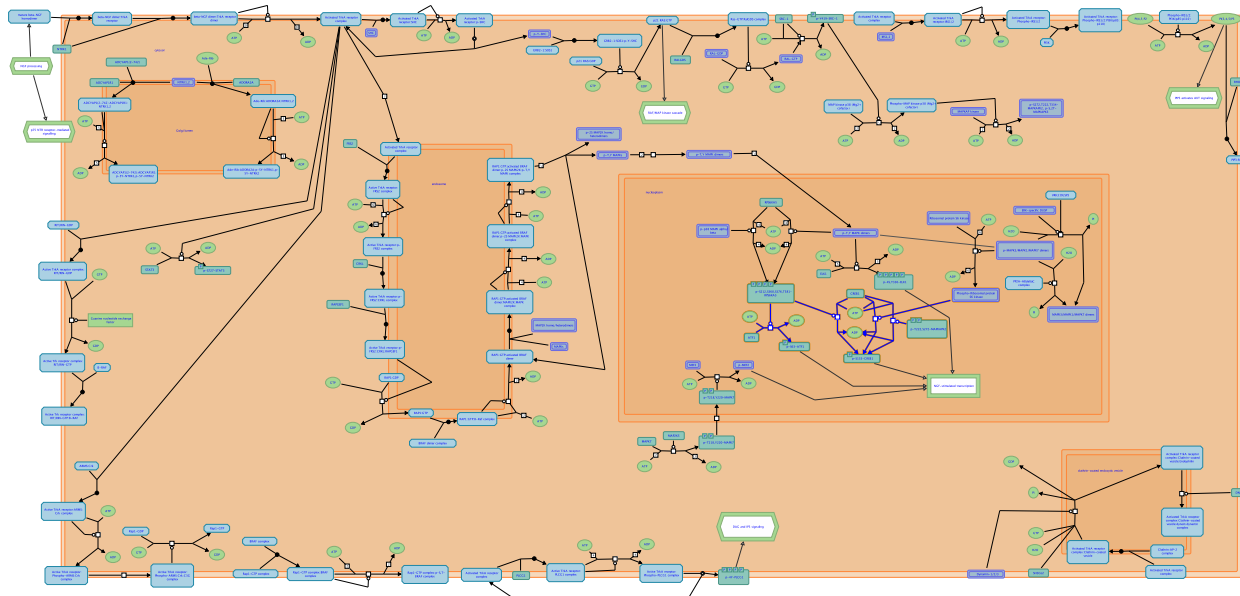


CREB phosphorylation



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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

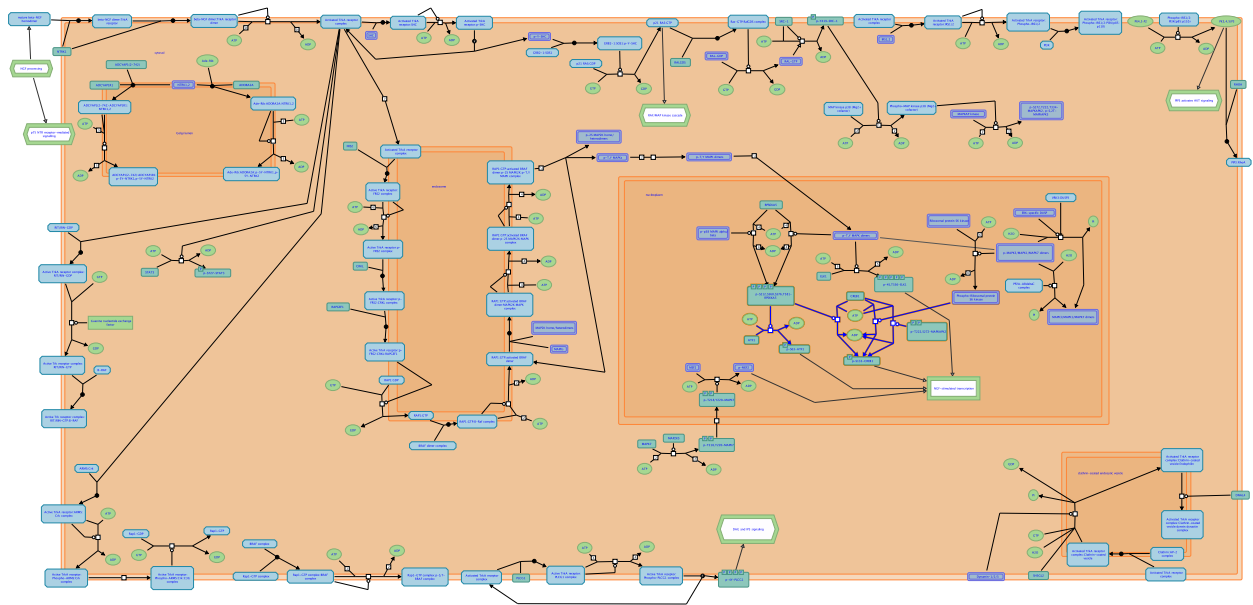
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Reactome database release: 77

This document contains 1 pathway and 4 reactions ([see Table of Contents](#))

CREB phosphorylation ↗

Stable identifier: R-HSA-199920



Nerve growth factor (NGF) activates multiple signalling pathways that mediate the phosphorylation of CREB at the critical regulatory site, serine 133. CREB phosphorylation at serine 133 is a crucial event in neurotrophin signalling, being mediated by ERK/RSK, ERK/MSK1 and p38/MAPKAPK2 pathways. Several kinases, such as MSK1, RSK1/2/3 (MAPKAPK1A/B/C), and MAPKAPK2, are able to directly phosphorylate CREB at S133. MSK1 is also able to activate ATF (Cyclic-AMP-dependent transcription factor). However, the NGF-induced CREB phosphorylation appears to correlate better with activation of MSK1 rather than RSK1/2/3, or MAPKAPK2. In retrograde signalling, activation of CREB occurs within 20 minutes after neurotrophin stimulation of distal axons.

Editions

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|------------|----------|------------------------|
| 2006-10-10 | Authored | Annibali, D., Nasi, S. |
| 2007-11-08 | Reviewed | Greene, LA. |

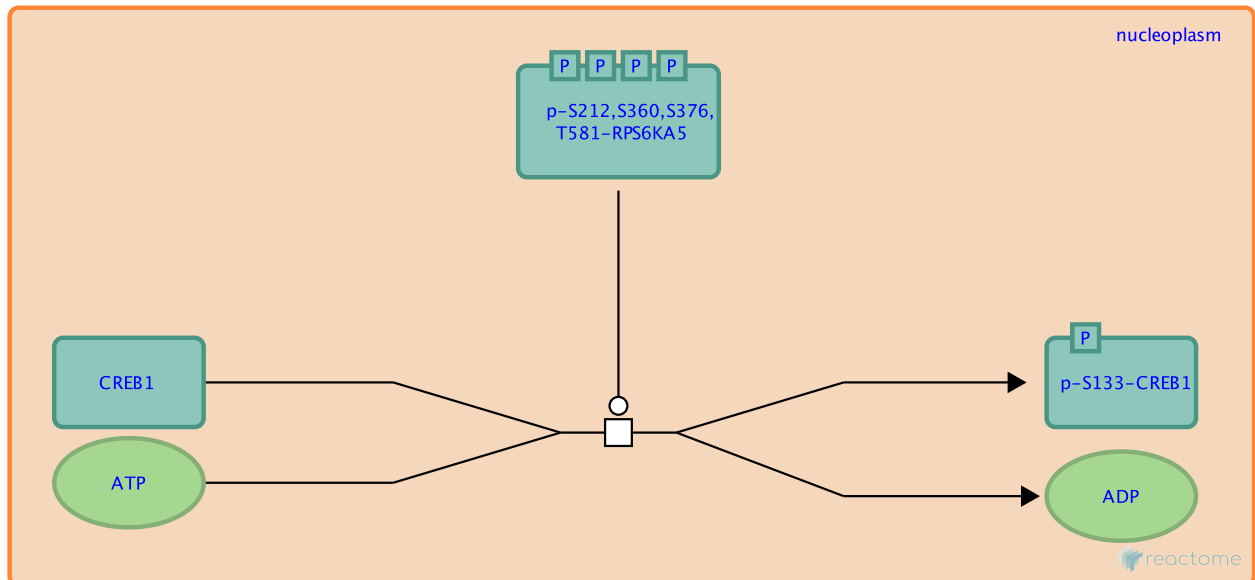
MSK1 activates CREB ↗

Location: CREB phosphorylation

Stable identifier: R-HSA-199935

Type: transition

Compartments: nucleoplasm



MSK1 is required for the mitogen-induced phosphorylation of the transcription factor, cAMP response element-binding protein (CREB).

Literature references

Deak, M., Clifton, AD., Lucocq, LM., Alessi, DR. (1998). Mitogen- and stress-activated protein kinase-1 (MSK1) is directly activated by MAPK and SAPK2/p38, and may mediate activation of CREB. *EMBO J*, 17, 4426-41. ↗

Editions

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| 2006-10-10 | Authored | Annibali, D., Nasi, S. |
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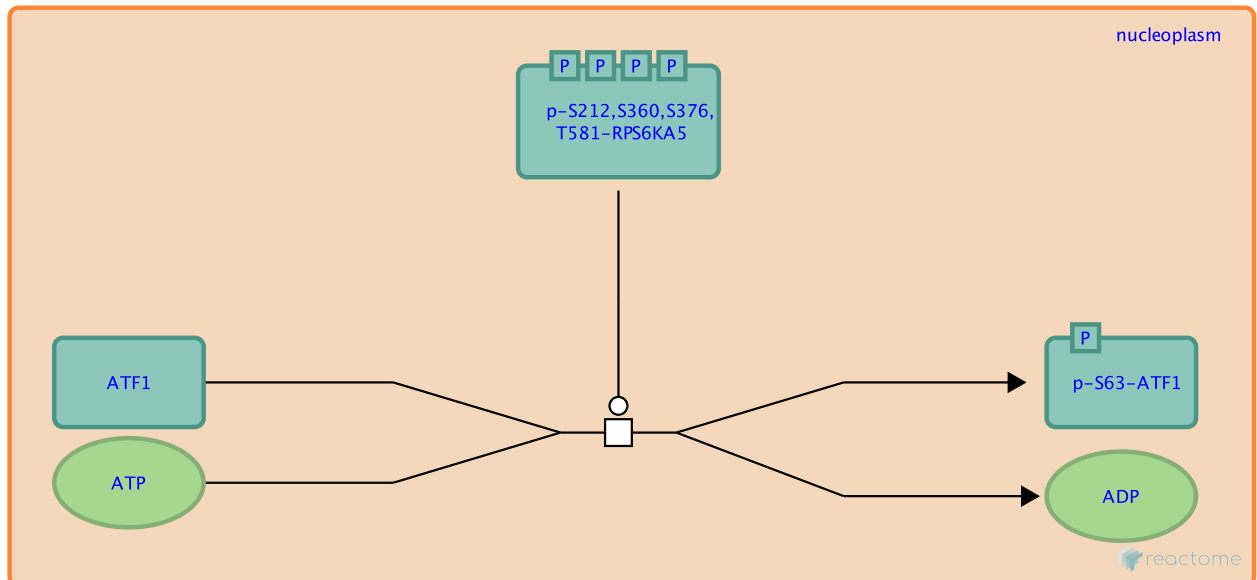
MSK1 activates ATF1 ↗

Location: CREB phosphorylation

Stable identifier: R-HSA-199910

Type: transition

Compartments: nucleoplasm



Cyclic-AMP-dependent transcription factor 1 (ATF1) can be phosphorylated at Serine 63 by MSK1, thus activating it.

Literature references

Gupta, P., Prywes, R. (2002). ATF1 phosphorylation by the ERK MAPK pathway is required for epidermal growth factor-induced c-jun expression. *J. Biol. Chem.*, 277, 50550-6. ↗

Editions

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| 2006-10-10 | Authored | Annibali, D., Nasi, S. |
| 2007-11-08 | Reviewed | Greene, LA. |

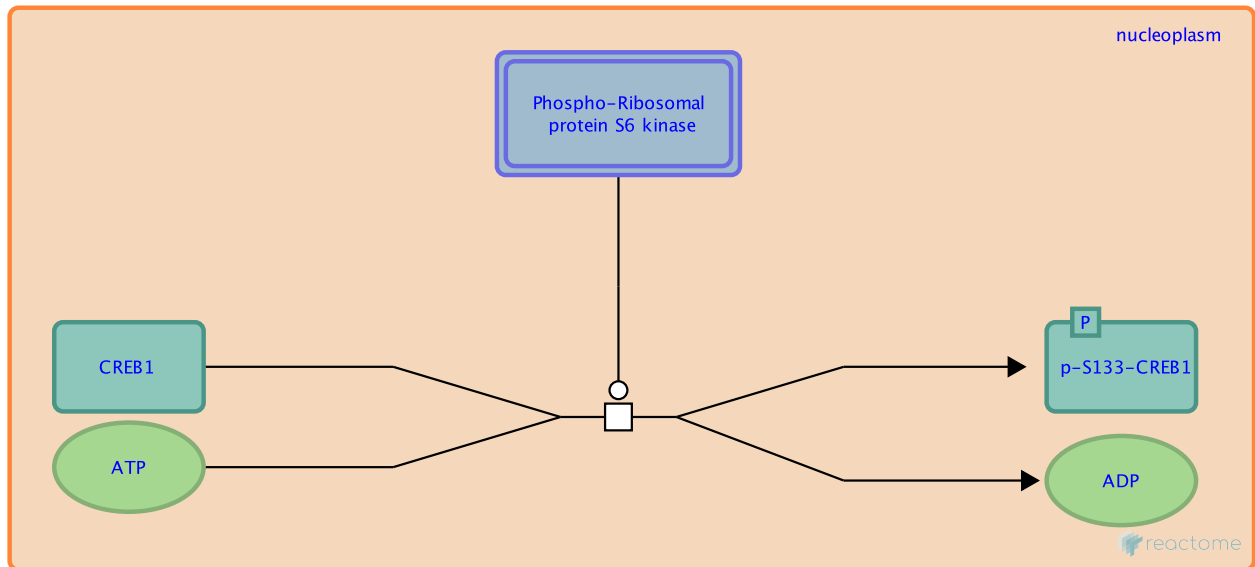
RSK1/2/3 phosphorylates CREB at Serine 133 ↗

Location: CREB phosphorylation

Stable identifier: R-HSA-199895

Type: transition

Compartments: nucleoplasm



CREB is phosphorylated at Serine 133 by RSK1/2/3.

Literature references

De Cesare, D., Jacquot, S., Hanauer, A., Sassone-Corsi, P. (1998). Rsk-2 activity is necessary for epidermal growth factor-induced phosphorylation of CREB protein and transcription of c-fos gene. *Proc Natl Acad Sci U S A*, 95, 12202-7. ↗

Editions

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| 2006-10-10 | Authored | Annibali, D., Nasi, S. |
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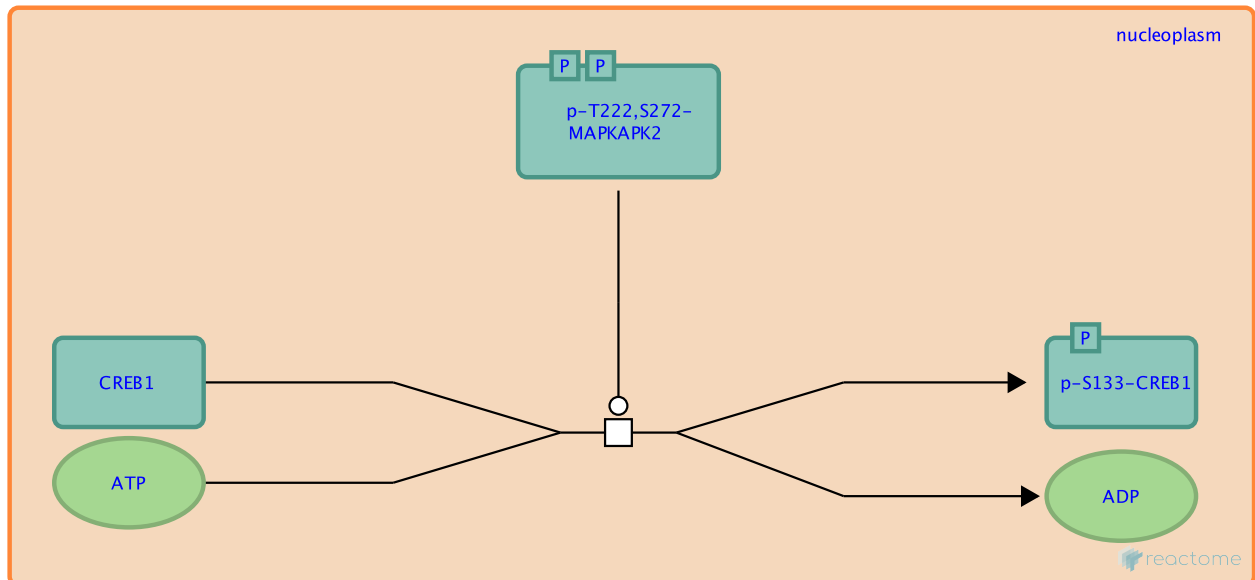
MAPKAPK2 phosphorylates CREB at Serine 133 [↗](#)

Location: [CREB phosphorylation](#)

Stable identifier: R-HSA-199917

Type: transition

Compartments: nucleoplasm



p38 MAPK activation leads to CREB Serine 133 phosphorylation through the activation of MAPKAP kinase 2 or the closely related MAPKAP kinase 3.

Literature references

Bonni, A., Ginty, DD., Dudek, H., Greenberg, ME. (1995). Serine 133-phosphorylated CREB induces transcription via a cooperative mechanism that may confer specificity to neurotrophin signals. *Mol. Cell. Neurosci.*, 6, 168-83. [↗](#)

Editions

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| 2006-10-10 | Authored | Annibali, D., Nasi, S. |
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