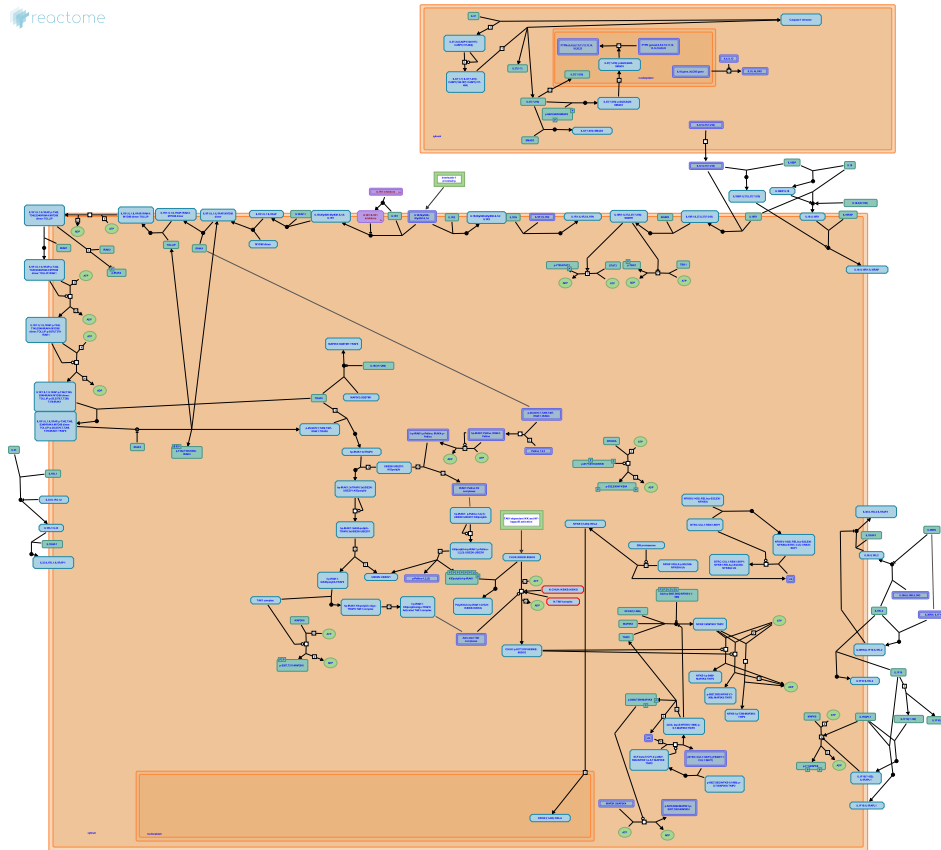


Interleukin-1 family signaling



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30/04/2024

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.

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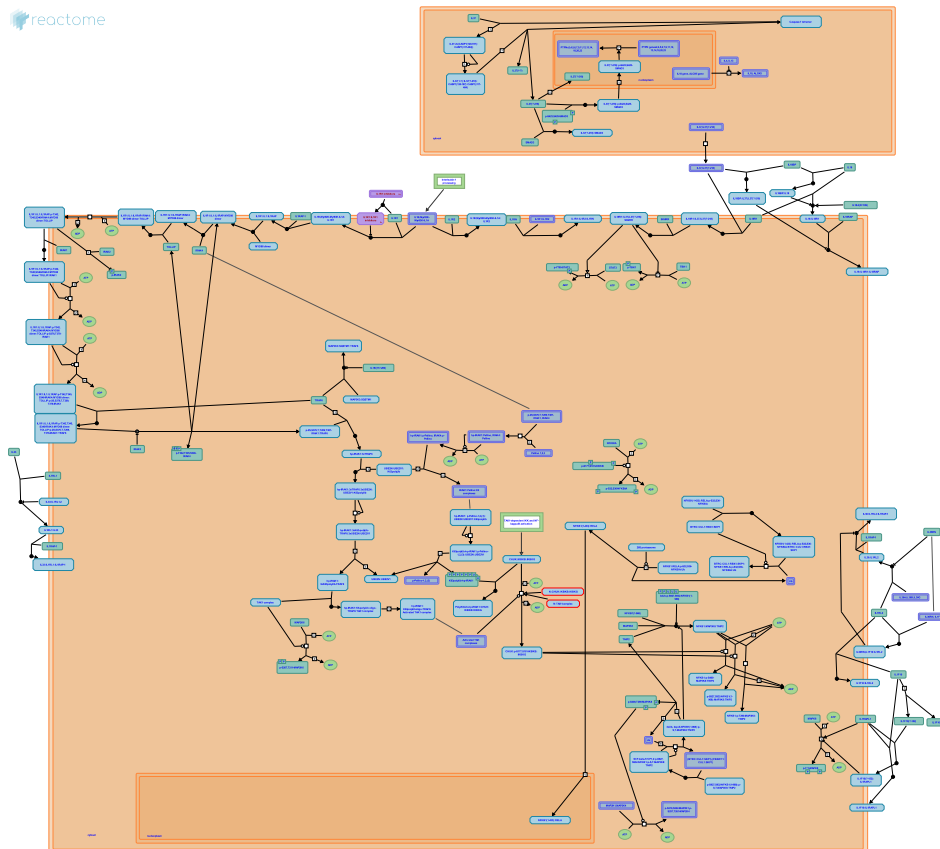
Reactome database release: 88

This document contains 8 pathways ([see Table of Contents](#))

Interleukin-1 family signaling ↗

Stable identifier: R-HSA-446652

Compartments: plasma membrane



The Interleukin-1 (IL1) family of cytokines comprises 11 members, namely Interleukin-1 alpha (IL1A), Interleukin-1 beta (IL1B), Interleukin-1 receptor antagonist protein (IL1RN, IL1RA), Interleukin-18 (IL18), Interleukin-33 (IL33), Interleukin-36 receptor antagonist protein (IL36RN, IL36RA), Interleukin-36 alpha (IL36A), Interleukin-36 beta (IL36B), Interleukin-36 gamma (IL36G), Interleukin-37 (IL37) and Interleukin-38 (IL38). The genes encoding all except IL18 and IL33 are on chromosome 2. They share a common C-terminal three-dimensional structure and with apart from IL1RN they are synthesized without a hydrophobic leader sequence and are not secreted via the classical reticulum endoplasmic-Golgi pathway. IL1B and IL18, are produced as biologically inactive propeptides that are cleaved to produce the mature, active interleukin peptide. The IL1 receptor (IL1R) family comprises 10 members: Interleukin-1 receptor type 1 (IL1R1, IL1RA), Interleukin-1 receptor type 2 (IL1R2, IL1RB), Interleukin-1 receptor accessory protein (IL1RAP, IL1RAcP, IL1R3), Interleukin-18 receptor 1 (IL18R1, IL18RA), Interleukin-18 receptor accessory protein (IL18RAP, IL18RB), Interleukin-1 receptor-like 1 (IL1RL1, ST2, IL33R), Interleukin-1 receptor-like 2 (IL1RL2, IL36R), Single Ig IL-1-related receptor (SIGIRR, TIR8), Interleukin-1 receptor accessory protein-like 1 (IL1RAPL1, TIGGIR2) and X-linked interleukin-1 receptor accessory protein-like 2 (IL1RAPL2, TIGGIR1). Most of the genes encoding these receptors are on chromosome 2. IL1 family receptors heterodimerize upon cytokine binding. IL1, IL33 and IL36 bind specific receptors, IL1R1, IL1RL1, and IL1RL2 respectively. All use IL1RAP as a co-receptor. IL18 binds IL18R1 and uses IL18RAP as co-receptor. The complexes formed by IL1 family cytokines and their heterodimeric receptors recruit intracellular signaling molecules, including Myeloid differentiation primary response protein MyD88 (MYD88), members of the IL1R-associated kinase (IRAK) family, and TNF receptor-associated factor 6 (TRAF6), activating Nuclear factor NF-kappa-B (NFkB), as well as Mitogen-activated protein kinase 14 (MAPK14, p38), c-Jun N-terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs) and other Mitogen-activated protein kinases (MAPKs).

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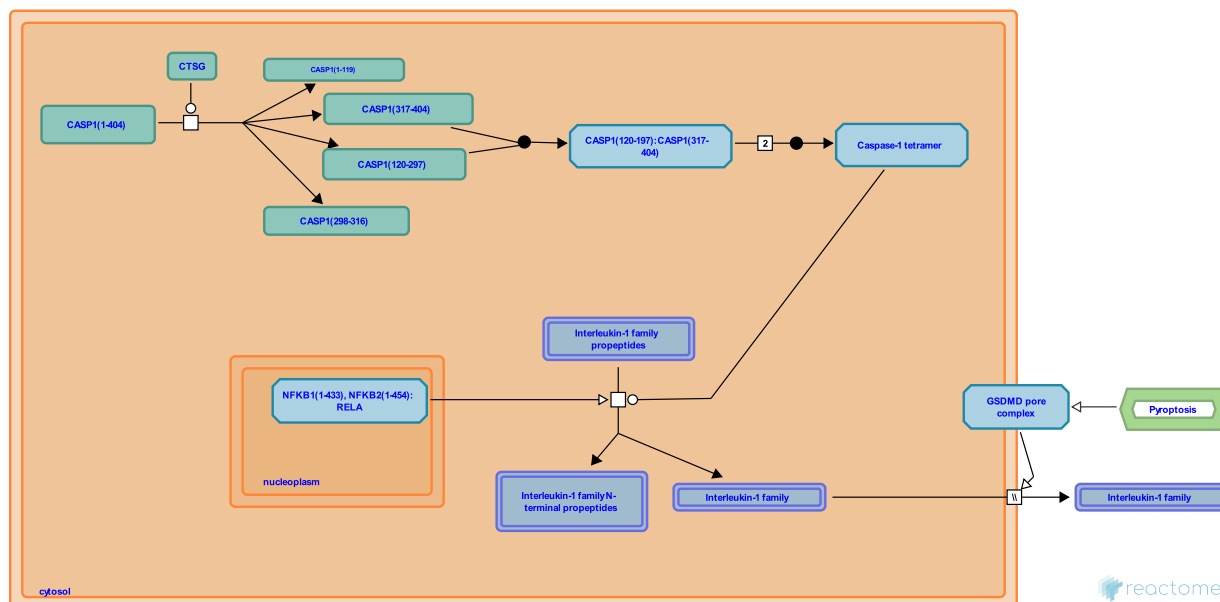
2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

Interleukin-1 processing ↗

Location: [Interleukin-1 family signaling](#)

Stable identifier: R-HSA-448706

Compartments: cytosol



The IL-1 family of cytokines that interact with the Type 1 IL-1R include IL-1 α (IL1A), IL-1 β (IL1B) and the IL-1 receptor antagonist protein (IL1RAP). IL1RAP is synthesized with a signal peptide and secreted as a mature protein via the classical secretory pathway. IL1A and IL1B are synthesised as cytoplasmic precursors (pro-IL1A and pro-IL1B) in activated cells. They have no signal sequence, precluding secretion via the classical ER-Golgi route (Rubartelli et al. 1990). Processing of pro-IL1B to the active form requires caspase-1 (Thornberry et al. 1992), which is itself activated by a molecular scaffold termed the inflammasome (Martinon et al. 2002). Processing and release of IL1B are thought to be closely linked, because mature IL1B is only seen inside inflammatory cells just prior to release (Brough et al. 2003). It has been reported that in monocytes a fraction of cellular IL1B is released by the regulated secretion of late endosomes and early lysosomes, and that this may represent a cellular compartment where caspase-1 processing of pro-IL1B takes place (Andrei et al. 1999). Shedding of microvesicles from the plasma membrane has also been proposed as a mechanism of secretion (MacKenzie et al. 2001). These proposals superseded previous models in which non-specific release due to cell lysis and passage through a plasma membrane pore were considered. However, there is evidence in the literature that supports all of these mechanisms and there is still controversy over how IL1B exits from cells (Brough & Rothwell 2007). A calpain-like protease has been reported to be important for the processing of pro-IL1A, but much less is known about how IL1A is released from cells and what specific roles it plays in biology.

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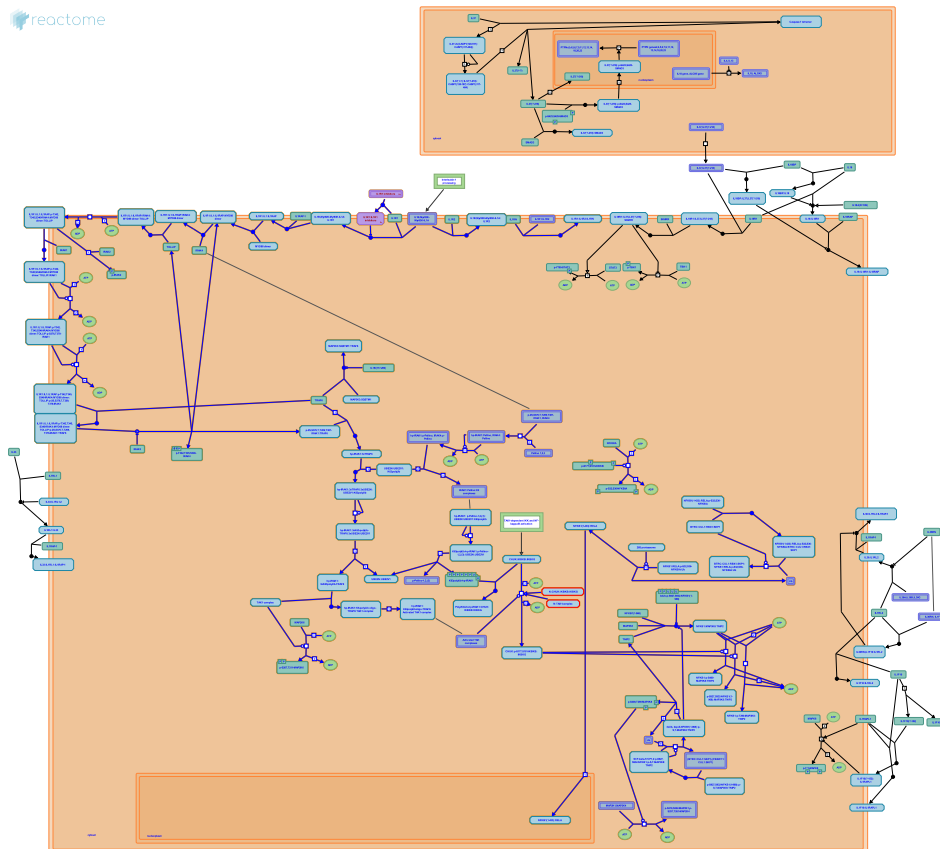
Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Pinteaux, E.

Interleukin-1 signaling ↗

Location: Interleukin-1 family signaling

Stable identifier: R-HSA-9020702



Interleukin 1 (IL1) signals via Interleukin 1 receptor 1 (IL1R1), the only signaling-capable IL1 receptor. This is a single chain type 1 transmembrane protein comprising an extracellular ligand binding domain and an intracellular region called the Toll/Interleukin-1 receptor (TIR) domain that is structurally conserved and shared by other members of the two families of receptors (Xu et al. 2000). This domain is also shared by the downstream adapter molecule MyD88. IL1 binding to IL1R1 leads to the recruitment of a second receptor chain termed the IL1 receptor accessory protein (IL1RAP or IL1RAcP) enabling the formation of a high-affinity ligand-receptor complex that is capable of signal transduction. Intracellular signaling is initiated by the recruitment of MyD88 to the IL1R1/IL1RAP complex. IL1RAP is only recruited to IL1R1 when IL1 is present; it is believed that a TIR domain signaling complex is formed between the receptor and the adapter TIR domains. The recruitment of MyD88 leads to the recruitment of Interleukin-1 receptor-associated kinase (IRAK)-1 and -4, probably via their death domains. IRAK4 then activates IRAK1 to autophosphorylate. Both IRAK1 and IRAK4 then dissociate from MyD88 (Brikos et al. 2007) which remains stably complexed with IL-1R1 and IL1RAP. They in turn interact with Tumor Necrosis Factor Receptor (TNFR)-Associated Factor 6 (TRAF6), which is an E3 ubiquitin ligase (Deng et al. 2000). TRAF6 is then thought to auto-ubiquitinate, attaching K63-polyubiquitin to itself with the assistance of the E2 conjugating complex Ubc13/Uev1a. K63-pUb-TRAF6 recruits Transforming Growth Factor (TGF) beta-activated protein kinase 1 (TAK1) in a complex with TAK1-binding protein 2 (TAB2) and TAB3, which both contain nuclear zinc finger motifs that interact with K63-polyubiquitin chains (Ninomiya-Tsuji et al. 1999). This activates TAK1, which then activates inhibitor of NF-kappaB (IkappaB) kinase 2 (IKK2 or IKKB) within the IKK complex, the kinase responsible for phosphorylation of IkappaB. The IKK complex also contains the scaffold protein NF-kappa B essential modulator (NEMO). TAK1 also couples to the upstream kinases for p38 and c-jun N-terminal kinase (JNK). IRAK1 undergoes K63-linked polyubiquitination; Pellino E3 ligases are important in this process. (Butler et al. 2007; Ordureau et al. 2008). The activity of these proteins is greatly enhanced by IRAK phosphorylation (Schauvliege et al. 2006), leading to K63-linked polyubiquitination of IRAK1. This recruits NEMO to IRAK1, with NEMO binding to polyubiquitin (Conze et al. 2008).

TAK1 activates IKKB (and IKK), resulting in phosphorylation of the inhibitory Ikb proteins and enabling translocation of NFkB to the nucleus; IKKB also phosphorylates NFkB p105, leading to its degradation and the subsequent release of active TPL2 that triggers the extracellular-signal regulated kinase (ERK)1/2 MAPK cascade. TAK1 can also trigger the p38 and JNK MAPK pathways via activating the upstream MKKs3, 4 and 6. The MAPK pathways activate a number of downstream kinases and transcription factors that co-operate with NFkB to induce the

expression of a range of TLR/IL-1R-responsive genes. There are reports suggesting that IL1 stimulation increases nuclear localization of IRAK1 (Bol et al. 2000) and that nuclear IRAK1 binds to the promoter of NFkB-regulated gene and Ikb α , enhancing binding of the NFkB p65 subunit to NFkB responsive elements within the Ikb α promoter. IRAK1 is required for IL1-induced Ser-10 phosphorylation of histone H3 in vivo (Liu et al. 2008). However, details of this aspect of IRAK1 signaling mechanisms remain unclear. Interleukin-18 is another Interleukin-1 related cytokine which signals through IL18R and IL18RAP subunit receptors (which share homology with IL1R and IL1RAP in the cytokine signaling cascade). Later it follows a MYD88/IRAK1/TRAF6 cascade signaling until reach the NFkB activation (Moller et al. 2002). Interleukin 33, 36, 37 and 38 are relatively recently discovered Interleukin-1 related cytokines which are also able to signal through IL1 receptor subunits or other as IL18R, IL37R (Schmitz et al. 2005, Yi et al. 2016, Lunding et al. 2015, van de Veendorck et al. 2012, Lin et al. 2001).

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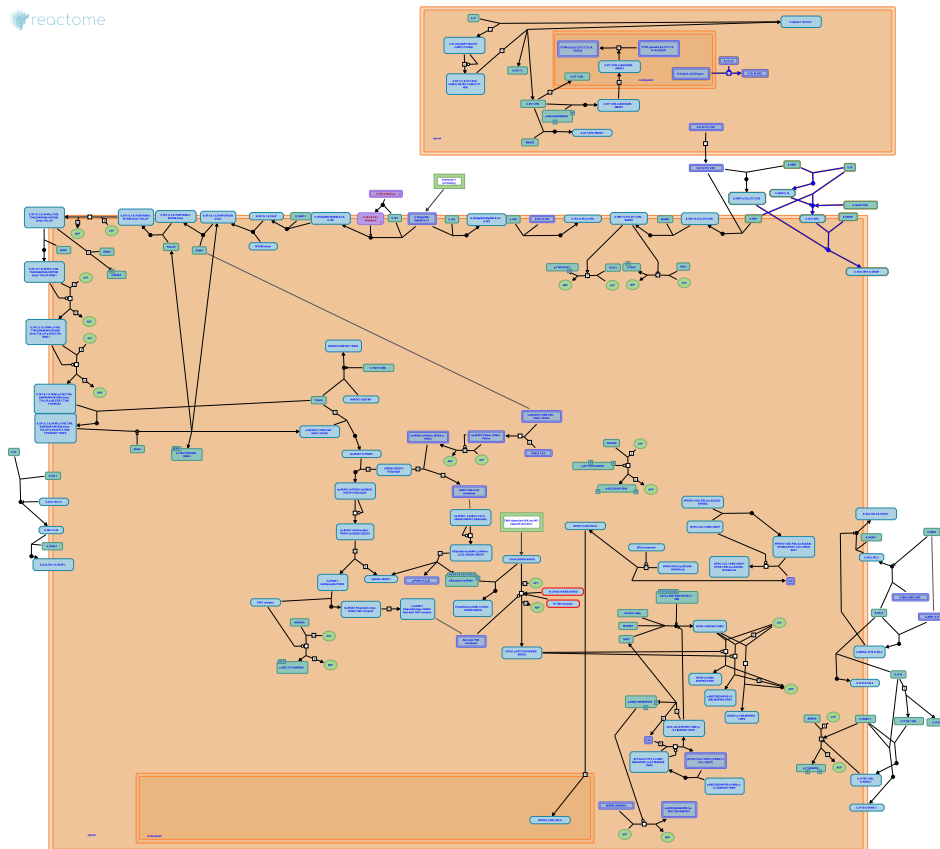
Editions

2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.
2017-11-09	Edited	Jupe, S.

Interleukin-18 signaling ↗

Location: Interleukin-1 family signaling

Stable identifier: R-HSA-9012546



Interleukin-18 (IL18, pro-IL18) is a pleiotropic and pro inflammatory cytokine. It belongs to the Interleukin-1 (IL1 superfamily (Alboni et al. 2010, Krumm et al. 2017, Dinarello 1999). IL18 is synthesized as an inactive 24-kDa precursor protein that is cleaved by extracellular proteases such as caspase-1, protease 3, serine protease, elastase or cathepsin G (Fantuzzi & Dinarello 1999, Gracie et al. 2004, Sugawara et al. 2001), forming an 18-kDa mature protein (Arend et al. 2008, Akita et al. 1997, Fantuzzi et al. 1998, Ghayur et al. 1997, Gu et al. 1997, Ushio et al. 1996).

IL18 also occurs as a short isoform, the result of an alternative splicing event that removes 57 bp/19 aa (IL18alpha) (Conti et al. 1997, Yang et al. 2005). This short isoform has a modest synergistic action with the IL18 canonical active form. The IL18 receptor (IL18R) belongs to the Interleukin-1 receptor/Toll like receptor superfamily. It consists of two subunits, Interleukin-18 receptor 1 (IL18R1, IL-18R α , IL1Rrp1, IL18R1, IL-1R5) and Interleukin-18 receptor accessory protein (IL18RAP, IL18RB, IL-18R β ,IL-18RacP, IL-18RII or IL-1R7). Both subunits have three extracellular immunoglobulin-like domains and one intracellular Toll/IL-1 receptor (TIR) domain (O'Neill & Dinarello 2000, Sims 2002). It is believed that IL18 binds first to IL18R1 and later recruits IL18RAP to form a high-affinity heterotrimeric complex (Sims 2002, Sergi & Pentilla 2004, Alboni et al. 2009). A short isoform of IL18R1 lacks the TIR domain (IL18R1 type II) (Alboni et al. 2009), which is required for signaling, leading to the suggestion that IL18R1 type II is a decoy receptor (Colotta et al. 1994). A truncated form of IL18RAP containing only one of the three immunoglobulin domains stabilizes IL18 binding to IL18R1 but prevents signaling.

IL-18 binding protein (IL18BP), a 38-kDa soluble protein, is another negative regulator of IL18 signaling. It has some sequence homology with IL18R1 (Im et al. 2002, Kim et al. 2002, Novick et al. 1999). IL18BP binds with high affinity to mature IL18, preventing its interaction with IL18R1. Several isoforms IL18BP have been described (Kim et al. 2000). Interleukin-37 (IL37, IL-1F7), another negative regulator of IL18 signaling, is able to bind IL18BP and IL18RAP preventing signaling (Bufler et al.2002, Pan et al. 2001, Kumar et al. 2002).

IL18 stimulates Interferon gamma (IFNG, IFN- γ) production from T-helper lymphocytes cells (Th1) and macrophages and enhances the cytotoxicity of natural killer (NK) cells. IL18 stimulated IFNG production is synergistically amplified by other Th1-related cytokines such as IL2, IL15, IL12 and IL23 (Boraschi & Dinarello 2006, Park et al. 2007, Dinarello 2007, Dinarello & Fantuzzi 2003).

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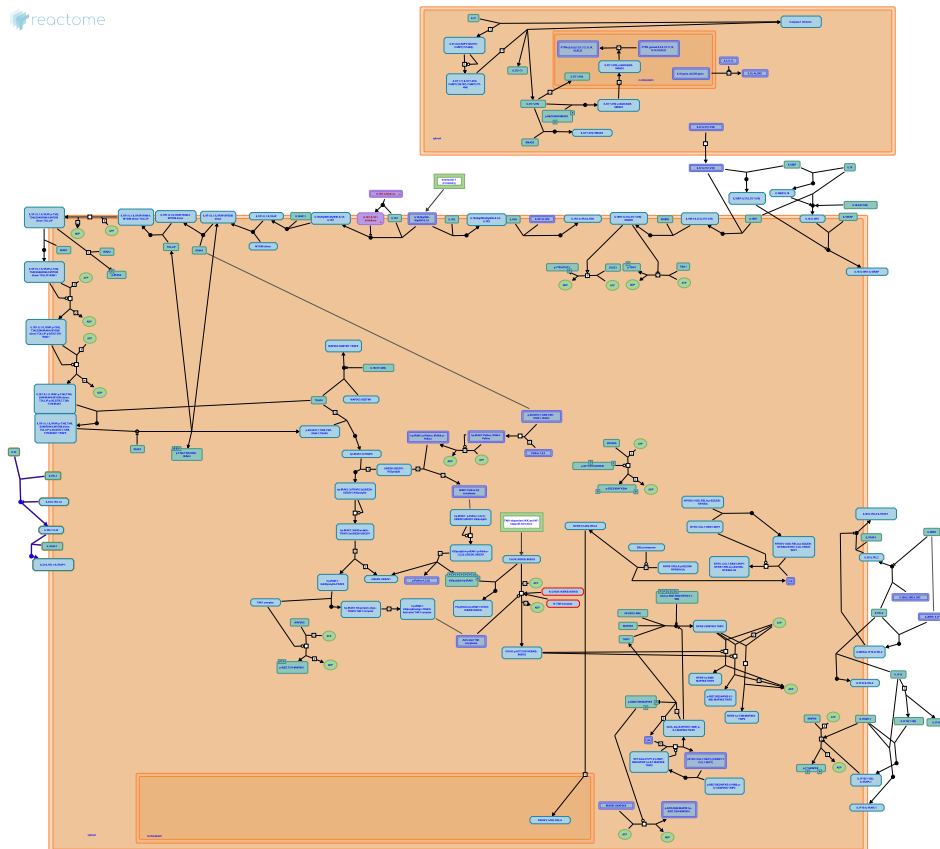
Editions

2016-01-28	Reviewed	Meldal, BH.
2017-08-08	Authored, Edited	Duenas, C.

Interleukin-33 signaling ↗

Location: [Interleukin-1 family signaling](#)

Stable identifier: R-HSA-9014843



Interleukin-33 (IL33) cytokine is a member of the Interleukin-1 family. It can be classified as an alarmin because it is released into the extracellular space during cell damage. It acts as an endogenous danger signal (Liew et al. 2010.) The gene product is biologically active (full-length IL33). Its potency has been reported to increase significantly (up to 30x) after cleavage at the N-terminus by inflammatory proteases such as Cathepsin G (CTSG) and Neutrophil elastase (ELANE) (Lefrançois et al. 2012, Lefrançois et al. 2014) but others have suggested that processing inactivates IL33 (Cayrol & Girard 2009). IL33 can act as an extracellular ligand and an intracellular signaling molecule (Martin et al. 2013, 2016). Full-length IL33 has a nuclear localization sequence and can translocate to the nucleus, where it binds heterochromatin (Moussion et al. 2008, Carriere et al. 2007, Roussel et al. 2008, Kuchler et al. 2008, Sundlisaeter et al. 2012, Baekkevold et al. 2003). IL33 that has undergone proteolytic processing is unable to translocate to the nucleus (Martin et al. 2013, Ali et al. 2010). Binding of extracellular IL33 to its receptor Interleukin-1 receptor-like 1 (IL1RL1, suppression of tumorigenicity 2, ST2) initiates several cellular signaling pathways. Cell injury or death are the dominant mechanisms by which IL33 reaches the extracellular environment, IL33 is not actively secreted by cells (Martin et al. 2016, Kaczmarek et al. 2013, Vancamelbeke et al. 2017). Because IL33 is expressed constitutively by endothelial and epithelial cells it is immediately available to the extracellular microenvironment after cell injury and necrosis (Lefrançois et al. 2012). Increases in extracellular ATP or mechanical stress correlate with increased IL33 secretion by mast cells or cardiomyocytes, respectively (Shimokawa et al. 2017, Kakkar et al. 2012, Zhao et al. 2012, Sanada et al. 2007, Chen et al. 2015). Soluble IL1RL1 (IL1RL1 Isoform C, ST2V) (Iwahana et al. 2005, Tominaga et al. 1999) shares the extracellular components of IL1RL1, including the ligand binding domain, but lacks the transmembrane and intracellular components of IL1RL1 (Kakkar et al. 2008, Iwahana et al. 1999). The IL33-IL1RL1 complex recruits a co-receptor, most commonly IL1 receptor accessory protein (IL1RAP, IL-1RAcP) (Schmitz et al. 2005, Lingel et al. 2009, Palmer et al. 2008, Liu et al. 2013).

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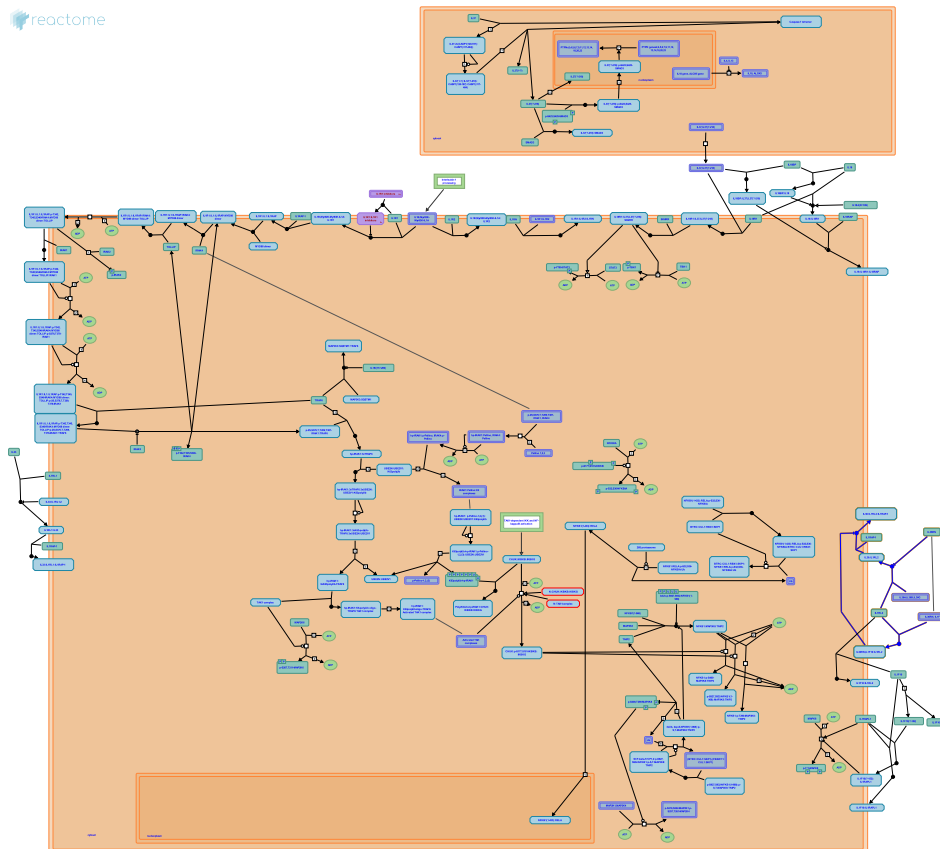
Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
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Interleukin-36 pathway ↗

Location: [Interleukin-1 family signaling](#)

Stable identifier: R-HSA-9014826



Interleukin-36 alpha (IL36A), IL36B and IL36G are collectively known as IL36. They are members of the Interleukin-1 family that signal through a receptor composed of Interleukin-1 receptor-like 2 (IL1RL2, IL36R) and Interleukin-1 receptor accessory protein (IL1RAP, IL-1R/AcP) to promote inflammatory responses. Interleukin-36 receptor antagonist protein (IL36RN, IL36Ra) is a natural antagonist. IL36 is expressed predominantly by epithelial cells and is implicated strongly through functional and genetic evidence in the pathology of psoriatic disorders.

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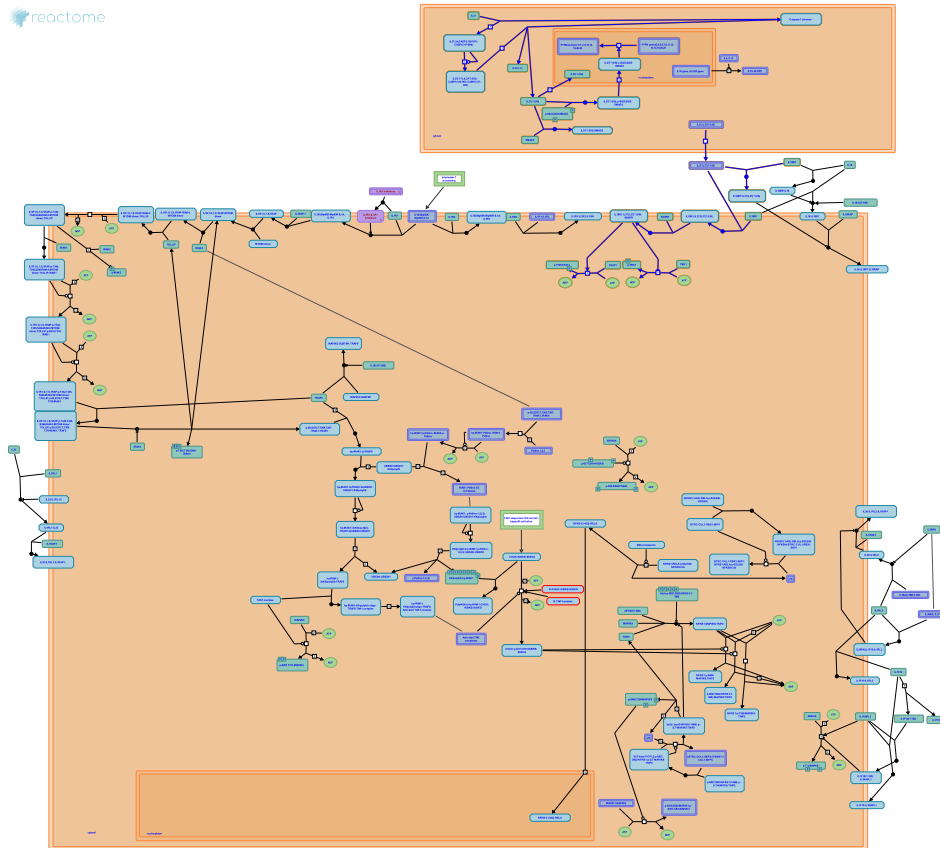
2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.

Interleukin-37 signaling ↗

Location: [Interleukin-1 family signaling](#)

Stable identifier: R-HSA-9008059

Compartments: plasma membrane, extracellular region, cytosol



Interleukins (IL) are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 37 (IL37), also known as IL 1F7, is a member of the IL 1 family (Sharma et al. 2008). Isoform b of IL37 (referred just as IL37) is synthesized as a precursor that requires processing (primarily by caspase 1) to attain full receptor agonist or antagonist function (Kumar et al. 2002). Both full length and processed IL37 can bind to the IL 18 binding protein (IL 18BP) and the Interleukin 18 receptor 1 (IL 18R1) (Shi et al. 2003). Upon binding to the IL18R1, IL37 recruits Single Ig IL 1 related receptor (SIGIRR) (Nold-Petry et al. 2015). The IL37:IL18R1 complex can activate phosphorylation of Signal transducer and activator of transcription 3 (STAT3), Tyrosine protein kinase Mer and Phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase and dual specificity protein phosphatase PTEN and can also inhibit Nuclear factor NF kappa B p105 subunit (NFkB) (Nold-Petry et al. 2015). Processed IL37 can be secreted from the cytosol to the extracellular space or translocated into the nucleus (Bulau et al. 2014). Full length IL37 can also be secreted from the cytosol to the extracellular space (Bulau et al. 2014). Processed IL37 can bind with Mothers against decapentaplegic homolog 3 (SMAD3) in the cytosol and then translocate to the nucleus, where it facilitates transcription of Tyrosine protein phosphatase non receptors (PTPNs) (Nold et al. 2010, Luo et al. 2017). These events ultimately lead to suppression of cytokine production in several types of immune cells resulting in reduced inflammation.

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Editions

2017-08-08

Authored, Edited

Varusai, TM.

2017-11-02

Reviewed

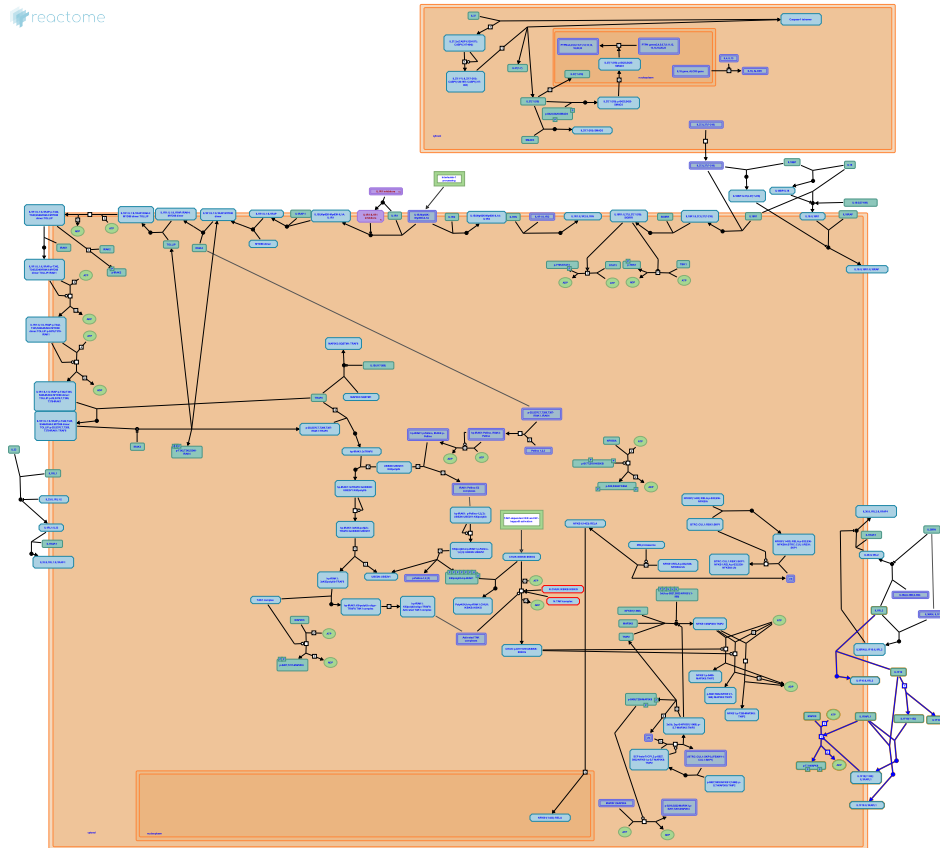
Mantovani, A., Garlanda, C., Carriero, R.

Interleukin-38 signaling ↗

Location: [Interleukin-1 family signaling](#)

Stable identifier: R-HSA-9007892

Compartments: nucleoplasm, extracellular region, cytosol



Interleukins are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 1 family member 10 (IL1F10, IL 38) is a member of the IL1 family (Lin et al. 2001, Bensen et al. 2001). IL1F10 is selectively produced by human apoptotic cells (Mora et al. 2016) and human epidermal keratinocytes (based on mRNA studies) (Boutet M A et al. 2016). IL1F10 can bind to interleukin 1 receptor like 2 (IL1RL2) and may result in the suppression of IL 17 and IL 22 and induction of IL 6 production (van de Veerdonk et al. 2012, Mora et al. 2016). IL1F10 is synthesized as precursors that require N terminal processing to attain full receptor agonist or antagonist function (Mora et al. 2016). Both full length (1 – 152 amino acids) and N terminal truncated (20 – 152 amino acids) IL1F10 can bind Interleukin 1 receptor accessory protein like 1 (IL1RAPL1) (Mora et al. 2016). The binding affinity of truncated IL1F10 is much higher than that of the full length. However, binding of the full length or truncated forms has distinct outcomes; the former induces IL6 and the latter suppresses IL6 via JNK and AP1 signaling (Mora et al. 2016).

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Editions

2017-07-28	Reviewed	Mora, J.
2017-08-08	Authored, Edited	Varusai, TM.

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