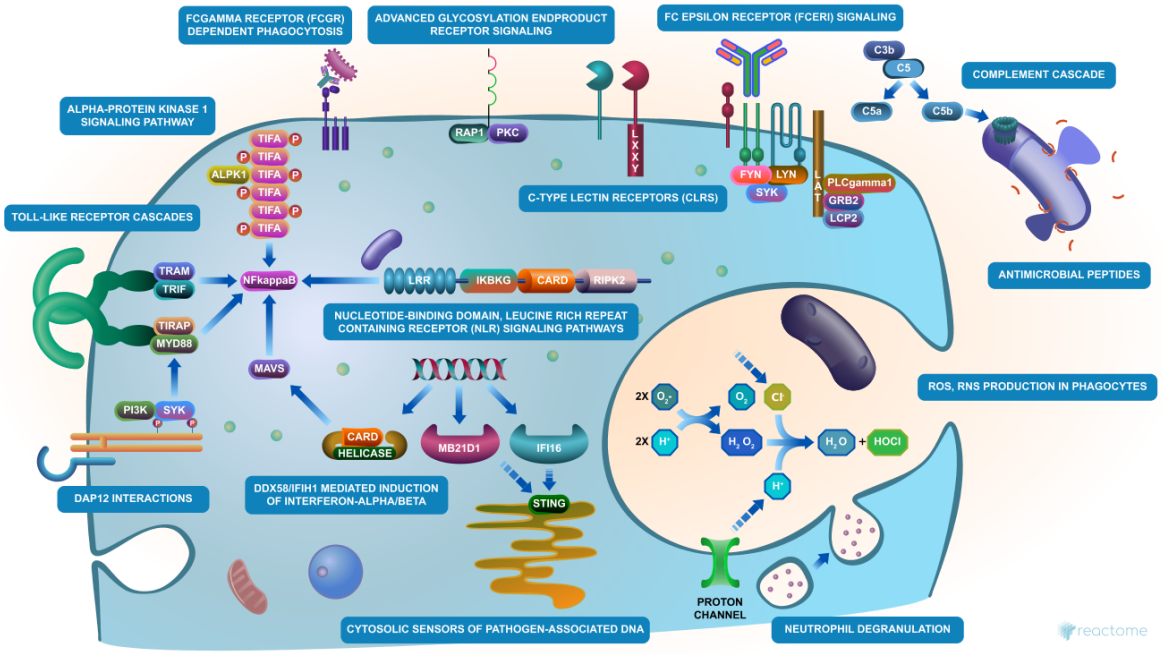
Innate Immune System



Akira, S., D'Eustachio, P., Gale M, Jr., Garapati, P V., Gay, NJ., Geijtenbeek, TB., Gillespie, ME., Hains, DS., Heegaard, N., Jassal, B., Jin, L., Jupe, S., Kawai, T., Kufer, TA., Lanier, LL., Luo, F., Mocarski, ES., Niarakis, A., Nüsse, O., Rittinger, K., Roncagalli, R., Rosales, C., Shamovsky, V., Shao, F., Stephan, R., Upton, JW., Warner, D., Wong, E., Wu, J., Yan, SD., de Bono, B.

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

14/09/2021

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

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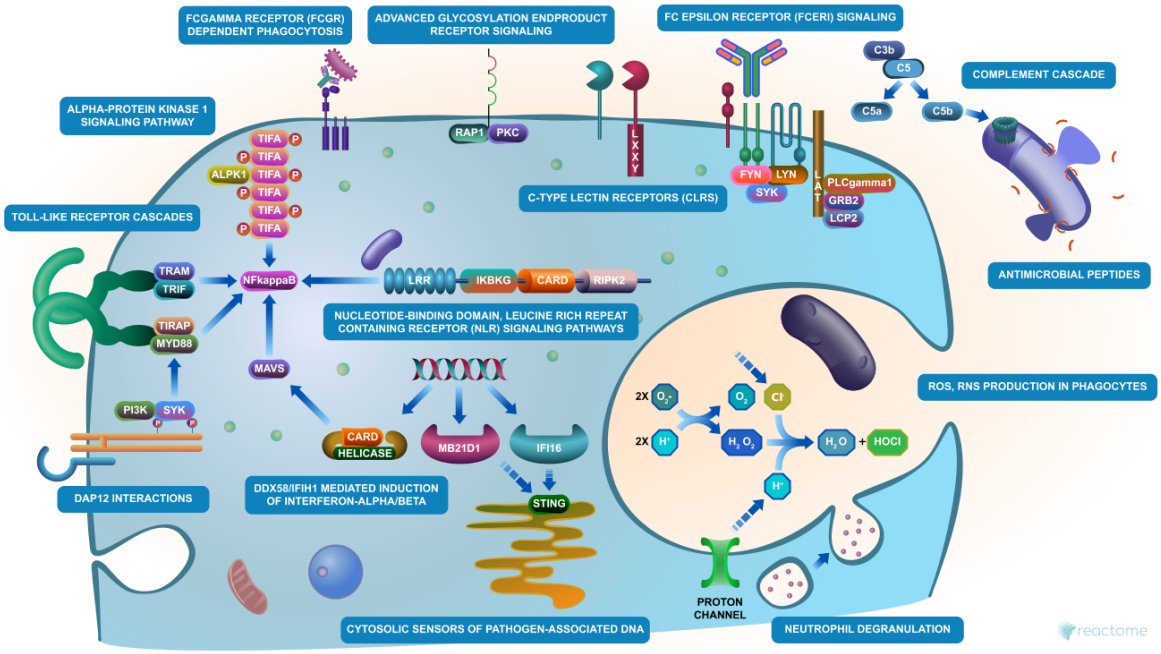
Reactome database release: 77

This document contains 15 pathways (see Table of Contents)

Innate Immune System ↗

Stable identifier: R-HSA-168249

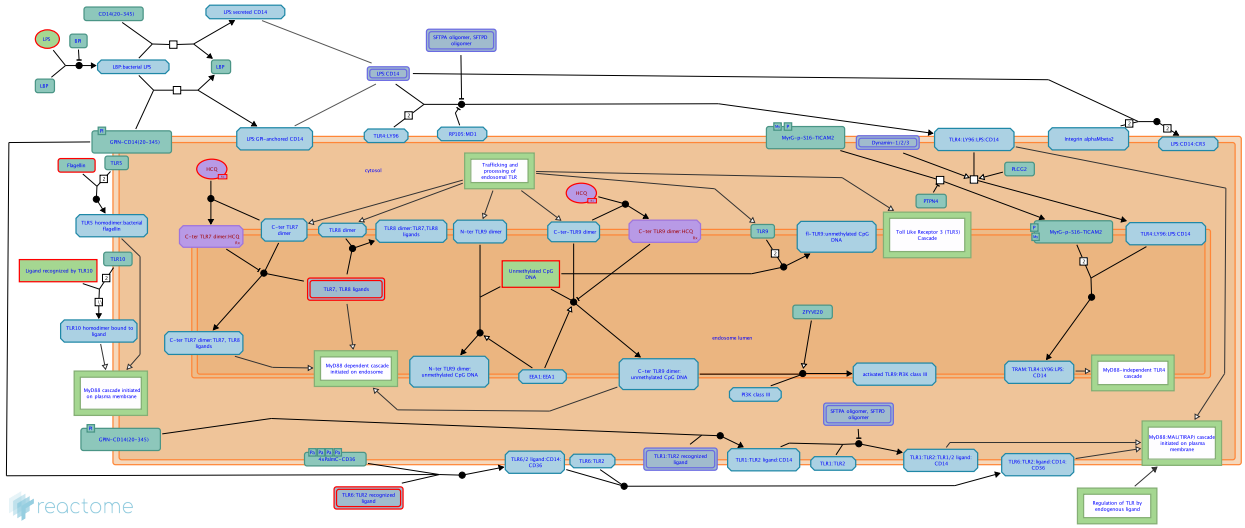


Innate immunity encompases the nonspecific part of immunity tha are part of an individual's natural biologic makeup

Toll-like Receptor Cascades ↗

Location: Innate Immune System

Stable identifier: R-HSA-168898



In human, ten members of the Toll-like receptor (TLR) family (TLR1-TLR10) have been identified (TLR11 has been found in mouse, but not in human). All TLRs have a similar Toll/IL-1 receptor (TIR) domain in their cytoplasmic region and an Ig-like domain in the extracellular region, where each is enriched with a varying number of leucine-rich repeats (LRRs). Each TLR can recognize specific microbial pathogen components. The binding pathogenic component to TLR initializes signaling pathways that lead to induction of Interferon alpha/beta and inflammatory cytokines. There are two main signaling pathways. The first is a MyD88-dependent pathway that is common to all TLRs, except TLR3; the second is a TRIF(TICAM1)-dependent pathway that is peculiar to TLR3 and TLR4. TLR4-mediated signaling pathway via TRIF requires adapter molecule TRAM (TRIF-related adapter molecule or TICAM2). TRAM is thought to bridge between the activated TLR4 complex and TRIF.(Takeda & Akira 2004; Akira 2003; Takeda & Akira 2005; Kawai 2005; Heine & Ulmer 2005). This pathway is organized as trafficking and processing of TLR, various TLR cascades (TLR10,TLR3,TLR5,TLR7/8,TLR9,TLR4,TLR2) and their regulation.

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Editions

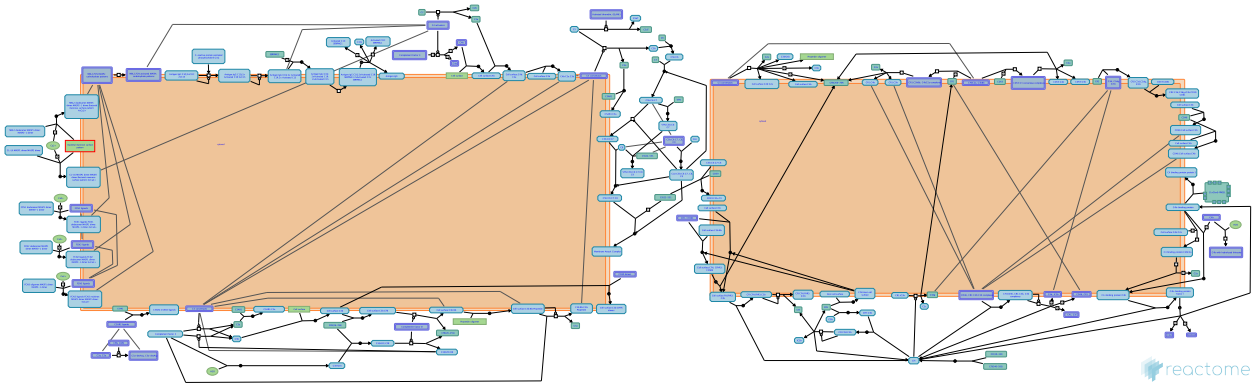
2006-10-31	Reviewed	D'Eustachio, P., Gay, NJ., Gale M, Jr.
2021-05-18	Authored	Gillespie, ME., de Bono, B., Gay, NJ., Luo, F.

Complement cascade ↗

Location: Innate Immune System

Stable identifier: R-HSA-166658

Compartments: extracellular region, plasma membrane



In the complement cascade, a panel of soluble molecules rapidly and effectively senses a danger or damage and triggers reactions to provide a response that discriminates among foreign intruders, cellular debris, healthy and altered host cells (Ricklin D et al. 2010). Complement proteins circulate in the blood stream in functionally inactive states. When triggered the complement cascade generates enzymatically active molecules (such as C3/C5 convertases) and biological effectors: opsonins (C3b, C3d and C4b), anaphylatoxins (C3a and C5a), and C5b, which initiates assembly of the lytic membrane attack complex (MAC). Three branches lead to complement activation: the classical, lectin and alternative pathways (Kang YH et al. 2009; Ricklin D et al. 2010). The classical pathway is initiated by C1 complex binding to immune complexes, pentraxins or other targets such as apoptotic cells leading to cleavage of C4 and C2 components and formation of the classical C3 convertase, C4bC2a. The lectin pathway is activated by binding of mannan-binding lectin (MBL) to repetitive carbohydrate residues, or by binding of ficolins to carbohydrate or acetylated groups on target surfaces. MBL and ficolins interact with MBL-associated serine proteases (MASP) leading to cleavage of C4 and C2 and formation of the classical C3 convertase, C4bC2a. The alternative pathway is spontaneously activated by the hydrolysis of the internal thioester group of C3 to give C3(H2O). Alternative pathway activation involves interaction of C3(H2O) and/or previously generated C3b with factor B, which is cleaved by factor D to generate the alternative C3 convertases C3(H2O)Bb and/or C3bBb. All three pathways merge at the proteolytic cleavage of component C3 by C3 convertases to form opsonin C3b and anaphylatoxin C3a. C3b covalently binds to glycoproteins scattered across the target cell surface. This is followed by an amplification reaction that generates additional C3 convertases and deposits more C3b at the local site. C3b can also bind to C3 convertases switching them to C5 convertases, which mediate C5 cleavage leading to MAC formation. Thus, the activation of the complement system leads to several important outcomes: opsonization of target cells to enhance phagocytosis, lysis of target cells via membrane attack complex (MAC) assembly on the cell surface, production of anaphylatoxins C3a/C5a involved in the host inflammatory response, C5a-mediated leukocyte chemotaxis, and clearance of antibody-antigen complexes. The complement system is able to distinguish between pathological and physiological challenges, i.e. the outcomes of complement activation are predetermined by the trigger and are tightly tuned by a combination of initiation events with several regulatory mechanisms. These regulatory mechanisms use soluble (e.g., C4BP, CFI and CFH) and membrane-bound regulators (e.g., CR1, CD46(MCP), CD55(DAF) and CD59) and are coordinated by complement receptors such as CR1, CR2, etc. In response to microbial infection complement activation results in flagging microorganisms with opsonins for facilitated phagocytosis, formation of MAC on cells such as Gram-negative bacteria leading to cell lysis, and release of C3a and C5a to stimulate downstream immune responses

and to attract leukocytes. Most pathogens can be eliminated by these complement-mediated host responses, though some pathogenic microorganisms have developed ways of avoiding complement recognition or blocking host complement attack resulting in greater virulence (Lambris JD et al. 2008; Serruto D et al. 2010). All three complement pathways (classical, lectin and alternative) have been implicated in clearance of dying cells (Mevorach D et al. 1998; Ogden CA et al. 2001; Gullstrand B et al.2009; Kemper C et al. 2008). Altered surfaces of apoptotic cells are recognized by complement proteins leading to opsonization and subsequent phagocytosis. In contrast to pathogens, apoptotic cells are believed to induce only a limited complement activation by allowing opsonization of altered surfaces but restricting the terminal pathway of MAC formation (Gershov D et al. 2000; Braunschweig A and Jozsi M 2011). Thus, opsonization facilitates clearance of dying cells and cell debris without triggering danger signals and further inflammatory responses (Fraser DA et al. 2007, 2009; Benoit ME et al. 2012). C1q-mediated complement activation by apoptotic cells has been shown in a variety of human cells: keratinocytes, human umbilical vein endothelial cells (HUVEC), Jurkat T lymphoblastoid cells, lung adenocarcinoma cells (Korb LC and Ahearn JM 1997; Mold C and Morris CA 2001; Navratil JS et al. 2001; Nauta AJ et al. 2004). In addition to C1q the opsonization of apoptotic Jurkat T cells with MBL also facilitated clearance of these cells by both dendritic cells (DC) and macrophages (Nauta AJ et al. 2004). Also C3b, iC3b and C4b deposition on apoptotic cells as a consequence of activation of the complement cascade may promote complement-mediated phagocytosis. C1q, MBL and cleavage fragments of C3/C4 can bind to several receptors expressed on macrophages (e.g. cC1qR (calreticulin), CR1, CR3, CR4) suggesting a potential clearance mechanism through this interaction (Mevorach D et al. 1998; Ogden CA et al. 2001). Apoptosis is also associated with an altered expression of complement regulators on the surface of apoptotic cells. CD46 (MCP) bound to the plasma membrane of a healthy cell protects it from complement-mediated attack by preventing deposition of C3b and C4b, and reduced expression of CD46 on dying cells may lead to enhanced opsonization (Elward K et al. 2005). Upregulation of CD55 (DAF) and CD59 on apoptotic cell surfaces may protect damaged cells against complement mediated lysis (Pedersen ED et al. 2007; Iborra A et al. 2003; Hensel F et al. 2001). In addition, fluid-phase complement regulators such as C4BP, CFH may also inhibit lysis of apoptotic cells by limiting complement activation (Trouw LA et al 2007; Braunschweig A and Jozsi M. 2011). Complement facilitates the clearance of immune complexes (IC) from the circulation (Chevalier J and Kazatchkine MD 1989; Nielsen CH et al. 1997). Erythrocytes bear clusters of complement receptor 1 (CR1 or CD35), which serves as an immune adherence receptor for C3 and/or C4 fragments deposited on IC that are shuttled to liver and spleen, where IC are transferred and processed by tissue macrophages through an Fc receptor-mediated process. Complement proteins are always present in the blood and a small percentage spontaneously activate. Inappropriate activation leads to host cell damage, so on healthy human cells any complement activation or amplification is strictly regulated by surface-bound regulators that accelerate decay of the convertases (CR1, CD55), act as a cofactor for the factor I (CFI)-mediated degradation of C3b and C4b (CR1, CD46), or prevent the formation of MAC (CD59). Soluble regulators such as C4BP, CFH and FHL1 recognize self surface pattern-like glycosaminoglycans and further impair activation. Complement components interact with other biological systems. Upon microbial infection complement acts in cooperation with Toll-like receptors (TLRs) to amplify innate host defense. Anaphylatoxin C5a binds C5a receptor (C5aR) resulting in a synergistic enhancement of the TLR and C5aR-mediated proinflammatory cytokine response to infection. This interplay is negatively modulated by co-ligation of TLR and the second C5a receptor, C5L2, suggesting the existence of complex immunomodulatory interactions (Kohl J 2006; Hajishengallis G and Lambris JD 2010). In addition to C5aR and C5L2, complement receptor 3 (CR3) facilitates TLR2 or TLR4 signaling pathways by promoting a recruitment of their sorting adaptor TIRAP (MAL) to the receptor complex (van Bruggen R et al. 2007; Kagan JC and Medzhitov R 2006). Complement may activate platelets or facilitate biochemical and morphological changes in the endothelium potentiating coagulation and contributing to homeostasis in response to injury (Oikonomopoulou K et al. 2012). The interplay of complement and coagulation also involves cleav-

age of C3 and C5 convertases by coagulation proteases, generating biologically active anaphylatoxins (Amara U et al. 2010). Complement is believed to link the innate response to both humoral and cell-mediated immunity (Toapanta FR and Ross TM 2006; Mongini PK et al. 1997). The majority of published data is based on experiments using mouse as a model organism. Further characterization of the influence of complement on B or T cell activation is required for the human system, since differences between murine models and the human system are not yet fully determined. Complement is also involved in regulation of mobilization and homing of hematopoietic stem/progenitor cells (HSPCs) from bone marrow to the circulation and peripheral tissue in order to accommodate blood cell replenishment (Reca R et al. 2006). Thus, the complement system orchestrates the host defense by sensing a danger signal and transmitting it into specific cellular responses while extensively communicating with associated biological pathways ranging from immunity and inflammation to homeostasis and development. Originally the larger fragment of Complement Factor 2 (C2) was designated C2a. However, complement scientists decided that the smaller of all C fragments should be designated with an 'a', the larger with a 'b', changing the nomenclature for C2. Recent literature may use the updated nomenclature and refer to the larger C2 fragment as C2b, and refer to the classical C3 convertase as C4bC2b. Throughout this pathway Reactome adheres to the original convention to agree with the current (Sep 2013) Uniprot names for C2 fragments. The complement cascade pathway is organised into the following sections: initial triggering, activation of C3 and C5, terminal pathway and regulation.

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Editions

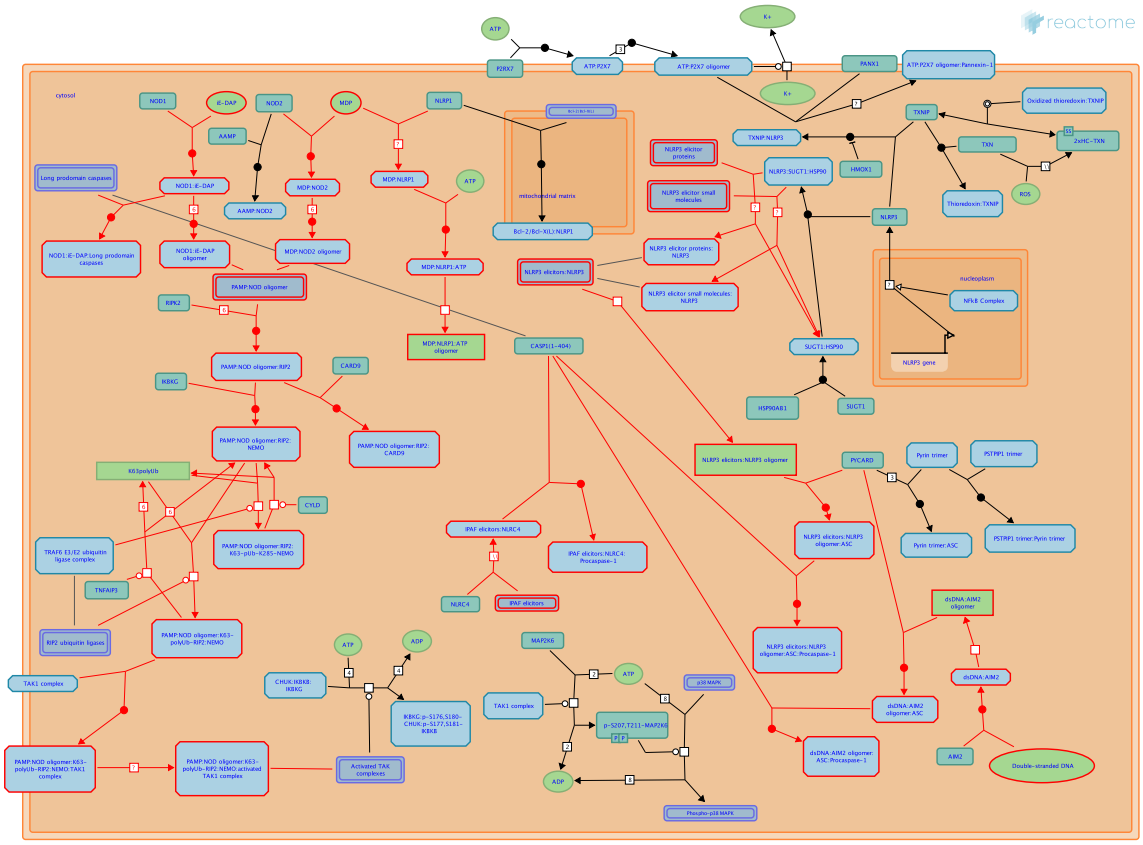
2004-08-04	Authored	de Bono, B.
2006-07-04	Reviewed	D'Eustachio, P.
2010-11-11	Edited, Revised	Jupe, S.

Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways ↗

Location: Innate Immune System

Stable identifier: R-HSA-168643

Compartments: cytosol



The innate immune system is the first line of defense against invading microorganisms, a broad specificity response characterized by the recruitment and activation of phagocytes and the release of antibacterial peptides. The receptors involved recognize conserved molecules present in microbes called pathogen-associated molecular patterns (PAMPs), and/or molecules that are produced as a result of tissue injury, the damage associated molecular pattern molecules (DAMPs). PAMPs are essential to the pathogen and therefore unlikely to vary. Examples are lipopolysaccharide (LPS), peptidoglycans (PGNs) and viral RNA. DAMPs include intracellular proteins, such as heat-shock proteins and extracellular matrix proteins released by tissue injury, such as hyaluronan fragments. Non-protein DAMPs include ATP, uric acid, heparin sulfate and dsDNA. The receptors for these factors are referred to collectively as pathogen- or pattern-recognition receptors (PRRs). The best studied of these are the membrane-associated Toll-like receptor family. Less well studied but more numerous are the intracellular nucleotide-binding domain, leucine rich repeat containing receptors (NLRs) also called nucleotide binding oligomerization domain (NOD)-like receptors, a family with over 20 members in humans and over 30 in mice. These recognise PAMPs/DAMPs from phagocytosed microorganisms or from intracellular infections (Kobayashi et al. 2003, Proell et al. 2008, Wilmanski et al. 2008). Some NLRs are involved in process unrelated to pathogen detection such as tissue homeostasis, apoptosis, graft-versus-host disease and early development (Kufer & Sansonetti 2011).

Structurally NLRs can be subdivided into the caspase-recruitment domain (CARD)-containing NLRCs (NODs) and the pyrin domain (PYD)-containing NLRPs (NALPs), plus outliers including ice protease (ca-

spase-1) activating factor (IPAF) (Martinon & Tschopp, 2005). In practical terms, NLRs can be divided into the relatively well characterized NOD1/2 which signal via RIP2 primarily to NFkappaB, and the remainder, some of which participate in macromolecular structures called Inflammasomes that activate caspases. Mutations in several members of the NLR protein family have been linked to inflammatory diseases, suggesting these molecules play important roles in maintaining host-pathogen interactions and inflammatory responses.

Most NLRs have a tripartite structure consisting of a variable amino-terminal domain, a central nucleotide-binding oligomerization domain (NOD or NACHT) that is believed to mediate the formation of self oligomers, and a carboxy-terminal leucine-rich repeat (LRR) that detects PAMPs/DAMPs. In most cases the amino-terminal domain includes protein-interaction modules, such as CARD or PYD, some harbour baculovirus inhibitor repeat (BIR) or other domains. For most characterised NLRs these domains have been attributed to downstream signaling

Under resting conditions, NLRs are thought to be present in an autorepressed form, with the LRR folded back onto the NACHT domain preventing oligomerization. Accessory proteins may help maintain the inactive state. PAMP/DAMP exposure is thought to triggers conformational changes that expose the NACHT domain enabling oligomerization and recruitment of effectors, though it should be noted that due to the lack of availability of structural data, the mechanistic details of NLR activation remain largely elusive.

New terminology for NOD-like receptors was adopted by the Human Genome Organization (HUGO) in 2008 to standardize the nomenclature of NLRs. The acronym NLR, once standing for NOD-like receptor, now is an abbreviation of 'nucleotide-binding domain, leucine-rich repeat containing' protein. The term NOD-like receptor is officially outdated and replaced by NLRC where the C refers to the CARD domain. However the official gene symbols for NOD1 and NOD2 still contain NOD and this general term is still widely used.

Literature references

Chen, G., Shaw, MH., Kim, YG., Nunez, G. (2009). NOD-like receptors: role in innate immunity and inflammatory disease. *Annu Rev Pathol, 4*, 365-98. ↗

Editions

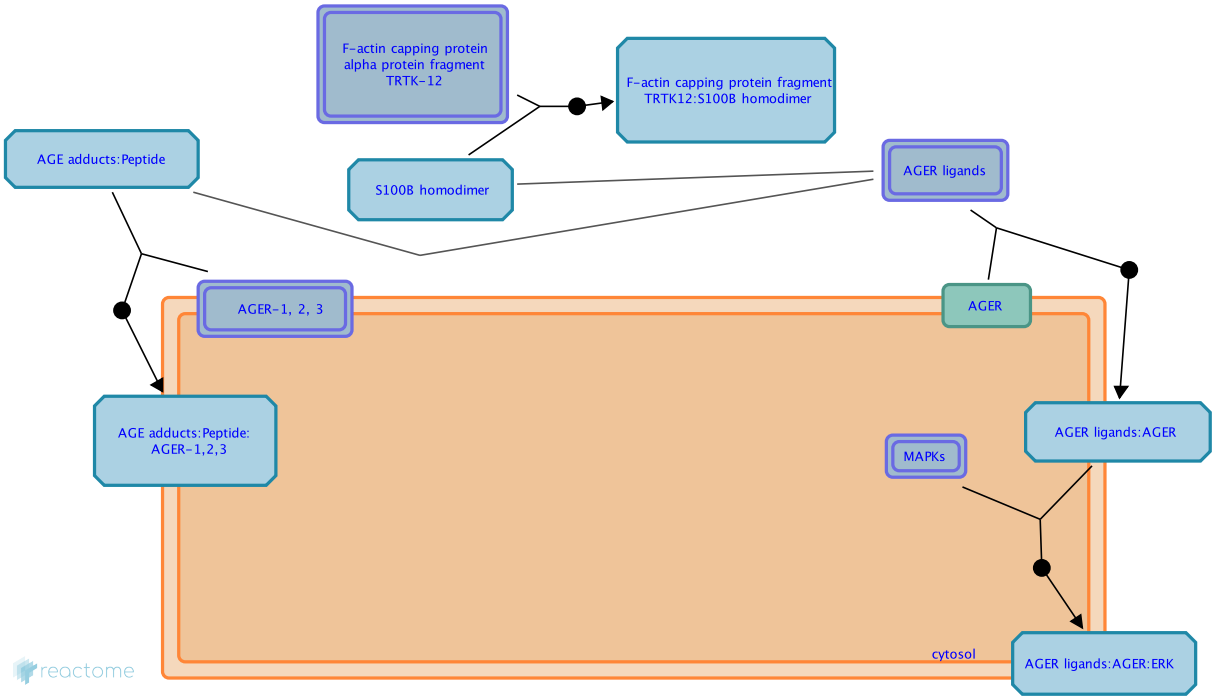
2010-04-22	Authored	Jupe, S.
2011-04-28	Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.

Advanced glycosylation endproduct receptor signaling ↗

Location: Innate Immune System

Stable identifier: R-HSA-879415

Compartments: plasma membrane, extracellular region



Advanced Glycosylation End- product-specific Receptor (AGER) also known as Receptor for Advanced Glycation End-products (RAGE) is a multi-ligand membrane receptor belonging to the immunoglobulin superfamily. It is considered to be a Pattern Recognition Receptor (Liliensiek et al. 2004). It recognizes a large variety of modified proteins known as advanced glycation/glycosylation endproducts (AGEs), a heterogenous group of structures that are generated by the Maillard reaction, a consequence of long-term incubation of proteins with glucose (Ikeda et al. 1996). Their accumulation is associated with diabetes, atherosclerosis, renal failure and ageing (Schmidt et al. 1999). The most prevalent class of AGE in vivo are N(6)-carboxymethyllysine (NECML) adducts (Kislinger et al. 1991). In addition to AGEs, AGER is a signal transduction receptor for amyloid-beta peptide (Ab) (Yan et al. 1996), mediating Ab neurotoxicity and promoting Ab influx into the brain. AGER also responds to the proinflammatory S100/calgranulins (Hofmann et al. 1999) and High mobility group protein B1 (HMGB1/Amphoterin/DEF), a protein linked to neurite outgrowth and cellular motility (Hori et al. 1995).

The major inflammatory pathway stimulated by AGER activation is NFkappaB. Though the signaling cascade is unclear, several pieces of experimental data suggest that activation of AGER leads to sustained activation and upregulation of NFkappaB, measured as NFkappaB translocation to the nucleus, and increased levels of de novo synthesized NFkappaB (Bierhaus et al. 2001). As this is clearly an indirect effect it is represented here as positive regulation of NFkappaB translocation to the nucleus. AGER can bind ERK1/2 and thereby activate the MAPK and JNK cascades (Bierhaus et al. 2005).

Literature references

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Editions

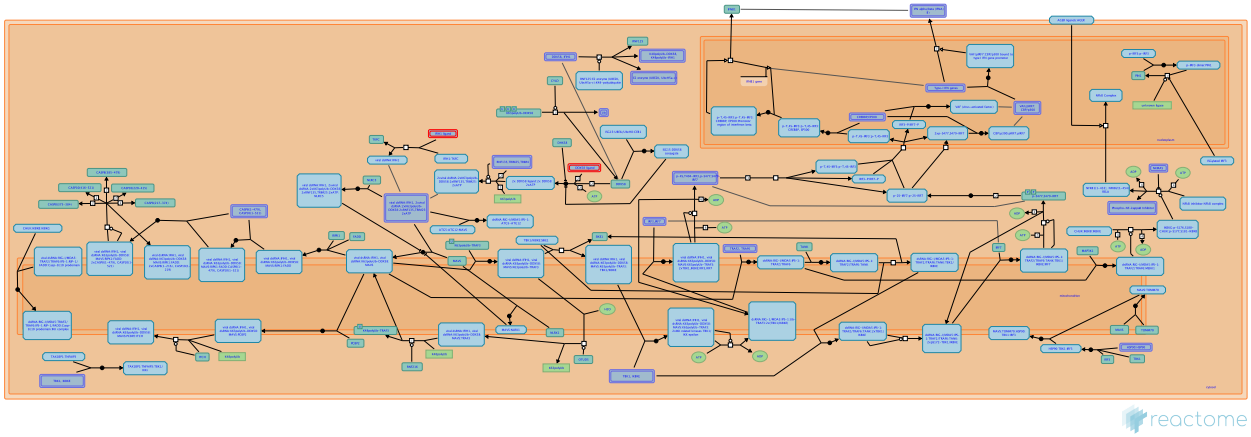
2010-06-01	Authored	Jupe, S.
2010-09-01	Edited	Jupe, S.
2010-11-09	Reviewed	Yan, SD.

DDX58/IFIH1-mediated induction of interferon-alpha/beta ↗

Location: Innate Immune System

Stable identifier: R-HSA-168928

Compartments: mitochondrial outer membrane



RIG-I-like helicases (RLHs) the retinoic acid inducible gene-I (RIG-I) and melanoma differentiation associated gene 5 (MDA5) are RNA helicases that recognize viral double-stranded RNA (dsRNA) present within the cytoplasm (Yoneyama M & Fujita T 2007, 2008). Upon viral infection dsRNA is generated by positive-strand RNA virus families such as Flaviviridae and Coronaviridae, negative-strand RNA virus families including Orthomyxoviridae and Paramyxoviridae, and DNA virus families such as Herpesviridae and Adenoviridae (Weber F et al. 2006; Son KN et al. 2015). Functionally RIG-I and MDA5 positively regulate the IFN genes in a similar fashion, however they differ in their response to different viral species. RIG-I is essential for detecting influenza virus, Sendai virus, VSV and Japanese encephalitis virus (JEV), whereas MDA5 is essential in sensing encephalomyocarditis virus (EMCV), Mengo virus and Theiler's virus, all of which belong to the picornavirus family. RIG-I and MDA5 signalling results in the activation of IKK epsilon and (TKK binding kinase 1) TBK1, two serine/threonine kinases that phosphorylate interferon regulatory factor 3 and 7 (IRF3 and IRF7). Upon phosphorylation, IRF3 and IRF7 translocate to the nucleus and subsequently induce interferon alpha (IFNA) and interferon beta (IFNB) gene transcription (Yoneyama M et al. 2004; Yoneyama M & Fujita T 2007, 2008).

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Yoneyama, M., Fujita, T. (2007). RIG-I family RNA helicases: cytoplasmic sensor for antiviral innate immunity. *Cytokine Growth Factor Rev, 18*, 545-51. ↗

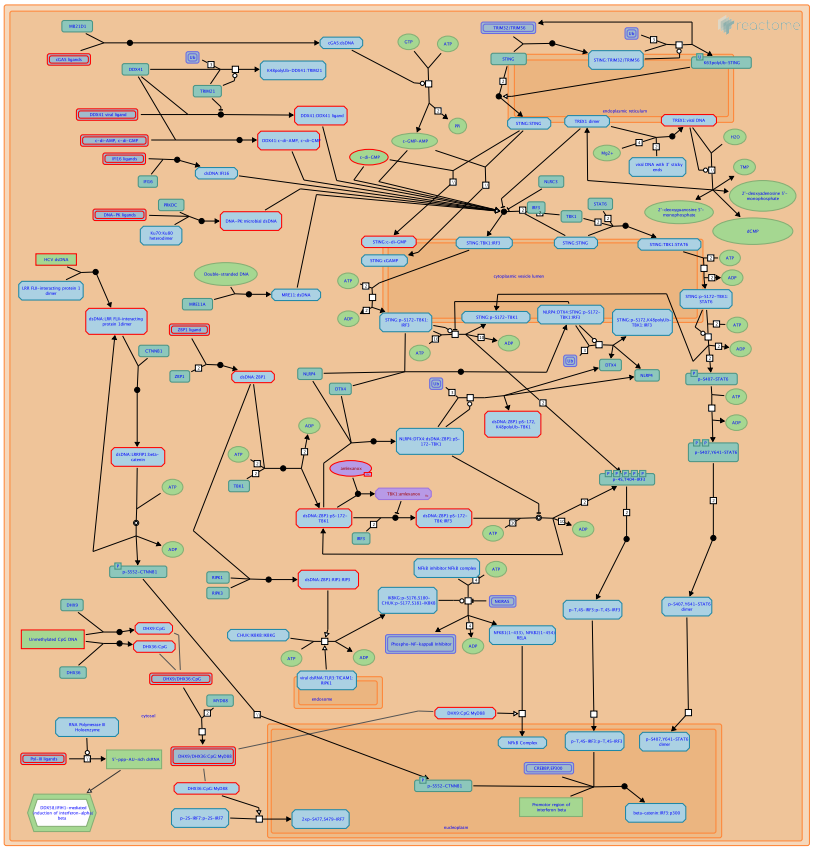
Editions

2010-08-02	Authored, Edited	Garapati, P V.
2010-10-30	Reviewed	Akira, S., Kawai, T.

Cytosolic sensors of pathogen-associated DNA ↗

Location: Innate Immune System

Stable identifier: R-HSA-1834949



Presence of pathogen-associated DNA in cytosol induces type I IFN production. Several intracellular receptors have been implicated to some degree. These include DNA-dependent activator of interferon (IFN)-regulatory factors (DAI) (also called Z-DNA-binding protein 1, ZBP1), absent in melanoma 2 (AIM2), RNA polymerase III (Pol III), IFN-inducible protein IFI16, leucine-rich repeat flightless interacting protein-1 (LRRFIP1), DEAH-box helicases (DHX9 and DHX36), DEAD-box helicase DDX41, meiotic recombination 11 homolog A (MRE11), DNA-dependent protein kinase (DNA-PK), cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING).

Detection of cytosolic DNA requires multiple and possibly redundant sensors leading to activation of the transcription factor NF-kappaB and TBK1-mediated phosphorylation of the transcription factor IRF3. Cytosolic DNA also activates caspase-1-dependent maturation of the pro-inflammatory cytokines interleukin IL-1beta and IL-18. This pathway is mediated by AIM2.

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Paludan, SR., Bowie, AG. (2013). Immune Sensing of DNA. *Immunity, 38*, 870-880. ↗

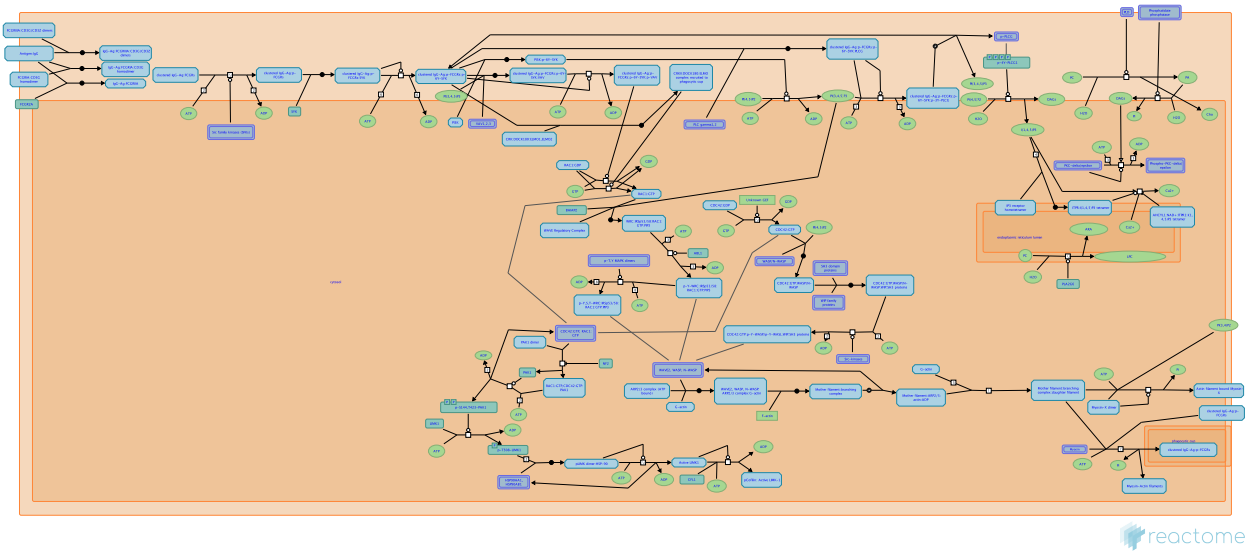
Editions

2011-09-21	Authored	Shamovsky, V.
2011-12-08	Reviewed	D'Eustachio, P.
2012-02-19	Reviewed	Upton, JW., Mocarski, ES.
2013-05-17	Edited	Shamovsky, V.
2013-05-22	Reviewed	Jin, L., Wu, J.

Fcgamma receptor (FCGR) dependent phagocytosis ↗

Location: Innate Immune System

Stable identifier: R-HSA-2029480



Phagocytosis is one of the important innate immune responses that function to eliminate invading infectious agents. Monocytes, macrophages, and neutrophils are the professional phagocytic cells. Phagocytosis is a complex process involving the recognition of invading foreign particles by specific types of phagocytic receptors and the subsequent internalization of the particles. Fc gamma receptors (FCGRs) are among the best studied phagocytic receptors that bind to Fc portion of immunoglobulin G (IgG). Through their antigen binding F(ab) end, antibodies bind to specific antigen while their constant (Fc) region binds to FCGRs on phagocytes. The clustering of FCGRs by IgG antibodies on the phagocyte initiates a variety of signals, which lead, through the reorganisation of actin cytoskeleton and membrane remodelling, to the formation of pseudopod and phagosome. Fc gamma receptors are classified into three classes: FCGRI, FCGRII and FCGRIII. Each class of these FCGRs consists of several individual isoforms. Among all these isoforms FCGRI, FCGRIIA and FCGRIIIA, are able to mediate phagocytosis (Joshi et al. 2006, Garcia Garcia & Rosales 2002, Nimmerjahn & Ravetch 2006).

Literature references

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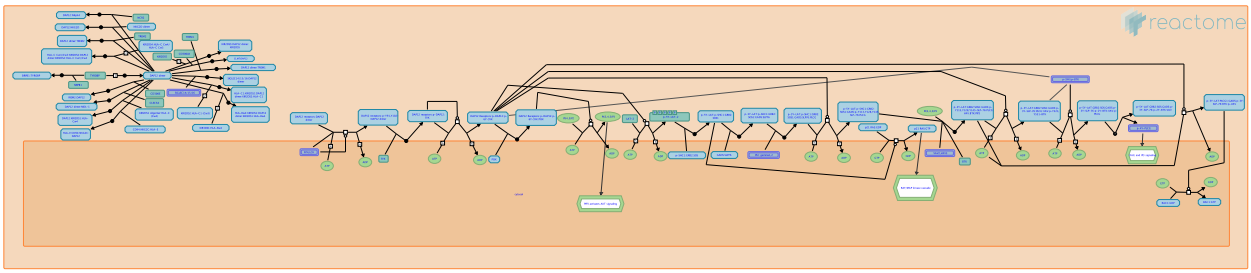
Editions

2012-01-04	Authored, Edited	Garapati, P V.
2012-05-15	Reviewed	Rosales, C.

DAP12 interactions ↗

Location: Innate Immune System

Stable identifier: R-HSA-2172127



DNAX activation protein of 12kDa (DAP12) is an immunoreceptor tyrosine-based activation motif (I-TAM)-bearing adapter molecule that transduces activating signals in natural killer (NK) and myeloid cells. It mediates signalling for multiple cell-surface receptors expressed by these cells, associating with receptor chains through complementary charged transmembrane amino acids that form a salt-bridge in the context of the hydrophobic lipid bilayer (Lanier et al. 1998). DAP12 homodimers associate with a variety of receptors expressed by macrophages, monocytes and myeloid cells including TREM2, Siglec H and SIRP-beta, as well as activating KIR, LY49 and the NKG2C proteins expressed by NK cells. DAP12 is expressed at the cell surface, with most of the protein lying on the cytoplasmic side of the membrane (Turnbull & Colonna 2007, Tessarz & Cerwenka 2008).

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Editions

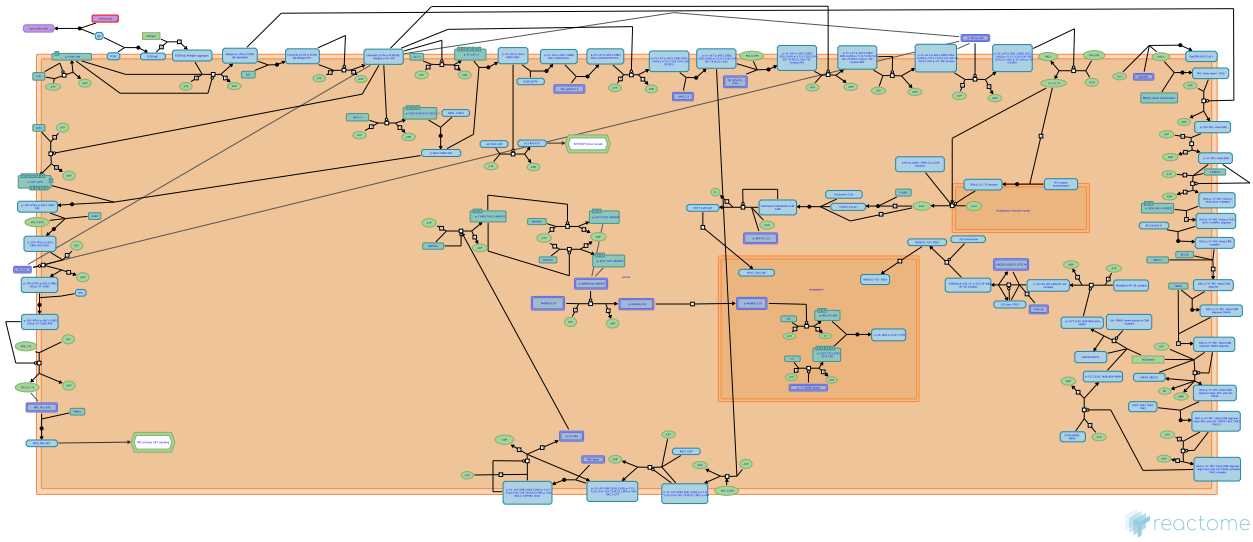
2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

Fc epsilon receptor (FCERI) signaling ↗

Location: Innate Immune System

Stable identifier: R-HSA-2454202

Compartments: plasma membrane



Mast cells (MC) are distributed in tissues throughout the human body and have long been recognized as key cells of type I hypersensitivity reactions. They also play important roles in inflammatory and immediate allergic reactions. Activation through FCERI-bound antigen-specific IgE causes release of potent inflammatory mediators, such as histamine, proteases, chemotactic factors, cytokines and metabolites of arachidonic acid that act on the vasculature, smooth muscle, connective tissue, mucous glands and inflammatory cells (Borish & Joseph 1992, Amin 2012, Metcalfe et al. 1993). FCERI is a multimeric cell-surface receptor that binds the Fc fragment of IgE with high affinity. On mast cells and basophils FCERI exists as a tetrameric complex consisting of one alpha-chain, one beta-chain, and two disulfide-bonded gamma-chains, and on dendritic cells, Langerhans cells, macrophages, and eosinophils it exists as a trimeric complex with one alpha-chain and two disulfide-bonded gamma-chains (Wu 2011, Kraft & Kinet 2007). FCERI signaling in mast cells includes a network of signaling molecules and adaptor proteins. These molecules coordinate ultimately leading to effects on degranulation, eicosanoid production, and cytokine and chemokine production and cell migration and adhesion, growth and survival.

The first step in FCERI signaling is the phosphorylation of the tyrosine residues in the ITAM of both the beta and the gamma subunits of the FCERI by LYN, which is bound to the FCERI beta-chain. The phosphorylated ITAM then recruits the protein tyrosine kinase SYK (spleen tyrosine kinase) which then phosphorylates the adaptor protein LAT. Phosphorylated LAT (linker for activation of T cells) acts as a scaffolding protein and recruits other cytosolic adaptor molecules GRB2 (growth-factor-receptor-bound protein 2), GADS (GRB2-related adaptor protein), SHC (SRC homology 2 (SH2)-domain-containing transforming protein C) and SLP76 (SH2-domain-containing leukocyte protein of 76 kDa), as well as the exchange factors and adaptor molecules VAV and SOS (son of sevenless homologue), and the signalling enzyme phospholipase C gamma1 (PLC-gamma1). Tyrosoine phosphorylation of enzymes and adaptors, including VAV, SHC GRB2 and SOS stimulate small GTPases such as RAC, RAS and RAF. These pathways lead to activation of the ERK, JNK and p38 MAP kinases, histamine release and cytokine production. FCERI activation also triggers the phosphorylation of PLC-gamma which upon membrane localisation hydrolyse PIP2 to form IP3 and 1,2-diacylglycerol (DAG) - second messengers that release Ca2+ from internal stores and activate PKC, respectively. Degranulation or histamine release follows the activation of PLC-gamma and protein kinase C (PKC) and the increased mobilization of calcium (Ca2+). Receptor aggregation also

results in the phosphorylation of adaptor protein NTAL/LAT2 which then recruits GAB2. PI3K associates with phosphorylated GAB2 and catalyses the formation of PIP3 in the membrane, which attracts many PH domain proteins like BTK, PLC-gamma, AKT and PDK. PI3K mediated activation of AKT then regulate the mast cell proliferation, development and survival (Gu et al. 2001).

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Editions

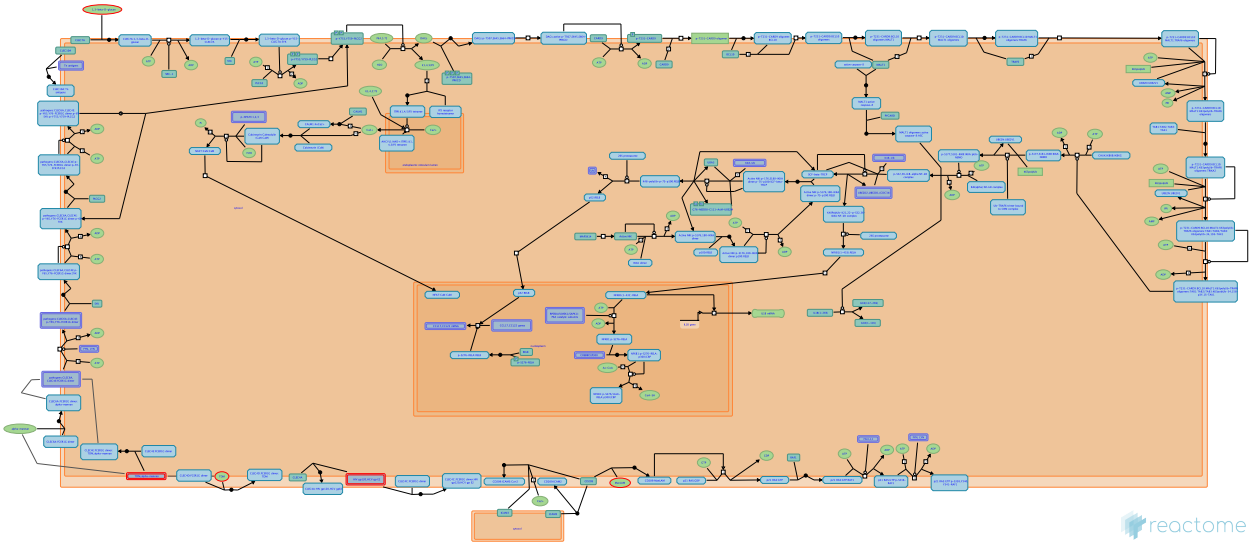
2012-08-22	Edited	Garapati, P V.
2012-12-21	Authored	Niarakis, A.
2013-02-13	Reviewed	Roncagalli, R.

C-type lectin receptors (CLRs) ↗

Location: Innate Immune System

Stable identifier: R-HSA-5621481

Compartments: cytosol, nucleoplasm, plasma membrane



Pathogen recognition is central to the induction of T cell differentiation. Groups of pathogens share similar structures known as pathogen-associated molecular patterns (PAMPs), which are recognised by pattern recognition receptors (PRRs) expressed on dendritic cells (DCs) to induce cytokine expression. PRRs include archetypical Toll-like receptors (TLRs) and non-TLRs such as retinoic acid-inducible gene I (RIG-I)-like receptors, C-type lectin receptors (CLRs) and intracellular nucleotide-binding domain and leucine-rich-repeat-containing family (NLRs). PRR recognition of PAMPs can lead to the activation of intracellular signalling pathways that elicit innate responses against pathogens and direct the development of adaptive immunity.

CLRs comprises a large family of receptors which bind carbohydrates, through one or more carbohydrate recognition domains (CRDs), or which possess structurally similar C-type lectin-like domains (CTLDs) which do not necessarily recognise carbohydrate ligands. Some CLRs can induce signalling pathways that directly activate nuclear factor-kB (NF-kB), whereas other CLRs affect signalling by Toll-like receptors. These signalling pathways trigger cellular responses, including phagocytosis, DC maturation, chemotaxis, the respiratory burst, inflammasome activation, and cytokine production.

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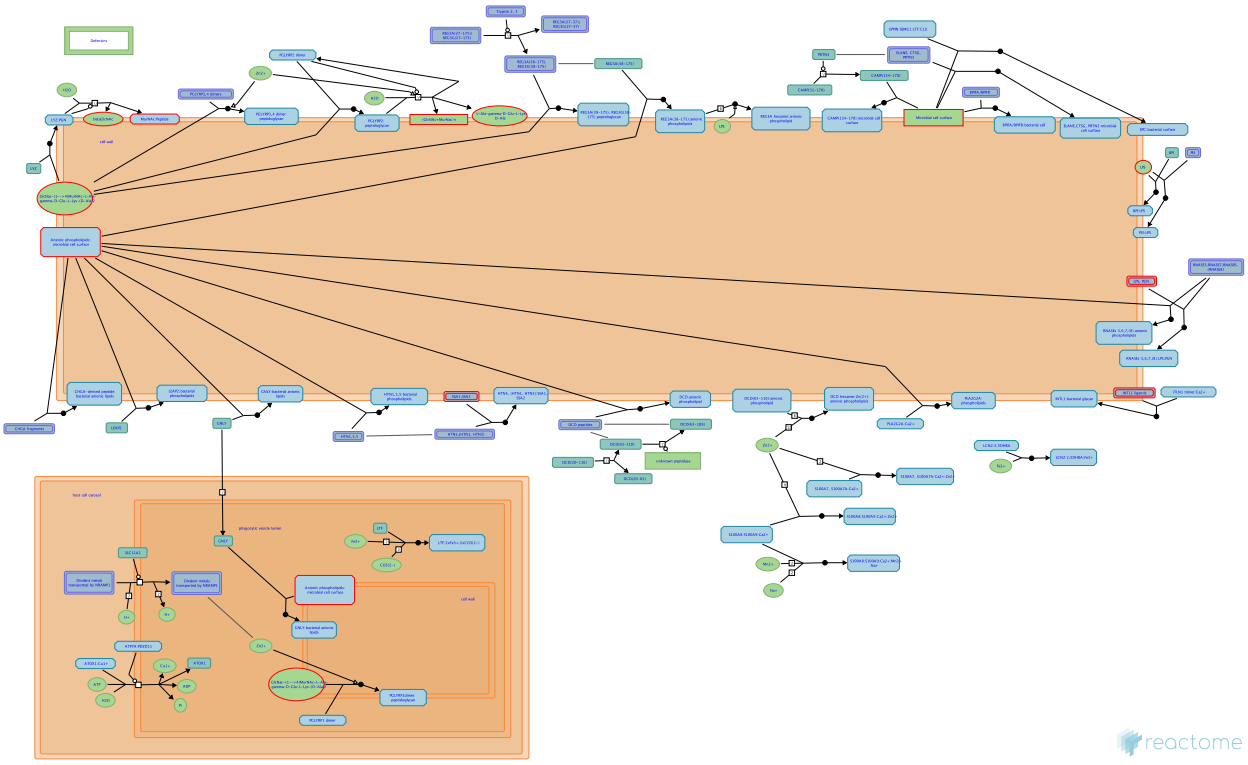
Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

Antimicrobial peptides ↗

Location: Innate Immune System

Stable identifier: R-HSA-6803157



Antimicrobial peptides (AMPs) are small molecular weight proteins with broad spectrum of antimicrobial activity against bacteria, viruses, and fungi (Zasloff M 2002; Radek K & Gallo R 2007). The majority of known AMPs are cationic peptides with common structural characteristics where domains of hydrophobic and cationic amino acids are spatially arranged into an amphipathic design, which facilitates their interaction with bacterial membranes (Shai Y 2002; Yeaman MR & Yount NY 2003; Brown KL & Hancock RE 2006; Dennison SR et al. 2005; Zelezetsky I & Tossi A 2006). It is generally excepted that the electrostatic interaction facilitates the initial binding of the positively charged peptides to the negatively charged bacterial membrane. Moreover, the structural amphiphilicity of AMPs is thought to promote their integration into lipid bilayers of pathogenic cells, leading to membrane disintegration and finally to the microbial cell death. In addition to cationic AMPs a few anionic antimicrobial peptides have been found in humans, however their mechanism of action remains to be clarified (Lai Y et al. 2007; Harris F et al. 2009; Paulmann M et al. 2012). Besides the direct neutralizing effects on bacteria AMPs may modulate cells of the adaptive immunity (neutrophils, T-cells, macrophages) to control inflammation and/or to increase bacterial clearance.

AMPs have also been referred to as cationic host defense peptides, anionic antimicrobial peptides/proteins, cationic amphipathic peptides, cationic AMPs, host defense peptides and alpha-helical antimicrobial peptides (Brown KL & Hancock RE 2006; Harris F et al. 2009; Groenink J et al. 1999; Bradshaw J 2003; Riedl S et al. 2011; Huang Y et al. 2010).

The Reactome module describes the interaction events of various types of human AMPs, such as cathelicidin, histatins and neutrophil serine proteases, with conserved patterns of microbial membranes at the host-pathogen interface. The module includes also proteolytic processing events for dermcidin (DCD) and cathelicidin (CAMP) that become functional upon cleavage. In addition, the module highlights an AMP-associated ability of the host to control metal quota at inflammation sites to influence host-patho-

gen interactions.

Literature references

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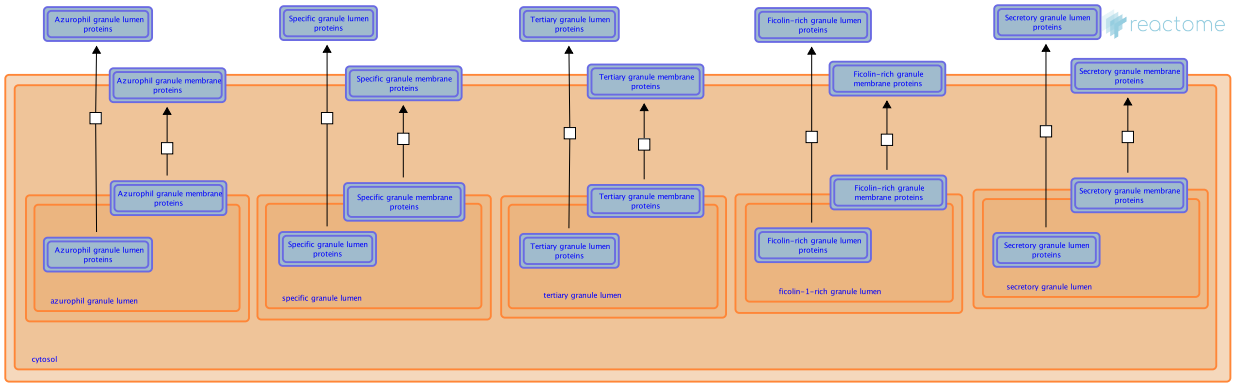
Editions

2015-10-05	Authored	Shamovsky, V.
2016-04-15	Reviewed	Jupe, S.
2016-08-02	Reviewed	Hains, DS.
2016-08-15	Edited	Shamovsky, V.

Neutrophil degranulation ↗

Location: Innate Immune System

Stable identifier: R-HSA-6798695



Neutrophils are the most abundant leukocytes (white blood cells), indispensable in defending the body against invading microorganisms. In response to infection, neutrophils leave the circulation and migrate towards the inflammatory focus. They contain several subsets of granules that are mobilized to fuse with the cell membrane or phagosomal membrane, resulting in the exocytosis or exposure of membrane proteins. Traditionally, neutrophil granule constituents are described as antimicrobial or proteolytic, but granules also introduce membrane proteins to the cell surface, changing how the neutrophil responds to its environment (Borregaard et al. 2007). Primed neutrophils actively secrete cytokines and other inflammatory mediators and can present antigens via MHC II, stimulating T-cells (Wright et al. 2010).

Granules form during neutrophil differentiation. Granule subtypes can be distinguished by their content but overlap in structure and composition. The differences are believed to be a consequence of changing protein expression and differential timing of granule formation during the terminal processes of neutrophil differentiation, rather than sorting (Le Cabec et al. 1996).

The classical granule subsets are Azurophil or primary granules (AG), secondary granules (SG) and gelatinase granules (GG). Neutrophils also contain exocytosable storage cell organelles, storage vesicles (SV), formed by endocytosis they contain many cell-surface markers and extracellular, plasma proteins (Borregaard et al. 1992). Ficolin-1-rich granules (FG) are like GGs highly exocytosable but gelatinase-poor (Rorvig et al. 2009).

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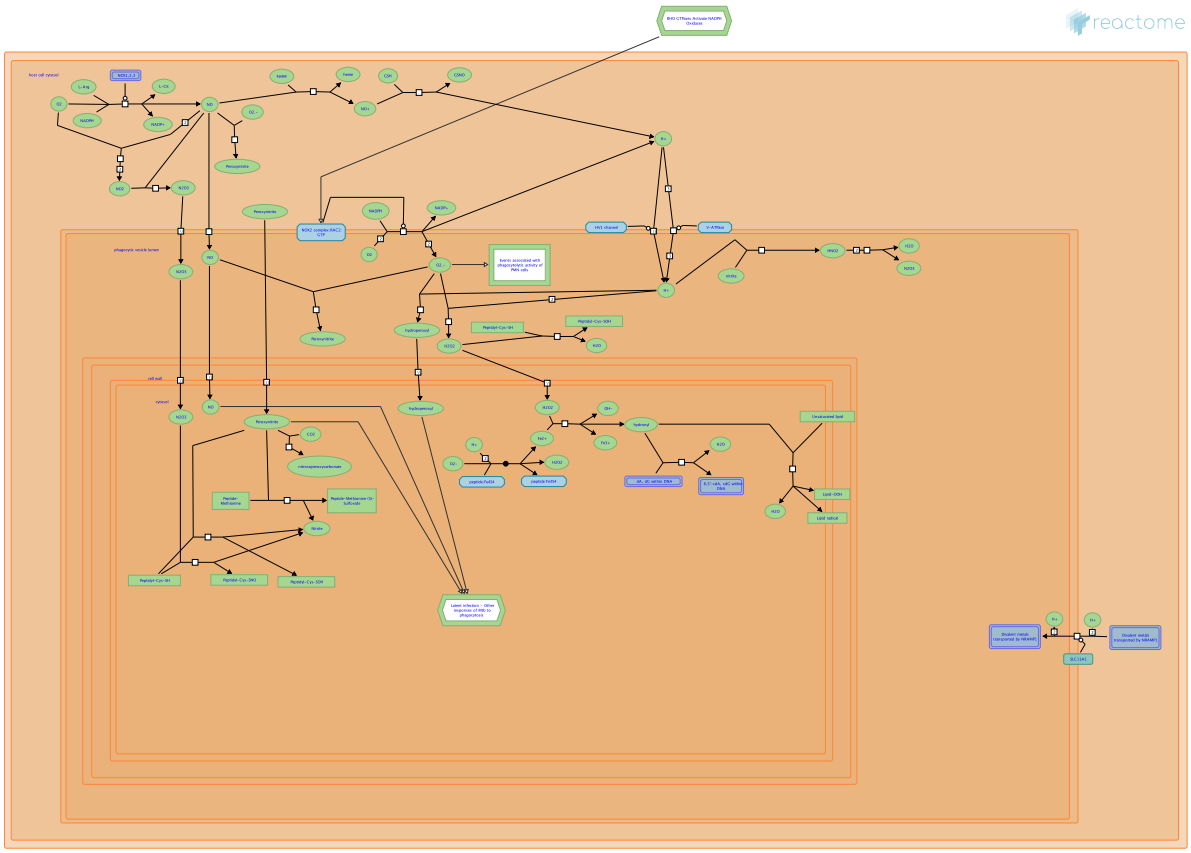
Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

ROS and RNS production in phagocytes ↗

Location: Innate Immune System

Stable identifier: R-HSA-1222556



The first line of defense against infectious agents involves an active recruitment of phagocytes to the site of infection. Recruited cells include polymorhonuclear (PMN) leukocytes (i.e., neutrophils) and monocytes/macrophages, which function together as innate immunity sentinels (Underhill DM & Ozinsky A 2002; Stuart LM & Ezekowitz RA 2005; Flannagan RS et al. 2012). Dendritic cells are also present, serving as important players in antigen presentation for ensuing adaptive responses (Savina A & Amigorena S 2007). These cell types are able to bind and engulf invading microbes into a membrane-enclosed vacuole - the phagosome, in a process termed phagocytosis. Phagocytosis can be defined as the receptor-mediated engulfment of particles greater than 0.5 micron in diameter. It is initiated by the cross-linking of host cell membrane receptors following engagement with their cognate ligands on the target surface (Underhill DM & Ozinsky A 2002; Stuart LM & Ezekowitz RA 2005; Flannagan RS et al. 2012). When engulfed by phagocytes, microorganisms are exposed to a number of host defense microbicidal events within the resulting phagosome. These include the production of reactive oxygen and nitrogen species (ROS and RNS, RONS) by specialized enzymes (Fang FC et al. 2004; Kohchi C et al. 2009; Gostner JM et al. 2013; Vatansever F et al. 2013). NADPH oxidase (NOX) complex consume oxygen to produce superoxide radical anion (O2.-) and hydrogen peroxide (H2O2) (Robinson et al. 2004). Induced NO synthase (iNOS) is involved in the production of NO, which is the primary source of all RNS in biological systems (Evans TG et al. 1996). The phagocyte NADPH oxidase and iNOS are expressed in both PMN and mononuclear phagocytes and both cell types have the capacity for phagosomal burst activity. However, the magnitude of ROS generation in neutrophils far exceeds that observed in macrophages (VanderVen BC et al. 2009). Macrophages are thought to produce considerably more RNS than neutrophils (Fang FC et al. 2004; Nathan & Shiloh 2000).

The presence of RONS characterized by a relatively low reactivity, such as H2O2, $O_2^{\cdot -}$ or NO, has no de-

leterious effect on biological environment (Attia SM 2010; Weidinger A & and Kozlov AV 2015). Their activity is controlled by endogenous antioxidants (both enzymatic and non-enzymatic) that are induced by oxidative stress. However the relatively low reactive species can initiate a cascade of reactions to generate more damaging “secondary” species such as hydroxyl radical (•OH), singlet oxygen or peroxinitrite (Robinson JM 2008; Fang FC et al. 2004). These "secondary" RONS are extremely toxic causing irreversible damage to all classes of biomolecules (Weidinger A & and Kozlov AV 2015; Fang FC et al. 2004; Kohchi C et al. 2009; Gostner JM et al. 2013; Vatansever F et al. 2013).

Although macrophages and neutrophils use similar mechanisms for the internalization of targets, there are differences in how they perform phagocytosis and in the final outcome of the process (Tapper H & Grinstein S 1997; Vierira OV et al. 2002). Once formed, the phagosome undergoes an extensive maturation process whereby it develops into a microbicidal organelle able to eliminate the invading pathogen. Maturation involves re-modeling both the membrane of the phagosome and its luminal contents (Vierira OV et al. 2002). In macrophages, phagosome formation and maturation follows a series of strictly coordinated membrane fission/fusion events between the phagosome and compartments of the endo-/lysosomal network gradually transforming the nascent phagosome into a phagolysosome, a degradative organelle endowed with potent microbicidal properties (Zimmerli S et al. 1996; Vierira OV et al. 2002). Neutrophils instead contain a large number of preformed granules such as azurophilic and specific granules that can rapidly fuse with phagosomes delivering antimicrobial substances (Karlsson A & Dahlgren C 2002; Naucler C et al. 2002; Nordenfelt P and Tapper H 2011). Phagosomal pH dynamics may also contribute to the maturation process by regulating membrane traffic events. The microbicidal activity of macrophages is characterized by progressive acidification of the lumen (down to pH 4–5) by the proton pumping vATPase. A low pH is a prerequisite for optimal enzymatic activity of most late endosomal/lysosomal hydrolases reported in macrophages. Neutrophil phagosome pH regulation differs significantly from what is observed in macrophages (Nordenfelt P and Tapper H 2011; Winterbourn CC et al. 2016). The massive activation of the oxidative burst is thought to result in early alkalization of neutrophil phagosomes which is linked to proton consumption during the generation of hydrogen peroxide (Segal AW et al. 1981; Levine AP et al. 2015). Other studies showed that neutrophil phagosome maintained neutral pH values before the pH gradually decreased (Jankowski A et al. 2002). Neutrophil phagosomes also exhibited a high proton leak, which was initiated upon activation of the NADPH oxidase, and this activation counteracted phagosomal acidification (Jankowski A et al. 2002).

The Reactome module describes ROS and RNS production by phagocytic cells. The module includes cell-type specific events, for example, myeloperoxidase (MPO)-mediated production of hypochlorous acid in neutrophils. It also highlights differences between phagosomal pH dynamics in neutrophils and macrophages. The module describes microbicidal activity of selective RONS such as hydroxyl radical or peroxynitrite. However, detection of any of these species in the phagosomal environment is subject to many uncertainties (Nüsse O 2011; Erard M et al. 2018). The mechanisms by which reactive oxygen/nitrogen species kill pathogens in phagocytic immune cells are still not fully understood.

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Editions

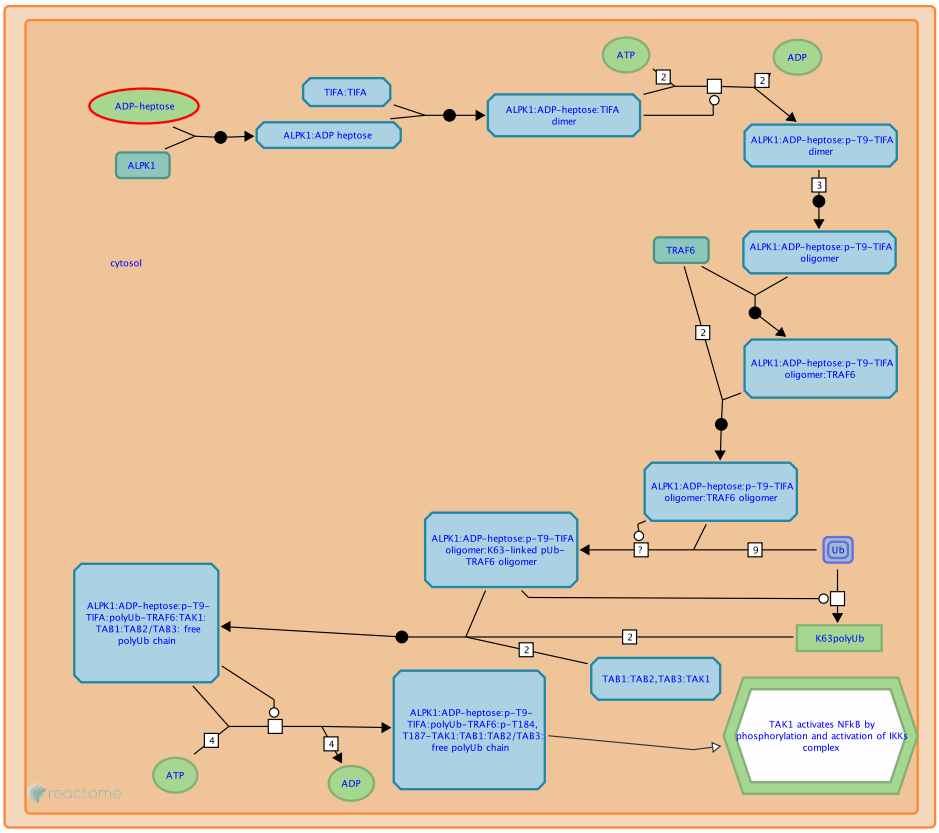
2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.
2018-11-07	Reviewed	Nüsse, O.
2018-11-07	Edited, Revised	Shamovsky, V.

Alpha-protein kinase 1 signaling pathway ↗

Location: Innate Immune System

Stable identifier: R-HSA-9645460

Compartments: cytosol



Immune recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRR) often activates proinflammatory nuclear factor kappa B (NF-κB) signalling. Lipopolysaccharide (LPS) is a well-known PAMP produced by gram-negative bacteria. LPS is recognized by toll like receptor 4 (TLR4) and is a strong activator of NF-κB inflammatory responses (Akashi S et al. 2003). LPS is also recognized in the cytosol by mouse caspase-11 and related human caspase-4 and caspase-5, which stimulate pyroptosis, a proinflammatory form of cell death (Kayagaki N et al. 2011; Shi J et al. 2015). Key metabolic intermediates in LPS biosynthesis, d-glycero-β-d-manno-heptose 1,7-bisphosphate (HBP) and ADP L-glycero-β-d-manno-heptose (ADP-heptose) were reported to activate the NF-κB pathway and trigger the innate immune responses (Milivojevic M et al. 2017; Zimmermann S et al. 2017; Zhou P et al. 2018; García-Weber D; 2018). ADP-heptose but not HBP can enter host cells autonomously (Zhou P et al. 2018). During infection, ADP-heptose or HBP translocate into the host cytosol where their presence is sensed by alpha-protein kinase 1 (ALPK1) (Zimmermann S et al. 2017; Zhou P et al. 2018). ADP-heptose directly binds and activates ALPK1 (Garcia-Weber D et al. 2018; Zhou P et al. 2018); instead, HBP is converted by host-derived adenylyltransferases, such as nicotinamide nucleotide adenylyltransferases, to ADP-heptose 7-P, a substrate which can then activate ALPK1 (Zhou P et al. 2018). The ADP-heptose binding to ALPK1 is thought to trigger conformational changes and stimulate the kinase domain of ALPK1 (Zhou P et al. 2018). ALPK1 kinase activity in turn leads to the phosphorylation-dependent oligomerization of the tumor necrosis factor (TNF-α) receptor–associated factor (TRAF)–interacting protein with the forkhead-associated domain (TIFA) (Zimmermann S et al. 2017; Zhou P et al. 2018). This process activates TRAF6 oligomerization and ubiquitination, and the recruitment of transforming growth factor β-activated kinase 1 (TAK1)-binding protein 2 (TAB2), a component of the TAK1 (MAP3K7) complex (Ea CK et al. 2004; Gaudet

RG et al. 2017). This TIFA oligomer signaling platform was given the term: TIFAsome. TIFAsome-activated TAK1 induces NF-κB nuclear translocation and proinflammatory gene expression. The ALPK1-TIFA signaling pathway has been identified in human embryonic kidney cells, intestinal epithelial cells, gastric cells and cervical cancer cells (Gaudet RG et al. 2015, 2017; Stein SC et al. 2017; Gall A et al. 2017; Zimmermann S et al. 2017; Milivojevic M et al. 2017; Zhou P et al. 2018). In vivo studies demonstrate that ADP-heptose and Burkholderia cenocepacia trigger massive inflammatory responses with increased production of several NF-κB-dependent cytokines and chemokines in wild type (WT), but not in Alpk1-/- mice (Zhou P et al. 2018).

This Reactome module describes ALPK1 as a cytosolic innate immune receptor for bacterial ADP-heptose.

Literature references

Zhou, P., She, Y., Dong, N., Li, P., He, H., Borio, A. et al. (2018). Alpha-kinase 1 is a cytosolic innate immune receptor for bacterial ADP-heptose. *Nature, 561*, 122-126. ↗

Hu, X., Yang, C., Wang, PG., Zhang, GL. (2019). ADP-heptose: A new innate immune modulator. *Carbohydr. Res., 473*, 123-128. ↗

Editions

2019-05-17	Authored	Shamovsky, V.
2019-06-03	Reviewed	Gillespie, ME.
2019-07-08	Reviewed	Shao, F.
2019-08-09	Edited	Shamovsky, V.

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