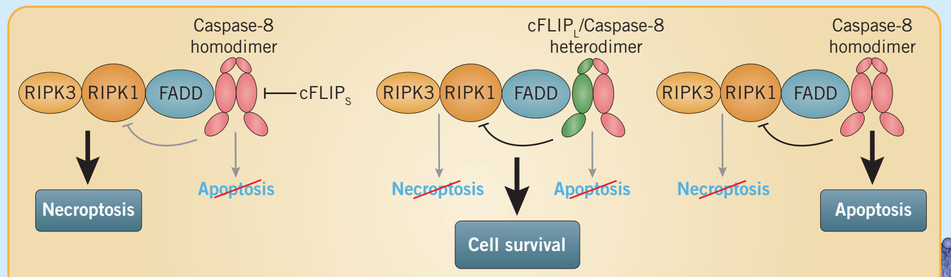
Programmed Cell Death

Bram van Raam[1] and Guy Salvesen[2]
[1]VIB/UGent Department for Molecular Biomedical Research, Technologiepark 927, 9052 Ghent, Belgium. Email: bramvr@dmbr.UGent.be
[2]Sanford-Burnham Medical Research Institute, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA. Email: gsalvesen@sanfordburnham.org

Two main forms of programmed cell death (PCD) are currently recognized: apoptosis and necroptosis. Apoptosis, a clean form of cellular demise that results in the quiet phagocytosis of unwanted cells, is the best known form of PCD and is executed through the sequential activation of a family of cysteine proteases, the caspases. Necroptosis, on the other hand, depends on activation of the RIP kinases and is a messy form of PCD wherein the cell's contents are spilled into the environment, resulting in sterile inflammation.[1,2] Caspase-8 activation at the Death Receptors prevents necroptotic signaling, while favoring either apoptosis or survival. Caspase-8 differentiates between these two tasks by forming either a homodimer or heterodimer with its inactive homolog FLIP$_L$ (see Box 1). Heterodimer formation is preferred, but limited to the amount of available FLIP$_L$.[3] Apoptosis is further regulated by the Bcl-2 family of proteins. Upon activation, the pro-apoptotic members of this family promote the release of pro-apoptotic factors from the mitochondria, resulting in the activation of downstream caspases and the execution of apoptosis.[4] Finally, the intracellular free Ca^{2+} balance plays an important role in the regulation of apoptosis.[5] Elevated free Ca^{2+} levels can lead to the activation of Ca^{2+}-dependent proteases, the calpains, which influence the apoptotic process at several levels. In addition, intracellular free Ca^{2+} regulates the activity of the cell membrane enzymes responsible for maintaining membrane asymmetry. This results in the net exposure of phosphatidylserine, an 'eat me' signal, on the outer membrane of apoptotic cells.[6]



Box 1: The influence of caspase-8 and cFLIP on cell fate following death receptor activation
Caspase-8 homodimers induce apoptosis via activation of downstream caspases and also inhibit necroptotic signaling. Heterodimers of caspase-8 and cFLIP$_L$ cannot induce apoptosis but still inhibit necroptosis, resulting in cell survival. Inhibition of the caspase-8 homodimer (e.g. by cFLIP$_S$) prevents apoptosis and removes its inhibitory effects on RIPK1, activating necroptosis.

References
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3. **van Raam and Salvesen** (2012) Proliferative versus apoptotic functions of caspase-8 Hetero or homo: the caspase-8 dimer controls cell fate. *Biochim. Biophys. Acta* **1824** 113.
4. **Kale** *et al* (2012) Shedding light on apoptosis at subcellular membranes. *Cell* **151** 1179.
5. **Decrock** *et al* (2013) IP$_3$, a small molecule with a powerful message. *Biochim. Biophys. Acta* Jan 2.
6. **Ravichandran** (2011) Beginnings of a good apoptotic meal: the find-me and eat-me signaling pathways. *Immunity* **35** 445.

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ASK1	NQDI 1
Bcl-2 Family	ARRY 520, AT 101, Bax channel blocker, Gambogic acid, iMAC2, SU 9516, TW 37
Calpains	Acetyl-Calpastatin (184-210) (human), Calpeptin, MG 132, PD 150606
Caspases	Apoptosis Activator 2, AZ 10417808, Z-DEVD-FMK, Z-VAD-FMK
DAPK	DAPK Substrate Peptide, TC-DAPK 6
eIF2α	Salubrinal
ERAD	Eeyarestatin I
IAPs	Embelin
IP$_3$ Receptors	2-APB, (-)-Xestospongin C
IRE1	4μ8C, Kaempferol, STF 083010
NF-κB Signaling	Caffeic acid phenethyl ester, IKK 16, IMD 0354, PF 184, TPCA-1
p53	HLI 373, Nutlin-3, Pifithrin-α, PRIMA-1
PARP-1	NU 1025, PJ 34
RIP1	Necrostatin-1

Glossary

AIF	Apoptosis inducing factor
Apaf-1	Apoptotic peptidase activating factor 1
ATF	Activating transcription factor
Bak	Bcl2 homologous antagonist killer
Bax	Bcl2-associated X protein
Bid	BH3-interacting domain death agonist
cFLIP$_L$	Cellular FLICE-like inhibitory protein (long)
cFLIP$_S$	Cellular FLICE-like inhibitory protein (short)
cIAP	Cellular inhibitor of apoptosis
CYLD	Protein encoded by the Cylindromatosis gene
DAPK	Death-associated protein kinase
eIF2α	Eukaryotic translation initiation factor 2 alpha
EndoG	Endonuclease G
ERAD	Endoplasmic reticulum-associated protein degradation
FADD	Fas-associated protein with death domain
IκBα	Inhibitor of κB alpha
IKK	Inhibitor of κB kinase
IRE1	Inositol-requiring protein 1
MDM2	Mouse double minute 2 protein
NEMO	NF-κB essential modulator
NF-κB	Nuclear factor-κB
PERK	PRKR-like endoplasmic reticulum kinase
RIPK	Receptor-interacting protein kinase
SMAC	Second mitochondria-derived activator of caspases
tBid	Truncated BH3-interacting domain death agonist
TNF-α	Tumor necrosis factor-α
TNFR1	Tumor necrosis factor receptor type 1
TRADD	Tumor necrosis factor receptor type 1-associated death domain
TRAF2	Tumor necrosis factor receptor-associated factor 2
UPR	Unfolded protein response
XBP	X-box-binding protein
XIAP	X-linked inhibitor of apoptosis

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