PLAN

P.LEMARCHAND

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Les différents types de mort cellulaire

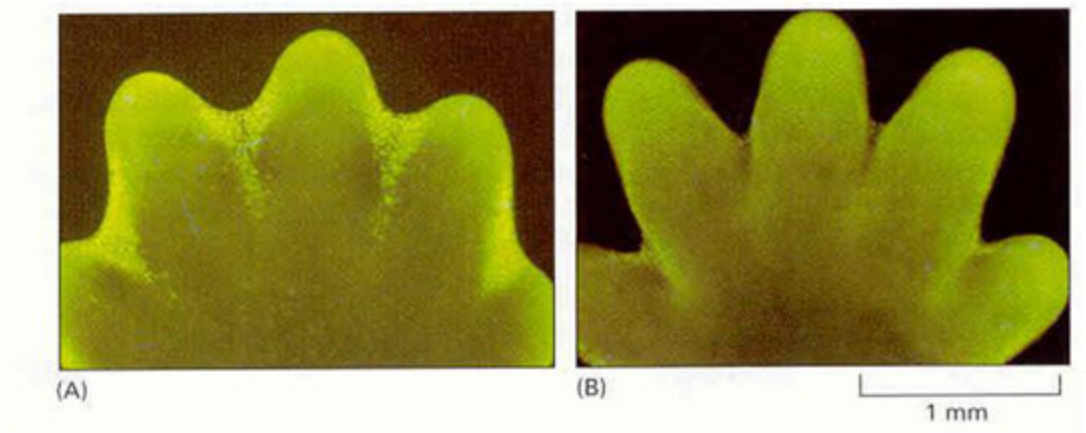
Table1 | **Characteristics of different types of cell death**

Type of cell death	Morphological changes			Biochemical features	Common detection methods
	Nucleus	*Cell membrane*	*Cytoplasm*		
Apoptosis	Chromatin condensation; nuclear fragmentation; DNA laddering	Blebbing	Fragmentation (formation of apoptotic bodies)	Caspase-dependent	Electron microscopy; TUNEL staining; annexin staining; caspase-activity assays; DNA-fragmentation assays; detection of increased number of cells in subG1/G0; detection of changes in mitochondrial membrane potential
Autophagy	Partial chromatin condensation; no DNA laddering	Blebbing	Increased number of autophagic vesicles	Caspase-independent; increased lysosomal activity	Electron microscopy; protein-degradation assays; assays for marker-protein translocation to autophagic membranes; MDC staining
Mitotic catastrophe	Multiple micronuclei; nuclear fragmentation	–	–	Caspase-independent (at early stage) abnormal CDK1/cyclin B activation	Electron microscopy; assays for mitotic markers (MPM2); TUNEL staining
Necrosis	Clumping and random degradation of nuclear DNA	Swelling; rupture	Increased vacuolation; organelle degeneration; mitochondrial swelling	–	Electron microscopy; nuclear staining (usually negative); detection of inflammation and damage in surrounding tissues
Senescence	Distinct heterochromatic structure (senescence-associated heterochromatic foci)	–	Flattening and increased granularity	SA-β-gal activity	Electron microscopy; SA-β-gal staining; growth-arrest assays; assays for increased p53, INK4A and ARF levels (usually increased); assays for RB phosphorylation (usually hypophosphorylated); assays for metalloproteinase activity (usually upregulated)

CDK1, cycline-dependent kinase 1; MDC, monodansylcadaverine; MPM2, mitotic phosphoprotein 2; SA-β-gal, senescence-associated β-galactosidase; RB, retinoblastoma protein.

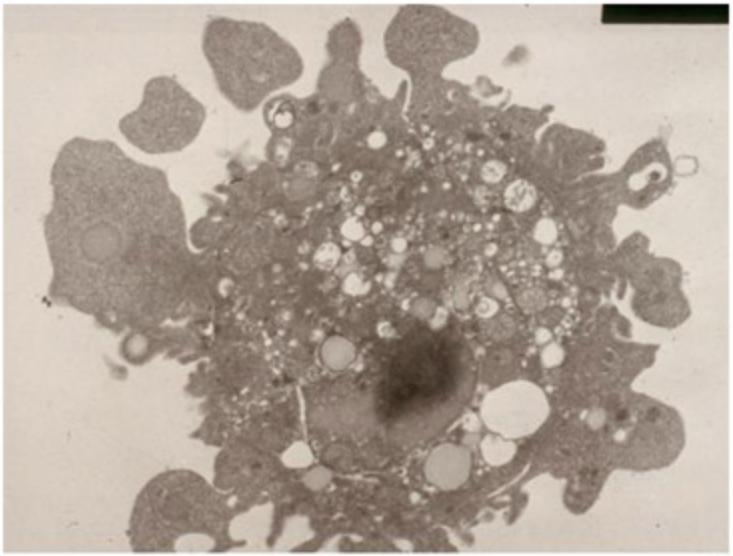
Nature Reviews Cancer **4**; 592-603 (2004)

Situations physiologiques

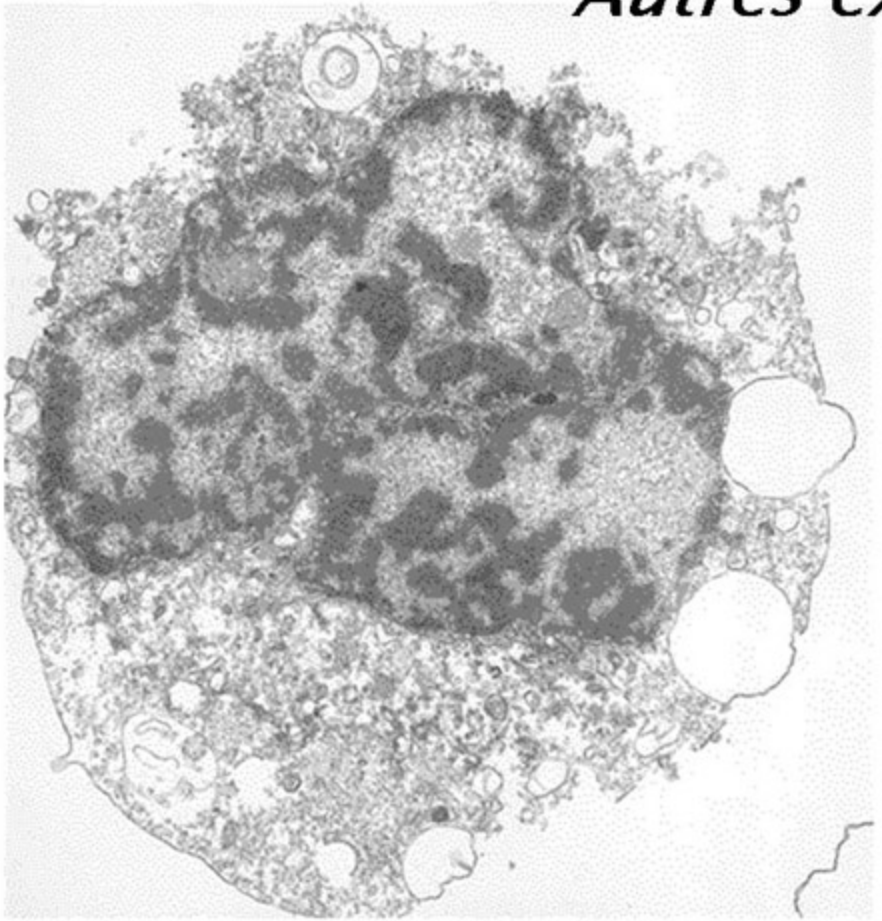


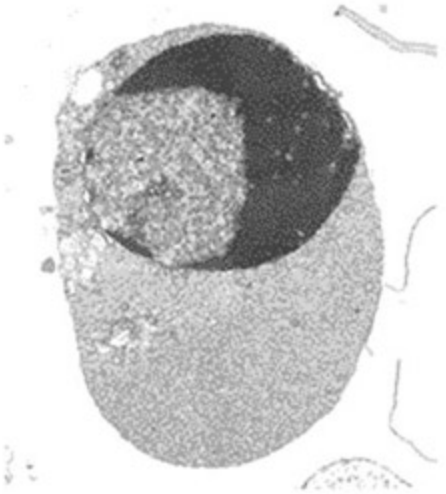
Development 2000;127:5245

Caractères morphologiques



Autres exemples





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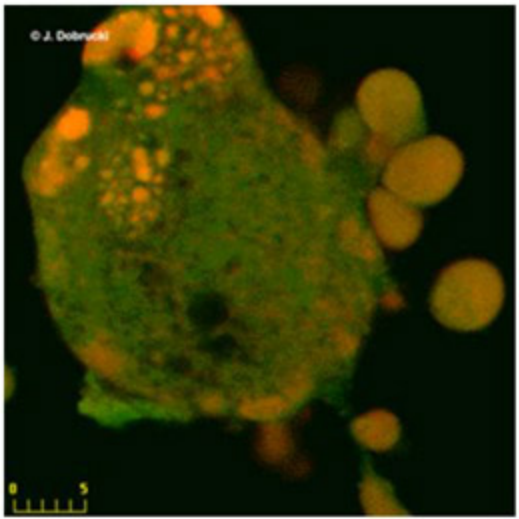
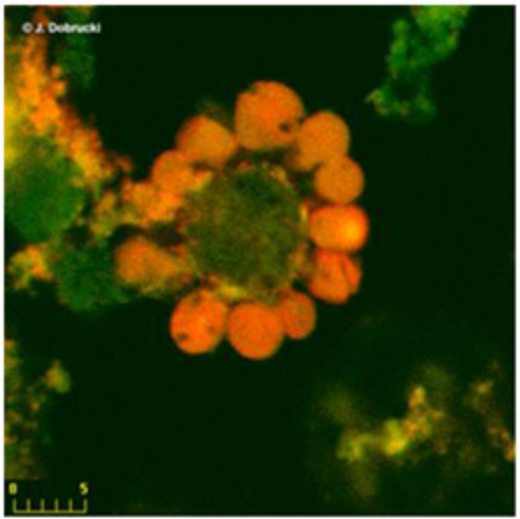
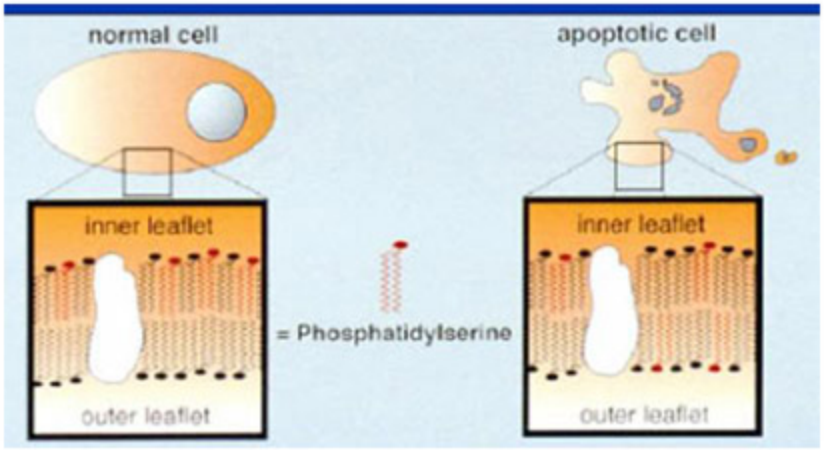




http://helios.mol.uj.edu.pl/

Caractères biochimiques

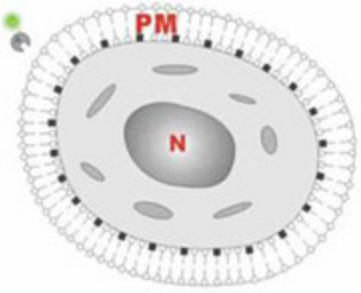


Phospholipid

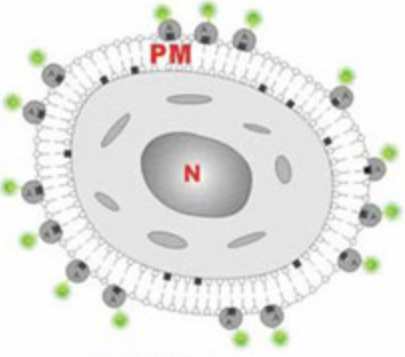
Phosphatidylserin

Annexin
with a green fluorescent label

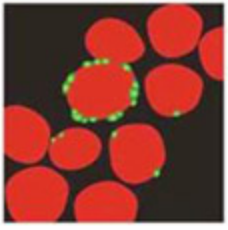
suite

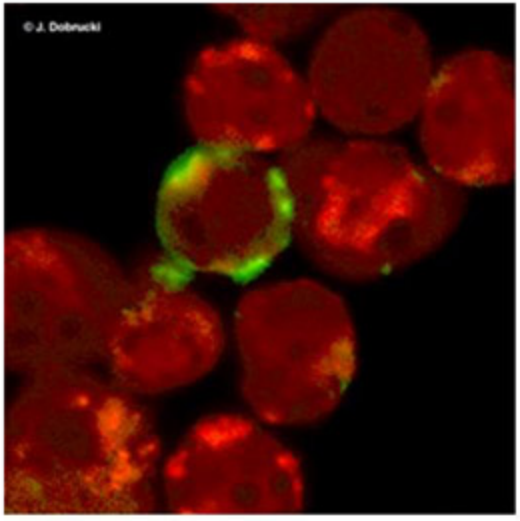


NORMAL, HEALTLHY CELL



APOPTOTIC CELL





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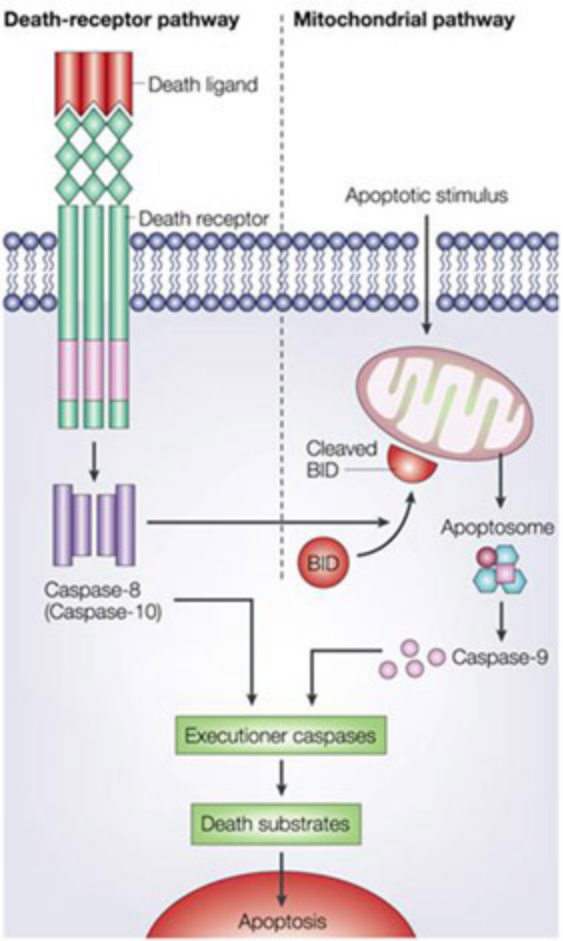
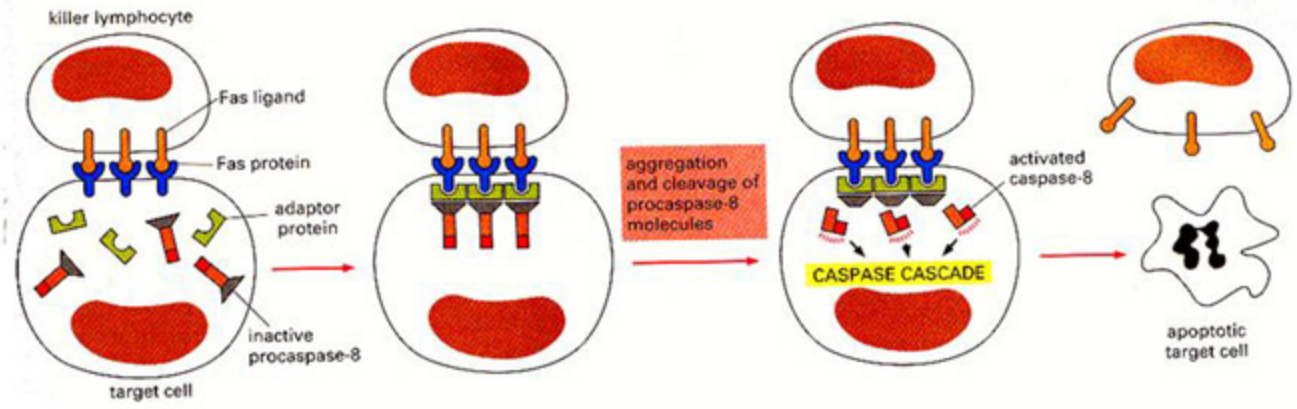
Signaux



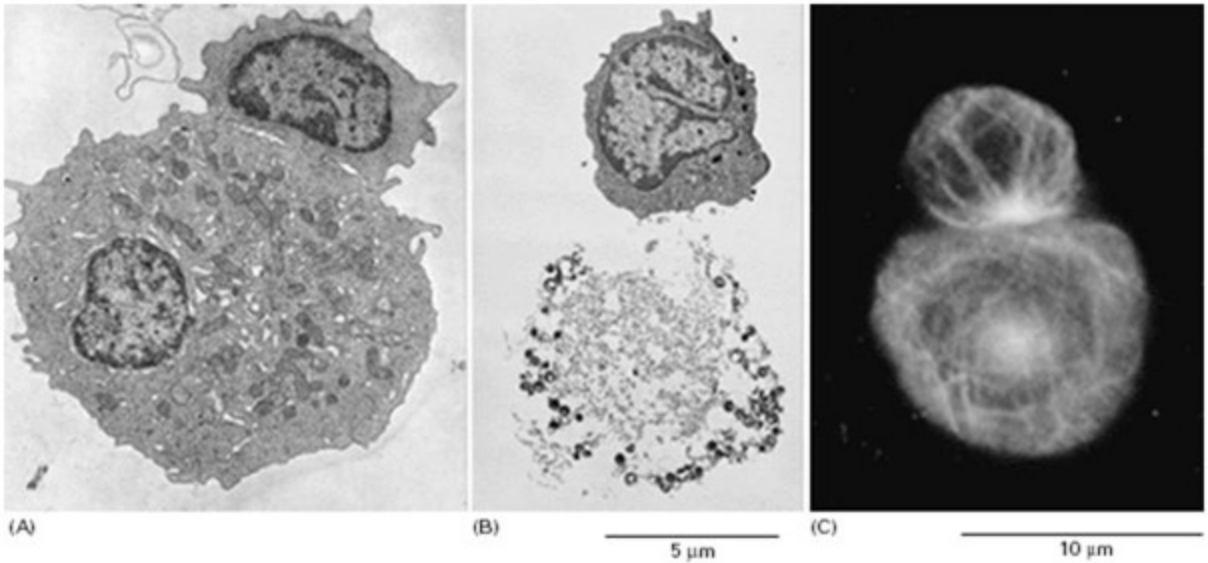
Nature Reviews Cancer **2**, 277-288 (2002)

Activation par récepteur transmembranaire



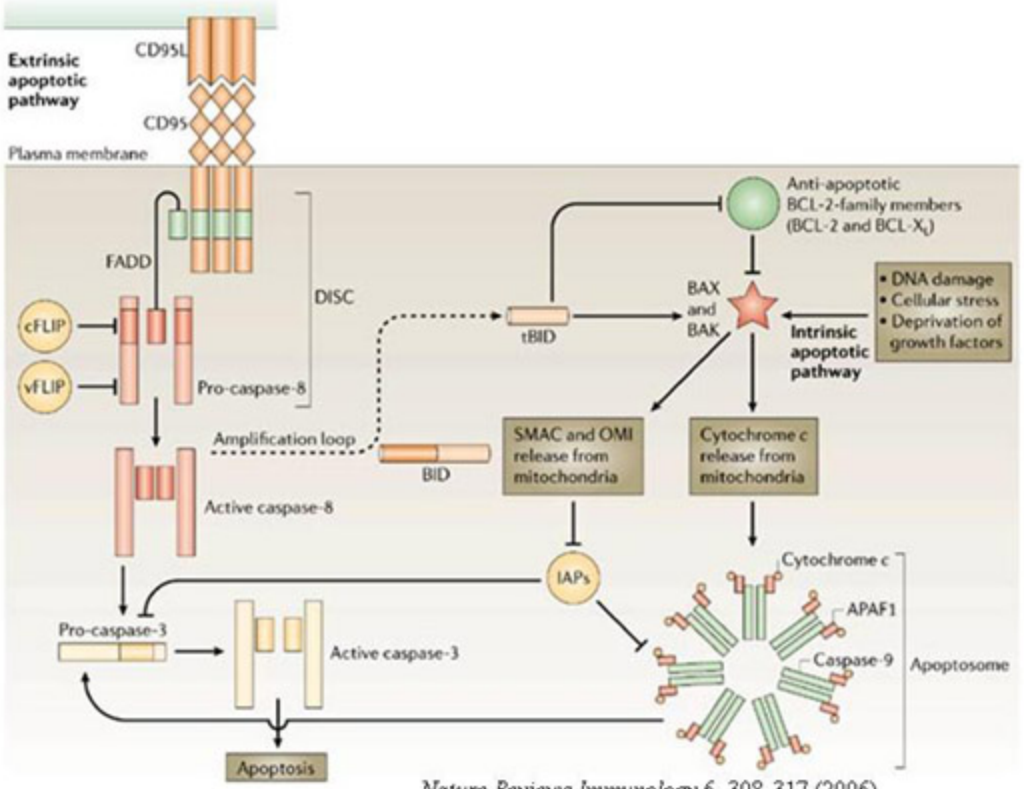
Molecular Biology of the Cell, 3ème édition

Activation par récepteur transmembranaire (II)



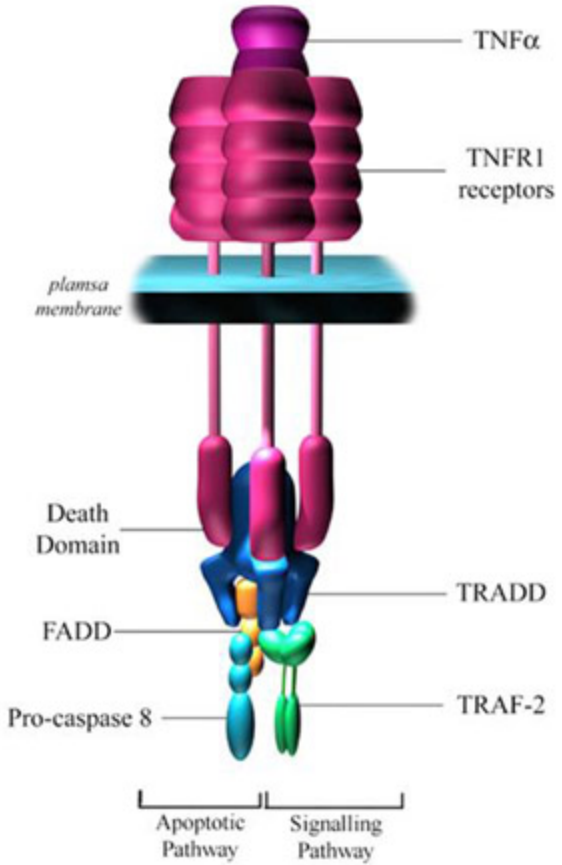
Molecular Biology of the Cell, 3ème édition

Activation de la voie Fas

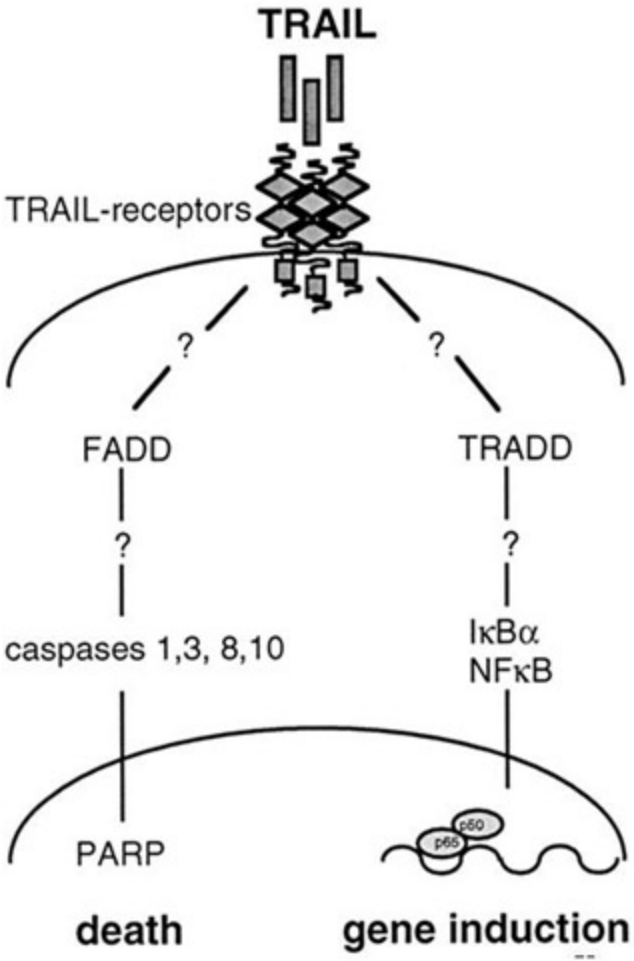


Nature Reviews Immunology 6, 308-317 (2006)

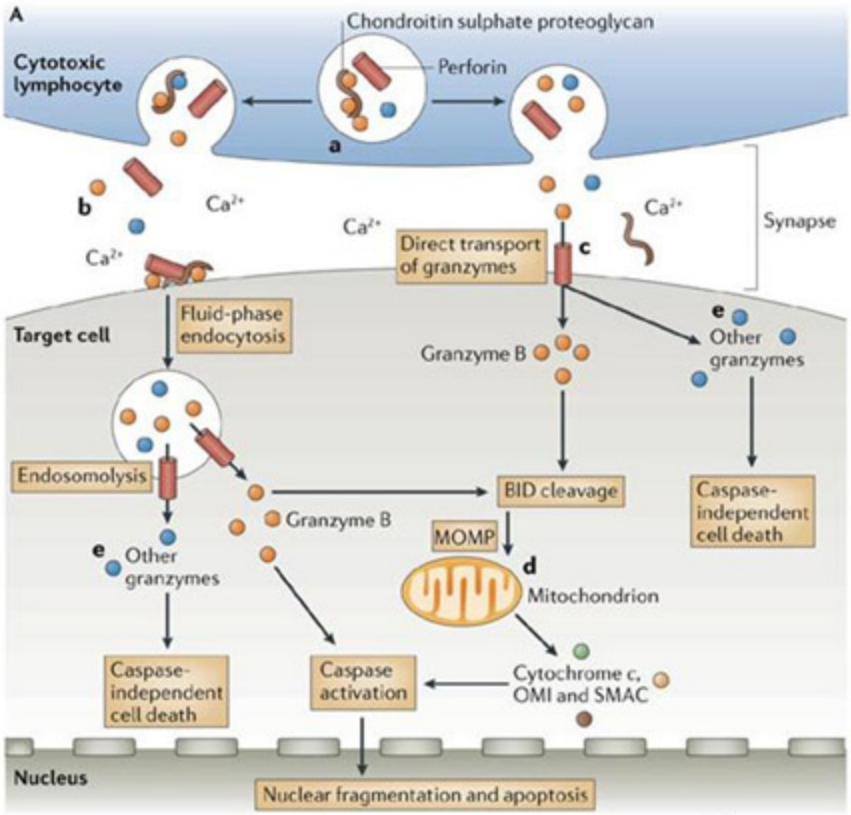
Activation de la voie TNF



Activation de la voie TRAIL

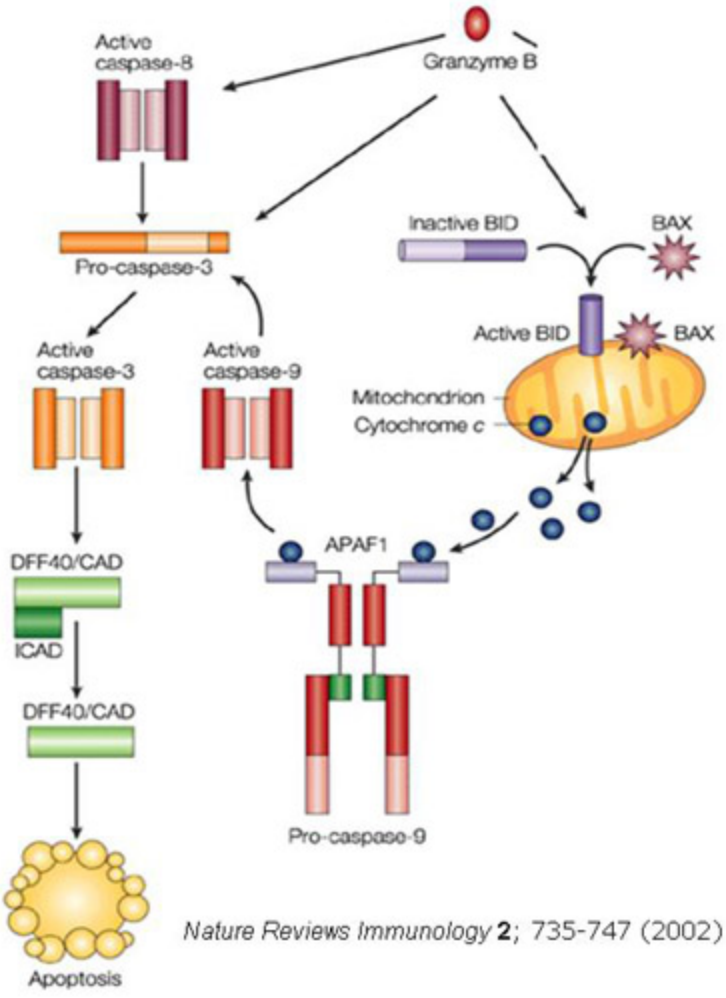


Cytotoxicité médiée par les granules



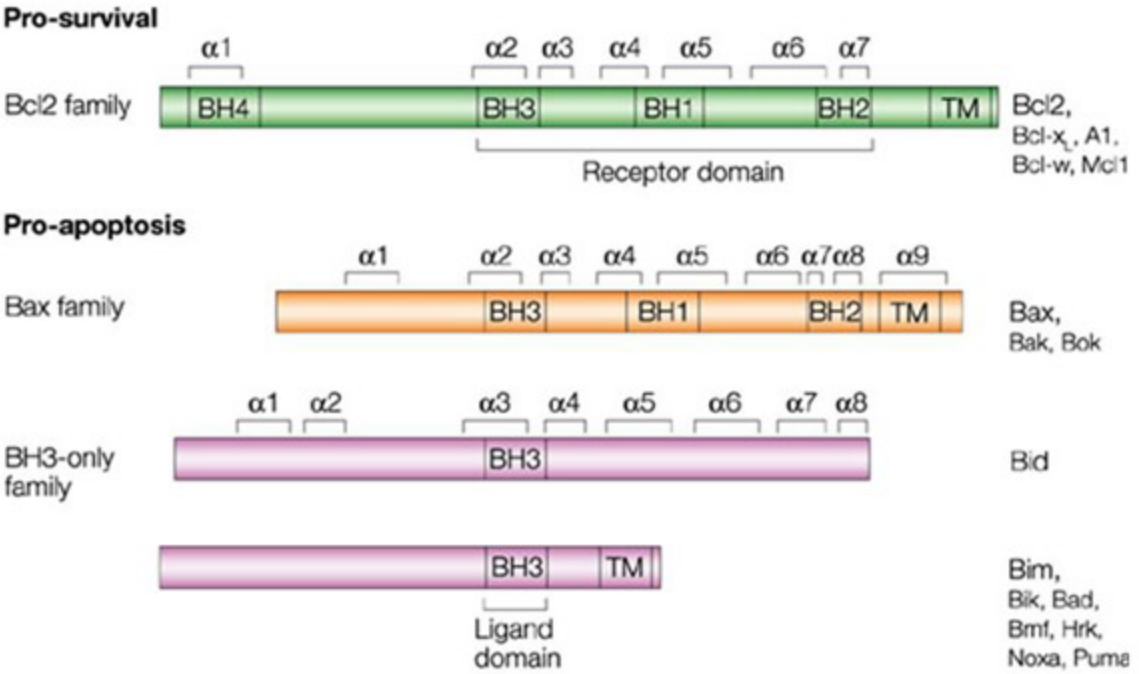
Nature Reviews Immunology 6, 940-952 (2006)

suite



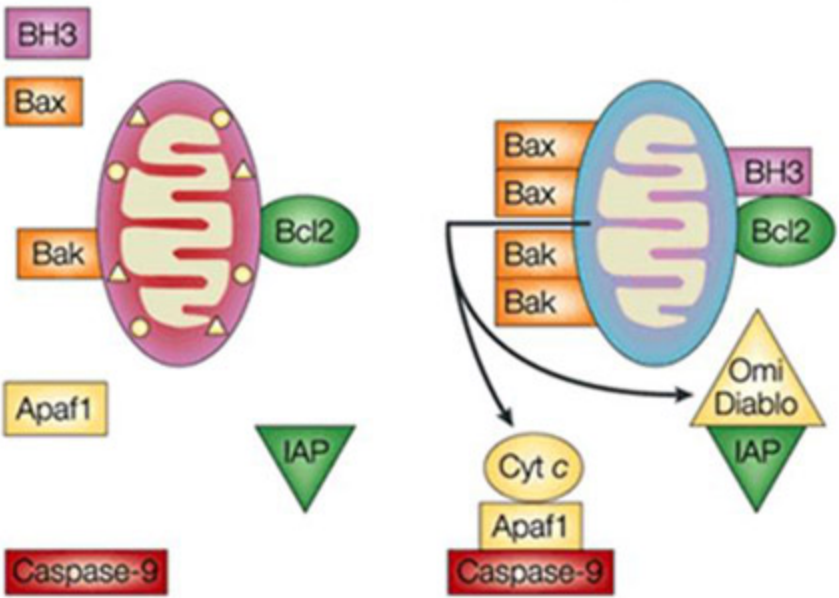
Nature Reviews Immunology **2**; 735-747 (2002)

Famille Bcl-2



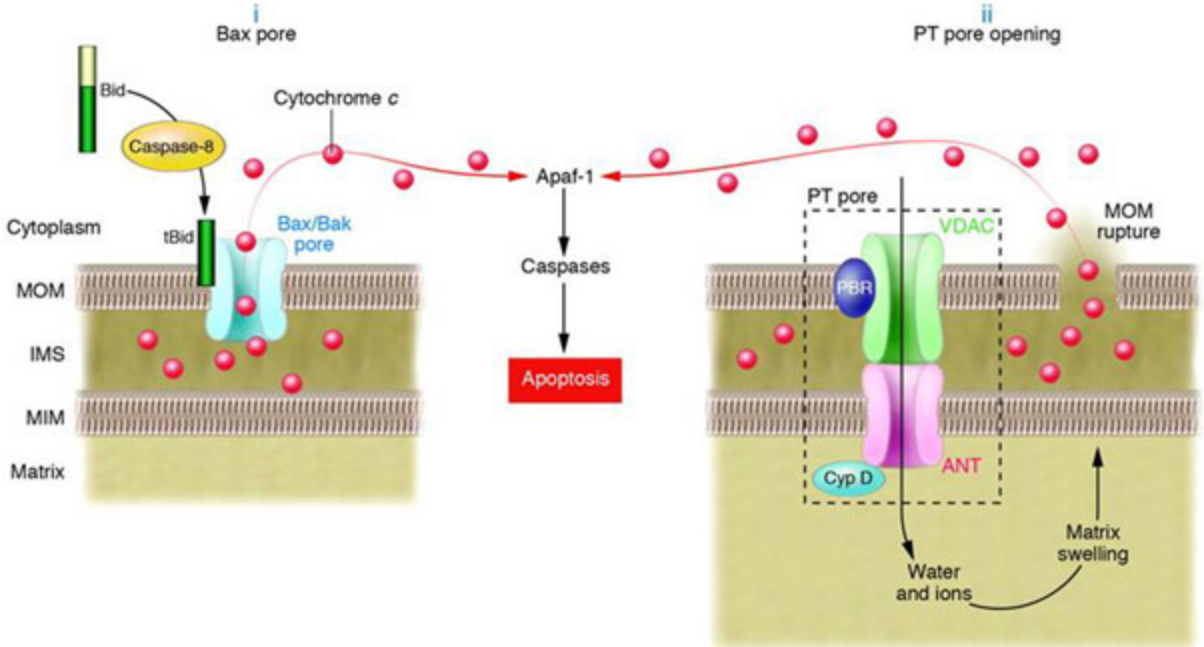
Nature Reviews Cancer **2**; 647-656 (2002)

Famille Bcl-2



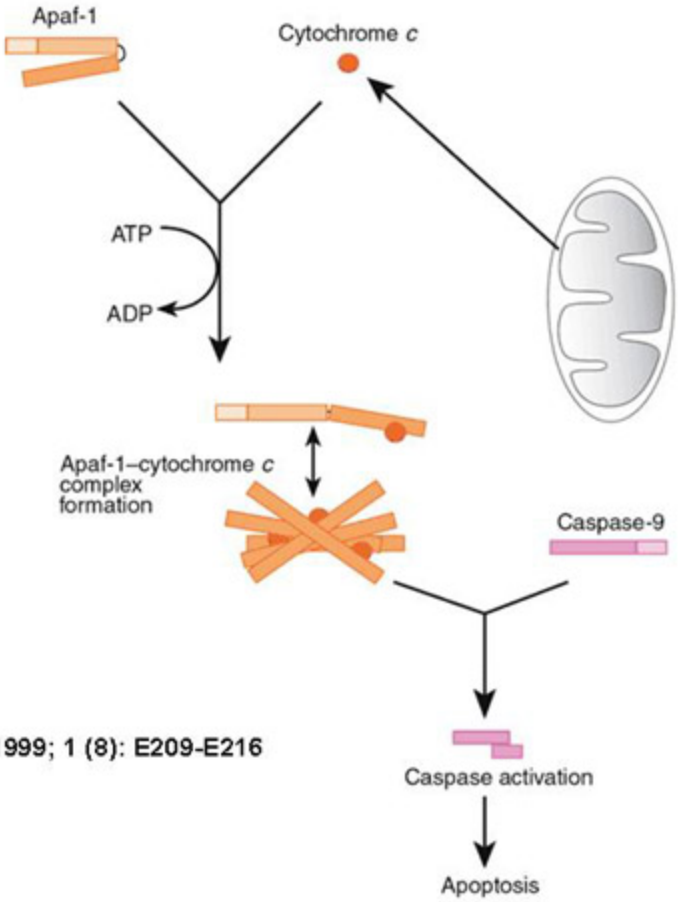
Nature Reviews Cancer **2**; 647-656 (2002)

Relargage par la mitochondrie



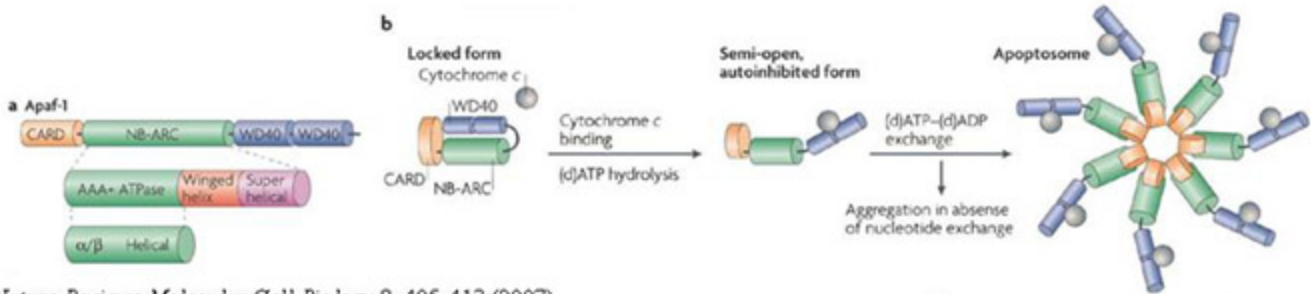
J. Clin. Invest. 115:2640-2647 (2005)

Activation par la mitochondrie

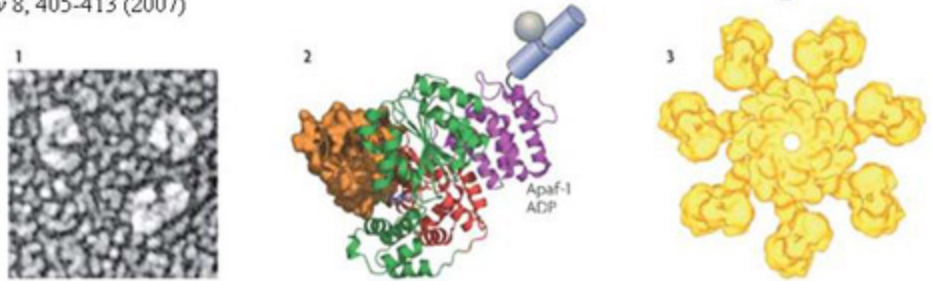


nature cell biology 1999; 1 (8): E209-E216

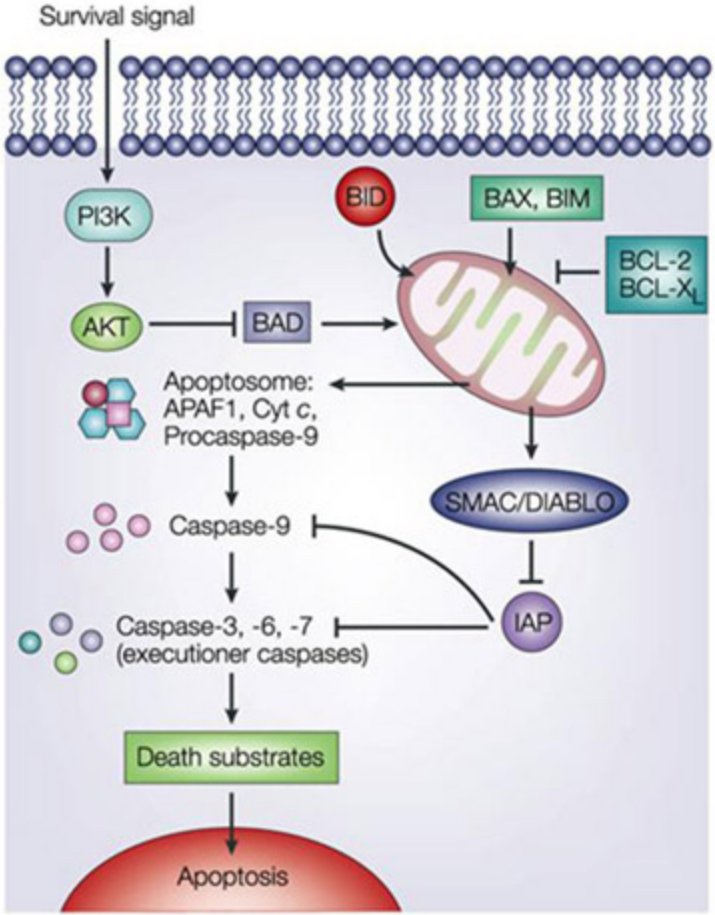
Apoptosome



Nature Reviews Molecular Cell Biology 8, 405-413 (2007)

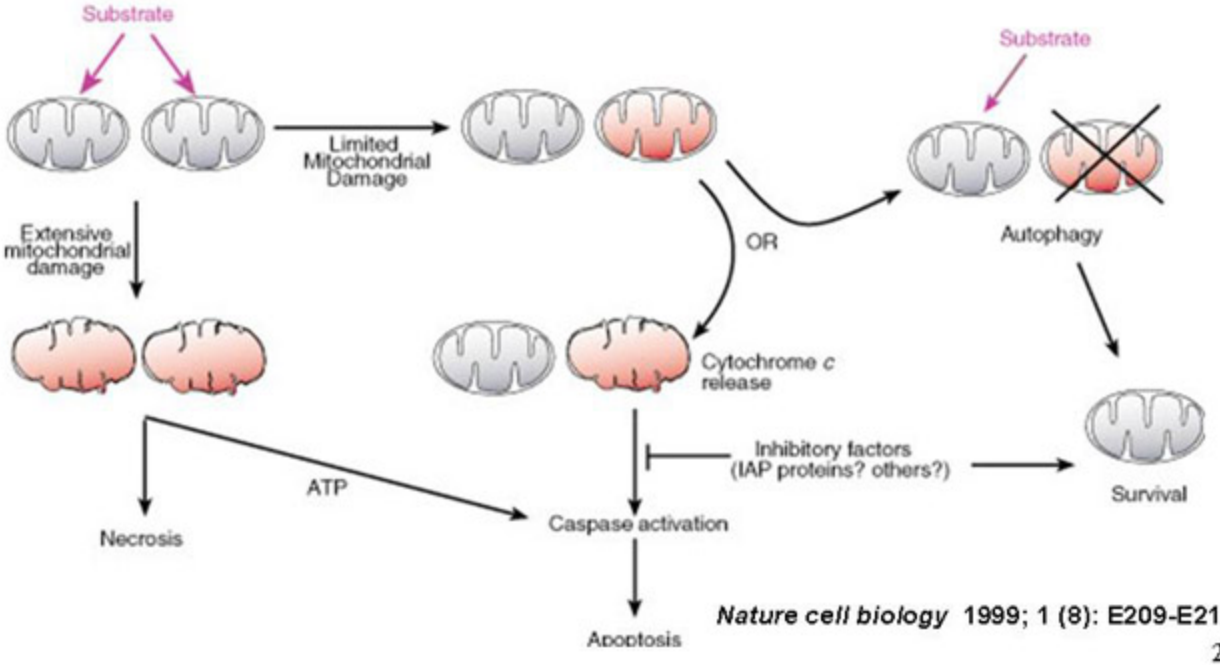


Activation directe



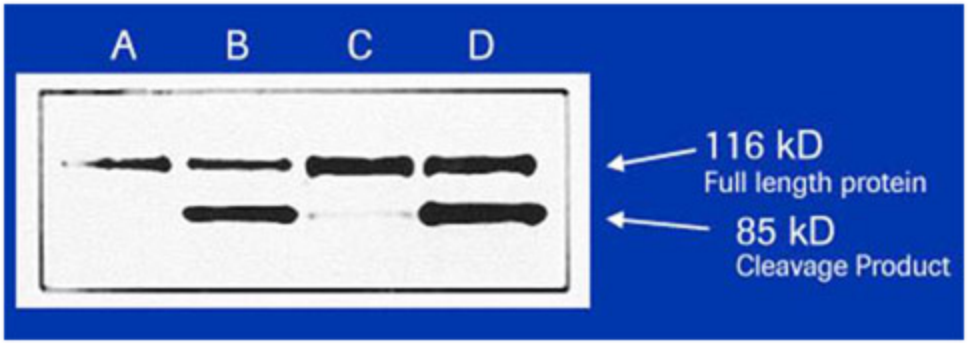
Nature Reviews Cancer **2**, 277-288 (2002)

Irréversibilité des lésions

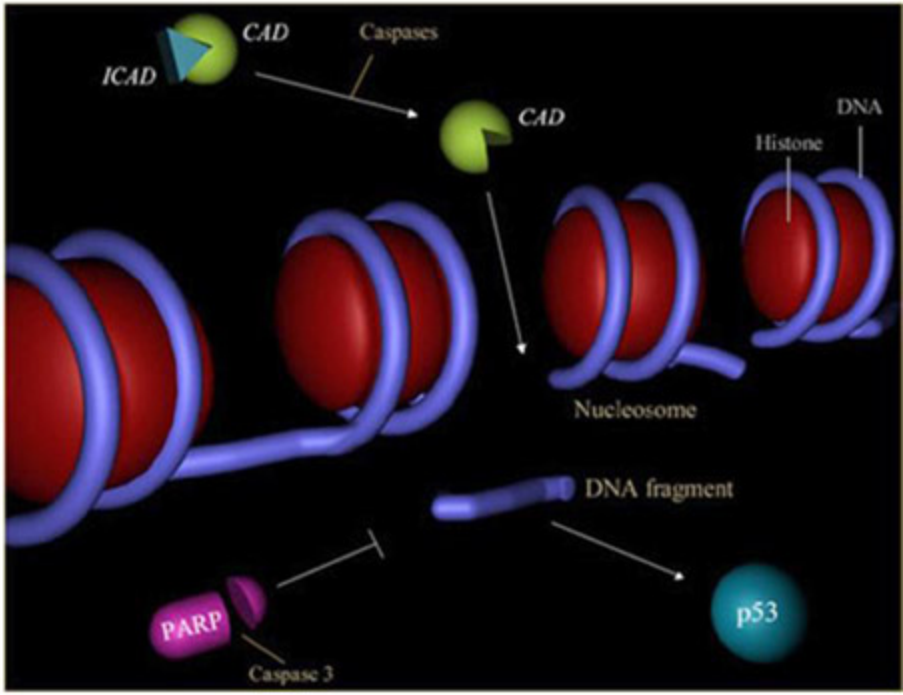


Nature cell biology 1999; 1 (8): E209-E216

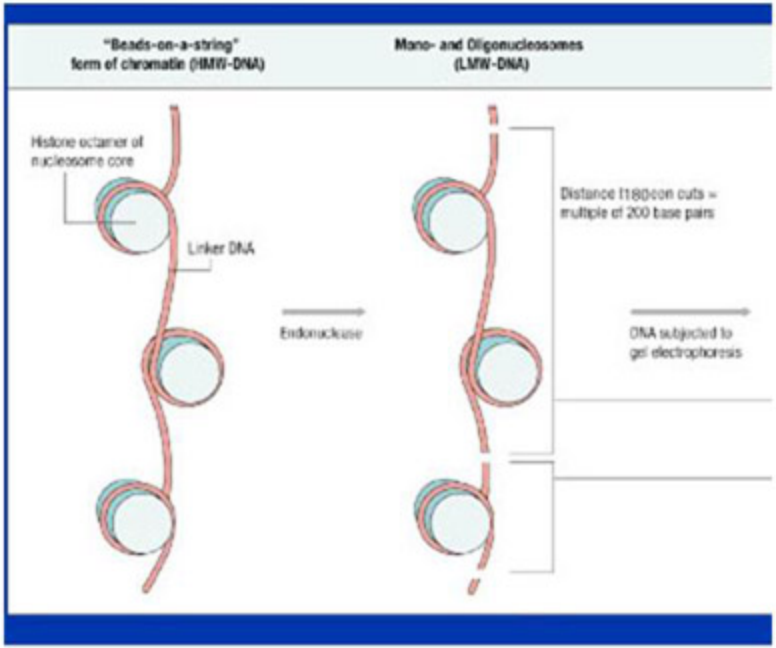
Phase d'exécution

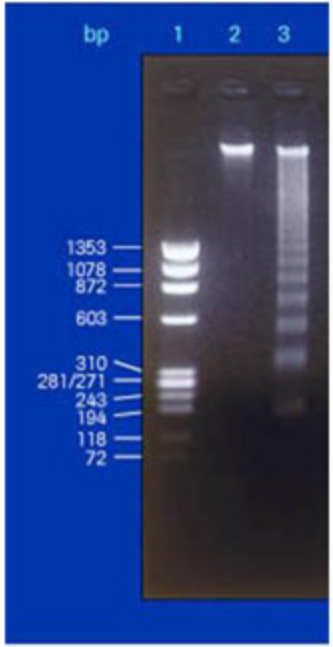


Effets nucléaires

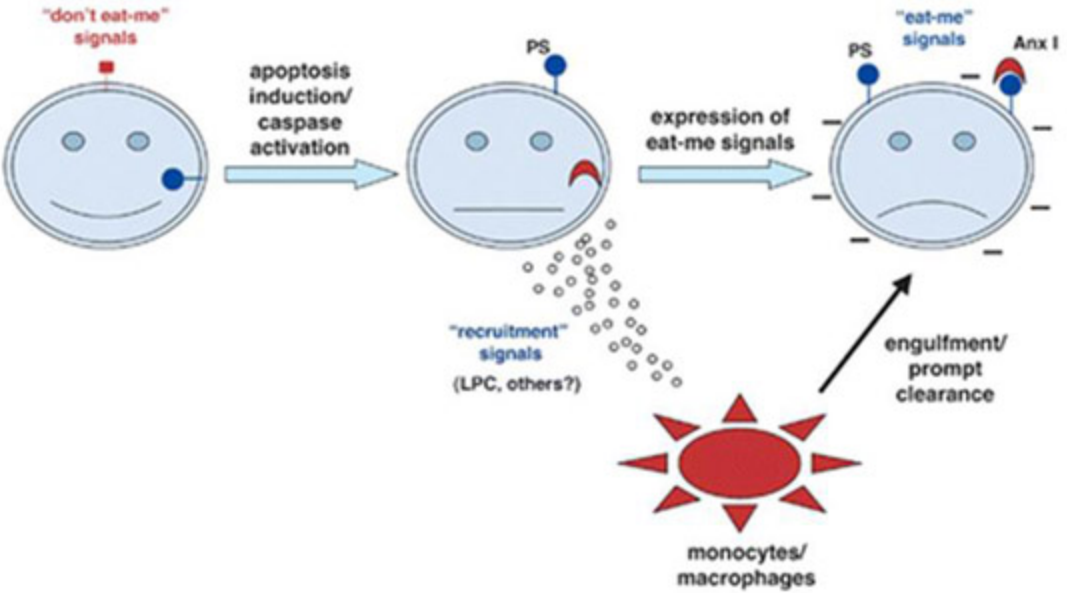


Mise en évidence de la fragmentation d'ADN



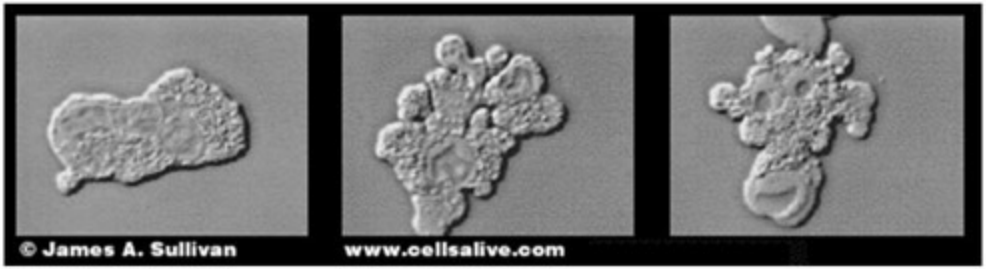


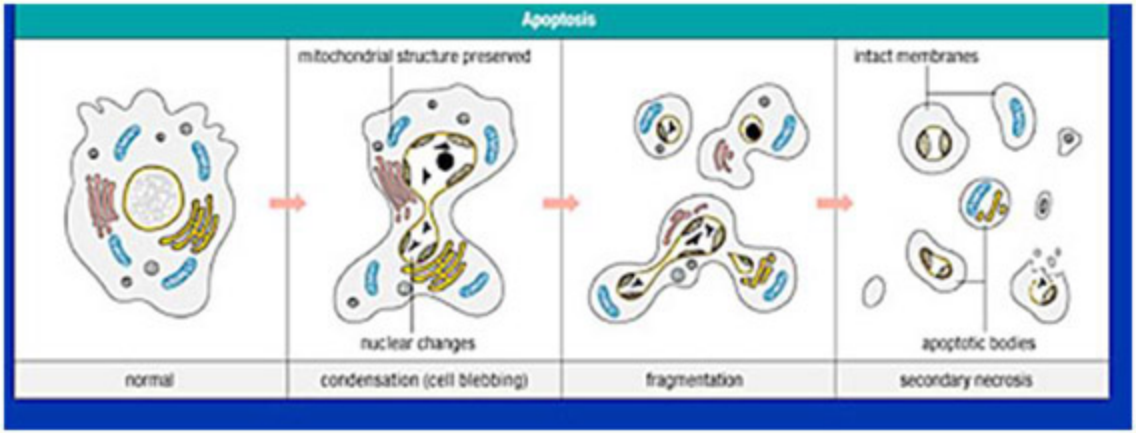
Clairance des cellules apoptotiques



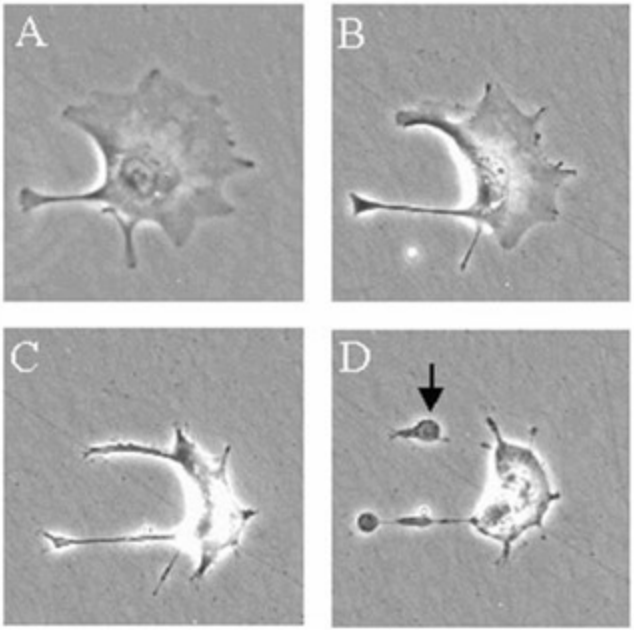
Cell, Vol 113, 817-820, 27 June 2003

Chronologie (1)





Microscopie time-lapse



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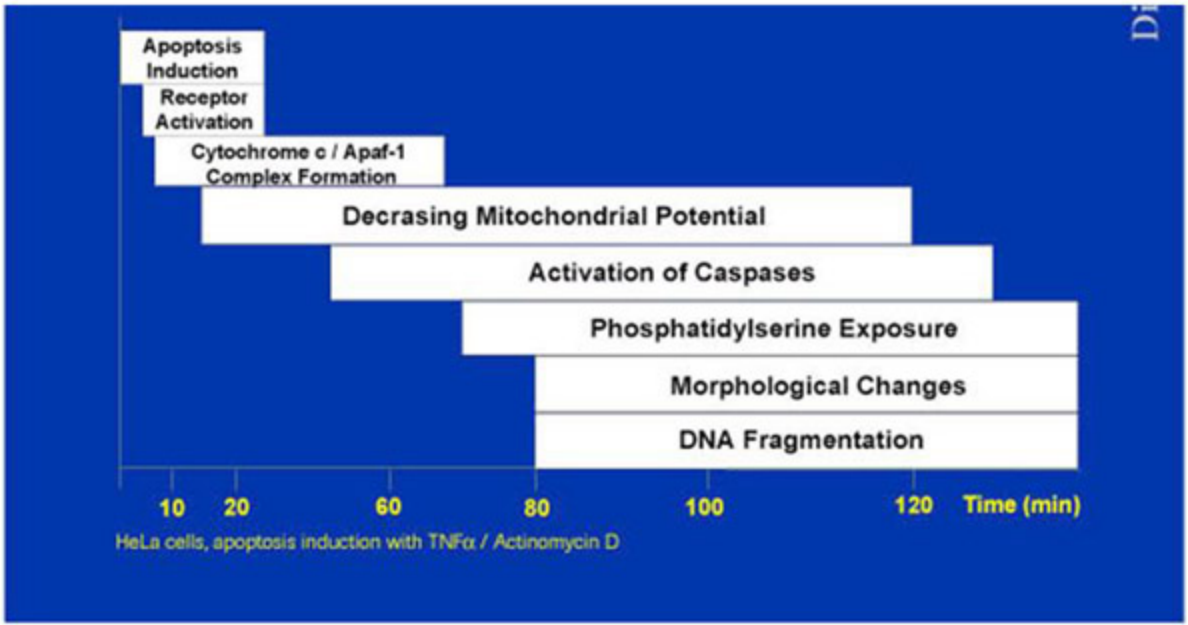

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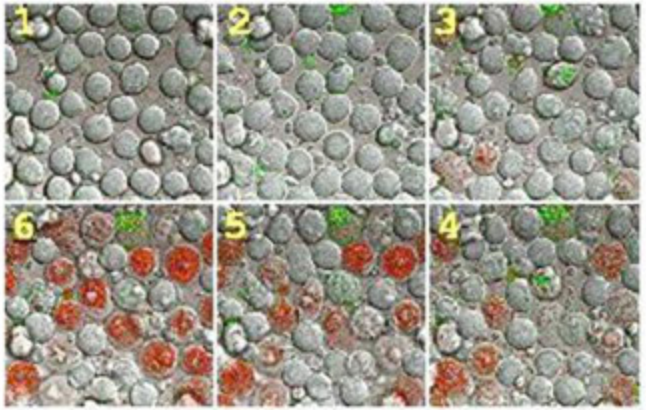
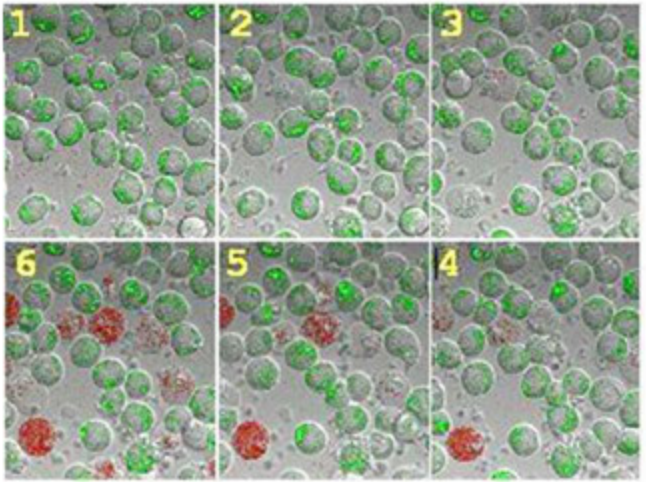
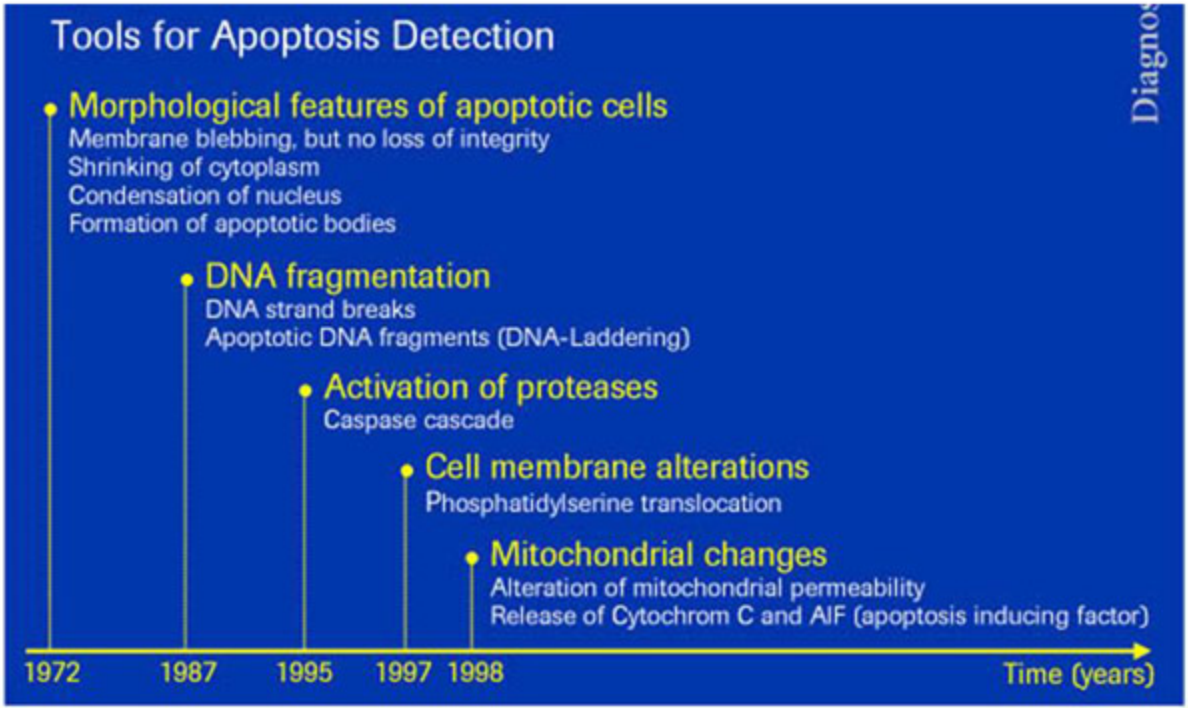
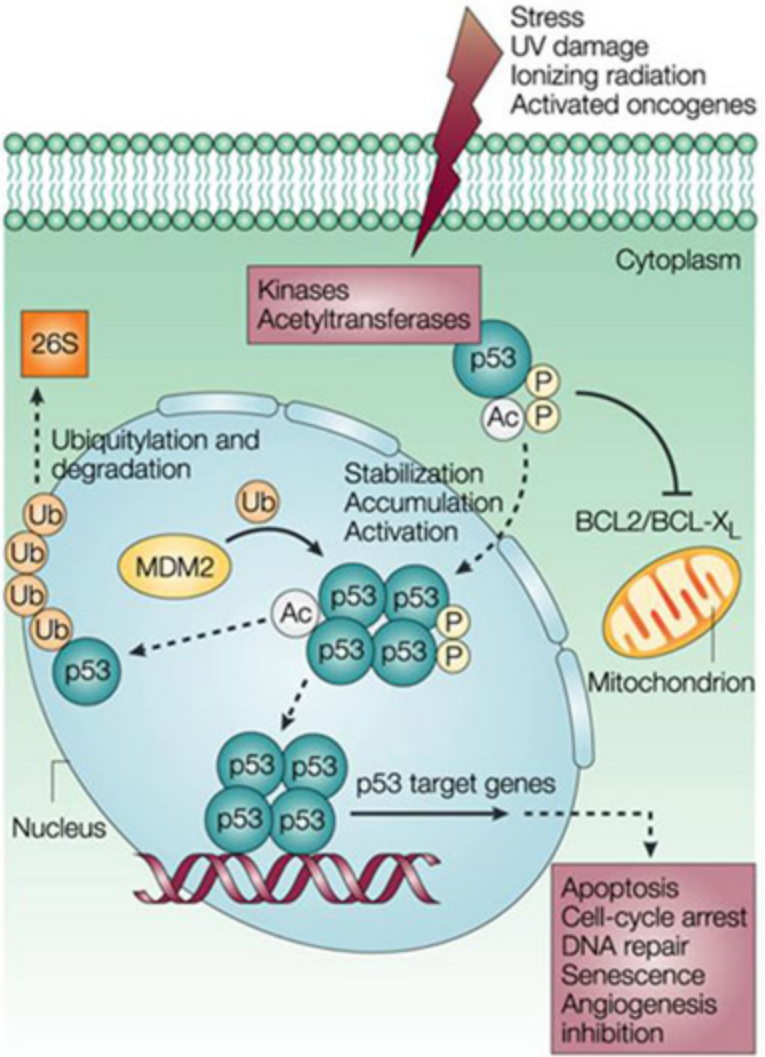




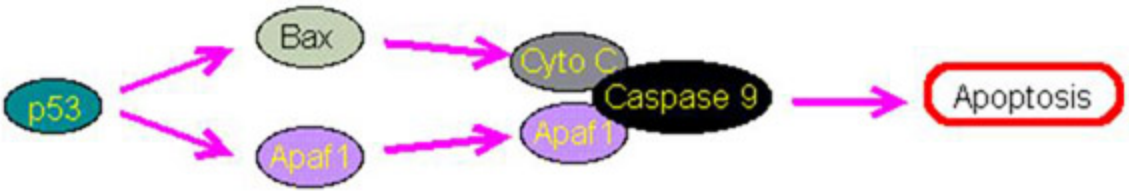

Tools for Apoptosis Detection
Diagnos
Morphological features of apoptotic cells
Membrane blebbing, but no loss of integrity
Shrinking of cytoplasm
Condensation of nucleus
Formation of apoptotic bodies
DNA fragmentation
DNA strand breaks
Apoptotic DNA fragments (DNA-Laddering)
Activation of proteases
Caspase cascade
Cell membrane alterations
Phosphatidylserine translocation
Mitochondrial changes
Alteration of mitochondrial permeability
Release of Cytochrom C and AIF (apoptosis inducing factor)
1972
1987
1995
1997
1998
Time (years)

Apoptose induite par p53

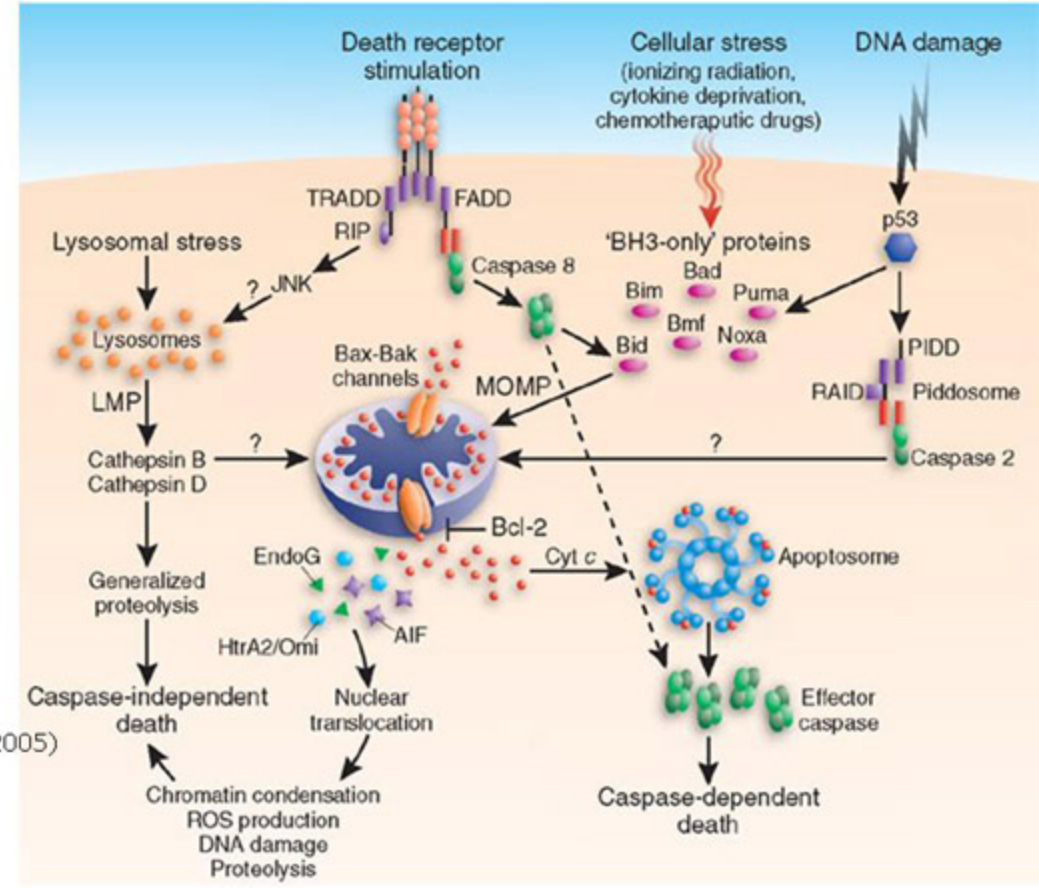


Nature Reviews Cancer **4**, 793-805 (2004)

Mécanismes – conséquences



Apoptose indépendante des caspases



Nature Medicine **11**, 725 - 730 (2005)

Apoptose et cancer

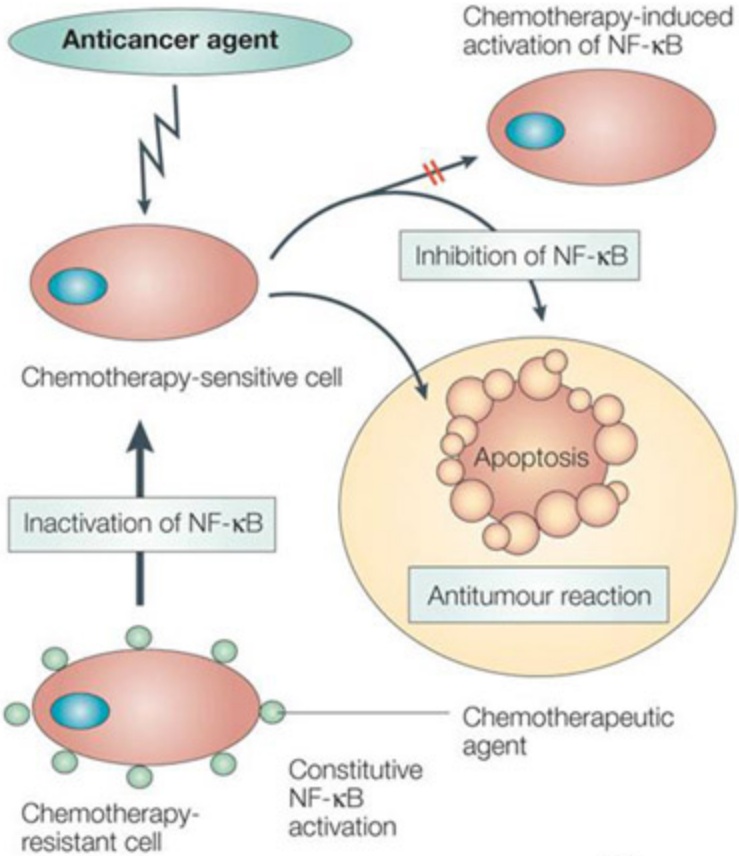
Table 1| **Mechanisms of tumour resistance to apoptosis**

Molecules		References
Expression of anti-apoptotic molecules		
BCL2 family members:	BCL2 BCL-X_L MCL1	75–80,82–84 80,85–88 89,90
FLIP		18,91–101
Soluble receptors for death ligands:	Soluble CD95 DcR3	102–105 5,6,106
IAPs:	Survivin cIAP2 ML-IAP	107–112 113 114
PI-9/SPI-6		111
Downregulation and mutation of pro-apoptotic genes		
BAX		116–122
APAF1		123
Caspase-8		124
Death receptors:	CD95 TRAIL-R1 TRAIL-R2	125–133 134–135 134,136,137
XAF1		138
Alterations of the p53 pathway		
p53		47,139–142
INK4A/ARF		48,143
ASPP		139
Alterations of the PI3K/AKT pathway		
PI3K		145–147
PTEN		143–145
AKT		146
Further mechanisms		
Expression of transporters:	MDR1/P-glycoprotein MRP	154,155 153
Alterations of NF-κB activity		157,158
Extracellular matrix		159

APAF1, apoptotic protease activating factor-1; ASPP, apoptosis stimulating protein of p53; DcR3, decoy receptor 3; FLIP, FAS-associated DD protein-like interleukin-1β-converting enzyme-like protease-inhibitory protein; IAP, inhibitor of apoptosis proteins; MCL1, myeloid cell leukaemia sequence 1; MDR1, multi-drug resistance protein-1; ML-IAP, melanoma IAP; NF-κB, nuclear factor κB; PI3K, phosphatidylinositol 3-kinase; PI-9/SPI-6, protease inhibitor 9/serine protease inhibitor 6; R, receptor; TRAIL, tumour-necrosis factor-related apoptosis-inducing ligand; XAF1, XIAP-associated factor 1.

Nature Reviews Cancer **2**, 277-288 (2002)

suite



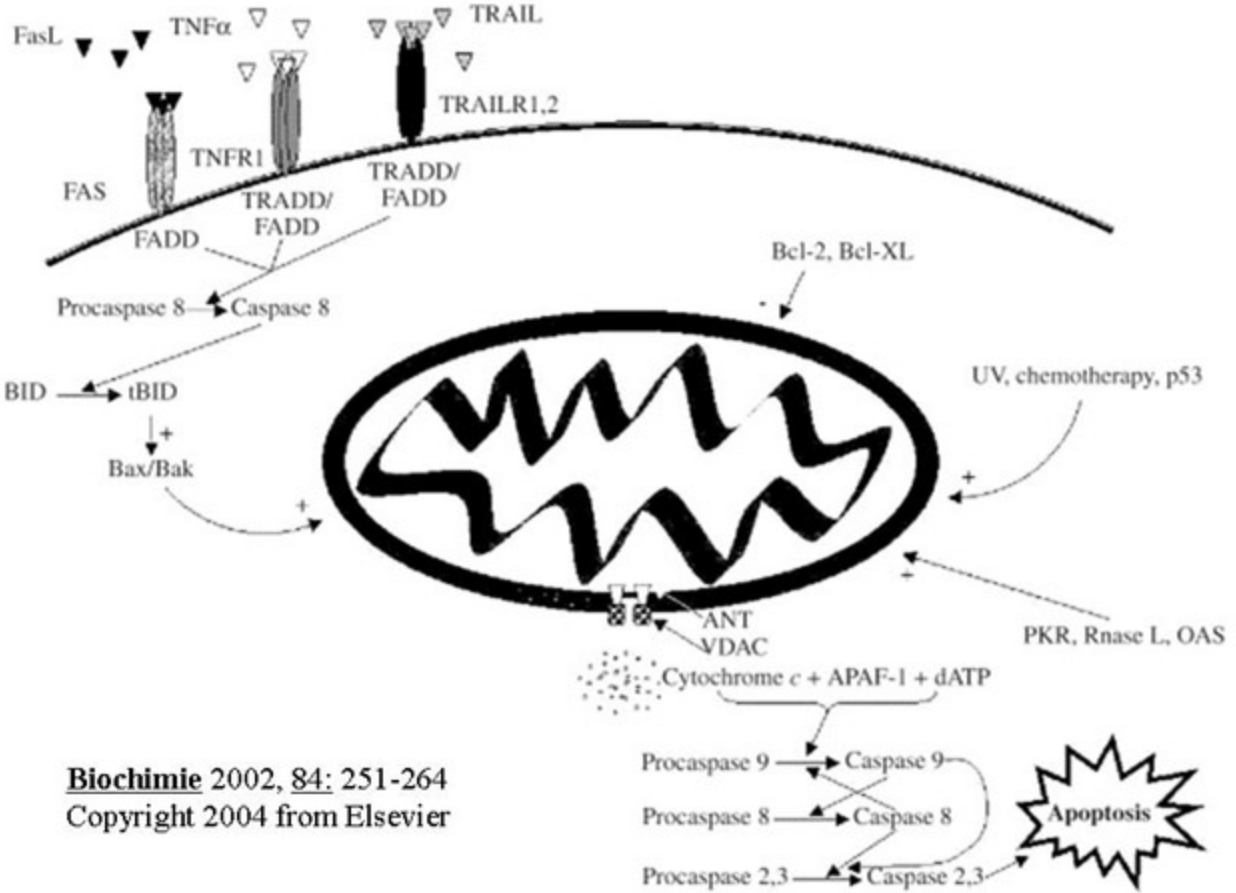
Nature Reviews Cancer **5**, 297-309 (2005)

Mécanismes de régulation de l'apoptose par le VIH

Stimulus	Mechanism
gp120	CD4 cross-linking
	↓ Bcl-2 expression
	↑ FasL expression
	caspase activation
	loss of $\Delta\psi_m$
Tat	↑ Fas/FasL expression
	↑ caspase 8 expression
	↓ Bcl-2 and ↑ Bax expression
	↑ TRAIL expression
	↑ Par-4 expression
	↓ $\Delta\psi_m$
	↓ SOD2 production
	↑ ROS production
Vpr	↓ $\Delta\psi_m$
	cytochrome *c* and AIF release
	caspase activation
	uncoupling of the electron transport chain and oxidative phosphorylation collapse
	G2/M cell cycle arrest
Protease	induces apoptosis
	cleavage of Bcl-2
	caspase 8 activation
	release of cytochrome *c*
	activation of caspases 9 and 3
Nef	↑ FasL expression
	enhances apoptosis
	↓ Bcl-2 and Bcl_{XL} expression
	↓ $\Delta\psi_m$
	activation of caspase 3
	cleavage of PARP
TAR	Rnase L- and OAS-mediated apoptosis
Unknown viral factor	↑ p53 expression and phosphorylation
HIV RNA	↓ $\Delta\psi_m$

Biochimie 2002, 84: 251-264

Apoptose



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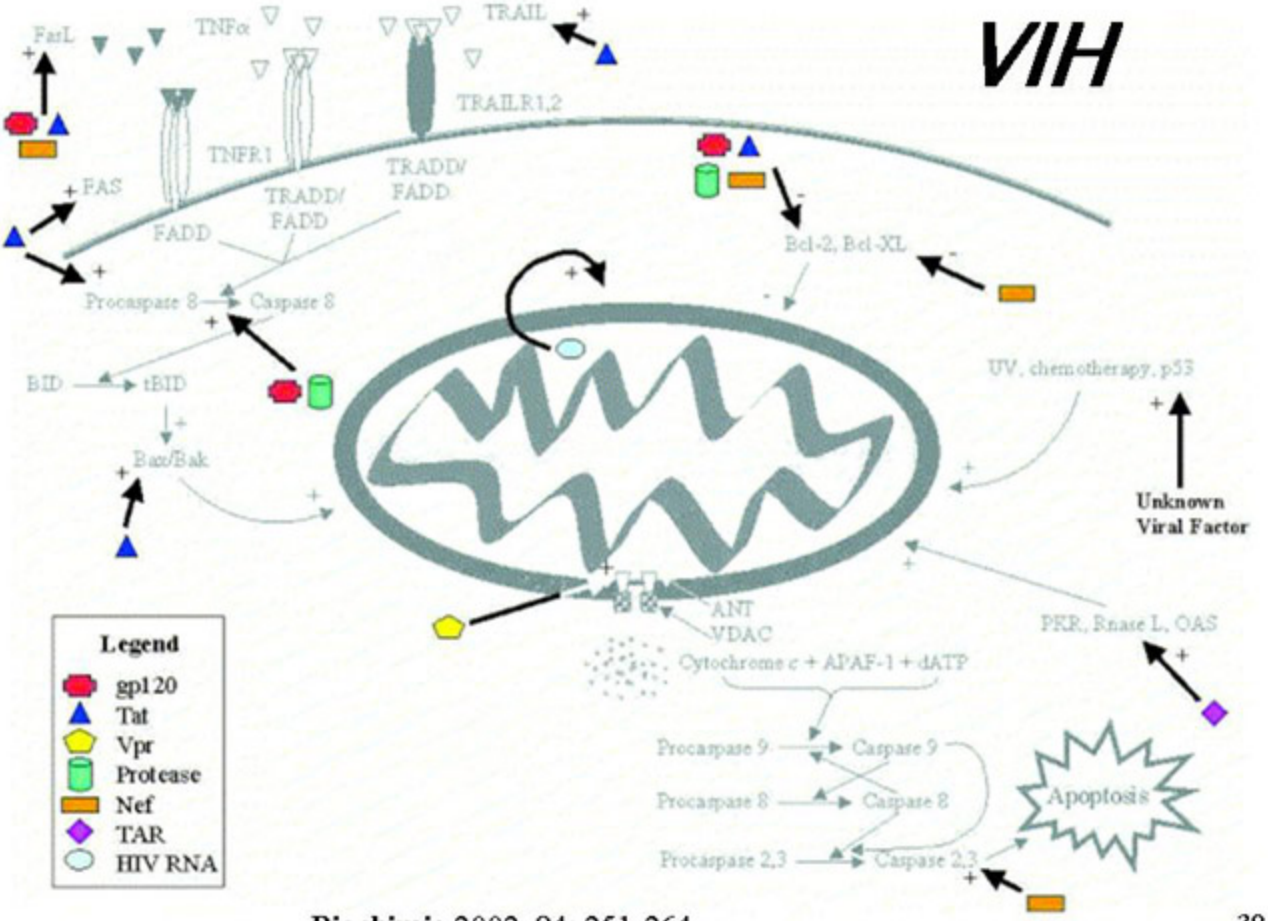

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Table 1 | **Apoptosis-based therapeutics in clinical trials**

Drug/ therapeutic	Company	Target	Type	Apoptosis effect	Disease indication(s)	Status
Core apoptosis targets						
IDN6556	Idun Pharmaceuticals	Caspases	Small molecule	Anti-	Acute liver injury, hepatitis	Ph II
VX-740	Vertex Pharmaceuticals	Caspase-1	Small molecule	Anti-	Arthritis, inflammation	Ph II
Genasense	Genta	BCL2	Antisense; oligonucleotide	Pro-	Cancer (melanoma, myeloma) (leukaemia, prostate, colon, lymphoma, breast)	Ph III Ph II
Inputs into apoptosis machinery						
TRAIL	Genentech/ Immunex	DR4, DR5	Biological (protein)	Pro-	Cancer	Ph I*
CDDO	National Cancer Institute	PPARγ, IKK and others	Small molecule	Pro-	Cancer	Ph I*
Vitaxin	Applied Molecular Evolution (lxsys)	αvβ3-integrin	Monoclonal (humanized) antibody	Pro-	Angiogenesis (cancer)	Ph III
EMD121974	E-Merck	αvβ3-integrin	Cyclic pentapeptide	Pro-	Angiogenesis (cancer)	Ph III
E1A gene therapy	Targeted Genetics	E1A	Gene (adenovirus)	Pro-	Cancer (head and neck, ovarian)	Ph III
ONYX-015	Onyx Pharmaceuticals	unknown	Adenovirus (p53-deficient cells) (dl1520)	Pro-	Cancer (head and neck)	Ph III
INGN201	Introgen Therapeutics	p53	Gene (adenovirus)	Pro-	Cancer (head and neck) (non-small-cell lung cancer)	Ph III Ph II
CGP3466B	Novartis	GAPDH	Small molecule	Anti-	Neuroprotection (Parkinson's disease)	Ph II
Exisulind	Cell Pathways	PDE5A (PKG)	Small molecule (NSAID)	Pro-	Cancer (colon)	Ph II
Memantine	Forest Laboratories	NMDAR	Small molecule; partial antagonist	Anti-	Neuroprotection (Alzheimer's disease; multi-infarct dementia)	Ph III‡
SAHA	Aton Pharma	HDAC	Small molecule	Pro-	Cancer	Ph I

*Phase I trials expected to begin this year.
‡Phase III trials completed. Drug awaiting approval for this indication.
DR, death receptor; E1A, adenovirus E1A protein; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HDAC, histone deacetylase; IKK, IκB kinase; NMDAR, *N*-methyl-D-aspartate receptor; NSAID, non-steroidal anti-inflammatory drug; PDE, phosphodiesterase 5A; PKG, protein kinases G; PPARγ, peroxisome proliferative-activated receptor-γ; TRAIL, tumour-necrosis factor (TNF)-related apoptosis-inducing ligand.

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