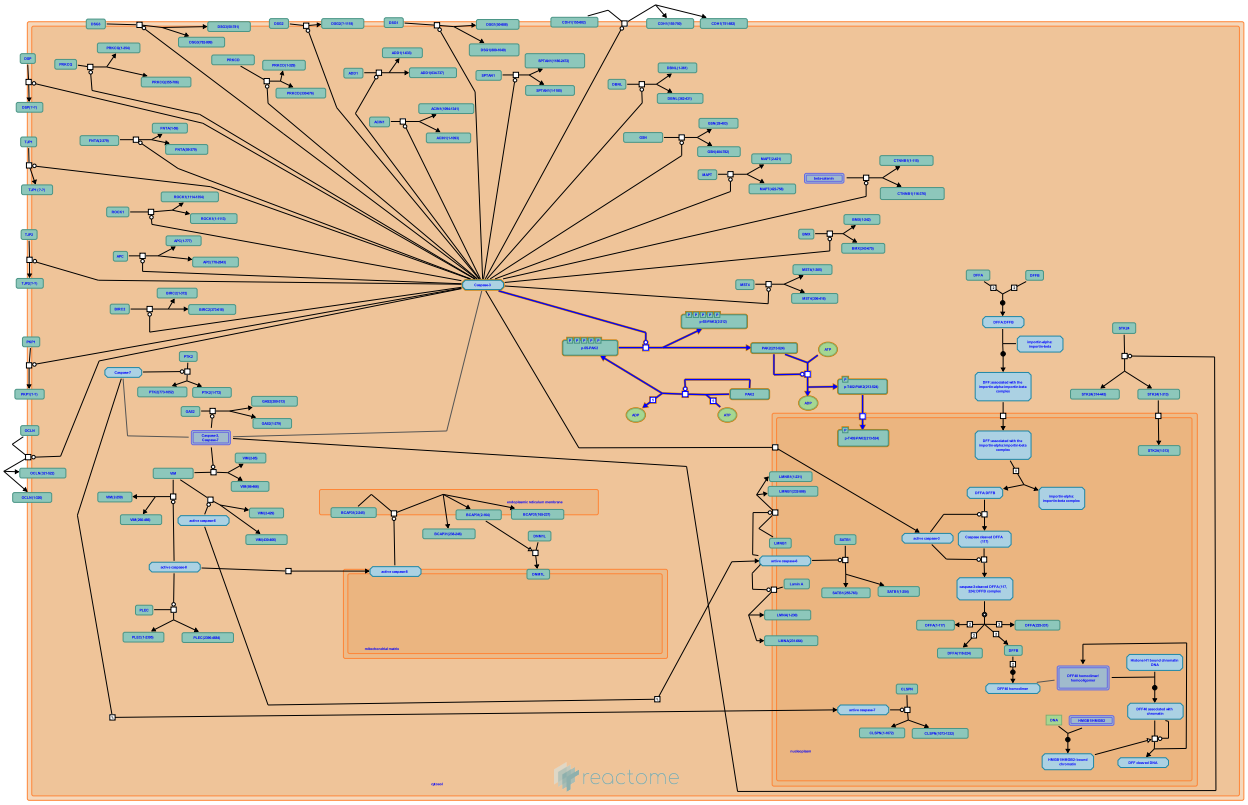
Stimulation of the cell death response by PAK-2p34



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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

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. ↗

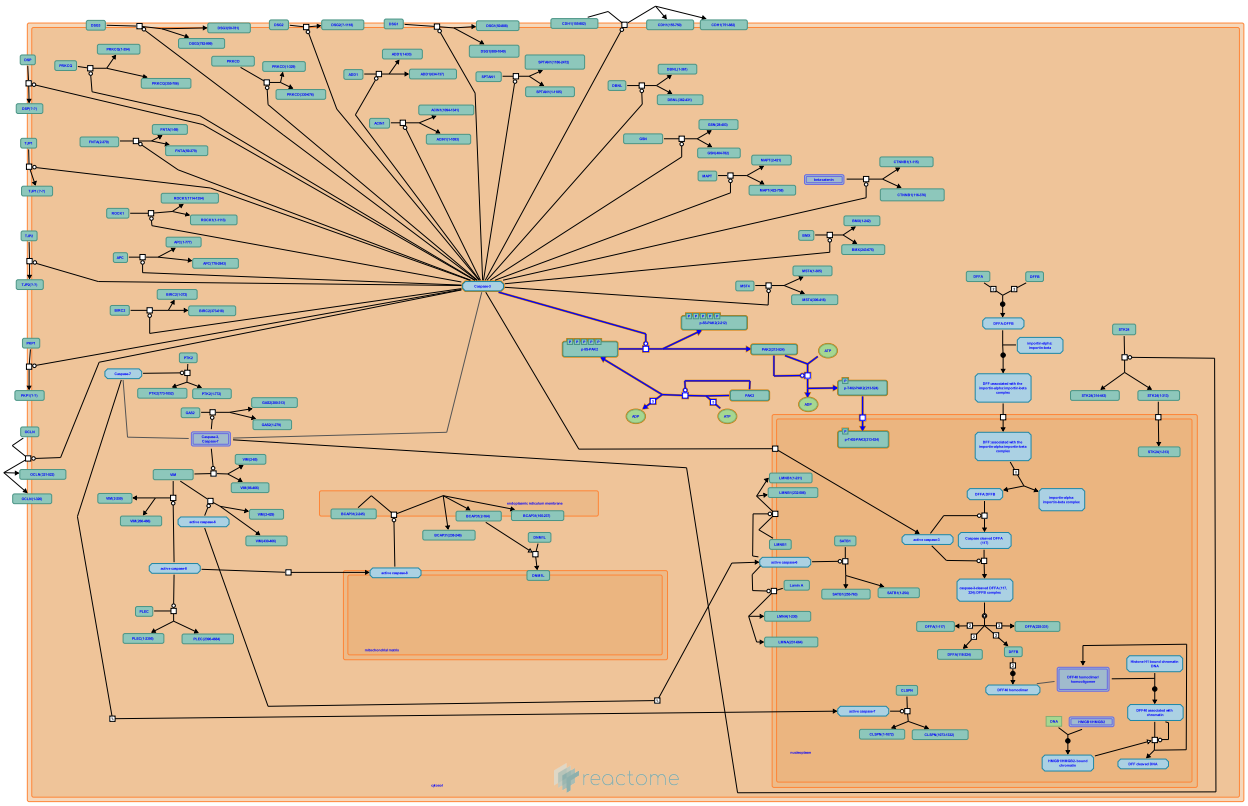
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Stimulation of the cell death response by PAK-2p34 ↗

Stable identifier: R-HSA-211736



In response to stress signals, the p21-activated protein kinase PAK-2 stimulates a cell death response characterized by increased cell rounding and apoptotic chromatin condensation (see Jakobi et al., 2003). PAK-2 is proteolytically cleaved by caspase-3 producing a constitutively active fragment, PAK-2p34. Following cleavage, PAK-2p34 is autophosphorylated at Thr 402 and transported to the nucleus where it accumulates due to the loss of its nuclear export signal motif (Jakobi et al., 2003). The activity of PAK-2p34 appears to be regulated both by proteosomal degradation (Jakobi et al., 2003) and by association with the GTPase-activating protein PS-GAP/ RHG-10. This interaction inhibits the kinase activity of PAK-2p34 and changes the localization of PAK-2p34 from the nucleus to the perinuclear region (Koeppel et al., 2004). PAK-2p34 may function in the down-regulation of translation initiation in apoptosis through phosphorylation of Mnk1 (Orton et al.,2004).

Literature references

Jakobi, R., Walter, BN., Huang, Z., Litwack, G., Traugh, JA., Tuazon, PT. et al. (1998). Cleavage and activation of p21-activated protein kinase gamma-PAK by CPP32 (caspase 3). Effects of autophosphorylation on activity. *J Biol Chem, 273*, 28733-9. ↗

Rhoads, RE., Korneeva, NL., Ling, J., Orton, KC., Traugh, JA., Waskiewicz, AJ. et al. (2004). Phosphorylation of Mnk1 by caspase-activated Pak2/gamma-PAK inhibits phosphorylation and interaction of eIF4G with Mnk. *J Biol Chem, 279*, 38649-57. ↗

Jakobi, R., Koeppel, MA., McCarthy, CC., Moertl, E. (2004). Identification and characterization of PS-GAP as a novel regulator of caspase-activated PAK-2. *J Biol Chem, 279*, 53653-64. ↗

Koeppel, MA., Jakobi, R., McCarthy, CC., Stringer, DK. (2003). Caspase-activated PAK-2 is regulated by subcellular targeting and proteasomal degradation. *J Biol Chem, 278*, 38675-85. ↗

Editions

2008-02-04	Edited	Matthews, L.
2008-02-05	Authored	Jakobi, R.
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2008-06-12	Edited	Matthews, L.

Cleavage of PAK-2 at 212 ↗

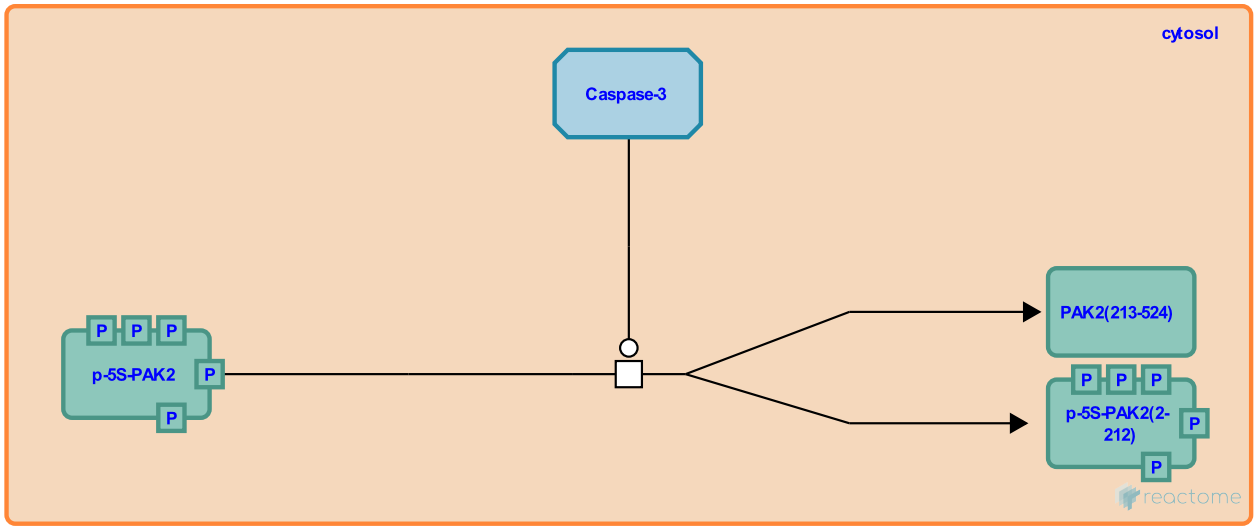
Location: Stimulation of the cell death response by PAK-2p34

Stable identifier: R-HSA-211651

Type: transition

Compartments: cytosol

Inferred from: Cleavage of PAK-2 at 212 (Oryctolagus cuniculus)



p21-activated protein kinase (PAK-2), also known as gamma-PAK, is cleaved by caspase-3 during apoptosis and plays a role in regulating cell death. Cleavage produces two peptides; 1-212 containing most of the regulatory domain and 213-524 containing 34 amino acids of the regulatory domain as well as the catalytic domain (Walter et al., 1998). Proteolytic cleavage of PAK by caspase-3 creates the constitutively active PAK-2p34 fragment (Jakobi et al., 2003). Evidence for this reaction comes from experiments using both human and rabbit proteins.

Preceded by: Partial autophosphorylation of PAK-2 at Ser-19, Ser-20, Ser-55, Ser-192, and Ser-197

Followed by: Autophosphorylation of PAK-2p34 in the activation loop

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2008-02-04	Edited	Matthews, L.
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Autophosphorylation of PAK-2p34 in the activation loop ↗

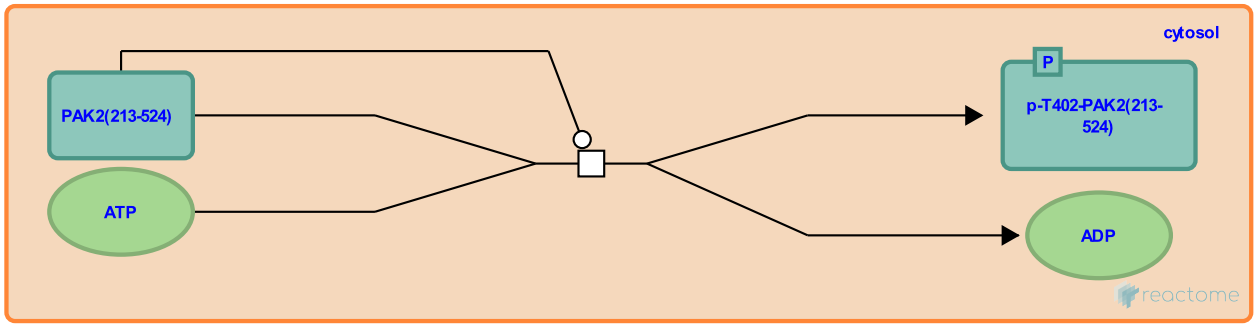
Location: Stimulation of the cell death response by PAK-2p34

Stable identifier: R-HSA-211650

Type: transition

Compartments: cytosol

Inferred from: Autophosphorylation of PAK-2p34 (Oryctolagus cuniculus)



Activation of PAK-2p34 coincides with autophosphorylation of Thr 402 in the the catalytic domain (Walter et al., 1998).

Preceded by: Cleavage of PAK-2 at 212

Followed by: Proteolytic PAK-2p34 fragment translocates to the nucleus

Editions

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Proteolytic PAK-2p34 fragment translocates to the nucleus ↗

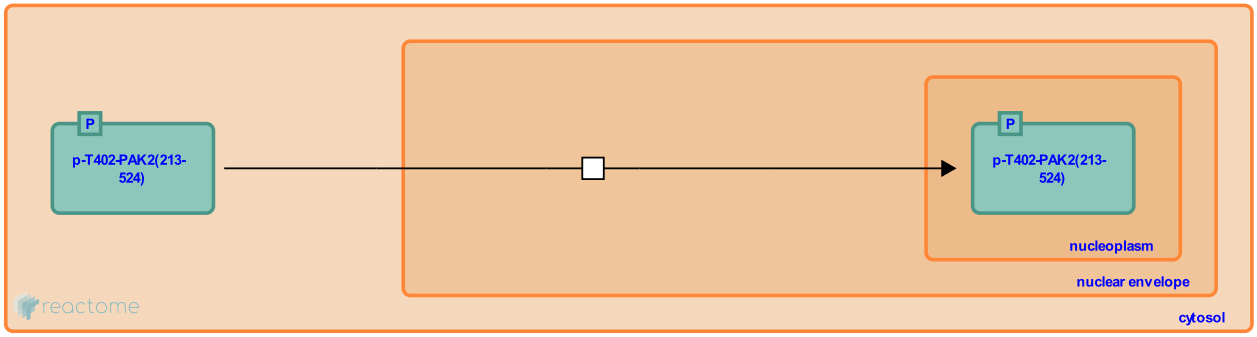
Location: Stimulation of the cell death response by PAK-2p34

Stable identifier: R-HSA-211712

Type: transition

Compartments: nuclear envelope

Inferred from: Proteolytic PAK-2p34 fragment translocates to the nucleus (Oryctolagus cuniculus)



The subcellular localization of PAK-2 is controlled by nuclear localization and nuclear export signal motifs (Jakobi et al.,2003). The regulatory domain contains a nuclear export signal motif that prevents the nuclear accumulation of full-length PAK-2. The activating proteolytic cleavage disrupts the nuclear export signal in PAK-2 and removes most its regulatory domain. The resulting activated PAK-2p34 fragment contains a nuclear localization signal and translocates to and is retained in the nucleus (Jakobi et al.,2003).

Preceded by: Autophosphorylation of PAK-2p34 in the activation loop

Editions

2008-02-04	Edited	Matthews, L.
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Partial autophosphorylation of PAK-2 at Ser-19, Ser-20, Ser-55, Ser-192, and Ser-197

↗

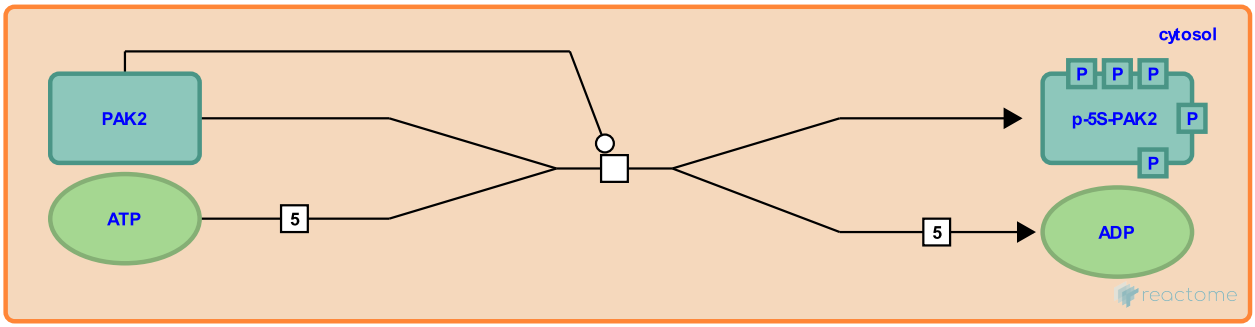
Location: Stimulation of the cell death response by PAK-2p34

Stable identifier: R-HSA-211583

Type: transition

Compartments: cytosol

Inferred from: Partial autophosphorylation of PAK-2 at Ser-19, Ser-20, Ser-55, Ser-192, and Ser-197 (Oryctolagus cuniculus)



Inactive PAK-2 can be partially autophosphorylated in the regulatory region without being activated (Gatti et al. 1999).

Followed by: Cleavage of PAK-2 at 212

Literature references

Traugh, JA., Jung, JH. (2005). Regulation of the interaction of Pak2 with Cdc42 via autophosphorylation of serine 141. *J Biol Chem, 280*, 40025-31. ↗

Editions

2008-02-05	Authored	Jakobi, R.
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