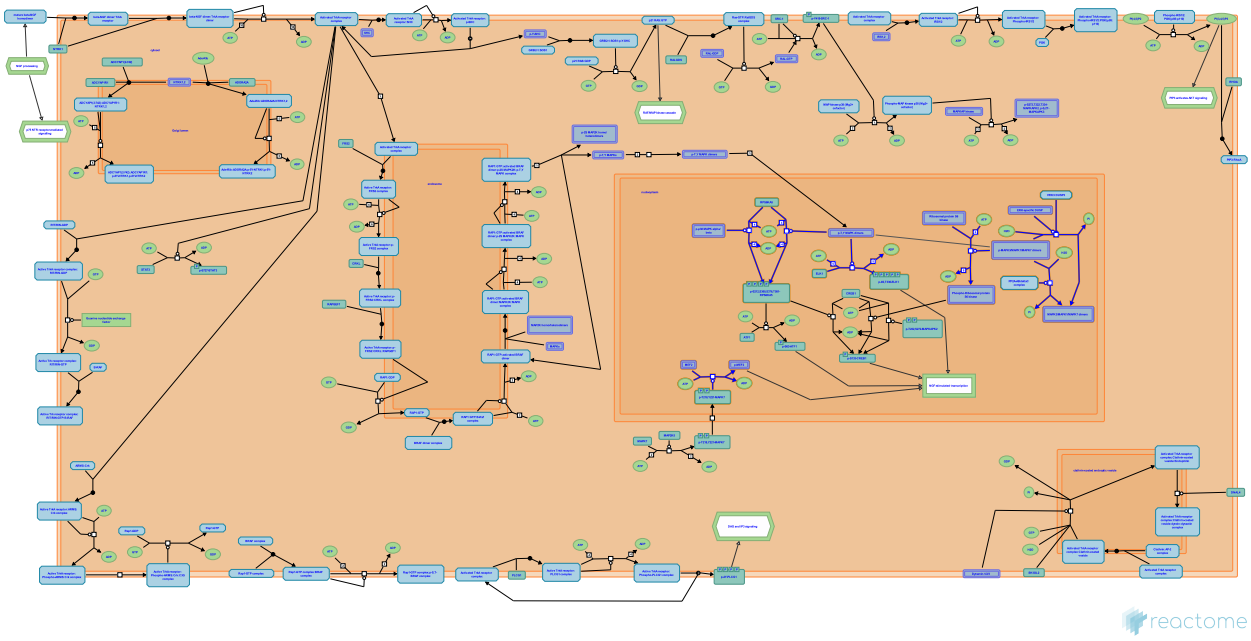
ERK/MAPK targets



Annibali, D., D'Eustachio, P., Greene, LA., Matthews, L., Nasi, S.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

27/04/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

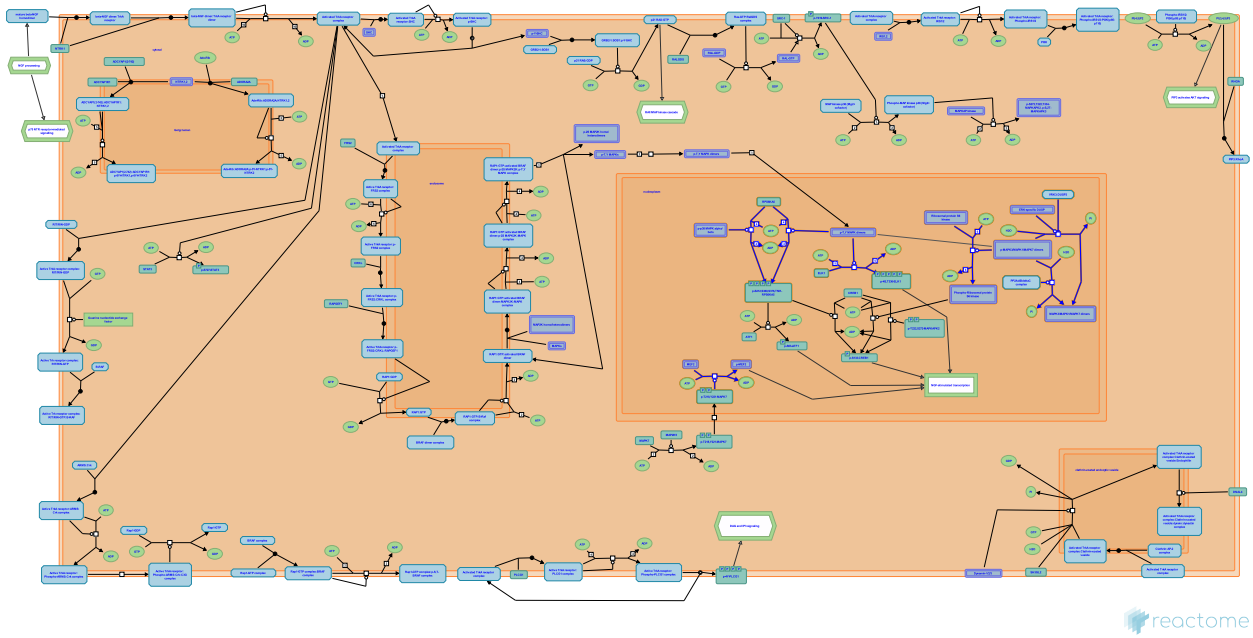
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

ERK/MAPK targets ↗

Stable identifier: R-HSA-198753



ERK/MAPK kinases have a number of targets within the nucleus, usually transcription factors or other kinases. The best known targets, ELK1, ETS1, ATF2, MITF, MAPKAPK2, MSK1, RSK1/2/3 and MEF2 are annotated here.

Editions

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

ERK1/2 activates ELK1 ↗

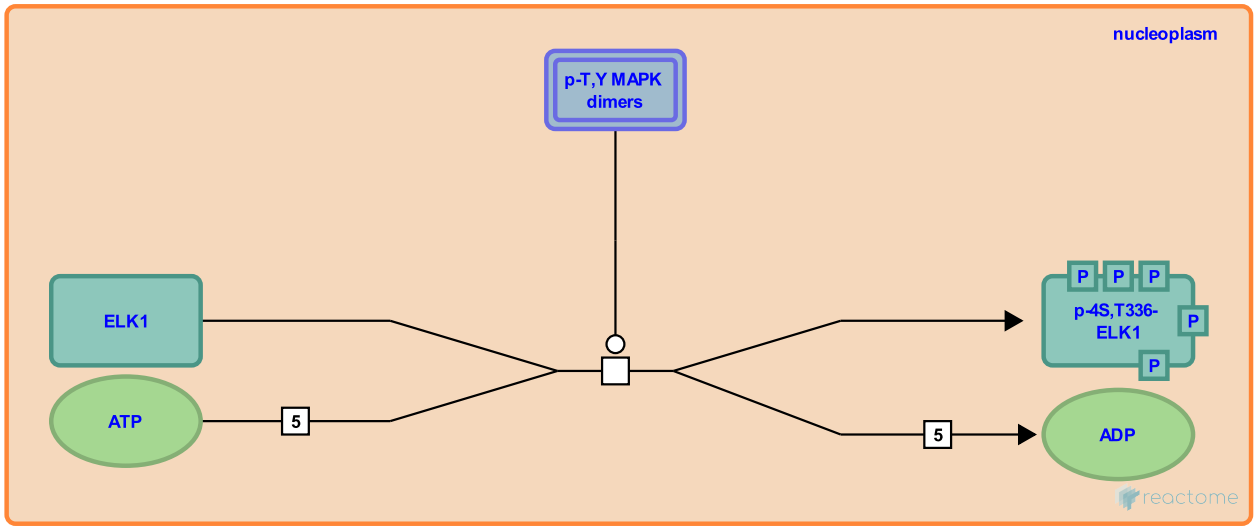
Location: ERK/MAPK targets

Stable identifier: R-HSA-198731

Type: transition

Compartments: nucleoplasm

Inferred from: ERK1/2 activates ELK1 (Mus musculus)



Following translocation to the nucleus, ERK1/2 directly phosphorylates key effectors, including the ubiquitous transcription factors ELK1 (Ets like protein 1). At least five residues in the C terminal domain of ELK1 are phosphorylated upon stimulation with growth factor stimulation. ELK1 can form a ternary complex with the serum response factor (SRF) and consensus sequences, such as serum response elements (SRE), on DNA, thus stimulating transcription of a set of immediate early genes like FOS (c-fos) (Marais et al, 1993; Gille et al, 1995; Duan et al, 1998; reviewed in Treisman, 1995).

Literature references

Treisman, R., Wynne, J., Marais, R. (1993). The SRF accessory protein Elk-1 contains a growth factor-regulated transcriptional activation domain. *Cell, 73*, 381-93. ↗

Treisman, R. (1995). Journey to the surface of the cell: Fos regulation and the SRE. *EMBO J., 14*, 4905-13. ↗

Xie, W., Safe, S., Duan, R., Burghardt, RC. (2001). Estrogen receptor-mediated activation of the serum response element in MCF-7 cells through MAPK-dependent phosphorylation of Elk-1. *J. Biol. Chem., 276*, 11590-8. ↗

Moomaw, C., Gille, H., Shaw, PE., Cobb, MH., Thomae, O., Slaughter, C. et al. (1995). ERK phosphorylation potentiates Elk-1-mediated ternary complex formation and transactivation. *EMBO J, 14*, 951-62. ↗

Editions

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

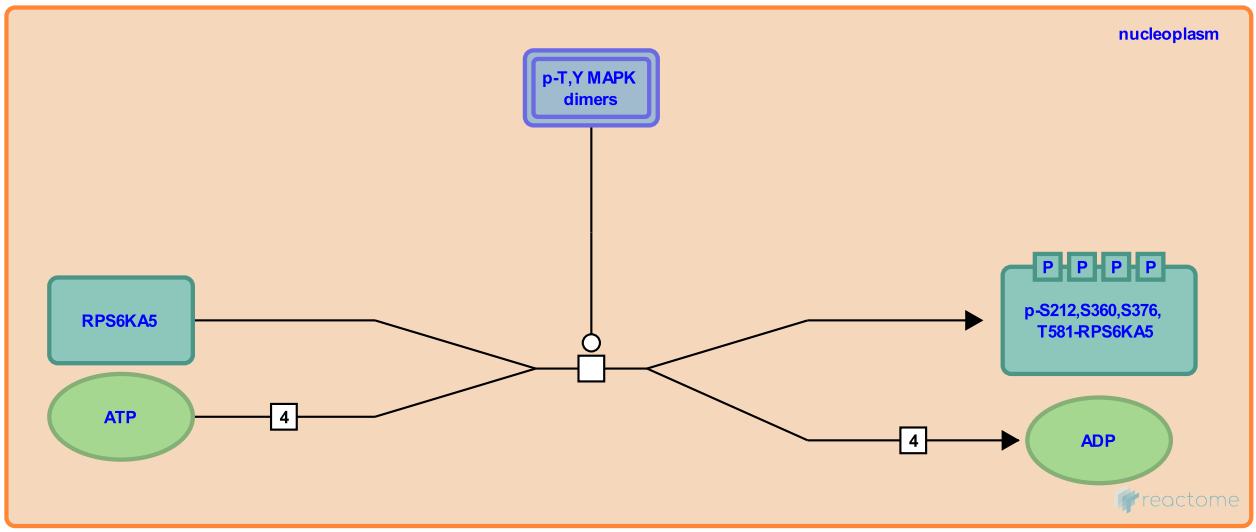
ERK1/2 phosphorylates MSK1 ↗

Location: ERK/MAPK targets

Stable identifier: R-HSA-198756

Type: transition

Compartments: nucleoplasm



MSK1 (Ribosomal protein S6 kinase alpha-5) is a serine/threonine kinase that is localised in the nucleus. It contains two protein kinase domains in a single polypeptide. It can be activated 5-fold by ERK1/2 through phosphorylation at four key residues.

Literature references

Lucocq, LM., Alessi, DR., Clifton, AD., Deak, M. (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

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

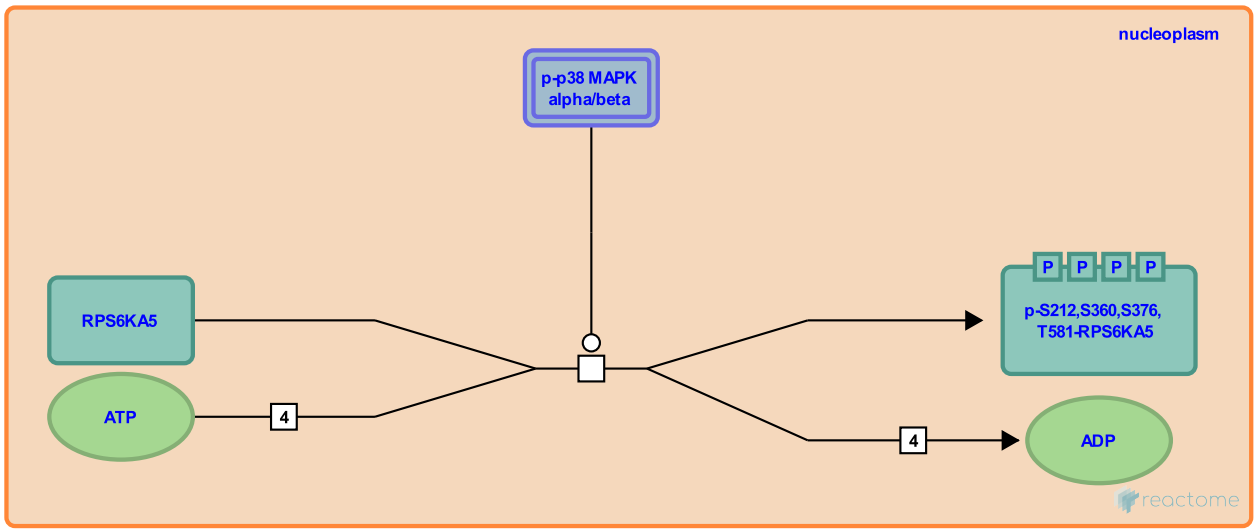
p38MAPK phosphorylates MSK1 ↗

Location: ERK/MAPK targets

Stable identifier: R-HSA-198669

Type: transition

Compartments: nucleoplasm



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Literature references

Lucocq, LM., Alessi, DR., Clifton, AD., Deak, M. (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

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

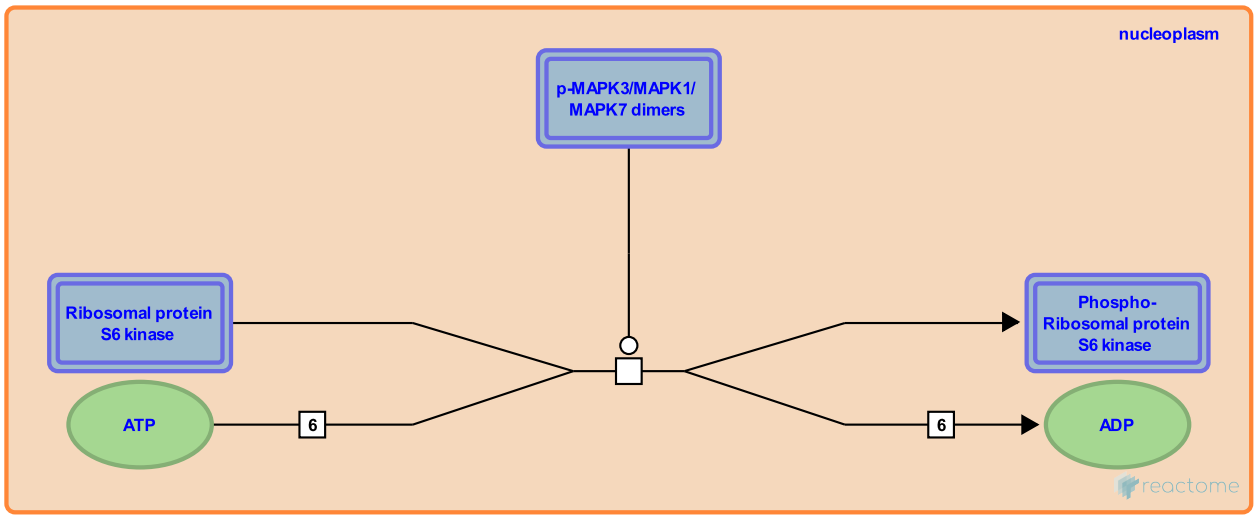
ERK1/2/5 activate RSK1/2/3 ↗

Location: ERK/MAPK targets

Stable identifier: R-HSA-198746

Type: transition

Compartments: nucleoplasm



The p90 ribosomal S6 kinases (RSK1-4) comprise a family of serine/threonine kinases that lie at the terminus of the ERK pathway. RSK family members are unusual among serine/threonine kinases in that they contain two distinct kinase domains, both of which are catalytically functional . The C-terminal kinase domain is believed to be involved in autophosphorylation, a critical step in RSK activation, whereas the N-terminal kinase domain, which is homologous to members of the AGC superfamily of kinases, is responsible for the phosphorylation of all known exogenous substrates of RSK.
RSKs can be activated by the ERKs (ERK1, 2, 5) in the cytoplasm as well as in the nucleus, they both have cytoplasmic and nuclear substrates, and they are able to move from nucleus to cytoplasm. Efficient RSK activation by ERKs requires its interaction through a docking site located near the RSK C terminus. The mechanism of RSK activation has been studied mainly with regard to ERK1 and ERK2. RSK activation leads to the phosphorylation of four essential residues Ser239, Ser381, Ser398, and Thr590, and two additional sites, Thr377 and Ser749 (the amino acid numbering refers to RSK1). ERK is thought to play at least two roles in RSK1 activation. First, activated ERK phosphorylates RSK1 on Thr590, and possibly on Thr377 and Ser381, and second, ERK brings RSK1 into close proximity to membrane-associated kinases that may phosphorylate RSK1 on Ser381 and Ser398.
Moreover, RSKs and ERK1/2 form a complex that transiently dissociates upon growth factor signalling. Complex dissociation requires phosphorylation of RSK1 serine 749, a growth factor regulated phosphorylation site located near the ERK docking site. Serine 749 is phosphorylated by the N-terminal kinase domain of RSK1 itself. ERK1/2 docking to RSK2 and RSK3 is also regulated in a similar way. The length of RSK activation following growth factor stimulation depends on the duration of the RSK/ERK complex, which, in turn, differs among the different RSK isoforms. RSK1 and RSK2 readily dissociate from ERK1/2 following growth factor stimulation stimulation, but RSK3 remains associated with active ERK1/2 longer, and also remains active longer than RSK1 and RSK2.

Literature references

Blenis, J., Richards, SA., Roux, PP. (2003). Phosphorylation of p90 ribosomal S6 kinase (RSK) regulates extracellular signal-regulated kinase docking and RSK activity. *Mol Cell Biol, 23*, 4796-804. ↗

Ranganathan, A., Cobb, MH., Sturgill, TW., Pearson, GW., Chrestensen, CA. (2006). The MAP kinase ERK5 binds to and phosphorylates p90 RSK. *Arch Biochem Biophys, 449*, 8-16. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
2013-07-15	Edited	D'Eustachio, P., Matthews, L.

ERK5 activates the transcription factor MEF2 ↗

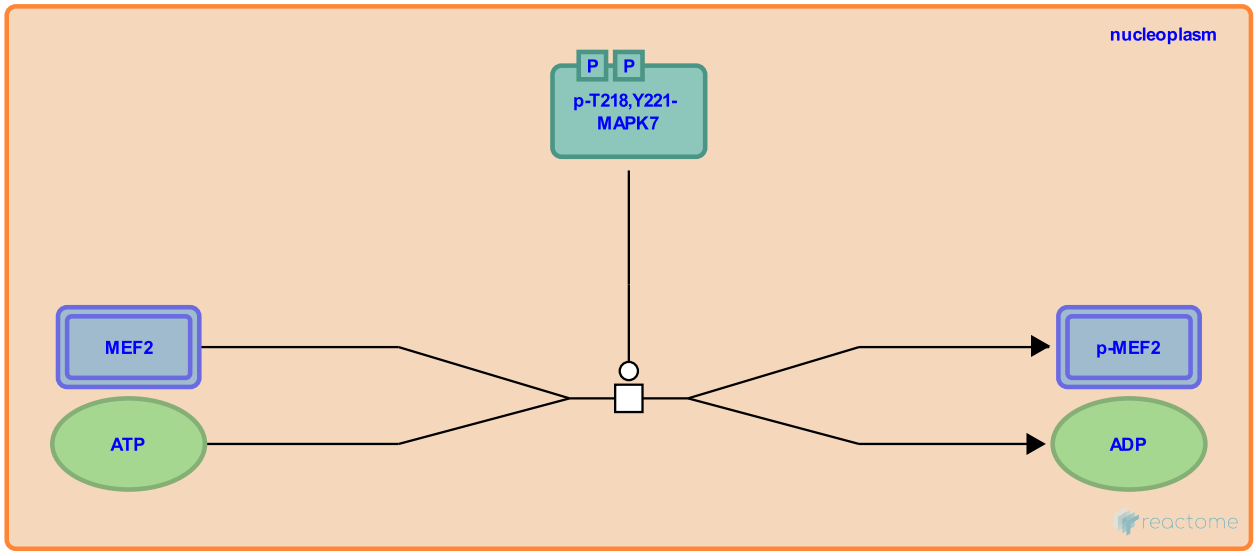
Location: ERK/MAPK targets

Stable identifier: R-HSA-199929

Type: transition

Compartments: nucleoplasm

Inferred from: ERK5 activates the transcription factor MEF2 (Rattus norvegicus)



The MEF2 (Myocyte-specific enhancer factor 2) proteins constitute a family of transcription factors: MEF2A, MEF2B, MEF2C, and MEF2D. MEF2A and MEF2C are known substrates of ERK5, and their transactivating activity can be stimulated by ERK5 via direct phosphorylation. MEF2A and MEF2C are expressed in developing and adult brain including cortex and cerebellum.

Editions

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

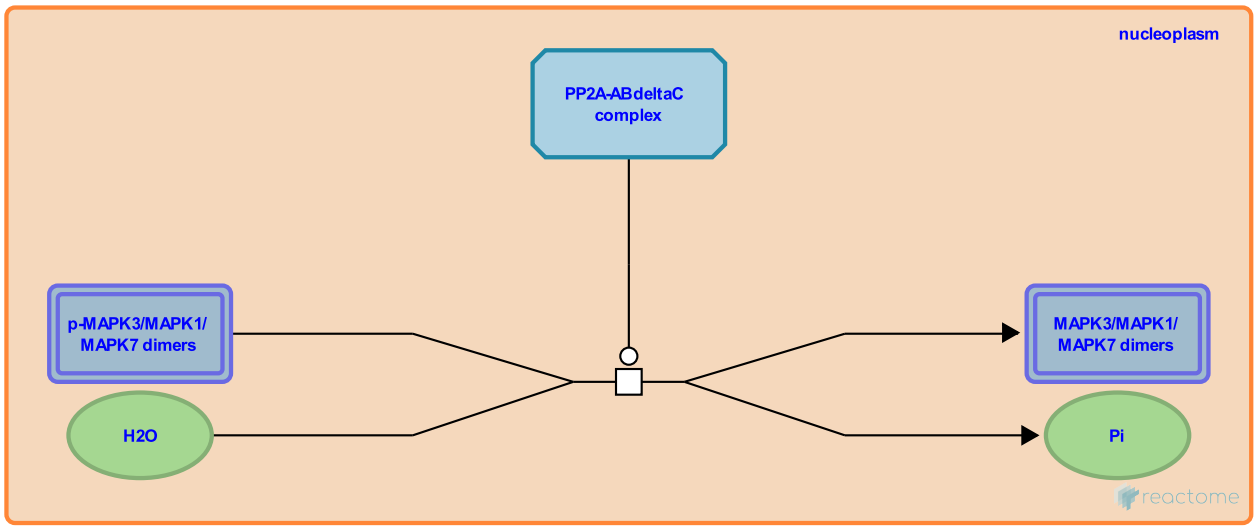
ERKs are inactivated by protein phosphatase 2A ↗

Location: ERK/MAPK targets

Stable identifier: R-HSA-199959

Type: transition

Compartments: nucleoplasm



ERKs are inactivated by the protein phosphatase 2A (PP2A). The PP2A holoenzyme is a heterotrimer that consists of a core dimer, composed of a scaffold (A) and a catalytic (C) subunit that associates with a variety of regulatory (B) subunits. The B subunits have been divided into gene families named B (or PR55), B0 (or B56 or PR61) and B00 (or PR72). Each family comprises several members. B56 family members of PP2A in particular, increase ERK dephosphorylation, without affecting its activation by MEK.
Induction of PP2A is involved in the extracellular signal-regulated kinase (ERK) signalling pathway, in which it provides a feedback control, as well as in a broad range of other cellular processes, including transcriptional regulation and control of the cell cycle.This diversity of functions is conferred by a diversity of regulatory subunits, the combination of which can give rise to over 50 different forms of PP2A. For example, five distinct mammalian genes encode members of the B56 family, called B56a, b, g, d and e, generating at least eight isoforms. Whether a specific holoenzyme dephosphorylates ERK and whether this activity is controlled during mitogenic stimulation is unknown.

Literature references

Rocher, G., Porteu, F., Letourneux, C. (2006). B56-containing PP2A dephosphorylate ERK and their activity is controlled by the early gene IEX-1 and ERK. *EMBO J, 25*, 727-38. ↗

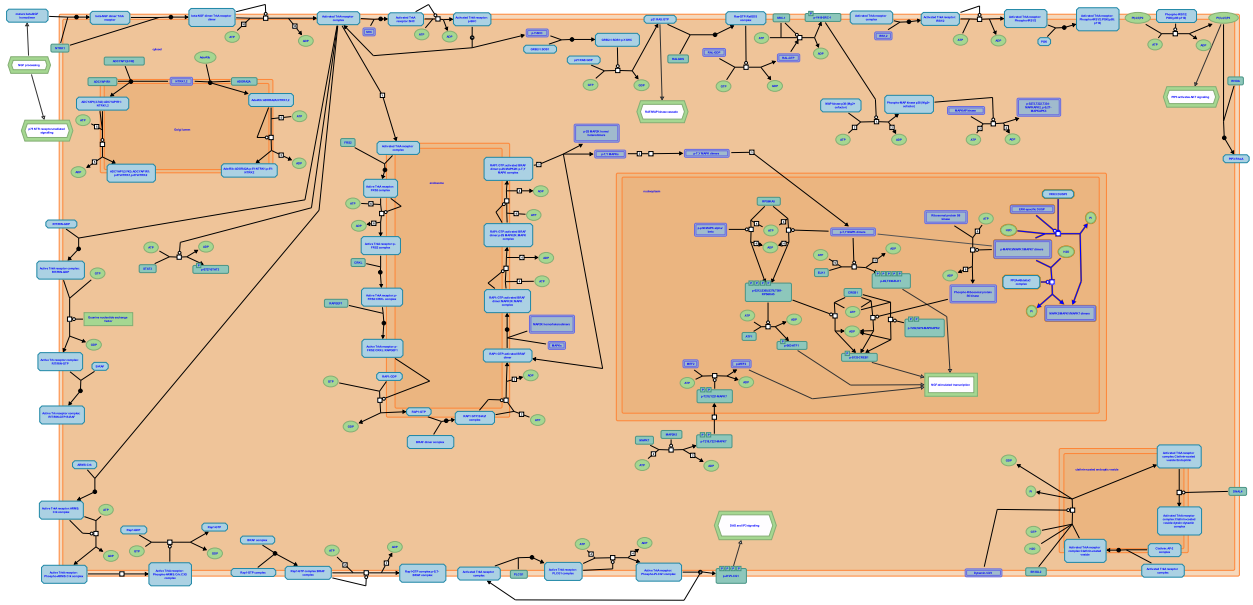
Editions

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

ERKs are inactivated ↗

Location: ERK/MAPK targets

Stable identifier: R-HSA-202670



MAP Kinases are inactivated by a family of protein named MAP Kinase Phosphatases (MKPs). They act through dephosphorylation of threonine and/or tyrosine residues within the signature sequence -pTXpY- located in the activation loop of MAP kinases (pT=phosphothreonine and pY=phosphotyrosine). MKPs are divided into three major categories depending on their preference for dephosphorylating; tyrosine, serine/threonine and both the tyrosine and threonine (dual specificity phoshatases or DUSPs). The tyrosine-specific MKPs include PTP-SL, STEP and HePTP, serine/threonine-specific MKPs are PP2A and PP2C, and many DUSPs acting on MAPKs are known. Activated MAP kinases trigger activation of transcription of MKP genes. Therefore, MKPs provide a negative feedback regulatory mechanism on MAPK signaling, by inactivating MAPKs via dephosphorylation, in the cytoplasm and the nucleus. Some MKPs are more specific for ERKs, others for JNK or p38MAPK.

Literature references

Farooq, A., Zhou, MM. (2004). Structure and regulation of MAPK phosphatases. *Cell Signal, 16*, 769-79. ↗

Siwak, D., Jacob-Hirsch, J., Lu, Y., Amit, I., Tarcic, G., Segal, E. et al. (2007). A module of negative feedback regulators defines growth factor signaling. *Nat Genet, 39*, 503-12. ↗

Editions

2007-11-08	Reviewed	Greene, LA.

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