Activation of the AP-1 family of transcription factors

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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: 73

This document contains 1 pathway and 5 reactions (see Table of Contents)
Activator protein-1 (AP-1) is a collective term referring to a group of transcription factors that bind to promoters of target genes in a sequence-specific manner. AP-1 family consists of hetero- and homodimers of bZIP (basic region leucine zipper) proteins, mainly of Jun-Jun, Jun-Fos or Jun-ATF.

AP-1 members are involved in the regulation of a number of cellular processes including cell growth, proliferation, survival, apoptosis, differentiation, cell migration. The ability of a single transcription factor to determine a cell fate critically depends on the relative abundance of AP-1 subunits, the composition of AP-1 dimers, the quality of stimulus, the cell type, the co-factor assembly.

AP-1 activity is regulated on multiple levels; transcriptional, translational and post-translational control mechanisms contribute to the balanced production of AP-1 proteins and their functions. Briefly, regulation occurs through:

1. effects on jun, fos, atf gene transcription and mRNA turnover.
2. AP-1 protein members turnover.
3. post-translational modifications of AP-1 proteins that modulate their transactivation potential (effect of protein kinases or phosphatases).
4. interactions with other transcription factors that can either induce or interfere with AP-1 activity.

**Literature references**


**Editions**

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**Phosphorylated MAPKs phosphorylate ATF-2**

**Location:** Activation of the AP-1 family of transcription factors

**Stable identifier:** R-HSA-168053

**Type:** transition

**Compartments:** nucleoplasm

At the beginning of this reaction, 1 molecule of 'ATP', and 1 molecule of 'ATF-2' are present. At the end of this reaction, 1 molecule of 'ADP', and 1 molecule of 'ATF-2-P' are present.

This reaction is mediated by the 'protein kinase activity' of 'MAPK1-P'.

the Raf–MEK–ERK pathway induces phosphorylation of ATF2 Thr71, whereas subsequent ATF2 Thr69 phosphorylation requires the Ral–RalGDS–Src–p38 pathway. Cooperation between ERK and p38 was found to be essential for ATF2 activation by these mitogens; the activity of p38 and JNK/SAPK in growth factor-stimulated fibroblasts is insufficient to phosphorylate ATF2 Thr71 or Thr69 + 71 significantly by themselves, while ERK cannot dual phosphorylate ATF2 Thr69 + 71 efficiently.

**Followed by:** Formation of Activated Protein 1 (AP-1) complex. ATF2/c-JUN heterodimer.

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Activated JNKs phosphorylate c-JUN

Location: Activation of the AP-1 family of transcription factors

Stable identifier: R-HSA-168136

Type: transition

Compartments: nucleoplasm

JNK (c-Jun N-terminal Kinase) phosphorylates several transcription factors including c-Jun after translocation to the nucleus.

Followed by: Formation of Activated Protein 1 (AP-1) complex. ATF2/c-JUN heterodimer. , Formation of Activated Protein 1 (AP-1) complex. cFOS/c-JUN heterodimer.

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**c-FOS activation by phospho ERK1/2**

**Location:** Activation of the AP-1 family of transcription factors

**Stable identifier:** R-HSA-450325

**Type:** transition

**Compartments:** nucleoplasm

The Fos proteins (c-Fos, FosB, Fra1 and Fra2), which cannot homodimerize, form stable heterodimers with Jun proteins and thereby enhance their DNA binding activity.

On activation of the MAPK pathway, Ser-374 of Fos is phosphorylated by ERK1/2 and Ser-362 is phosphorylated by RSK1/2, the latter kinases being activated by ERK1/2. If stimulation of the MAPK pathway is sufficiently sustained, ERK1/2 can dock on an upstream FTYP amino acid motif, called the DEF domain (docking site for ERKs, FXFP), and phosphorylate Thr-331 and Thr-325.

Phosphorylation at specific sites enhances the transactivating potential of several AP-1 proteins, including Jun and Fos, without having any effect on their DNA binding activities. Thus, phosphorylation of Ser-362 and Ser-374 stabilizes c-Fos but has no demonstrated role in the control of transcriptional activity. On the contrary, phosphorylation of Thr-325 and Thr-331 enhances c-Fos transcriptional activity but has no demonstrated effect on protein turnover.

**Followed by:** Formation of Activated Protein 1 (AP-1) complex. cFOS/c-JUN heterodimer.

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https://www.reactome.org
Formation of Activated Protein 1 (AP-1) complex. ATF2/c-JUN heterodimer.

**Location:** Activation of the AP-1 family of transcription factors

**Stable identifier:** R-HSA-168440

**Type:** binding

**Compartments:** nucleoplasm

At the beginning of this reaction, 1 molecule of 'c-Jun-P', and 1 molecule of 'ATF-2-P' are present. At the end of this reaction, 1 molecule of 'AP-1' is present.

**Preceded by:** Activated JNKs phosphorylate c-JUN, Phosphorylated MAPKs phosphorylate ATF-2

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Formation of Activated Protein 1 (AP-1) complex. cFOS/c-JUN heterodimer.

**Location:** Activation of the AP-1 family of transcription factors

**Stable identifier:** R-HSA-450292

**Type:** binding

**Compartments:** nucleoplasm

The bZIP domains of Jun and Fos form an X-shaped helical structure, which binds to the palindromic AP-1 site (TGAGTCA) (Glover and Harrison, 1995).

**Preceded by:** Activated JNKs phosphorylate c-JUN, c-FOS activation by phospho ERK1/2

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