MAPK activation in TLR cascade

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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.

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: 74

This document contains 4 pathways (see Table of Contents)
The mitogen activated protein kinase (MAPK) cascade, one of the most ancient and evolutionarily conserved signaling pathways, is involved in many processes of immune responses. The MAP kinases cascade transduces signals from the cell membrane to the nucleus in response to a wide range of stimuli (Chang and Karin, 2001; Johnson et al, 2002).

There are three major groups of MAP kinases

- the extracellular signal-regulated protein kinases ERK1/2,
- the p38 MAP kinase
- and the c-Jun NH-terminal kinases JNK.

ERK1 and ERK2 are activated in response to growth stimuli. Both JNKs and p38-MAPK are activated in response to a variety of cellular and environmental stresses. The MAP kinases are activated by dual phosphorylation of Thr and Tyr within the tripeptide motif Thr-Xaa-Tyr. The sequence of this tripeptide motif is different in each group of MAP kinases: ERK (Thr-Glu-Tyr); p38 (Thr-Gly-Tyr); and JNK (Thr-Pro-Tyr).

MAPK activation is mediated by signal transduction in the conserved three-tiered kinase cascade: MAPKKKK (MAP4K or MKKKK or MAPKKK Kinase) activates the MAPKKK. The MAPKKKs then phosphorylates a dual-specificity protein kinase MAPKK, which in turn phosphorylates the MAPK.

The dual specificity MAP kinase kinases (MAPKK or MKK) differ for each group of MAPK. The ERK MAP kinases are activated by the M KK1 and M KK2; the p38 MAP kinases are activated by M KK3, M KK4, and M KK6; and the JNK pathway is activated by M KK4 and M KK7. The ability of MAP kinase kinases (MKKs, or MEKs) to recognize their cognate MAPKs is facilitated by a short docking motif (the D-site) in the M KK N-terminus, which binds to a complementary region on the MAPK. MAPKs then recognize many of their targets using the same strategy, because many MAPK substrates also contain D-sites.
The upstream signaling events in the TLR cascade that initiate and mediate the ERK signaling pathway remain unclear.

**Literature references**


**Editions**

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Activated TAK1 mediates Jun kinases (JNK) phosphorylation and activation

Location: MAPK activation in TLR cascade

Stable identifier: R-GGA-437986

Compartments: cytosol

Inferred from: JNK (c-Jun kinases) phosphorylation and activation mediated by activated human TAK1 (Homo sapiens)

C-Jun NH2 terminal kinases are stress activated MAPKs, also known as SAPKs. The JNK pathway is activated by heat shock, or inflammatory cytokines, or UV radiation. The JNKs are encoded by at least three genes: JNK1/SAPK-gamma, JNK2/SAPK-alpha and JNK3/ SAPK-beta.

Activation of JNKs is mediated by activated TAK1 which phosphorylates two dual specificity enzymes MKK4 (MAPK kinase 4) and MKK7(MAPK kinase 7).

Literature references


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## Editions

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Activated TAK1 mediates p38 MAP kinase phosphorylation

**Location:** MAPK activation in TLR cascade

**Stable identifier:** R-GGA-437980

**Inferred from:** activated TAK1 mediates p38 MAPK activation (Homo sapiens)

p38 mitogen-activated protein kinase (MAPK) belongs to a highly conserved family of serine/threonine protein kinases.

The p38 MAPK-dependent signaling cascade is activated by pro-inflammatory or stressful stimuli such as ultraviolet radiation, oxidative injury, heat shock, cytokines, and other pro-inflammatory stimuli. p38 MAPK exists as four isoforms (alpha, beta, gamma, and delta). Of these, p38alpha and p38beta are ubiquitously expressed while p38gamma and p38delta are differentially expressed depending on tissue type. Each isoform is activated by upstream kinases including MAP kinase kinases (MKK) 3, 4, and 6, which in turn are phosphorylated by activated TAK1 at the typical Ser-Xaa-Ala-Xaa-Thr motif in their activation loops.

Once p38 MAPK is phosphorylated it activates numerous downstream substrates, including MAPK-activated protein kinase-2 and 3 (MAPKAPK-2 or 3) and mitogen and stress-activated kinase-1/2 (MSK1/2). MAPKAPK-2/3 and MSK1/2 function to phosphorylate heat shock protein 27 (HSP27) and cAMP-response element binding protein transcriptional factor, respectively. Other transcription factors, including activating transcription factor 2, Elk, CHOP/GADD153, and myocyte enhancer factor 2, are known to be regulated by these kinases.

**Literature references**


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ERK activation

Location: MAPK activation in TLR cascade

Stable identifier: R-GGA-451478

Lipopolysaccharide and flagellin were shown to stimulate ERK activation in chicken heterophils.

Bioinformatic analysis reveals no evidence of ERK1 in the chicken genome, although chicken orthologs to other mediators of MEK-ERK signaling (MEK1, MEK2, ERK2 etc.) were identified. In this Reactome model we show ERK2 activation and assume that chicken MEK-ERK mediators behave like their human counterparts.

Literature references


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