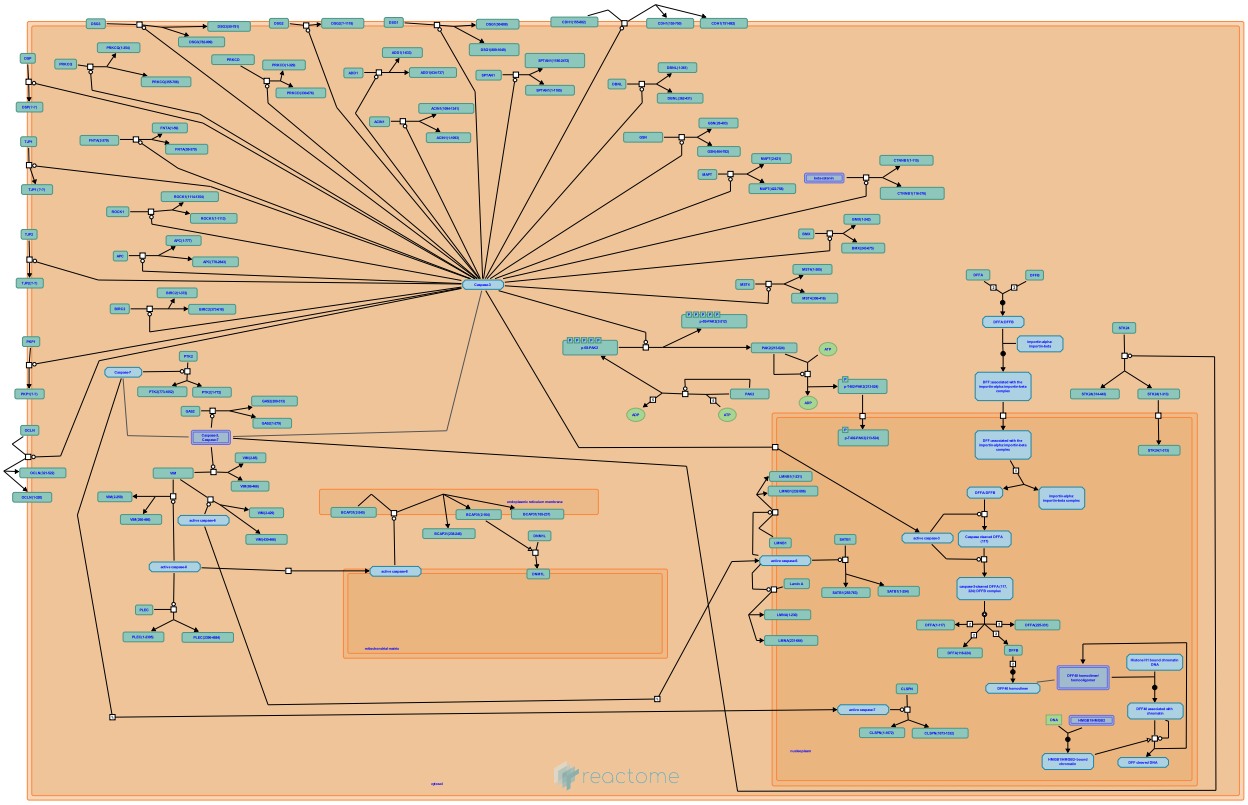
Apoptotic execution phase



Alnemri, E., Chang, E., Gillespie, ME., Jakobi, R., Matthews, L., Ranganathan, S., Schulze-Osthoff, K., Shamovsky, V., Widlak, P.

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.

17/05/2024

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. ↗

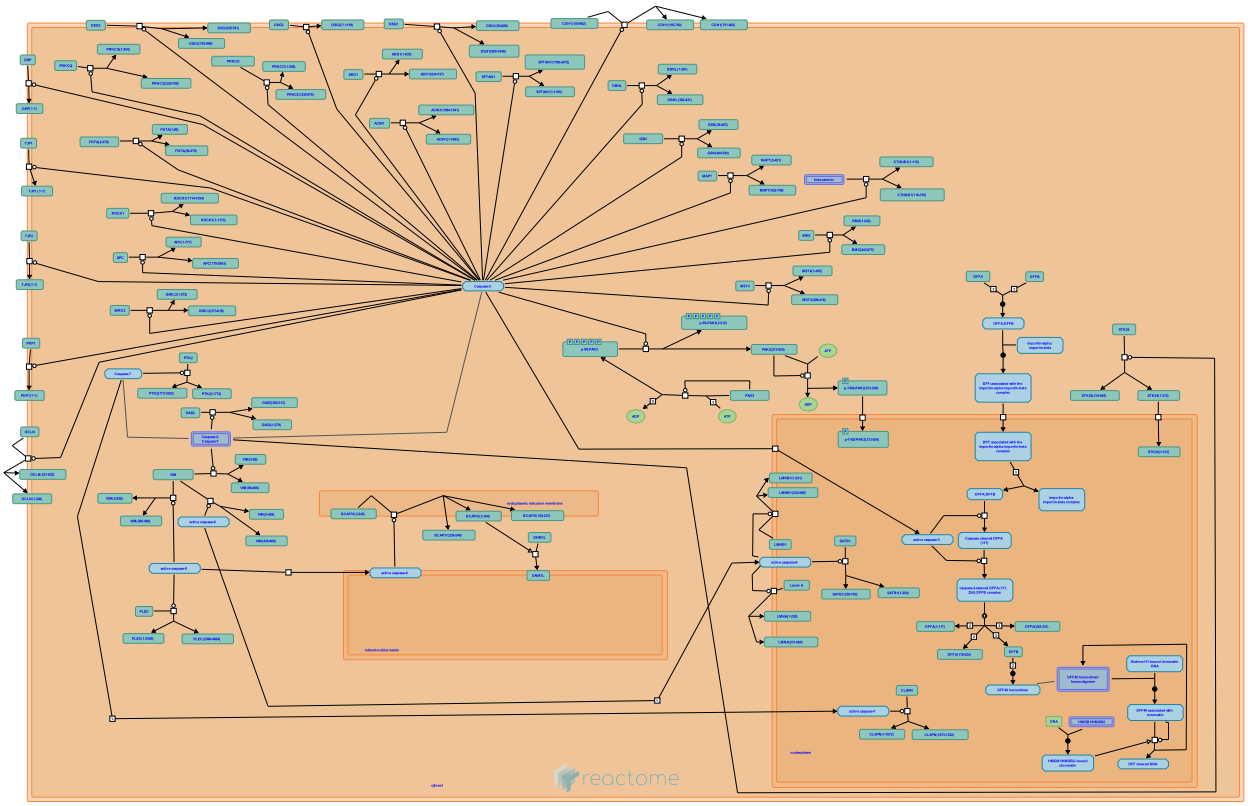
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Apoptotic execution phase ↗

Stable identifier: R-HSA-75153



In the execution phase of apoptosis, effector caspases cleave vital cellular proteins leading to the morphological changes that characterize apoptosis. These changes include destruction of the nucleus and other organelles, DNA fragmentation, chromatin condensation, cell shrinkage and cell detachment and membrane blebbing (reviewed in Fischer et al., 2003).

Literature references

Janicke, RU., Schulze-Osthoff, K., Fischer, U. (2003). Many cuts to ruin: a comprehensive update of caspase substrates. *Cell Death Differ, 10*, 76-100. ↗

Editions

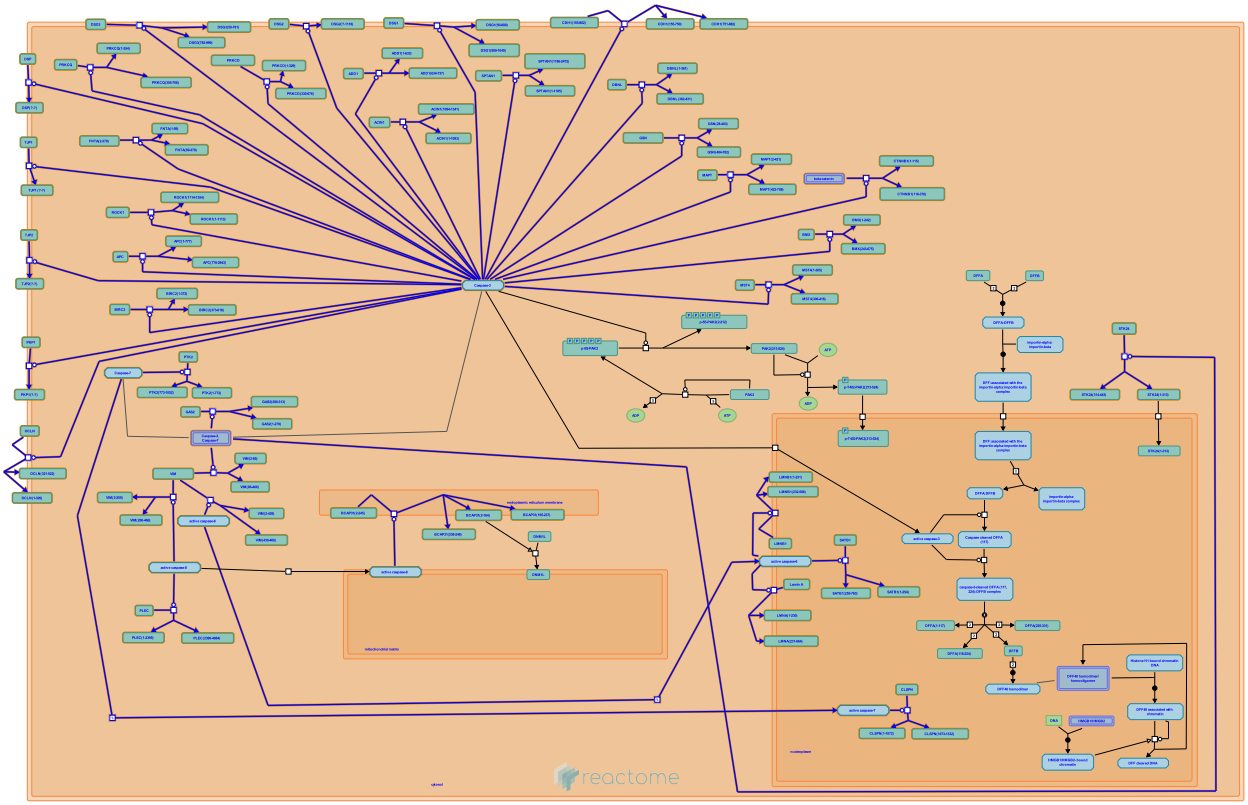
2004-02-17	Authored	Alnemri, E.
2007-11-23	Reviewed	Ranganathan, S.
2008-02-12	Edited	Matthews, L.
2008-05-20	Revised	Matthews, L.

Apoptotic cleavage of cellular proteins ↗

Location: Apoptotic execution phase

Stable identifier: R-HSA-111465

Compartments: cytosol



Apoptotic cell death is achieved by the caspase-mediated cleavage of various vital proteins. Among caspase targets are proteins such as E-cadherin, Beta-catenin, alpha fodrin, GAS2, FADK, alpha adducin, HIP-55, and desmoglein involved in cell adhesion and maintenance of the cytoskeletal architecture. Cleavage of proteins such as APC and CIAP1 can further stimulate apoptosis by produce proapoptotic proteins (reviewed in Fischer et al., 2003. See also Wee et al., 2006 and the CASVM Caspase Substrates Database: http://www.casbase.org/casvm/squery/index.html).

Literature references

Tan, TW., Ranganathan, S., Wee, LJ. (2006). SVM-based prediction of caspase substrate cleavage sites. *BMC Bioinformatics, 7*, S14. ↗

Janicke, RU., Schulze-Osthoff, K., Fischer, U. (2003). Many cuts to ruin: a comprehensive update of caspase substrates. *Cell Death Differ, 10*, 76-100. ↗

Tan, TW., Ranganathan, S., Wee, LJ. (2007). CASVM: web server for SVM-based prediction of caspase substrates cleavage sites. *Bioinformatics, 23*, 3241-3. ↗

Editions

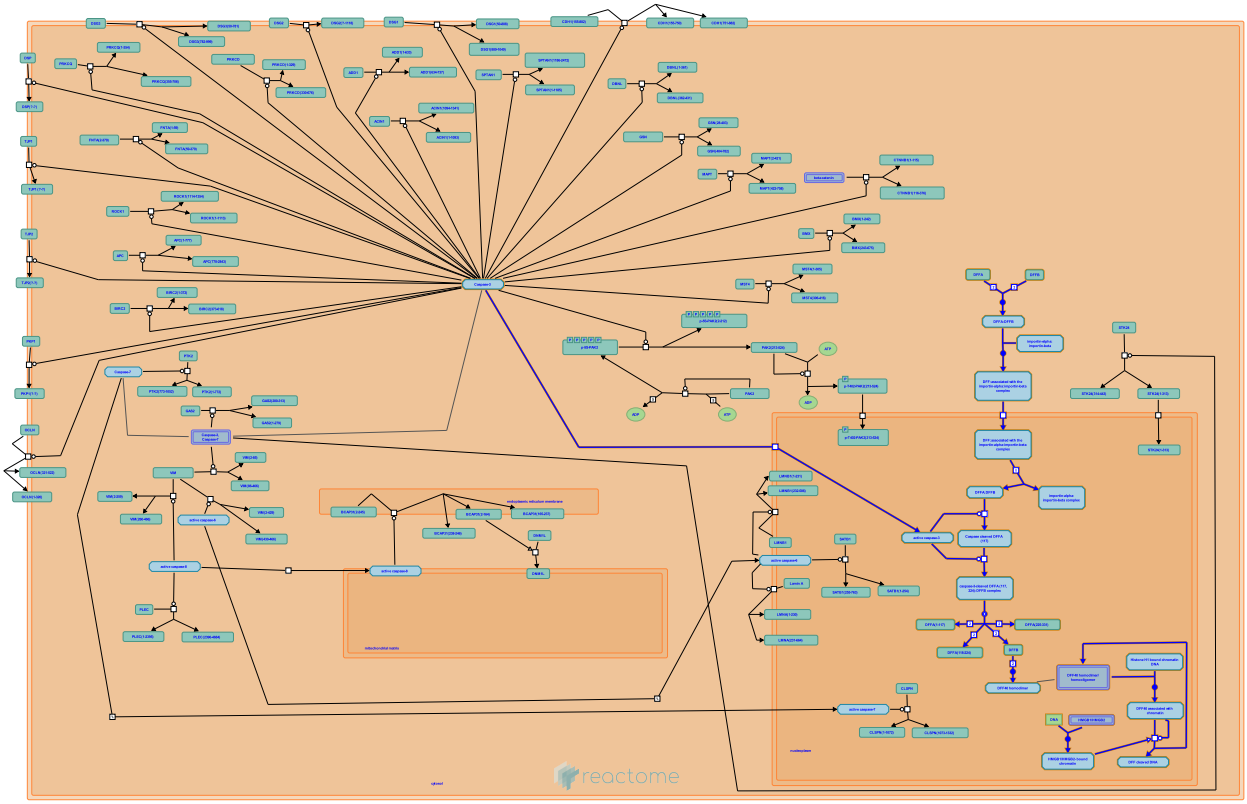
2007-09-03	Authored	Schulze-Osthoff, K.
2007-11-23	Reviewed	Ranganathan, S.
2008-02-08	Edited	Matthews, L.
2008-05-18	Revised	Matthews, L.

Apoptosis induced DNA fragmentation ↗

Location: Apoptotic execution phase

Stable identifier: R-HSA-140342

Compartments: nucleoplasm, cytosol



DNA fragmentation in response to apoptotic signals is achieved, in part, through the activity of apoptotic nucleases, termed DNA fragmentation factor (DFF) or caspase-activated DNase (CAD) (reviewed in Widlak and Garrard, 2005). In non-apoptotic cells, DFF is a nuclear heterodimer consisting of a 45 kD chaperone and inhibitor subunit (DFF45)/inhibitor of CAD (ICAD-L)] and a 40 kD nuclease subunit (DFF40/CAD)(Liu et al. 1997, 1998; Enari et al. 1998). During apoptosis, activated caspase-3 or -7 cleave DFF45/ICAD releasing active DFF40/CAD nuclease. The activity of DFF is tightly controlled at multiple stages. During translation, DFF45/ICAD, Hsp70, and Hsp40 proteins play a role in insuring the appropriate folding of DFF40 during translation(Sakahira and Nagata, 2002). The nuclease activity of DFF40 is enhanced by the chromosomal proteins histone H1, Topoisomerase II and HMGB1/2(Widlak et al., 2000). In addition, the inhibitors (DFF45/35; ICAD-S/L) are produced in stoichiometric excess (Widlak et al., 2003).

Literature references

Widlak, P., Garrard, WT. (2005). Discovery, regulation, and action of the major apoptotic nucleases DFF40/CAD and endonuclease G. *J Cell Biochem, 94*, 1078-87. ↗

Li, P., Wang, X., Widlak, P., Garrard, WT. (2000). Cleavage preferences of the apoptotic endonuclease DFF40 (caspase-activated DNase or nuclease) on naked DNA and chromatin substrates. *J Biol Chem, 275*, 8226-32. ↗

Garrard, W., Liu, X., Wang, X., Widlak, P., Zou, H. (1999). Activation of the apoptotic endonuclease DFF40 (caspase-activated DNase or nuclease). Oligomerization and direct interaction with histone H1. *J Biol Chem, 274*, 13836-40. ↗

Cary, RB., Lanuszewska, J., Widlak, P., Garrard, WT. (2003). Subunit structures and stoichiometries of human DNA fragmentation factor proteins before and after induction of apoptosis. *J Biol Chem, 278*, 26915-22. ↗

Yokoyama, H., Nagata, S., Okawa, K., Enari, M., Iwamatsu, A., Sakahira, H. (1998). A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD. *Nature, 391*, 43-50. ↗

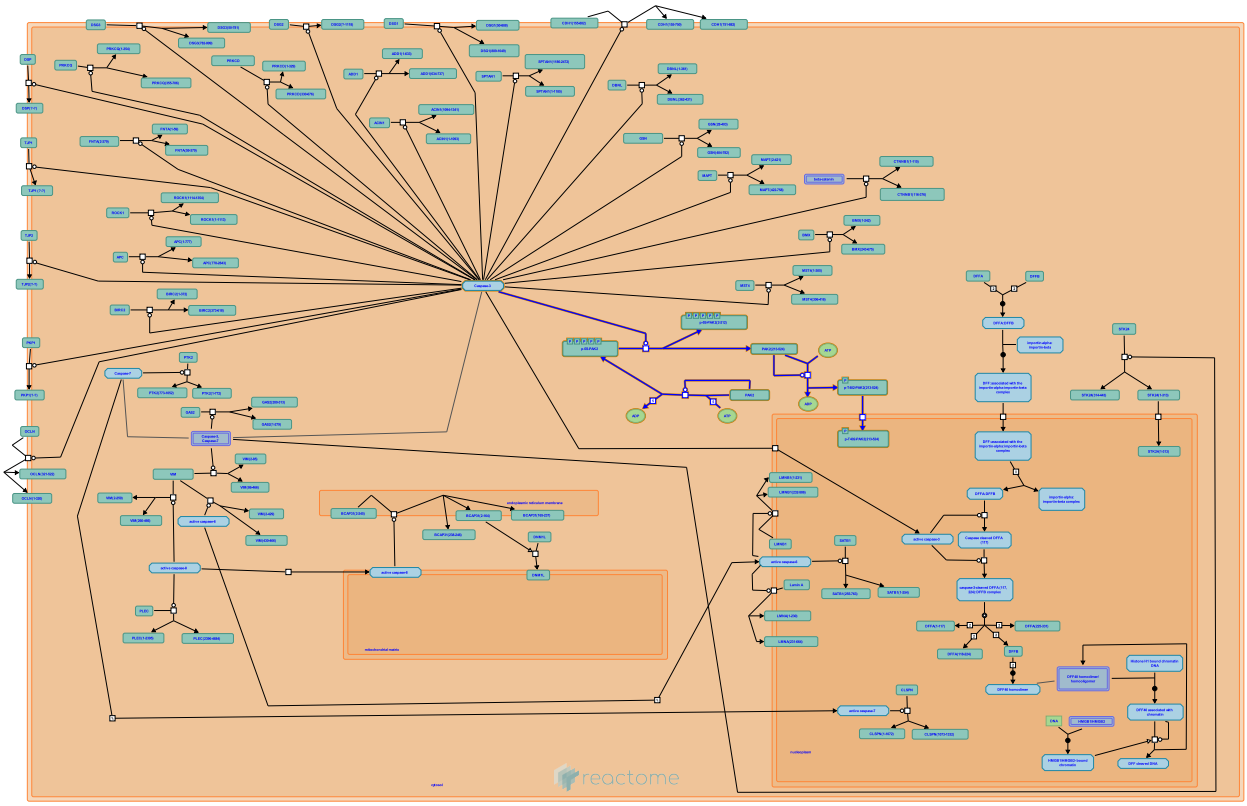
Editions

2008-04-25	Authored	Matthews, L.
2008-04-25	Reviewed	Widlak, P.
2008-05-18	Edited, Revised	Matthews, L.

Stimulation of the cell death response by PAK-2p34

Location: Apoptotic execution phase

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.
2008-05-21	Reviewed	Chang, E.
2008-06-12	Edited	Matthews, L.

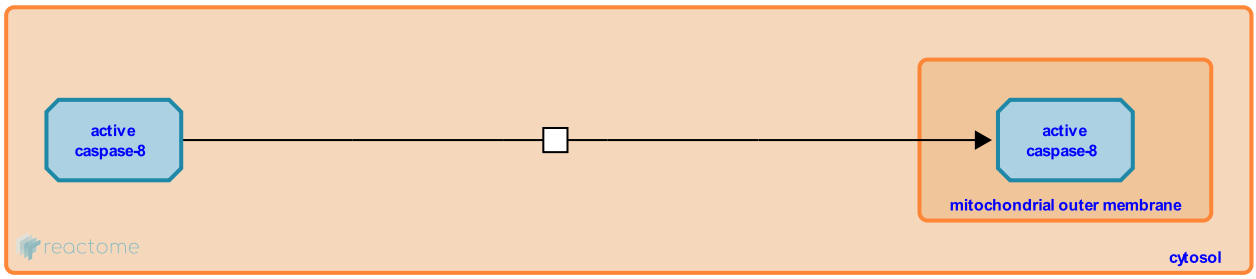
Translocation of active caspase-8 to the mitochondrial membrane ↗

Location: Apoptotic execution phase

Stable identifier: R-HSA-351863

Type: transition

Compartments: cytosol, mitochondrial outer membrane



Active caspase 8 associates with the membranes during apoptosis caused by multiple stimuli (Chandra et al., 2004). OMM-localized active caspase 8 can activate cytosolic caspase 3 and ER-localized BAP31 (Chandra et al., 2004) .

Literature references

Deng, X., Chandra, D., Bhatia, B., Tang, DG., Daniel, P., Choy, G. (2004). Association of active caspase 8 with the mitochondrial membrane during apoptosis: potential roles in cleaving BAP31 and caspase 3 and mediating mitochondrion-endoplasmic reticulum cross talk in etoposide-induced cell death. *Mol Cell Biol, 24*, 6592-607. ↗

Editions

2008-05-18	Authored	Schulze-Osthoff, K.
2008-05-27	Edited	Matthews, L.
2008-06-11	Reviewed	Ranganathan, S.
2012-11-19	Reviewed	Gillespie, ME.
2012-11-26	Edited	Shamovsky, V.

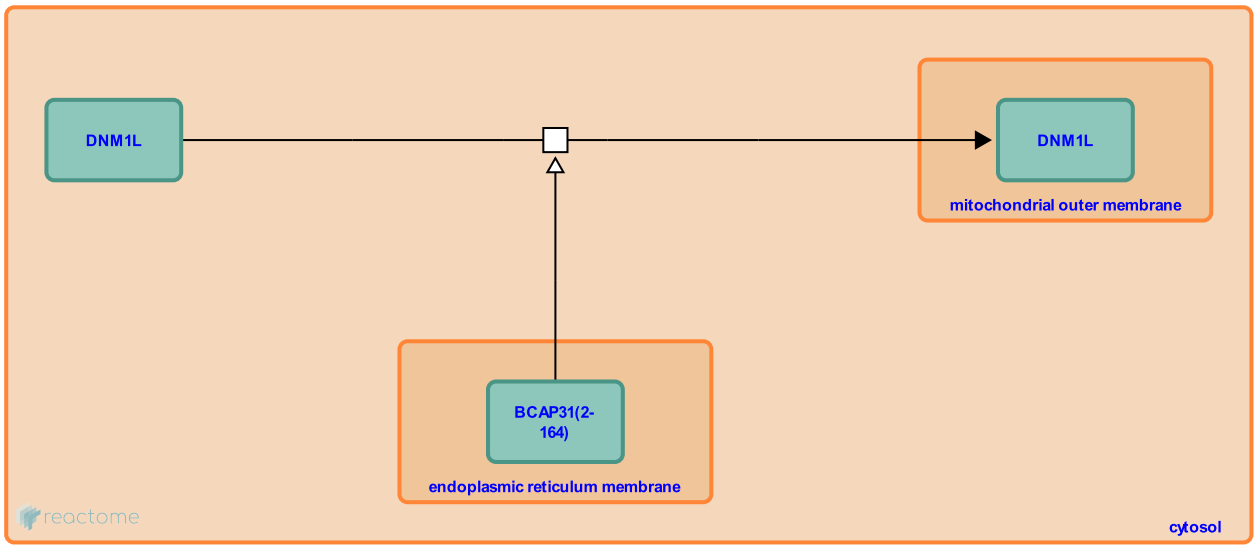
Mitochondrial recruitment of Drp1 ↗

Location: Apoptotic execution phase

Stable identifier: R-HSA-351948

Type: transition

Compartments: cytosol, mitochondrial outer membrane



Adenoviral expression of the BAP31 cleavage product, p20 causes early release of Ca2+ from the ER, concomitant uptake of Ca2+ into mitochondria, and recruitment of Drp1 to the mitochondria (Breckenridge et al., 2003). Drp1 mediates scission of the outer mitochondrial membrane, resulting in dramatic fragmentation and fission of the mitochondrial network.

Literature references

Stojanovic, M., Marcellus, RC., Shore, GC., Breckenridge, DG. (2003). Caspase cleavage product of BAP31 induces mitochondrial fission through endoplasmic reticulum calcium signals, enhancing cytochrome c release to the cytosol. *J Cell Biol, 160*, 1115-27. ↗

Editions

2008-05-18	Authored	Schulze-Osthoff, K.
2008-06-03	Edited	Matthews, L.
2008-06-11	Reviewed	Ranganathan, S.

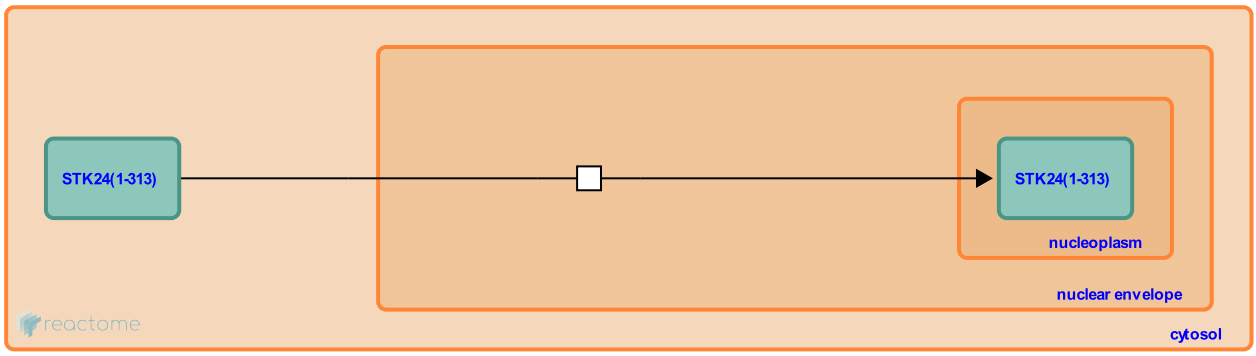
Nuclear translocation of catalytic domain of Mst3

Location: Apoptotic execution phase

Stable identifier: R-HSA-351947

Type: transition

Compartments: nuclear envelope



Proteolytic cleavage of the COOH-terminal domain of Mst3 by caspases promotes nuclear translocation of the catalytic domain (Huang et al., 2002).

Literature references

Huang, CY., Hsu, CY., Fang, HI., Robinson, DR., Wu, YM., Huang, CL. et al. (2002). Caspase activation of mammalian sterile 20-like kinase 3 (Mst3). Nuclear translocation and induction of apoptosis. *J Biol Chem, 277*, 34367-74.

Editions

2008-05-18	Authored	Schulze-Osthoff, K.
2008-06-02	Edited	Matthews, L.
2008-06-11	Reviewed	Ranganathan, S.

Table of Contents