FCERI mediated NF-kB activation

Garapati, P V., Geijtenbeek, TB., Niarakis, A., Roncagalli, R., Rudd, C.E., Trowsdale, J., de Bono, B.

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05/04/2020
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: 72

This document contains 1 pathway and 19 reactions (see Table of Contents)
The increase in intracellular Ca+2 in conjunction with DAG also activates PKC and RasGRP, which in turn contributes to cytokine production by mast cells (Kambayashi et al. 2007). Activation of the FCERI engages CARMA1, BCL10 and MALT1 complex to activate NF-kB through PKC-theta (Klemm et al. 2006, Chen et al. 2007). FCERI stimulation leads to phosphorylation, and degradation of IkB which allows the release and nuclear translocation of the NF-kB proteins. Activation of the NF-kB transcription factors then results in the synthesis of several cytokines. NF-kB activation by FCERI is critical for proinflammatory cytokine production during mast cell activation and is crucial for allergic inflammatory diseases (Klemm et al. 2006).

**Literature references**


RasGRP interacts with DAG and Ca2+

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730871

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Inferred from:** RasGRP interacts with DAG and Ca2+ (Mus musculus)

Ras guanyl nucleotide-releasing proteins (RasGRPs) are guanyl nucleotide exchange factors (GEFs) that activate Ras ultimately leading to MAPK activation. RasGRPs have a catalytic domain composed of Ras exchange motif (REM) and a CDC25 domain, an atypical pair of EF hands that bind calcium and a DAG-binding C1 domain. After PIP2 hydrolysis, RasGRPs are recruited to the plasma membrane by binding to DAG and calcium (Stone 2011, Liu et al. 2007). Upon T-cell activation RasGRP1 specifically interacts with and activates Ras on Golgi instead of the plasma membrane (Bivona et al. 2003). It remains to be determined whether activation of N-Ras by RasGRP1 in mast cells occurs in the Golgi or the plasma membrane (Liu et al. 2007). RasGRP4 is mast cell specific and is involved in the controls Ras activation.

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Translocation of PKC theta to plasma membrane

Location: FCERI mediated NF-kB activation

Stable identifier: R-HSA-202328

Type: binding

Compartments: cytosol, plasma membrane

DAG along with intracellular calcium signals cooperatively to activate PKCs, which then trigger other pathways such as the NF-κB pathway, ultimately leading to mast cell (MC) degranulation and cytokine production (Wu 2011). PKC theta is a member of the Ca++ independent and DAG dependent, novel PKC subfamily expressed mainly in T cells. It contains, N-term C2 like domain, a pseudosubstrate (PS), DAG binding (C1) domain and a C-term kinase domain. The PS sequence resembles an ideal substrate with the exception that it contains an alanine residue instead of a substrate serine residue, is bound to the kinase domain in the resting state. As a result, PKC theta is maintained in a closed inactive state, which is inaccessible to cellular substrates.

MCs express several Protein kinase C (PKC) isozymes and these kinases are involved in both the activation and termination of the degranulation process. PKC-delta is a negative regulator of FCERI mediated mast cell degranulation, whereas PKC-theta facilitates in degranulation (Leitges et al. 2002, Liu et al. 2001). In response to FCERI activation PKC-theta translocates to membrane by binding to DAG with its C1 domain. PKC-theta exists in two conformations closed/inactive and open/active state. In resting state, PKC-theta is autoinhibited where the pseudosubstrate sequence in the N-terminal regulatory region of PKC-theta forms intramolecular interaction with the substrate-binding region in the catalytic domain. This prevents the catalytic domain gaining access to substrates. The allosteric change of PKC-theta from closed to open state involves two important mechanisms: DAG binding to the C1 domains and autophosphorylation of T538 on the activation loop. Interaction with DAG induces conformational change resulting in the exposure of the activation loop of PKC-theta (Wang et al. 2012, Melowic et al. 2007).

Followed by: Phosphorylation of PKC-theta

Literature references


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Phosphorylation of PKC-theta

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730882

**Type:** transition

**Compartments:** plasma membrane, cytosol

Raft localized PKC-theta is phosphorylated and is activated. Phosphorylation of both tyrosine and serinethreonine residues is important in the regulation of PKC function. Six phosphorylation sites have been identified on PKC-theta: Y90, T219, T538, S676, S685, and S695. Phosphorylation of Y90 positively regulates NF-AT and NF-kB activation in T-cells. In mast cells Src family members Src and LYN have been shown to be involved in phosphorylating Y90 (Wang et al. 2012, Liu et al. 2001).

**Preceded by:** Translocation of PKC theta to plasma membrane

**Followed by:** Autophosphorylation of PKC-theta

**Literature references**


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Autophosphorylation of PKC-theta

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730835

**Type:** transition

**Compartments:** cytosol, plasma membrane

T219, T538 at the activation loop, S676 at the turn motif and S695 at the hydrophobic motif are autophosphorylated in cis-manner. Phosphorylation of T538 is critical for kinase activation and it stabilises the open active conformation. Some studies suggest the involvement of PDK1 (3-phosphoinositide-dependent protein kinase 1) and GLK kinases in the phosphorylation T538.

**Preceded by:** Phosphorylation of PKC-theta

**Followed by:** Phosphorylation of CARMA1 by PKC-theta

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Phosphorylation of CARMA1 by PKC-theta

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730863

**Type:** transition

**Compartments:** plasma membrane, cytosol

CARMA1 (CARD11/Caspase recruitment domain-containing protein 11), BCL10 (B-cell lymphoma/leukemia 10) and MALT1 (Mucosa-associated lymphoid tissue lymphoma translocation protein 1)/paracaspase have been identified as signaling components that act downstream of PKC-theta. CARMA1 is a scaffold protein and recruits BCL10, MALT1, PKC and TRAF6 to form a multi protein complex. CARMA1 exists in an inactive conformation in which the linker region binds to and blocks the accessibility of the CARD motif. Upon stimulation S552 and S645 linker residues are phosphorylated by PKC-theta and this may weaken this interaction, inducing an open conformation of CARMA1. Further phosphorylation studies have revealed other phosphorylation sites (S109, S551 and S555) that may also promote activation of CARMA1. Serine/threonine kinases PKC-beta, IKKbeta, HPK1 and CaMKII are involved in triggering CARMA1 activation (Thome et al. 2010, Rueda & Thome 2005). (only phosphorylated S552 and S645 are represented in this reaction)

**Preceded by:** Autophosphorylation of PKC-theta

**Followed by:** Oligomerization of p-CARMA1

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Oligomerization of p-CARMA1

Location: FCERI mediated NF-kB activation

Stable identifier: R-HSA-2730902

Type: omitted

Compartments: plasma membrane, cytosol

CARMA1 phosphorylation initiates its oligomerization and the coiled-coil (CC) domain of CARMA1 is hypothesized to mediate this clustering (Tanner et al. 2007).

Preceded by: Phosphorylation of CARMA1 by PKC-theta

Followed by: Interaction of BCL10:MALT1 with CARMA1 to form CBM complex

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Interaction of BCL10:MALT1 with CARMA1 to form CBM complex

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730836

**Type:** binding

**Compartments:** cytosol, plasma membrane

**Inferred from:** Interaction of Bcl10:Malt1 with Carma1 to form CBM complex (Mus musculus)

Phosphorylation of CARMA1 causes conformational change such that its CARD motif is exposed and is free to interact with BCL10 CARD motif. BCL10 constitutively associated with MALT1 and exists as a pre-formed complex in the cytoplasm. BCL10 and MALT1 have been identified as key positive regulators of FCERI-dependent NF-kB activation (Klemm et al. 2006). The resulting CARMA1-BCL10-MALT1 (CBM) complex may be stabilized by interactions between the CARMA1 coiled coil (CC) domain and a C-terminal MALT1 region that lacks the DD and first two Ig domains (Thome et al. 2010, Che et al. 2004). The CBM complex transmits activating signals that ultimately result in ubiquitination (Ub) and degradation of the NF-kB inhibitor, IkBα.

**Preceded by:** Oligomerization of p-CARMA1

**Followed by:** Oligomerization of BCL10 and MALT1

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Oligomerization of BCL10 and MALT1

Location: FCERI mediated NF-kB activation

Stable identifier: R-HSA-2730899

Type: uncertain

Compartments: plasma membrane, cytosol

BCL10 and MALT1 proteins form high molecular weight oligomers and only these oligomeric forms can activate IKK in vitro (Sun et al. 2004). BCL10 proteins form homo-oligomers through CARD-CARD interactions whereas in MALT1 the tandem Ig-like domains naturally form oligomers with a tendency towards dimers and tetramers (Dong et al. 2006, Qiu & Dhe-Paganon 2011). These CBM oligomers provides the molecular platform, which can facilitate dimerization or serve as scaffolds on which proteases and kinases involved in NF-kB activation are assembled and activated.

Preceded by: Interaction of BCL10:MALT1 with CARMA1 to form CBM complex

Followed by: Recruitment of TRAF6 to CBM complex by binding to MALT1

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Recruitment of TRAF6 to CBM complex by binding to MALT1

Location: FCERI mediated NF-kB activation

Stable identifier: R-HSA-2730864

Type: binding

Compartments: plasma membrane, cytosol

TRAF6 is a ubiquitin ligase that plays a central role in the IKK-dependent canonical NF-kB pathway. It is recruited to the CBM complex by binding to MALT1. The MALT1 C-terminal Ig domain and extension contain two binding motifs for TRAF6 (Noels et al 2007). After oligomerization TRAF6, together with Ubc13/Uev1A, activates TAK1 and IKK. It also acts as an E3 ligase for MALT1 and mediates lysine 63-linked ubiquitination (Oeckinghaus et al. 2007).

Preceded by: Oligomerization of BCL10 and MALT1

Followed by: Oligomerization of TRAF6

Literature references


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Oligomerization of TRAF6

Location: FCERI mediated NF-kB activation

Stable identifier: R-HSA-2730903

Type: omitted

Compartments: plasma membrane, cytosol

BCL10-MALT1 oligomers bind to TRAF6 and this in turn promotes the oligomerization of TRAF6 and activates its E3 ligase activity (Sun et al. 2004).

Preceded by: Recruitment of TRAF6 to CBM complex by binding to MALT1

Followed by: Auto-ubiquitination of TRAF6

Literature references

Sun, L., Deng, L., Ea, CK., Xia, ZP., Chen, ZJ. (2004). The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. Mol Cell, 14, 289-301.

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Auto-ubiquitination of TRAF6

**Location:** FCERI mediated NF-κB activation

**Stable identifier:** R-HSA-2730904

**Type:** omitted

**Compartments:** plasma membrane, cytosol

TRAF6 possesses ubiquitin ligase activity and undergoes K-63-linked auto-ubiquitination after its oligomerization. In the first step, ubiquitin is activated by an E1 ubiquitin activating enzyme. The activated ubiquitin is transferred to a E2 conjugating enzyme (a heterodimer of proteins Ubc13 and Uev1A) forming the E2-Ub thioester. Finally, in the presence of ubiquitin-protein ligase E3 (TRAF6, a RING-domain E3), ubiquitin is attached to the target protein (TRAF6 on residue Lysine 124) through an isopeptide bond between the C-terminus of ubiquitin and the epsilon-amino group of a lysine residue in the target protein. In contrast to K-48-linked ubiquitination that leads to the proteosomal degradation of the target protein, K-63-linked polyubiquitin chains act as a scaffold to assemble protein kinase complexes and mediate their activation through proteosome-independent mechanisms. This K63 polyubiquitinated TRAF6 activates the TAK1 kinase complex.

**Preceded by:** Oligomerization of TRAF6

**Followed by:** Recruitment of TAK1 kinase complex to oligo-K63-pUb-TRAF6

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Recruitment of TAK1 kinase complex to oligo-K63-pUb-TRAF6

Location: FCERI mediated NF-kB activation

Stable identifier: R-HSA-2730861

Type: binding

Compartments: plasma membrane, cytosol

K-63 linked polyubiquitin (pUb) chain on TRAF6 provides a scaffold to recruit downstream effector molecules to activate NF-kB. Transforming growth factor beta-activated kinase 1 (TAK1) is a member of the mitogen-activated protein kinase (MAPK) kinase kinase family is shown to be an essential intermediate that transmits the upstream signals from the receptor complex to the downstream MAPKs and to the NF-kB pathway (Broglie et al. 2009). TAK1-binding protein 1 (TAB1), TAB2 and TAB3 constitutively bound to TAK1. TAB1 acts as the activation subunit of the TAK1 complex, aiding in the autophosphorylation of TAK1, whereas TAB2 and its homologue TAB3, act as adaptors of TAK1 that facilitate the assembly of TAK1 complex to TRAF6. The highly conserved C-terminal zinc finger domain of TAB2 and TAB3 binds preferentially to the K-63-linked polyubiquitin chains on TRAF6 (Broglie et al. 2009, Besse et al. 2007).

Preceded by: Auto-ubiquitination of TRAF6

Followed by: Activation of TAK1 complex bound to pUb-TRAF6

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Activation of TAK1 complex bound to pUb-TRAF6

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730900

**Type:** omitted

**Compartments:** plasma membrane, cytosol

Binding of TAB2 and TAB3 to K63-linked polyubiquitin chains leads to the activation of TAK1 by an uncertain mechanism. Phosphorylation of TAK1 within the activation loop of the kinase is absolutely required for TAK1 activity. TAB1 is known to augment TAK1 catalytic activity by mediating spontaneous oligomerization and induces autophosphorylation of TAK1 (Kishimoto et al. 2000). The binding of TAB2/3 to polyubiquitinated TRAF6 may facilitate polyubiquitination of TAB2/3 by TRAF6 (Ishitani et al. 2003), which might result in conformational changes within the TAK1 complex that leads to the activation of TAK1. Some biochemical studies revealed that free K63 polyubiquitin chains, which are not conjugated to any cellular protein, can directly activate the TAK1 kinase complex (Xia et al. 2009).

**Preceded by:** Recruitment of TAK1 kinase complex to oligo-K63-pUb-TRAF6

**Followed by:** Phosphorylation of IKK-beta by TAK1

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Phosphorylation of IKK-beta by TAK1

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730876

**Type:** transition

**Compartments:** cytosol, plasma membrane

In humans, the IkB kinase (IKK) complex serves as the master regulator for the activation of NF-kB by various stimuli. It contains two catalytic subunits, IKK alpha and IKK beta, and a regulatory subunit, IKKgamma/NEMO. The activation of IKK complex is dependent on the phosphorylation of IKK alpha/beta at its activation loop and the K63-linked ubiquitination of NEMO. This basic trimolecular complex is referred to as the IKK complex.

IKK subunits have a N-term kinase domain a leucine zipper (LZ) motifs, a helix-loop-helix (HLH) and a C-ter NEMO binding domain (NBD). IKK catalytic subunits are dimerized through their LZ motifs. IKK beta is the major IKK catalytic subunit for NF-kB activation. Activated TAK1 phosphorylate IKK beta on S177 and S181 (S176 and S180 in IKK alpha) in the activation loop and thus activate the IKK kinase activity, leading to the IkB alpha phosphorylation and NF-kB activation.

**Preceded by:** Activation of TAK1 complex bound to pUb-TRAF6

**Followed by:** Ubiquitination of NEMO by TRAF6

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During the phosphorylation of the IKK beta, the regulatory subunit NEMO undergoes K-63-linked polyubiquitination. Ubiquitinated TRAF6 trimer, acts as a E3 ligase and induces this ubiquitination. The ubiquitin target sites in NEMO are not yet clearly identified. Studies of different NF-kB signaling pathways revealed several potential ubiquitination sites on NEMO (e.g., K285, K277, K309 and K399) (Fuminori et al. 2009).

**Preceded by:** Phosphorylation of IKK-beta by TAK1

**Followed by:** p-S177,S181-IKKB:IKKA:pUb-NEMO phosphorylates IκB-alpha:NF-kB

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p-S177,S181-IKKB:IKKA:pUb-NEMO phosphorylates IkB-alpha:NF-kB

Location: FCERI mediated NF-kB activation

Stable identifier: R-HSA-202541

Type: transition

Compartments: plasma membrane

NF-kB is sequestered in the cytosol of unstimulated cells through the interactions with a class of inhibitor proteins, called IkBs, which mask the nuclear localization signal (NLS) of NF-kB and prevent its nuclear translocation. A key event in NF-kB activation involves phosphorylation of IkB (at sites equivalent to Ser32 and Ser36 of IkB-alpha or Ser19 and Ser22 of IkB-beta) by IKK. The phosphorylated IkB-alpha is recognized by the E3 ligase complex and targeted for ubiquitin-mediated proteasomal degradation, releasing the NF-kB dimer p50/p65 into the nucleus to turn on target genes. (Karin & Ben-Neriah 2000)

Preceded by: Ubiquitination of NEMO by TRAF6

Followed by: beta-TRCP ubiquitinates IkB-alpha in p-S32,33-IkB-alpha:NF-kB complex

Literature references


Editions

2008-01-24 Authored de Bono, B., Garapati, P V., Rudd, C.E.
2008-02-26 Reviewed Trowsdale, J.
Two major signaling steps are required for the removal of IkappaB (IkB) alpha an inhibitor of NF-kB: activation of the IkB kinase (IKK) and degradation of the phosphorylated IkB alpha. IKK activation and IkB degradation involve different ubiquitination modes; the former is mediated by K63-ubiquitination and the later by K48-ubiquitination. Mutational analysis of IkB alpha has indicated that K21 and K22 are the primary sites for addition of multiubiquitination chains while K38 and K47 are the secondary sites. In a transesterification reaction the ubiquitin is transferred from the ubiquitin-activating enzyme (E1) to an E2 ubiquitin-conjugating enzyme, which may, in turn, transfer the ubiquitin to an E3 ubiquitin protein ligase. UBE2D2 (UBC4) or UBE2D1 (UBCH5) or CDC34 (UBC3) acts as the E2 and SCF (SKP1-CUL1-F-box)-beta-TRCP complex acts as the E3 ubiquitin ligase (Strack et al. 2000, Wu et al. 2010). beta-TRCP (beta-transducin repeats-containing protein) is the substrate recognition subunit for the SCF-beta-TRCP E3 ubiquitin ligase. beta-TRCP binds specifically to phosphorylated IkB alpha and recruits it to the SCF complex, allowing the associated E2, such as UBC4 and or UBC5 to ubiquitinate Ikappa B alpha (Baldi et al. 1996, Rodriguez et al. 1996, Scherer et al. 1995, Alkalay et al. 1995).

Preceded by: p-S177,S181-IKKB:IKKA:pUb-NEMO phosphorylates IkB-alpha:NF-kB

Followed by: 26S proteasome processes K48PolyUb-K21,22-p-S32,36-IkBA:NF-kB complex to form NF-kB complex

Literature references


## Editions

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<td>Reviewed</td>
<td>Geijtenbeek, TB.</td>
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**26S proteasome processes K48PolyUb-K21,22-p-S32,36-IkBA:NF-kB complex to form NF-kB complex**

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-5607724

**Type:** omitted

**Compartments:** cytosol

Following ubiquitination Ikappa B-alpha (IKBA) is rapidly degraded by 26S-proteasome, allowing NF-kB to translocate into the nucleus where it activates gene transcription (Spencer et al. 1999).

**Preceded by:** beta-TRCP ubiquitinates IkB-alpha in p-S32,33-IkB-alpha:NF-kB complex

**Followed by:** NFKB1:RELA translocates from the cytosol to the nucleus

**Literature references**


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https://reactome.org
**NFkB1:RELA translocates from the cytosol to the nucleus**

**Location:** FCERI mediated NF-kB activation

**Stable identifier:** R-HSA-2730894

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

The released NF-kB transcription factor (p50/p65) with unmasked nuclear localization signal (NLS) moves in to the nucleus. Once in the nucleus, NF-kB binds DNA and regulate the expression of genes encoding cytokines, cytokine receptors, and apoptotic regulators.

**Preceded by:** 26S proteasome processes K48PolyUb-K21,22-p-S32,36-IkBA:NF-kB complex to form NF-kB complex

**Literature references**


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