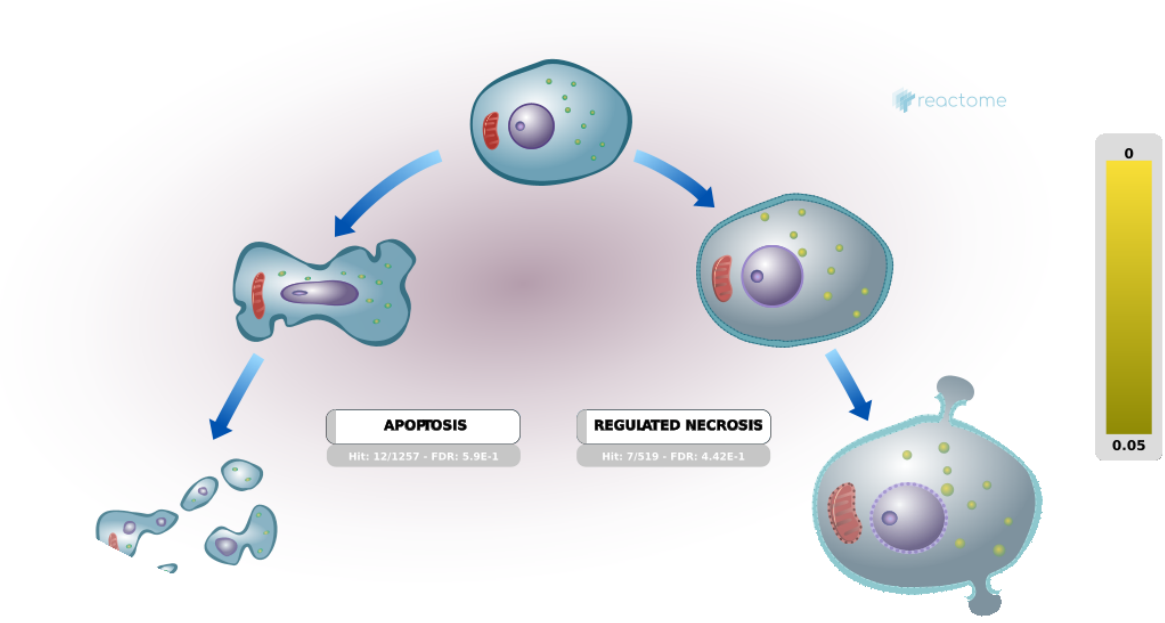
Programmed Cell Death



Alnemri, E., Chan, FK., Gillespie, ME., Gopinathrao, G., Hardwick, JM., Hengartner, M., Joshi-Tope, G., Matthews, L., Ranganathan, S., Shamovsky, V., Tschopp, J., Tsujimoto, Y., Vaux, DL.

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

01/09/2022

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. ↗

Reactome database release: 81

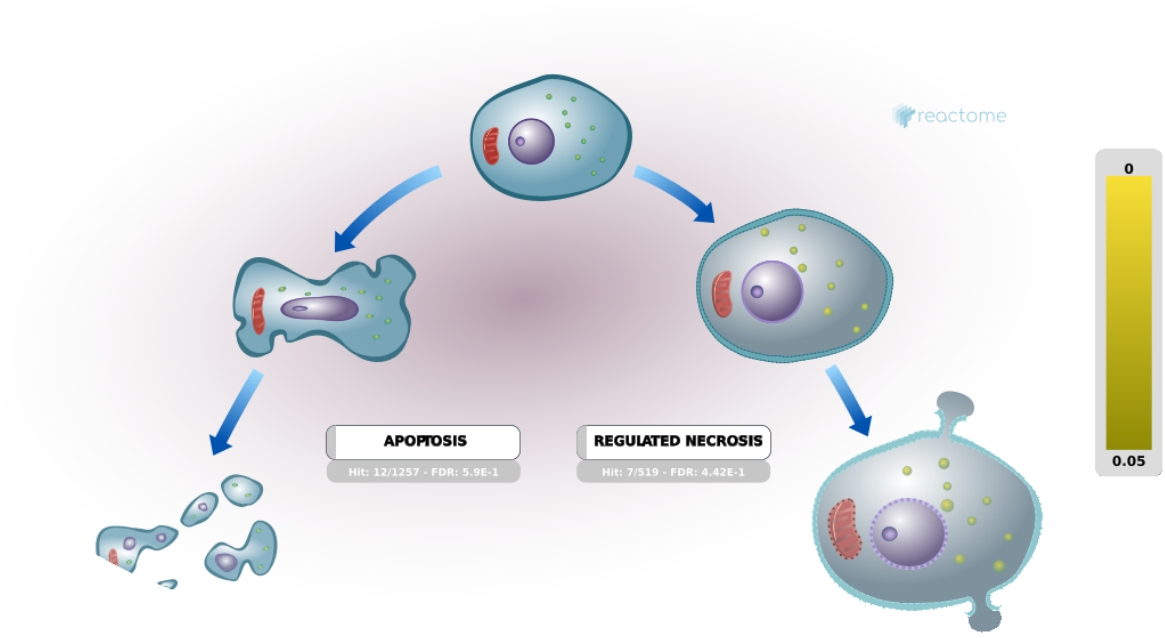
This document contains 3 pathways (see Table of Contents)

Analysis properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method. See more
- 39 out of 39 identifiers in the sample were found in Reactome, where 1141 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjA5MDEwNDA3MzZfMzEyNTc%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

Programmed Cell Death ↗

Stable identifier: R-HSA-5357801



Cell death is a fundamental cellular response that has a crucial role in shaping our bodies during development and in regulating tissue homeostasis by eliminating unwanted cells. There are a number of different forms of cell death, each with a corresponding number of complex subprocesses. The first form of regulated or programmed cell death to be characterized was apoptosis. Evidence has emerged for a number of regulated non-apoptotic cell death pathways, including some with morphological features that were previously attributed to necrosis. More recently necrosis has been subdivided into parts including programmed necrotic cell death processes, such as RIP1-mediated regulated necrosis or pyroptosis.

Reactome currently represents programmed cell death using the model of extrinsic signalling that leads to a molecular decision point pivoting on caspase-8 activation or inhibition. Caspase-8 activation tilts the cell towards apoptosis, while caspase-8 inhibition tilts the cell towards Regulated Necrosis.

The terminology and molecular definitions of cell death-related events annotated here are consistent with the 2015 recommendations of the Nomenclature Committee on Cell Death (NCCD) (Galluzzi L et al. 2015).

Literature references

Szabadkai, G., Kepp, O., Nunez, G., Aaronson, SA., Bredesen, DE., Abrams, JM. et al. (2015). Essential versus accessory aspects of cell death: recommendations of the NCCD 2015. *Cell Death Differ., 22*, 58-73. ↗

Editions

2014-11-18	Authored, Edited	Shamovsky, V.

6 submitted entities found in this pathway, mapping to 8 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BAX	Q07812	BCL2	P10415	IL1B	P01583, P01584
MAPK	P28482	STAT3	P40763	p53	P04637

Input	Ensembl Id
BCL2	ENSG00000171791

Interactors found in the analysis (9)

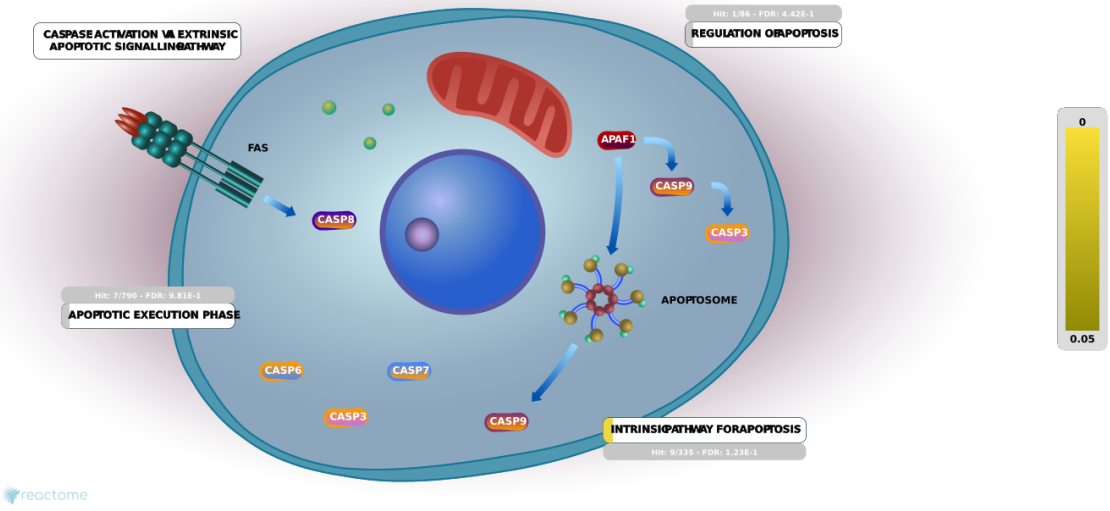
Input	UniProt Id	Interacts with
BAX	Q07812, Q07813-1	Q07817, Q16611, O43521, P10415, Q07812, P55957
EGFR	P00533	P10636, P12830, Q8WUM4, P45983, P06396, Q05397
NFKB1	P19838	P35222
STAT3	P40763	P51813
p53	P04637	P09429, Q05655, P10415, Q8N726, Q05397

Input	UniProt Id	Interacts with
BCL2	P10415, P10415-1	P51572, Q92934, Q16611, O43521, P10415, Q07812, P55957, Q13794, Q9BXH1
Myc	P01106	O60313, P06396
PARP1	P09874	P09429
TNF	P01375	Q13546, Q13490

Apoptosis ↗

Location: Programmed Cell Death

Stable identifier: R-HSA-109581



Apoptosis is a distinct form of cell death that is functionally and morphologically different from necrosis. Nuclear chromatin condensation, cytoplasmic shrinking, dilated endoplasmic reticulum, and membrane blebbing characterize apoptosis in general. Mitochondria remain morphologically unchanged. In 1972 Kerr et al introduced the concept of apoptosis as a distinct form of "cell-death", and the mechanisms of various apoptotic pathways are still being revealed today.

The two principal pathways of apoptosis are (1) the Bcl-2 inhibitable or intrinsic pathway induced by various forms of stress like intracellular damage, developmental cues, and external stimuli and (2) the caspase 8/10 dependent or extrinsic pathway initiated by the engagement of death receptors

The caspase 8/10 dependent or extrinsic pathway is a death receptor mediated mechanism that results in the activation of caspase-8 and caspase-10. Activation of death receptors like Fas/CD95, TNFR1, and the TRAIL receptor is promoted by the TNF family of ligands including FASL (APO1L OR CD95L), TNF, LT-alpha, LT-beta, CD40L, LIGHT, RANKL, BLYS/BAFF, and APO2L/TRAIL. These ligands are released in response to microbial infection, or as part of the cellular, humoral immunity responses during the formation of lymphoid organs, activation of dendritic cells, stimulation or survival of T, B, and natural killer (NK) cells, cytotoxic response to viral infection or oncogenic transformation.

The Bcl-2 inhibitable or intrinsic pathway of apoptosis is a stress-inducible process, and acts through the activation of caspase-9 via Apaf-1 and cytochrome c. The rupture of the mitochondrial membrane, a rapid process involving some of the Bcl-2 family proteins, releases these molecules into the cytoplasm. Examples of cellular processes that may induce the intrinsic pathway in response to various damage signals include: auto reactivity in lymphocytes, cytokine deprivation, calcium flux or cellular damage by cytotoxic drugs like taxol, deprivation of nutrients like glucose and growth factors like EGF, anoikis, transactivation of target genes by tumor suppressors including p53.

In many non-immune cells, death signals initiated by the extrinsic pathway are amplified by connections to the intrinsic pathway. The connecting link appears to be the truncated BID (tBID) protein a proteolytic

cleavage product mediated by caspase-8 or other enzymes.

Literature references

MacFarlane, M., Williams, AC. (2004). Apoptosis and disease: a life or death decision. *EMBO Rep, 5*, 674-8.

Kerr, JF. (2002). History of the events leading to the formulation of the apoptosis concept. *Toxicology, 181*, 471-4.

Adams, JM. (2003). Ways of dying: multiple pathways to apoptosis. *Genes Dev, 17*, 2481-95.

Adams, JM., Huang, DC., Cory, S. (2003). The Bcl-2 family: roles in cell survival and oncogenesis. *Oncogene, 22*, 8590-607.

Currie, AR., Kerr, JF., Wyllie, AH. (1972). Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer, 26*, 239-57.

Editions

2004-01-16	Authored	Tsujimoto, Y., Hengartner, M., Alnemri, E., Hardwick, JM., Tschopp, J.
2013-11-25	Edited	Gillespie, ME., Gopinathrao, G., Matthews, L., Joshi-Tope, G.
2022-05-18	Reviewed	Hengartner, M., Vaux, DL., Ranganathan, S.

5 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BAX	Q07812	BCL2	P10415	MAPK	P28482
STAT3	P40763	p53	P04637		

Input	Ensembl Id
BCL2	ENSG00000171791

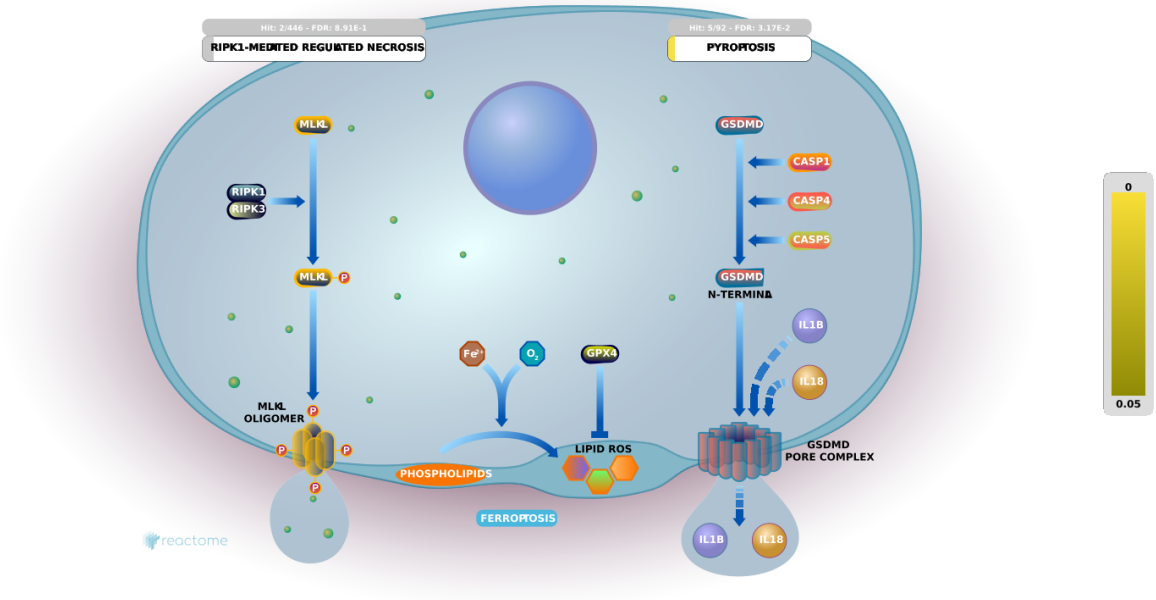
Interactors found in the analysis (8)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BAX	Q07812, Q07813-1	Q07817, Q16611, O43521, P10415, Q07812, P55957	BCL2	P10415, P10415-1	P51572, Q92934, Q16611, O43521, P10415, Q07812, Q13794, P55957, Q9BXH1
EGFR	P00533	P10636, P12830, P45983, P06396, Q05397	Myc	P01106	O60313, P06396
NFKB1	P19838	P35222	STAT3	P40763	P51813
TNF	P01375	Q13490	p53	P04637	P10415, Q8N726, Q05655, Q05397

Regulated Necrosis ↗

Location: Programmed Cell Death

Stable identifier: R-HSA-5218859



Necrosis has traditionally been considered as a passive, unregulated cell death. However, accumulating evidence suggests that necrosis, like apoptosis, can be executed by genetically controlled and highly regulated cellular process that is morphologically characterized by a loss of cell membrane integrity, intracellular organelles and/or the entire cell swelling (oncosis) (Rello S et al. 2005; Galluzzi L et al. 2007; Berghe TV et al. 2014; Ros U et al. 2020). The morphological hallmarks of the nectotic death have been associated with different forms of programmed cell death including (but not limited to) parthanatos, necroptosis, glutamate-induced oxytosis, ferroptosis, inflammasome-mediated necrosis etc. Each of them can be triggered under certain pathophysiological conditions. For example UV, ROS or alkylating agents may induce poly(ADP-ribose) polymerase 1 (PARP1) hyperactivation (parthanatos), while tumor necrosis factor (TNF) or toll like receptor ligands (LPS and dsRNA) can trigger necrosome-mediated necroptosis. The initiation events, e.g., PARP1 hyperactivation, necrosome formation, activation of NADPH oxidases, in turn trigger one or several common intracellular signals such as NAD+ and ATP-depletion, enhanced Ca2+ influx, dysregulation of the redox status, increased production of reactive oxygen species (ROS) and the activity of phospholipases. These signals affect cellular organelles and membranes leading to osmotic swelling, massive energy depletion, lipid peroxidation and the loss of lysosomal membrane integrity. Different mechanisms of permeabilization have emerged depending on the cell death form. Pore formation by gasdermins (GSDMs) is a hallmark of pyroptosis, while mixed lineage kinase domain-like (MLKL) protein facilitates membrane permeabilization in necroptosis, and phospholipid peroxidation leads to membrane damage in ferroptosis. This diverse repertoire of mechanisms leading to membrane permeabilization contributes to define the specific inflammatory and immunological outcome of each type of regulated necrosis. Regulated or programmed necrosis eventually leads to cell lysis and release of cytoplasmic content into the extracellular region that is often associated with a tissue damage resulting in an intense inflammatory response.

The Reactome module describes necroptosis and pyroptosis.

Literature references

Vandenabeele, P., Jouan-Lanhouet, S., Vanden Berghe, T., Linkermann, A., Walczak, H. (2014). Regulated necrosis: the expanding network of non-apoptotic cell death pathways. *Nat. Rev. Mol. Cell Biol., 15*, 135-47. ↗

Mocarski, ES., Upton, JW., Kaiser, WJ., Livingston-Rosanoff, D., Daley-Bauer, LP. (2014). True grit: programmed necrosis in antiviral host defense, inflammation, and immunogenicity. *J. Immunol., 192*, 2019-26. ↗

Nikoletopoulou, V., Tavernarakis, N., Palikaras, K., Markaki, M. (2013). Crosstalk between apoptosis, necrosis and autophagy. *Biochim. Biophys. Acta, 1833*, 3448-59. ↗

Editions

2013-12-20	Authored	Shamovsky, V.
2014-10-31	Reviewed	Gillespie, ME.
2015-02-10	Edited	Shamovsky, V.
2015-02-15	Reviewed	Chan, FK.

3 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BAX	Q07812	IL1B	P01583, P01584	p53	P04637

Interactors found in the analysis (4)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	Q8WUM4	PARP1	P09874	P09429
TNF	P01375	Q13546	p53	P04637	P09429

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