Activation of NF-kappaB in B cells

May, B., Wienands, J.

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

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25/06/2019
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: 69

This document contains 1 pathway and 10 reactions (see Table of Contents)
Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1169091

Compartments: cytosol, nucleoplasm, plasma membrane


Literature references


PRKCB (Protein kinase C beta, PKC-beta) binds diacylglycerol and phosphatidyserine

**Location:** Activation of NF-kappaB in B cells

**Stable identifier:** R-HSA-1168373

**Type:** binding

**Compartments:** cytosol, plasma membrane

Human Protein kinase C beta (PKC-beta) is activated by calcium ions, diacylglycerol, and binds phosphatidyserine (Kochs et al. 1991). Experiments in mice have shown that knocking out PKC-beta causes severe defects in B cells, leading to the conclusion that PKC-beta is the predominant signaling PKC in these cells (Leitges et al. 1996, Su et al. 2002, Saijo et al. 2002).

**Followed by:** PRKCB (PKC-beta) phosphorylates CARMA1

**Literature references**


**Editions**

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PRKCB (PKC-beta) phosphorylates CARMA1

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168635

Type: omitted

Compartments: cytosol, plasma membrane

CARMA1 is phosphorylated at serines 559, 644, and 652 by Protein Kinase C beta (PKC-beta) (Sommer et al. 2005). CARMA1 is constitutively oligomerized (Tanner et al. 2007) and most CARMA1 in unstimulated cells is cytosolic (Sommer et al. 2005, Tanner et al. 2007), though a portion is constitutively associated with the plasma membrane (Gaide et al. 2002, Sommer et al. 2005). After phosphorylation, CARMA1 is associated with lipid rafts in the plasma membrane (Sommer et al. 2005). Note that some publications refer to CARMA1 with a different N-terminal methionine that is 7 amino acids shorter. In this case the phosphorylated serines are 552, 537, and 645.

Preceded by: PRKCB (Protein kinase C beta, PKC-beta) binds diacylglycerol and phosphatidylinerine

Followed by: CARMA1 recruits MALT1 and BCL10 forming CBM Complex

Literature references


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CARMA1 recruits MALT1 and BCL10 forming CBM Complex

**Location:** Activation of NF-kappaB in B cells

**Stable identifier:** R-HSA-1168644

**Type:** binding

**Compartments:** cytosol, plasma membrane

CARMA1 is phosphorylated and recruits BCL10 and MALT1 to the plasma membrane to form the CBM complex (Sommer et al. 2005, Tanner et al. 2007). Evidence from T cells (Jurkat cells) indicates that MALT1 and BCL10 oligomerize to activate the IKK complex (Zhou 2004).

**Preceded by:** PRKCB (PKC-beta) phosphorylates CARMA1

**Followed by:** CARMA1:BCL10:MALT1 complex recruits TAK1 and IKK

**Literature references**


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CARMA1:BCL10:MALT1 complex recruits TAK1 and IKK

**Location:** Activation of NF-kappaB in B cells

**Stable identifier:** R-HSA-1168637

**Type:** omitted

**Compartments:** cytosol, plasma membrane

**Inferred from:** CARMA1 recruits TAK1 and the IKK complex (Gallus gallus)

TAK1 and the IKK complex are observed to migrate from the cytosol to lipid rafts containing the CARMA1:BCL10:MALT1 (CBM) complex (Sommer et al. 2005, Shinohara et al. 2005 using chicken cells). By analogy with activation of NF-KappaB signaling in T cells, TAK1 in B cells may also be bound to TAB1 and TAB2 or TAB3, which bind K63-conjugated polyubiquitin on a TRAF protein bound to the CBM complex (reviewed in Shinohara et al. 2009).

**Preceded by:** CARMA1 recruits MALT1 and BCL10 forming CBM Complex

**Followed by:** TAK1 associated with the CBM complex phosphorylates IKKbeta

**Literature references**


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TAK1 associated with the CBM complex phosphorylates IKKbeta

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168641

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylation of IKKs complex by activated TAK1 (Gallus gallus), Activated TAK1 mediates phosphorylation of the IKK Complex (Homo sapiens)

TAK1 phosphorylates IKK-beta (Wang et al. 2001). As inferred from chicken B cells, the reaction in human B cells may occur when TAK1 and the IKK complex are associated with the CARMA1:BCL10:MALT1 (CBM) complex. During T cell activation TAK1 forms a complex with TAB1 and TAB2, which binds K-63 conjugated polyubiquitin attached to TRAF6 associated with the CBM complex (Sun et al. 2004, reviewed in Shinohara et al. 2009). TRAF6 also polyubiquitinates IKK-gamma in T cells (Zhou et al. 2004). B cells contain functional TRAF6 and TRAF2 (Zhang et al. 2010) so the same mechanism may occur during activation of B cells.

Preceded by: CARMA1:BCL10:MALT1 complex recruits TAK1 and IKK

Followed by: Activated IKK phosphorylates I-kappaB

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Activated IKK phosphorylates I-kappaB

**Location:** Activation of NF-kappaB in B cells

**Stable identifier:** R-HSA-1168638

**Type:** transition

**Compartments:** cytosol


**Preceded by:** TAK1 associated with the CBM complex phosphorylates IKKbeta

**Followed by:** SCF with beta-TrCP1 or beta-TrCP2 binds NF-kappaB:phospho-IkB

**Literature references**


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SCF with beta-TrCP1 or beta-TrCP2 binds NF-kappaB:phospho-IkB

**Location:** Activation of NF-kappaB in B cells

**Stable identifier:** R-HSA-1168642

**Type:** binding

**Compartments:** cytosol


**Preceded by:** Activated IKK phosphorylates I-kappaB

**Followed by:** SCF-beta-TrCP ubiquitinylates IkB

**Literature references**


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SCF-beta-TrCP ubiquitinylates IkB

**Location:** Activation of NF-kappaB in B cells

**Stable identifier:** R-HSA-1168643

**Type:** omitted

**Compartments:** cytosol


**Preceded by:** SCF with beta-TrCP1 or beta-TrCP2 binds NF-kappaB:phospho-IkB

**Followed by:** Ubiquitinated IkB is degraded

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Ubiquitinated IkB is degraded

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168640

Type: omitted

Compartments: cytosol


Preceded by: SCF-beta-TrCP ubiquitinylates IkB

Followed by: NF-kappaB translocates from the cytosol to the nucleus

Literature references


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**NF-kappaB translocates from the cytosol to the nucleus**

**Location:** Activation of NF-kappaB in B cells

**Stable identifier:** R-HSA-1168633

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

Nf-kappaB subunits contain nuclear localization sequences and, in the absence of IkB, are translocated to the nucleus (Baeuerle and Baltimore 1988, Blank et al. 1991, Ghosh et al. 2008, Fagerlund et al. 2008). c-Rel binds to importins alpha5, alpha6, and alpha7; RelB binds to importins alpha5 and alpha6; p52 binds importin alpha3, alpha4, alpha5, and alpha6 (Fagerlund et al. 2008)

**Preceded by:** Ubiquitinated IkB is degraded

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  - CARMA1:BCL10:MALT1 complex recruits TAK1 and IKK
  - TAK1 associated with the CBM complex phosphorylates IKKbeta
  - Activated IKK phosphorylates I-kappaB
  - SCF with beta-TrCP1 or beta-TrCP2 binds NF-kappaB:phospho-IkB
  - SCF-beta-TrCP ubiquitinylates IkB
  - Ubiquitinated IkB is degraded
  - NF-kappaB translocates from the cytosol to the nucleus