

Functional groups

Protein name	Functional group
BAD	1
BAK	1
BAX(A_B)	1
BCL-2	1
BCL-W	1
BCL-XL	1
BID	1
BIM(EL)	1
BNIP3	1
NOXA	1
PUMA	1
ACINUS	2
GELSOLIN	2
ICAD-L/S	2
MLC1	2
PARP-1	2
BRUCE(APOLLON)	3
HIAP1(CIAP2)	3
HIAP2(CIAP1)	3
SURVIVIN	3
XIAP	3
C-FLIP	4
CRADD(RAIDD)	4
FADD	4
FAS	4
FASL	4
LRDD(PIDD)	4
RIP1	4
TNF	4
TNFR(P55)	4
TNFRSF10A	4
TNFRSF10B	4
TNFSF10	4
TRADD	4
TRAF1	4
TRAF2	4
CASP10	5
CASPASE2	5
CASPASE3	5
CASPASE4	5
CASPASE7	5
CASPASE8	5
CASPASE9	5
AKT	6
ERK1(MAPK3)	6
ERK2(MAPK1/2)	6
MEK1	6
MEK2	6
RAF1	6
RRAS(RAS)	6
RSK1	6
RSK2	6
OMI/HTRA2	7
SMAC/DIABLO	7

Group ID	Group name
1	The Bcl-2 family
2	Substrates of Caspases
3	IAP (inhibitors of apoptosis)
4	Extrinsic pathway
5	Caspases
6	Signaling kinases
7	IAP inhibitors
8	Apoptosome
9	DAPK family
10	Calpains
11	JNK-related proteins
12	DNA fragmentation
13	Membrane blebbing
14	Cathepsins
15	Membrane blebbing
16	Cathepsins

APAF-1	8
CASPASE9	8
CYTOCHROME-C	8
DAPK	9
DAPK2(DRP-1)	9
DAPK3(ZIPK)	9
DRAK1	9
DRAK2	9
CALPAIN1	10
CALPAIN2	10
ASK1	11
JNK1	11
JNK2	11
CAD	12
ENDOG	12
MLC1	13
DAPK	13
DAPK3(ZIPK)	13
ROCK1	13
CATHEPSIND	14
CTSB	14
ATG5	Not classified
DAP3	Not classified
DRAM	Not classified
EIF2	Not classified
DAP5	Not classified
BIF-1	Not classified
P14ARF	Not classified

Anchor points

We consider a subgroup of six caspase substrates to act as the anchor points of the apoptosis core machinery. These proteins and the events to which they are responsible and lead to the collapse of the cell are listed below

Protein	Process	Reference (Pubmed ID)
ACINUS	chromatin condensation	10490026
ENDOG	DNA fragmentation	15723341
CAD	DNA fragmentation	15723341
MLC1	Disruption of the cell's cytoskeleton	9456322
GELSOLIN	Disruption of the cell's cytoskeleton	9323209
PARP-1	Inhibition of DNA repair	12101391

Additioal interactions and references

Protein 1	Protein 2	Reference for interaction (Pumed ID)
Bruce (apollon)	caspase7	15200957
Bcl-W	Bax (a,b)	18178565
Bcl-W	Bak	18178565
caspase9	caspase7	17899380, 9922454
caspase7	PARP-1	18511888, 16374543
Bim(EL)	Bax (a,b)	12198137, 15721256
caspase3	PARP-1	15660421
ROCK1	MLC1	11283606
LRDD(PIDD)	RIP1	16360037
caspase2	caspase3	16977332
caspase2	TRAF2	15590671
FADD	Atg5	15778222
DAPK3 (ZIPk)	MLC1	17487247, 15096528
DAPK	MLC1	15002035
DAPK	DAPK3(ZIPk)	15367680
DAPK	PKD	17703233
DAPK	DAPK2(DRP-1)	15367680
DAPK	CAMKKb	15209507
CAMKKb	AMPK(catalytic_sub:a1,a2)	17244528
PKD	ASK1	15755722
Atg7	Atg5	11265251
ERK1(MAPK3)	TSC2	16244323
RSK1	TSC2	16244323
RSK2	TSC2	16244323
RSK1	DAPK	16213824
RSK2	DAPK	16213824
JNK1	PARP-1	17218956
Bif-1	Bax (a,b)	11259440
UVRAG	Bif-1	17891140

Pubmed ID	Details
15200957	Dual role of BRUCE as an antiapoptotic IAP and a chimeric E2/E3 ubiquitin ligase. Bruce et. al Mol Cell. 2004 Jun 18;14(6):801-11
18178565	Differential regulation of Bax and Bak by anti-apoptotic Bcl-2 family proteins Bcl-B and Mcl-1 Zahi et. al J Biol Chem. 2008 Apr 11;283(15):9580-6.
17899380	Delineation of the caspase-9 signaling cascade. Guerrero et al, Apoptosis. 2008 Jan;13(1):177-86
9922454	Ordering the cytochrome c-initiated caspase cascade: hierarchical activation of caspases-2, -3, -6, -7, -8, and -10 in a caspase-9-dependent manner. Slee et al, J Cell Biol. 1999 Jan 25;144(2):281-92.
18511888	Apoptotic cell death in TrkA-overexpressing cells: kinetic regulation of ERK phosphorylation and caspase-7 activation. Jung et al, Mol Cells. 2008 Jul 31;26(1):12-7.
16374543	Nuclear caspase-3 and caspase-7 activation, and poly(ADP-ribose) polymerase cleavage are early events in camptothecin-induced apoptosis. Rodríguez-Hernández et al, Apoptosis. 2006 Jan;11(1):131-9.

- 12198137 Bcl-XL protects BimEL-induced Bax conformational change and cytochrome C release independent of interacting with Bax or BimEL. Yamaguchi et al, *J Biol Chem.* 2002 Nov 1;277(44):41604-12.
- 15721256 BH3 domains of BH3-only proteins differentially regulate Bax-mediated mitochondrial membrane permeabilization both directly and indirectly. Kuwana et al, *Mol Cell.* 2005 Feb 18;17(4):525-35.
- 15660421 In vivo activated caspase-3 cleaves PARP-1 in rat liver after administration of the hepatocarcinogen N-nitrosomorpholine (NNM) generating the 85 kDa fragment. Wesierska-Gadek et al, *J Cell Biochem.* 2004 Nov 1;93(4):774-87.
- 11283606 Membrane blebbing during apoptosis results from caspase-mediated activation of ROCK I. Coleman et al, *Nat Cell Biol.* 2001 Apr;3(4):339-45.
- 16360037 PIDD mediates NF-kappaB activation in response to DNA damage. Janssens et al, *Cell.* 2005 Dec 16;123(6):1079-92.
- 16977332 Apoptosome: a platform for the activation of initiator caspases. Bao et al, *Cell Death Differ.* 2007 Jan;14(1):56-65.
- 15590671 A novel caspase-2 complex containing TRAF2 and RIP1. Lamkanfi et al, *J Biol Chem.* 2005 Feb 25;280(8):6923-32.
- 15778222 Essential roles of Atg5 and FADD in autophagic cell death: dissection of autophagic cell death into vacuole formation and cell death. Pyo et al, *J Biol Chem.* 2005 May 27;280(21):20722-9.
- 17487247 The regulation of smooth muscle contractility by zipper-interacting protein kinase. Ihara et al, *Can J Physiol Pharmacol.* 2007 Jan;85(1):79-87.
- 15096528 ZIP kinase is responsible for the phosphorylation of myosin II and necessary for cell motility in mammalian fibroblasts. Komatsu et al, *J Cell Biol.* 2004 Apr 26;165(2):243-54.
- 15002035 DAP-kinase-mediated morphological changes are localization dependent and involve myosin-II phosphorylation. Bialik et al, *Cell Death Differ.* 2004 Jun;11(6):631-44.
- 15367680 Death-associated protein kinase phosphorylates ZIP kinase, forming a unique kinase hierarchy to activate its cell death functions. Shani et al, *Mol Cell Biol.* 2004 Oct;24(19):8611-26.
- 17703233 DAP kinase regulates JNK signaling by binding and activating protein kinase D under oxidative stress. Eisenberg-Lerner et al, *Cell Death Differ.* 2007 Nov;14(11):1908-15.
- 15209507 A calmodulin-regulated protein kinase linked to neuron survival is a substrate for the calmodulin-regulated death-associated protein kinase. Schumacher et al, *Biochemistry.* 2004 Jun 29;43(25):8116-24.
- 17244528 Control of macroautophagy by calcium, calmodulin-dependent kinase kinase-beta, and Bcl-2. Høyer-Hansen et al, *Mol Cell.* 2007 Jan 26;25(2):193-205.
- 15755722 Protein kinase D specifically mediates apoptosis signal-regulating kinase 1-JNK signaling induced by H₂O₂ but not tumor necrosis factor. Zhang et al, *J Biol Chem.* 2005 May 13;280(19):19036-44.
- 11265251 Molecular dissection of autophagy: two ubiquitin-like systems. Oshumi et al, *Nat Rev Mol Cell Biol.* 2001 Mar;2(3):211-6.
- 16244323 Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways. Kwiatkowski et al, *Hum Mol Genet.* 2005 Oct 15;14 Spec No. 2:R251-8.
- 16213824 The tumor suppressor DAP kinase is a target of RSK-mediated survival signaling. Anjum et al, *Curr Biol.* 2005 Oct 11;15(19):1762-7.
- 17218956 c-Jun N-terminal kinase mediates hydrogen peroxide-induced cell death via sustained poly(ADP-ribose) polymerase-1 activation. Zhang et al, *Cell Death Differ.* 2007 May;14(5):1001-10.
- 11259440 Molecular cloning and characterization of Bif-1. A novel Src homology 3 domain-containing protein that associates with Bax. Cuddeback et al, *J Biol Chem.* 2001 Jun 8;276(23):20559-65.

17891140

Bif-1 interacts with Beclin 1 through UVRAG and regulates autophagy and tumorigenesis. Takahashi et al, *Nat Cell Biol.* 2007 Oct;9(10):1142-51.