Active p38 MAPK phosphorylates MAPKAPK2 or 3

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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

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. ↗

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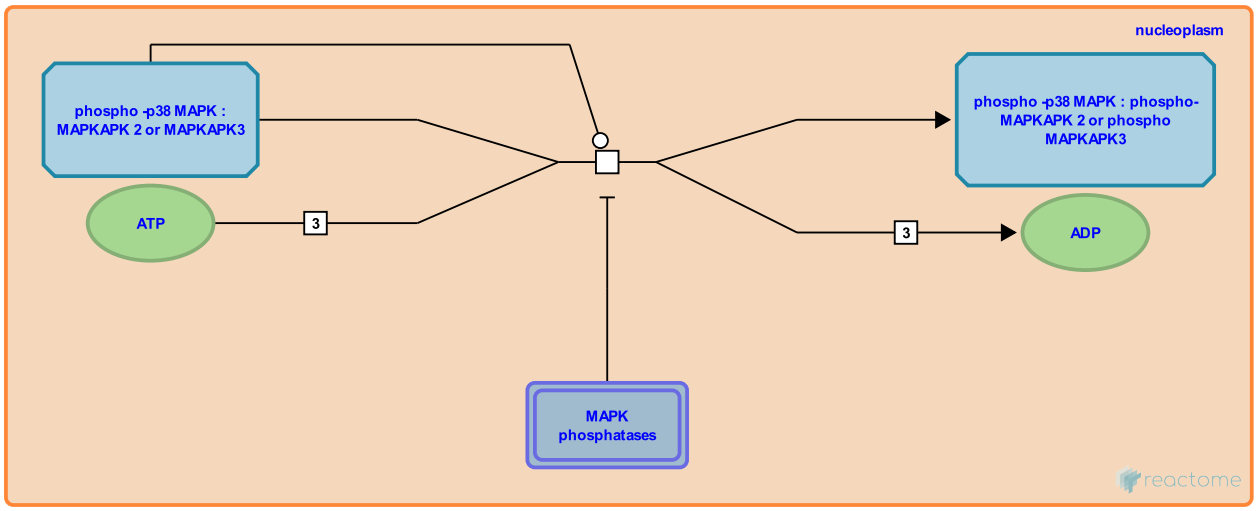
Stable identifier: R-GGA-442913

Type: transition

Compartments: nucleoplasm

Inferred from: Active p38 MAPK phosphorylates MAPKAPK2 or 3 (Homo sapiens)



Human p38 MAPK alpha forms a complex with MK2 even when the signaling pathway is not activated. This heterodimer is found mainly in the nucleus. The crystal structure of the unphosphorylated p38alpha-MK2 heterodimer was determined. The C-terminal regulatory domain of MK2 binds in the docking groove of p38 MAPK alpha, and the ATP-binding sites of both kinases are at the heterodimer interface (ter Haar et al. 2007).

Upon activation, p38 MAPK alpha activates MK2 by phosphorylating Thr-222, Ser-272, and Thr-334 (Ben-Levy et al. 1995).

The phosphorylation of MK2 at Thr-334 attenuates the affinity of the binary complex MK2:p38 alpha by an order of magnitude and leads to a large conformational change of an autoinhibitory domain in MK2. This conformational change unmasks not only the MK2 substrate-binding site but also the MK2 nuclear export signal (NES) thus leading to the MK2:p38 alpha translocation from the nucleus to the cytoplasm. Cytoplasmic active MK2 then phosphorylates downstream targets such as the heat-shock protein HSP27 and tristetraprolin (TTP) (Meng et al. 2002, Lukas et al. 2004, White et al. 2007).

MAPKAPK (MAPK-activated protein) kinase 3 (MK3, also known as 3pK) has been identified as the second p38 MAPK-activated kinase that is stimulated by different stresses (McLaughlin et al. 1996; Sithanandam et al. 1996; reviewed in Gaestel 2006). MK3 shows 75% sequence identity to MK2 and, like MK2, is activated by p38 MAPK alpha and p38 MAPK beta. MK3 phosphorylates peptide substrates with kinetic constants similar to MK2 and phosphorylates the same serine residues in HSP27 at the same relative rates as MK2 (Clifton et al. 1996) indicating an identical phosphorylation-site consensus sequence. Hence, it is assumed that its substrate spectrum is either identical to or at least overlapping with MK2.

Literature references

Studts, JM., Farmer BT, 2nd., Werneburg, BG., Pargellis, CA., White, A. (2007). Molecular basis of MAPK-activated protein kinase 2:p38 assembly. *Proc Natl Acad Sci U S A, 104*, 6353-8. ↗

Marshall, CJ., Ben-Levy, R., Attwood, P., Morrice, N., Leighton, IA., Cohen, P. et al. (1995). Identification of novel phosphorylation sites required for activation of MAPKAP kinase-2. *EMBO J, 14*, 5920-30. ↗

Liu, X., Lepre, C., Prabhakar, P., Ter Haar, E. (2007). Crystal structure of the p38 alpha-MAPKAP kinase 2 heterodimer. *J Biol Chem, 282*, 9733-9. ↗

Wildeson, J., Lukas, SM., Ingraham, RH., Frego, L., Peet, GW., Labadia, ME. et al. (2004). Catalysis and function of the p38 alpha.MK2a signaling complex. *Biochemistry, 43*, 9950-60. ↗

Editions

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