TAK1 activates NFkB by phosphorylation and activation of IKKs complex


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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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Literature references


Reactome database release: 74

This document contains 1 pathway and 5 reactions (see Table of Contents)
TAK1 activates NFkB by phosphorylation and activation of IKKs complex

Stable identifier: R-HSA-445989

Compartments: cytosol, nucleoplasm

NF-kappaB is sequestered in the cytoplasm in a complex with inhibitor of NF-kappaB (IkB). Almost all NF-kappaB activation pathways are mediated by IkB kinase (IKK), which phosphorylates IkB resulting in dissociation of NF-kappaB from the complex. This allows translocation of NF-kappaB to the nucleus where it regulates gene expression.

Literature references


Editions

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IKBKA, IKBKB and IKBKG form IKK complex

Location: TAK1 activates NFkB by phosphorylation and activation of IKKs complex

Stable identifier: R-HSA-5609665

Type: binding

Compartments: cytosol

The multimeric I kappa B kinase (IKK) complex is a key regulator of NFkB signaling, which is responsible for the phosphorylation of inhibitor kB (IkB). The phosphorylation by IKK triggers K48-linked ubiquitination of IkB leading proteasomal degradation of IkB, allowing translocation of NFkB factor to the nucleus, where it can activate transcription of a variety of genes participating in the immune and inflammatory response, cell adhesion, growth control, and protection against apoptosis (Alkalay I et al. 1995; Collins T et al. 1995; Kaltschmidt B et al. 2000; Oeckinghaus A and Ghosh S 2009). The IKK complex is composed of the two catalytic subunits, IKKA (IKBKA) and IKKB (IKBKB) kinases, and a regulatory subunit, NFkB essential modulator (IKBKG/NEMO/IKKG). IKBKG (NEMO) associates with the unphosphorylated IKK kinase C-termini and activates the IKK complex’s catalytic activity (Rothwarf DM et al. 1998). The molecular composition and stoichiometry of the IKK complex remains debatable, although the core IKK complex that range from 700 to 900 kDa is thought to consist of an IKBKA:IKBKB heterodimer associated with an IKBKG dimer or higher oligomeric assemblies (DiDonato JA et al. 1997; May J et al. 2002; Tegethoff S et al. 2003; Marienfeld RB et al. 2006; Rushe M et al. 2008).

Literature references


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Activated TAK1 mediates phosphorylation of the IKK Complex

**Location:** TAK1 activates NFkB by phosphorylation and activation of IKKs complex

**Stable identifier:** R-HSA-168184

**Type:** transition

**Compartments:** cytosol

In humans, the IKKs - IkB kinase (IKK) complex serves as the master regulator for the activation of NF-kB by various stimuli. The IKK complex contains two catalytic subunits, IKK alpha and IKK beta associated with a regulatory subunit, NEMO (IKKgamma). The activation of the IKK complex and the NFkB mediated antiviral response are dependent on the phosphorylation of IKK alpha/beta at its activation loop and the ubiquitination of NEMO [Solt et al 2009; Li et al 2002]. NEMO ubiquitination by TRAF6 is required for optimal activation of IKKalpha/beta; it is unclear if NEMO subunit undergoes K63-linked or linear ubiquitination.

This basic trimolecular complex is referred to as the IKK complex. Each catalytic IKK subunit has an N-terminal kinase domain and leucine zipper (LZ) motifs, a helix-loop-helix (HLH) and a C-terminal 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. Phosphorylation in the activation loop of IKK beta requires Ser177 and Ser181 and thus activates the IKK kinase activity, leading to the IkB alpha phosphorylation and NF-kB activation.

**Followed by:** Phospho-IKK Complex phosphorylates NFkB inhibitor within the NFkB inhibitor:NFkB complex

**Literature references**


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NFkB inhibitor binds NFkB complex

Location: TAK1 activates NFkB by phosphorylation and activation of IKKs complex

Stable identifier: R-HSA-9630923

Type: binding

Compartments: cytosol

NFkB is sequestered in the cytosol of unstimulated cells through the interactions with a class of inhibitor proteins, called NFkB inhibitors (IkBs). IkB proteins such as NFKBIA or NFKBIB are characterized by the presence of six to seven ankyrin repeat motifs, which mediate interaction with the Rel homology domain (RHD). RHD mediates DNA binding, dimerization and nuclear localization (Jacobs MD & Harrison SC 1998; Manavalan B et al. 2010). NFkB inhibitors (IkBs) mask the nuclear localization signal (NLS) of NFkB preventing its nuclear translocation (Jacobs MD & Harrison SC 1998; Cervantes CF et al. 2011). A key event in NFkB activation involves phosphorylation of IkB (at sites equivalent to Ser32 and Ser36 of NFKBIA (IkB-alpha) or Ser19 and Ser22 of NFKBIB (IkB-beta)) by the IκB kinase (IKK) complex. The phosphorylated NFKBIA is recognized by the E3 ligase complex and targeted for ubiquitin-mediated proteasomal degradation, releasing the NFkB dimer p50/p65 into the nucleus to turn on target genes (Karin M & Ben-Neriah Y 2000, Kanarek N & Ben-Neriah Y 2012; Hoffmann A et al. 2006). Crystal structures of NFkB inhibitors:NFkB complexes revealed that an NFkB dimer binds to one IkB molecule (Jacobs MD & Harrison SC 1998; Ghosh G et al 2012).

Followed by: Phospho-IKK Complex phosphorylates NFkB inhibitor within the NFkB inhibitor:NFkB complex

Literature references

Phospho-IKK Complex phosphorylates NFkB inhibitor within the NFkB inhibitor:NFkB complex

**Location:** TAK1 activates NFkB by phosphorylation and activation of IKKs complex

**Stable identifier:** R-HSA-168140

**Type:** transition

**Compartments:** cytosol

In human, IkB is an inhibitory protein that sequesters NF-kB in the cytoplasm, by masking a nuclear localization signal, located just at the C-terminal end in each of the NF-kB subunits.

A key event in NF-kB activation involves phosphorylation of IkB by an IkB kinase (IKK). The phosphorylation and ubiquitination of IkB kinase complex is mediated by two distinct pathways, either the classical or alternative pathway. In the classical NF-kB signaling pathway, the activated IKK (IkB kinase) complex, predominantly acting through IKK beta in an IKK gamma-dependent manner, catalyzes the phosphorylation of IkBs (at sites equivalent to Ser32 and Ser36 of human IkB-alpha or Ser19 and Ser22 of human IkB-beta); Once phosphorylated, IkB undergoes ubiquitin-mediated degradation, releasing NF-kB.

**Preceded by:** Activated TAK1 mediates phosphorylation of the IKK Complex, NFkB inhibitor binds NFkB complex

**Followed by:** NFkB complex is transported from cytosol to nucleus

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NFkB complex is transported from cytosol to nucleus

**Location:** TAK1 activates NFkB by phosphorylation and activation of IKKs complex

**Stable identifier:** R-HSA-168166

**Type:** transition

**Compartments:** cytosol, nucleoplasm

NFkB is a family of transcription factors that play pivotal roles in immune, inflammatory, and antiapoptotic responses. There are five NF-kB/Rel family members, p65 (RelA), RelB, c-Rel, p50/p105 (NF-kappa-B1) and p52/p100 (NFkappa-B2). All members of the NFkB family contain a highly conserved DNA-binding and dimerization domain called Rel-homology region (RHR). The RHR is responsible for homo- or heterodimerization. Therefor, NF-kappa-B exists in unstimulated cells as homo or heterodimers; the most common heterodimer is p65/p50. NF-kappa-B 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 of NF-kB and prevent its nuclear translocation. Various stimuli induce the activation of the IkB kinase (IKK) complex, which then phosphorylates IkBs. The phosphorylated IkBs are ubiquitinated and then degraded through the proteasome-mediated pathway. The degradation of IkBs releases NF-kappa-B and and it can be transported into nucleus where it induces the expression of target genes.

**Preceded by:** Phospho-IKK Complex phosphorylates NFkB inhibitor within the NFkB inhibitor:NFkB complex

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