Apoptose, Nécrose/Nécroptose, Pyroptose et Autophagie : Caractéristiques et Méthodes d'Etudes

Gérard LIZARD - INSERM

EA7270 - Equipe 'Biochimie du Peroxysome, inflammation et Métabolisme Lipidique'

Faculté des Sciences Gabriel

6, Bd Gabriel

21000 Dijon - FRANCE

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Master Pro – Univ Tunis El Manar
Tunisie

Gérard Lizard

MULTIPLICITY OF THE MODES OF CELL DEATH

- Typical modes of cell death

* Apoptosis
* Autophagy
* Cornification
* Necrosis/Necroptosis

-Atypical modes of cell death

* Mitotic catastrophe
* Anoikis
* Excitotoxicity
* Wallerian degeneration
* Paraptosis
* Pyroptosis
* Pyronecrosis
* Entosis

Kroemer G et al. Cell Death Differ 2009, 16: 3-11.

CLASSIFICATION OF CELL DEATH

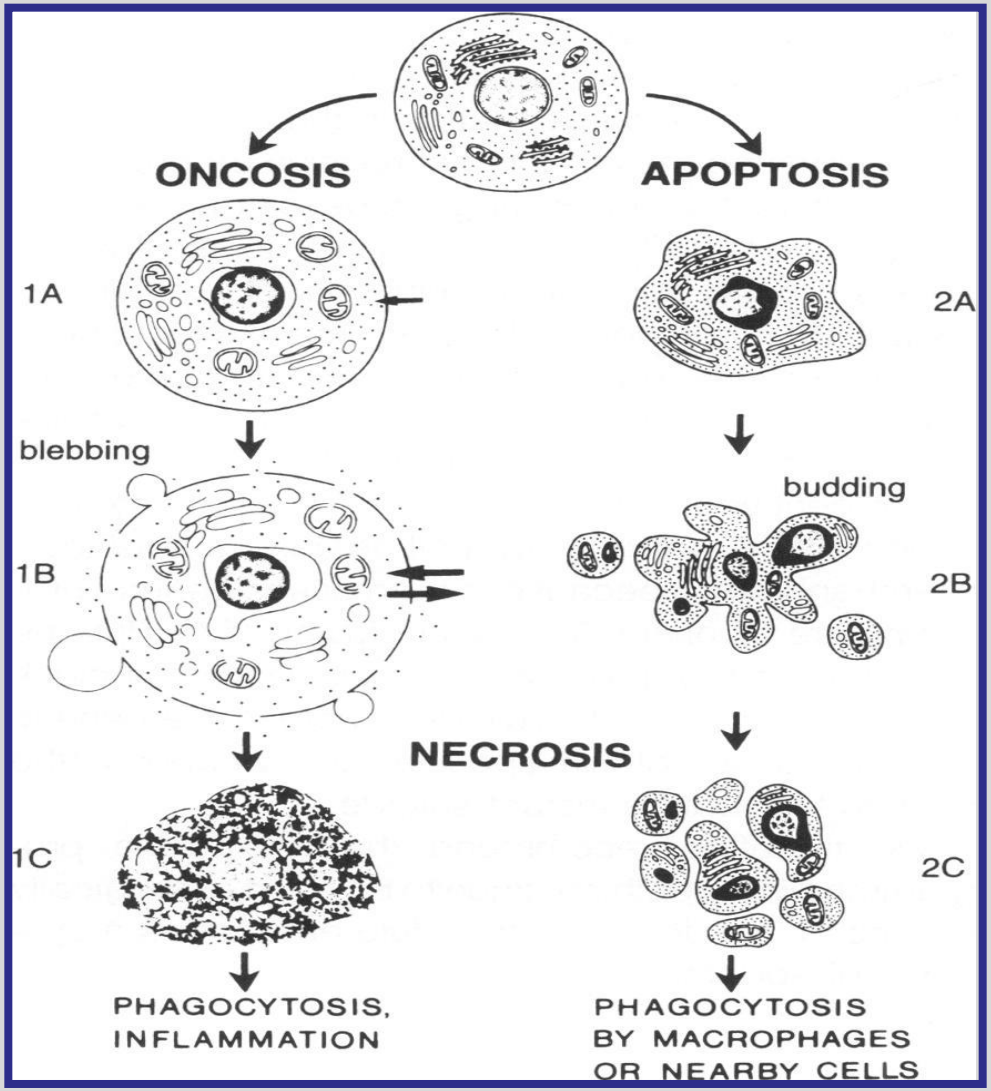
Physiological and pathological cell death have been classified according to morphological criteria into at least three categories:

* **type I** cell death : **apoptosis**

* **type II** cell death : **autophagy**

* **type III** cell death : necrosis

Boya G & Kroemer G et al. Oncogene 2008, 27: 6434-6451.



Two pathways of cell death leading to necrosis and apoptosis. At the top is shown a normal cell. 1A: Swelling. 1B: Vacuolization, blebbing, and increased permeability. 1C: Necrotic changes. ie, coagulation, shrinkage, and karyolysis. 2A: Shrinkage and pyknosis. 2B: Budding and karyorhexis. 2C: Necrotic changes, ie, breakup into a cluster of apoptotic bodies.

Majno G & Joris I Am J Pathol 1995, 146: 3 - 15.

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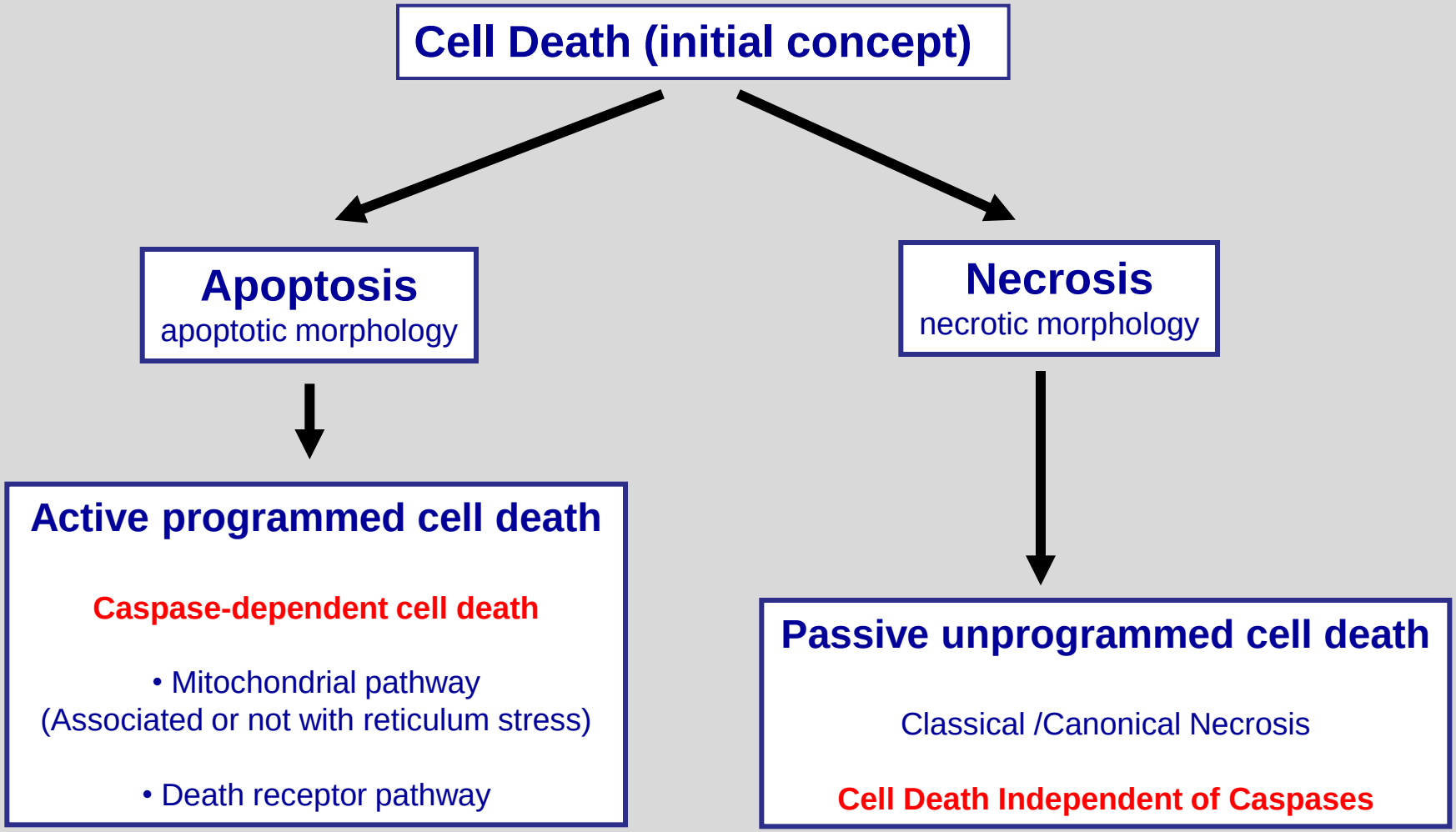
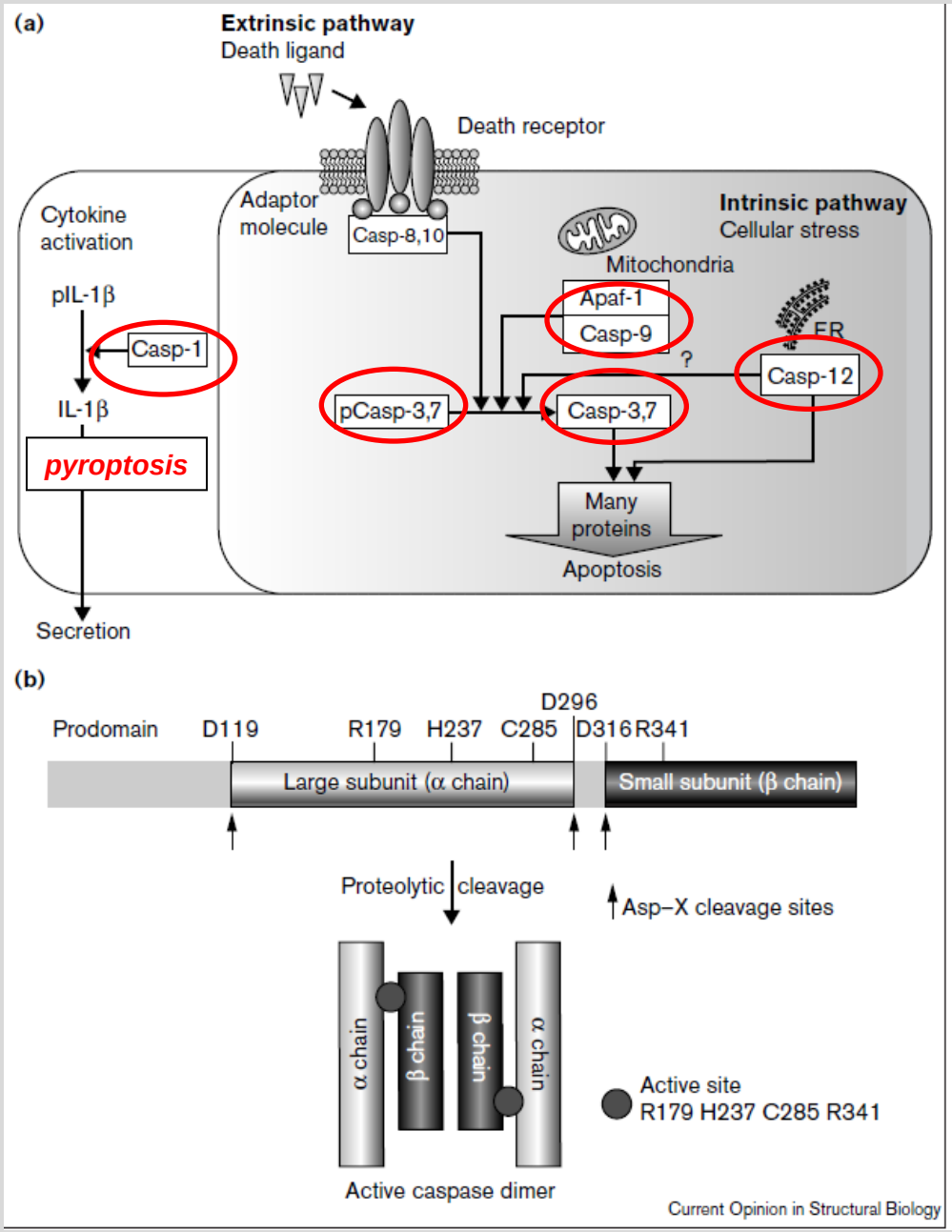


Kitanaka C & Kuchino Y Cell Death Differ 1999, 6: 508-515.



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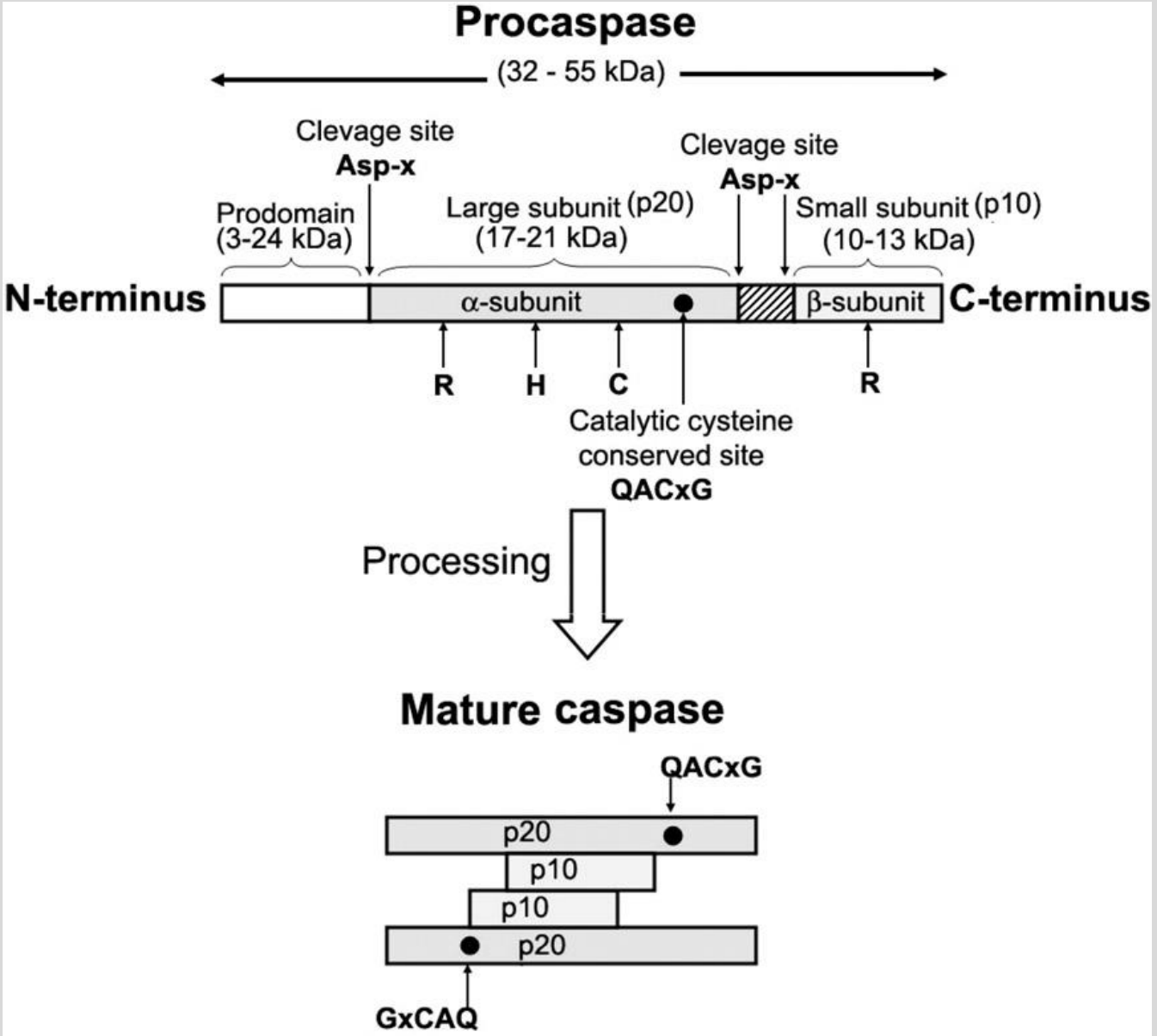
Grütter MG. Caspases: key players in programmed cell death. Curr Opin Struct Biol. 2000 Dec;10(6):649-55.



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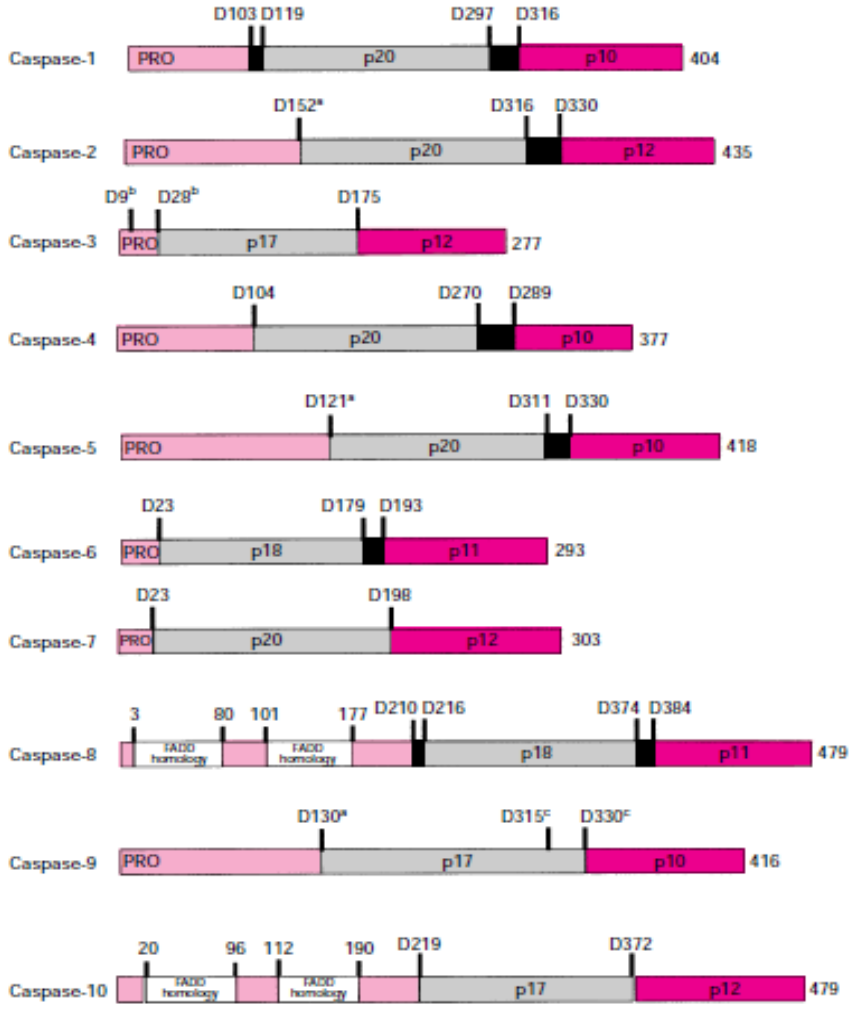
Chowdhury I, Tharakan B, Bhat GK. Caspases - an update. Comp Biochem Physiol B Biochem Mol Biol. 2008 ;151(1):10-27.



Proenzyme organization of the caspases

Caspases are synthesized as proenzymes, with a N-terminal peptide or prodomain (PRO), and two subunits sometimes separated by a linker peptide (black box). Based on caspase-1 and caspase-3, active enzymes are heterotetramers of two large (~ 20 kDa; p20) and two small (~ 10 kDa; p10) subunits. The proenzymes are cleaved at specific Asp residues (D*n*, where *n* is the position in the protein). The numbers at the right-hand side are the numbers of amino acids in the protein. [a]Exact cleavage site not known; [b]the cleavage site of caspase-3 may be at Asp-9 or Asp-28 [65–67]; [c]caspase-9 is cleaved preferentially at Asp-330 by caspase-3 and at Asp-315 by granzyme B [82]. Caspase-2 cleavage sites are based on equivalent sites being present in Nedd2 [60,61]. FADD represents the domains of caspase-8 and caspase-10 that are homologous to the DED of FADD/MORT1.

Cohen GM. Caspases: the executioners of apoptosis. Biochem J. 1997 Aug 15;326 (Pt 1):1-16.

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Caspases-3, -7 and -9 have only one cleavage site between the large and small subunits, whereas the other caspases have two potential aspartate cleavage sites, resulting in removal of a linker region. Degrees of inhibition by cowpox viral serpin CrmA: +++, potent inhibition; ±, very weak inhibition; ?, not known.

Caspase	Other names	Active site	Cleavage site(s) between large and small subunits	CrmA inhibition
Caspase-1	ICE	QACRG	WFKD ↓ S; FEDD ↓ A	+++
Caspase-2	Nedd2, ICH-1	QACRG	DQQD ↓ G; EESD ↓ A	±
Caspase-3	CPP32, Yama, apopain	QACRG	IETD ↓ S	±
Caspase-4	ICE_{rel}II, TX, ICH-2	QACRG	WRVD ↓ S; LEED ↓ A	+++
Caspase-5	ICE_{rel}III, TY	QACRG	WRVD ↓ S; LEAD ↓ S	?
Caspase-6	Mch2	QACRG	DVVD ↓ N; TEVD ↓ A	±
Caspase-7	Mch3, ICE-LAP3, CMH-1	QACRG	IDAD ↓ S	±
Caspase-8	MACH, FLICE, Mch5	QACQG	VETD ↓ S; LEMD ↓ L	+++
Caspase-9	ICE-LAP6, Mch6	QACGG	DQLD ↓ A	?
Caspase-10	Mch4	QACQG	SDTD ↓ V; IEAD ↓ A	±

Cohen GM. Caspases: the executioners of apoptosis. Biochem J. 1997 Aug 15;326 (Pt 1):1-16.

Caspase substrate specificities*.

Specificity group		P4–P1. Optimal recognition motif	Consensus
Group I	Caspase-1	WEHD	
	Caspase-4	WEHD	WEHD
	Caspase-5	WEHD	
	Caspase-13	WEHD	
Group II	Caspase-2	DEHD	
	Caspase-3	DEVD	DEXD
	Caspase-7	DEVD	
Group III	Caspase-6	VEHD	
	Caspase-8	LETD	(I/V/L)EXD
	Caspase-9	LEHD	
	Caspase-10	LEXD	

Grütter MG. Caspases: key players in programmed cell death. Curr Opin Struct Biol. 2000 Dec;10(6):649-55.

Protein substrates of caspases

Abbreviation: SREBP, sterol regulatory element binding protein.

Protein substrate	Cleavage motif	Caspase(s)	Function of substrate	References
PARP	DEVD ↓ G	3,7	DNA repair enzyme	68, 104
U1-70 kDa	DGPD ↓ G	3	Splicing of RNA	106
DNA-PK$_{cs}$	DEVD ↓ N	3	DNA double-strand-break repair	106, 107
Gas2	SRVD ↓ G	?	Component of microfilament system	126
Protein kinase C δ	DMQD ↓ N	3	Cleaved to active form in apoptosis	130, 131
Pro-IL-1β	YVHD ↓ A	1	Cleaved to mature active cytokine	32–34
D4-GDP dissociation inhibitor	DELD ↓ S	3	Regulator of Rho GTPases	110
Lamin A	VEID ↓ N	6	Assist in maintaining nuclear shape	113–116
Heteroribonuclear proteins C1 and C2	?	3,7	Processing of pre-mRNA	108
Huntingtin	DXXD	3	Huntington disease gene product	111
SREBP-1 and SREBP-2	DEPD ↓ S	3,7	Sterol regulatory element binding proteins	109
Fodrin	DETD ↓ S?	?	Membrane-associated cytoskeletal protein	127–129
Rb (see the text)	DEAD ↓ G	3	Cell cycle regulatory protein	112, 133, 134

Cholesterol metabolism

Cohen GM. Caspases: the executioners of apoptosis. Biochem J. 1997 Aug 15;326 (Pt 1):1-16.

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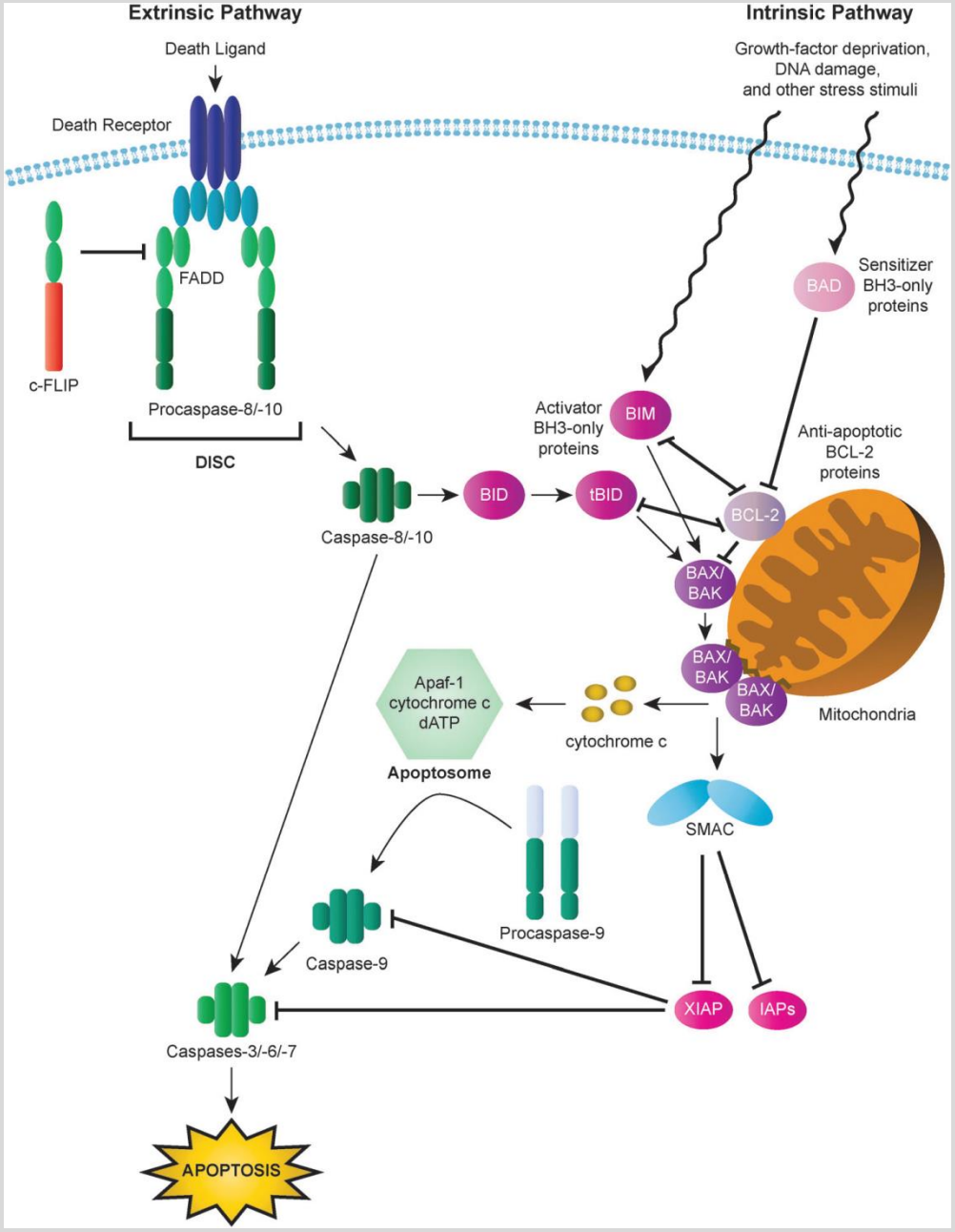

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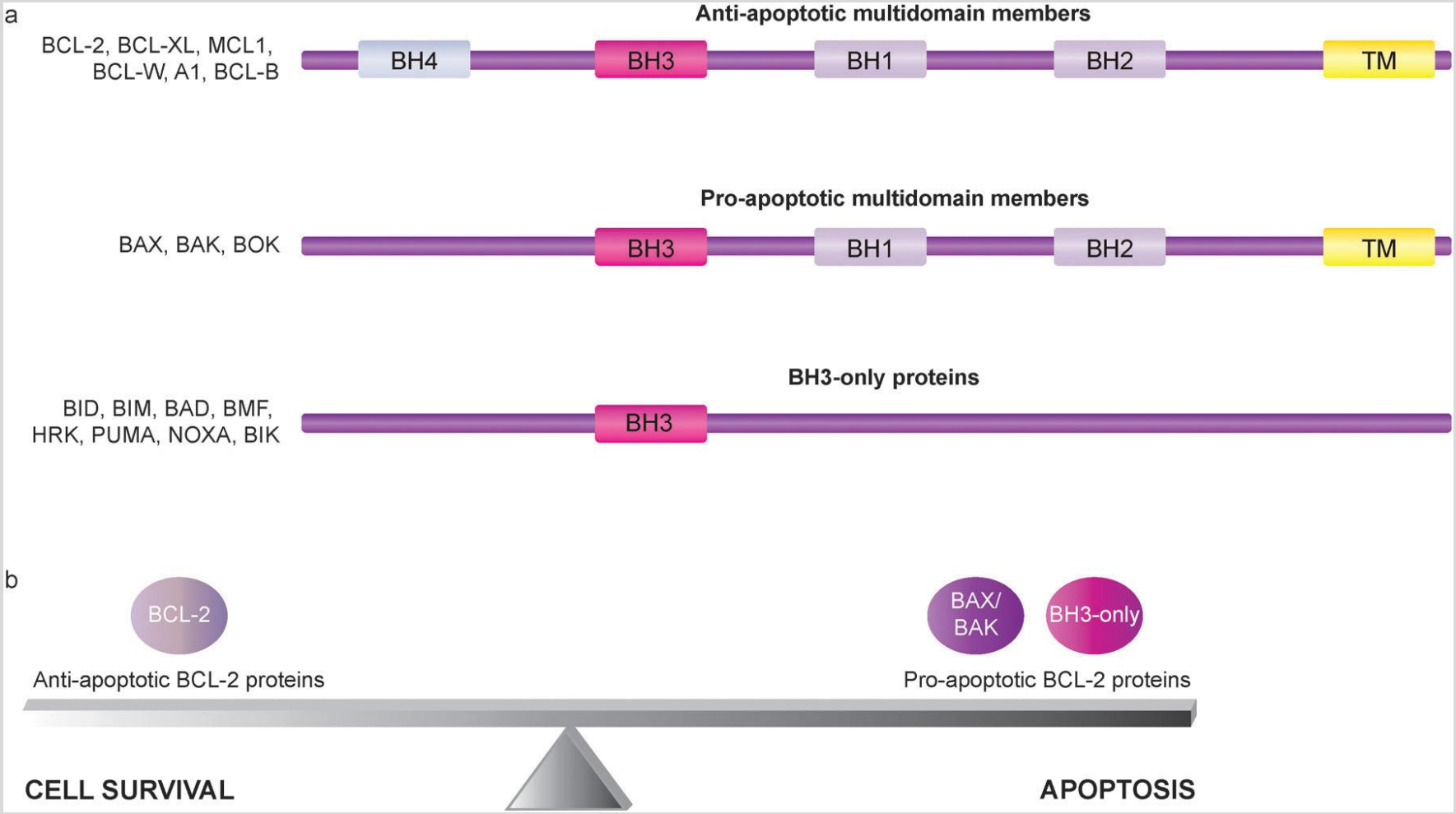
Plati J, Bucur O, Khosravi-Far R. Apoptotic cell signaling in cancer progression and therapy. Integr Biol (Camb). 2011 ;3(4):279-96.



Subgroups of BCL-2 family members with representative members of each subfamily. (a) BCL-2 family members can be classified into three subgroups according to function and BH domain composition. All BCL-2 family members possess at least one of four BCL-2 homology (BH) domains, termed BH1, BH2, BH3, and BH4, and many also include a transmembrane (TM) domain. The anti-apoptotic multidomain members have three to four BH domains, with some members lacking a BH4 domain. Similar to the anti-apoptotic multidomain members, the pro-apoptotic multidomain members contain BH1, BH2, and BH3 domains. The BH3-only proteins are a subset of pro-apoptotic proteins that only bear a single BH motif, the BH3 domain. Some BH3-only proteins also include a TM domain. (b) BCL-2 proteins play a key role in mediating the delicate balance between cell survival and cell death. Disruption of this balance by cellular alterations that increase the functional activity of anti-apoptotic BCL-2 proteins relative to pro-apoptotic BCL-2 proteins can enable the evasion of apoptosis, which tips the balance to favor cell survival and thus promotes the development and progression of cancer.

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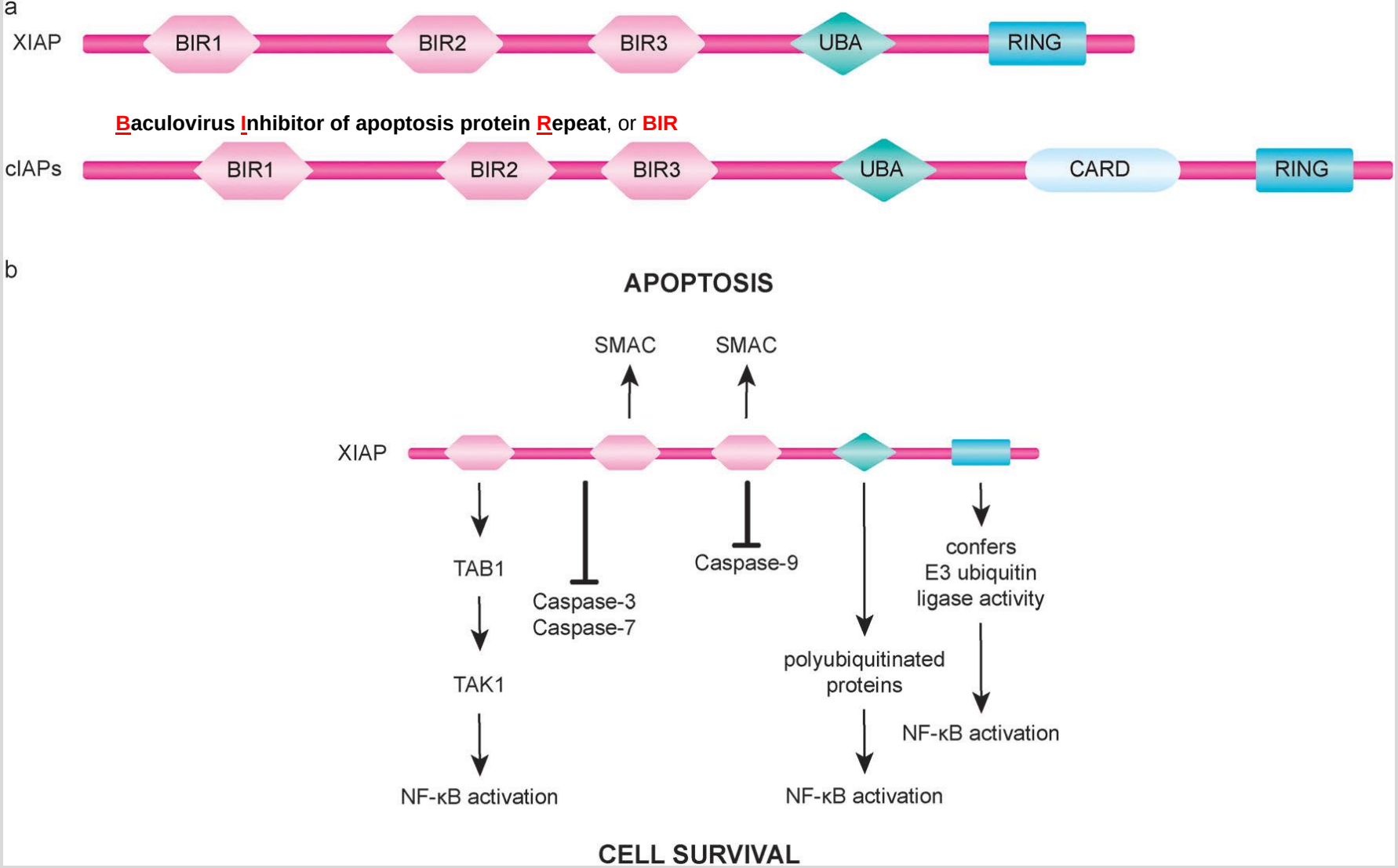
Plati J, Bucur O, Khosravi-Far R. Apoptotic cell signaling in cancer progression and therapy. Integr Biol (Camb). 2011 ;3(4):279-96.



Domain organization and function of inhibitors of apoptosis (IAP) proteins. (a) XIAP, a well studied human IAP family member, and the structurally similar family members cIAP1 and cIAP2 (cIAPs) each have three tandem BIR domains followed by an ubiquitin-associated (UBA) domain and a C-terminal RING finger domain. cIAPs also possess a caspase recruitment domain (CARD) of unknown function located between the UBA and the RING domains. (b) The BIR2 domain of XIAP, along with residues in its N-terminal flanking linker region, mediates the binding and inhibition of caspase-3 and caspase-7. Inactivation of caspase-9 by XIAP involves the BIR3 domain of XIAP binding to caspase-9. In addition to blocking caspase activity, XIAP can also promote cell survival through regulation of important cellular signaling pathways, including signaling mechanisms of NF-kB activation. IAP-binding motif (IBM)-containing proteins, such as SMAC, interact with the BIR2 and BIR3 domains of XIAP to neutralize its anti-apoptotic activity.

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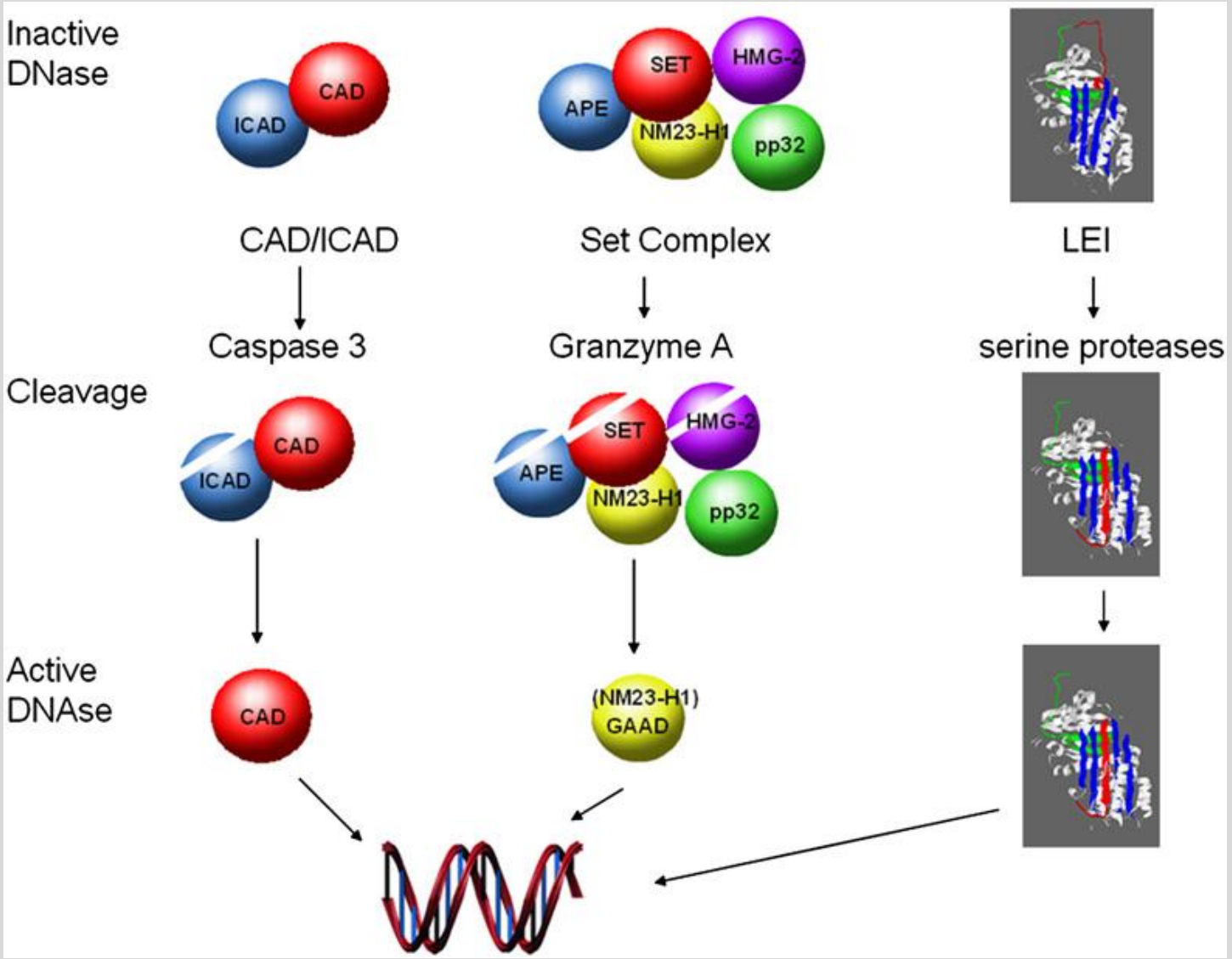
Plati J, Bucur O, Khosravi-Far R. Apoptotic cell signaling in cancer progression and therapy. Integr Biol (Camb). 2011 ;3(4):279-96.



Sequence of activation of different nucleases in apoptosis. In regard to events occurring upstream of DNase activation during apoptosis, three systems have been characterized to date. The first and most widely known is the activation of CAD by cleavage of its inhibitor ICAD by effector caspases like caspases 3 or 7. This mode of activation is found again during the activation of GAAD. Several proteins of the SET complex are cleaved by Granzyme A liberating an active GAAD endonuclease. Finally a proteolytic cleavage of LEI, by the action of serine proteases, transforms this protein into L-DNase II. It is interesting to note that in every case the increase of the proteolytic activity in the cell triggers endonuclease activation. So, the activated DNase depends on the molecular pathways activated upstream.

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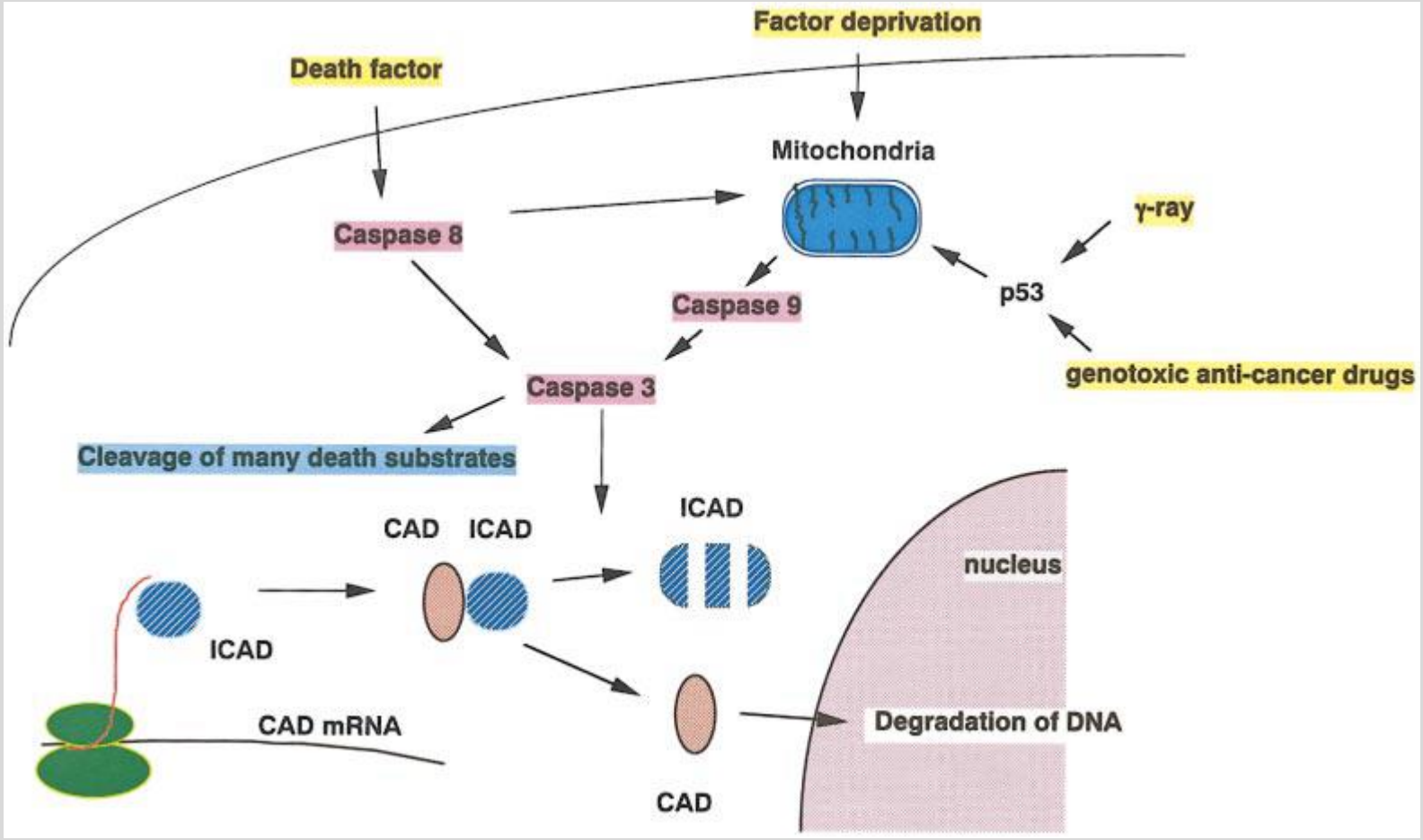
Counis MF, Torriglia A. Acid DNases and their interest among apoptotic endonucleases. Biochimie. 2006 ; 88(12):1851-8.



CAD-mediated apoptotic DNA fragmentation. When CAD is synthesized, ICAD helps its correct and productive folding. CAD thus exists as an inactive enzyme complexed with ICAD in proliferating cells. Various apoptotic signals such as death factors, factor-deprivation, or genotoxic agents activate the caspase cascade. Caspase 3 downstream of the cascade cleaves ICAD at two positions and inactivates its CAD-inhibitory activity. CAD, thus released from ICAD, degrades chromosomal DNA.

Nagata S. Apoptotic DNA fragmentation. Exp Cell Res. 2000;256(1):12-8

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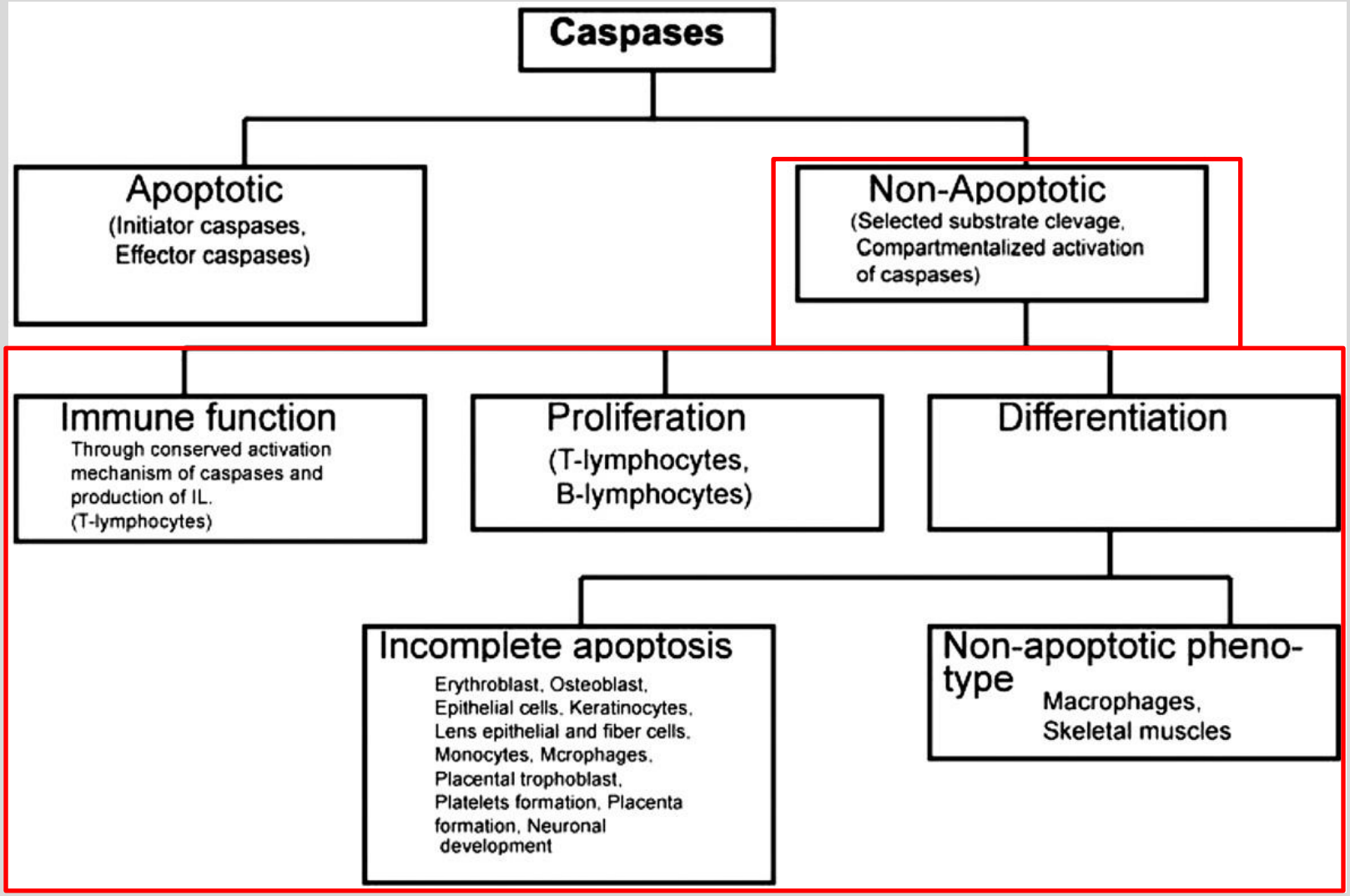

Chowdhury I, Tharakan B, Bhat GK. Caspases - an update. Comp Biochem Physiol B Biochem Mol Biol. 2008 ;151(1):10-27.

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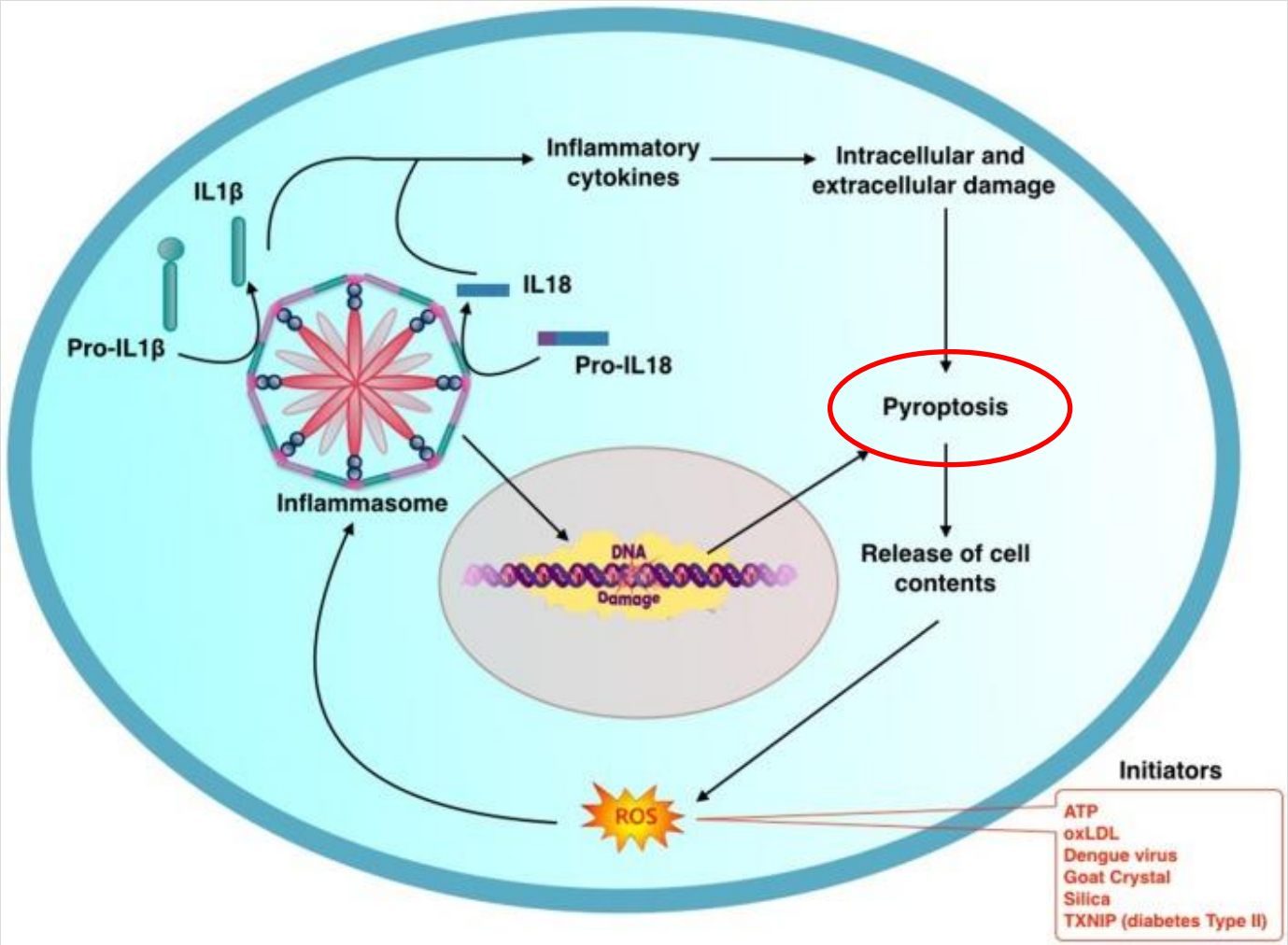
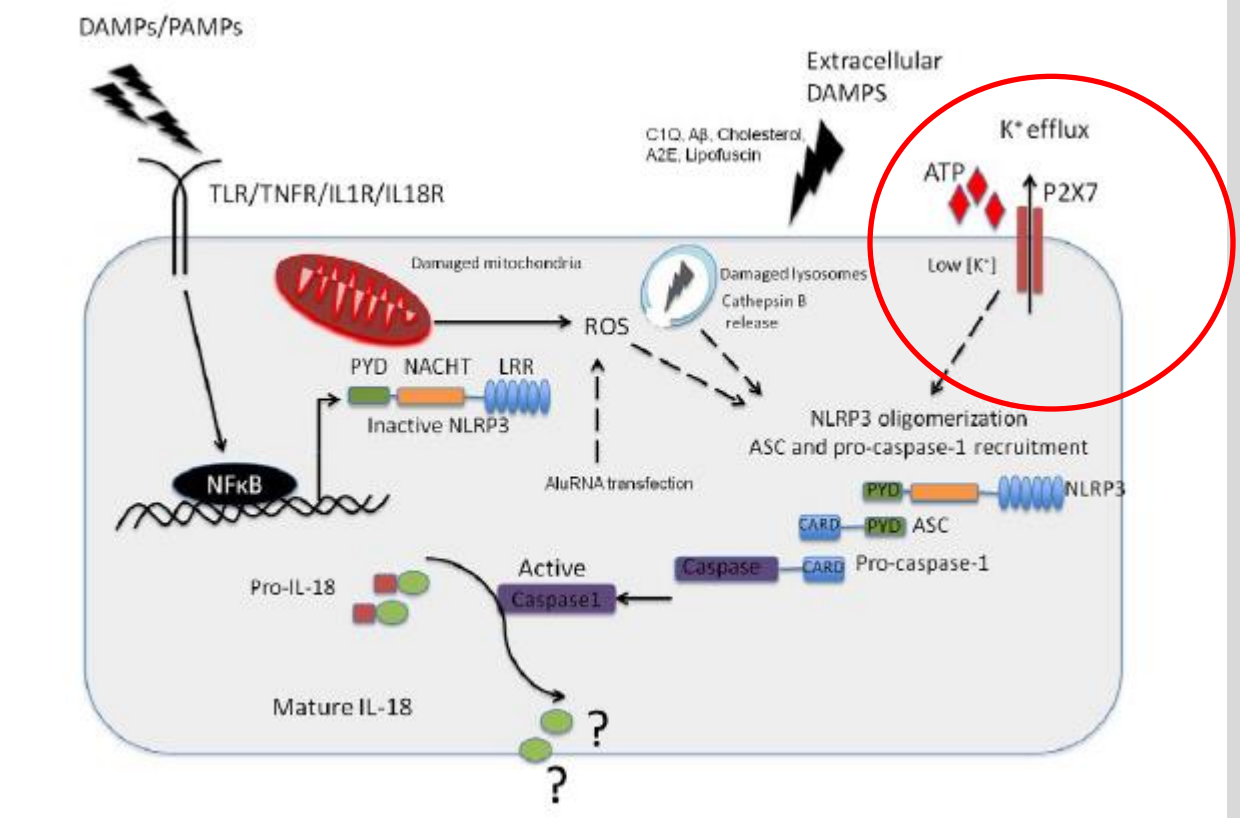
Crosstalk between caspase activation, inflammation and ROS overproduction
The part taken by inflammasome



General schema describing the process of activation of inflammasome: initiating factors activate production of reactive oxygen species (ROS) which in turntriggers the inflammasome mediated inflammatory cascade. Oligomerization of components results in assembly of Inflammasome. This in turn activates Il-1β and Il-18 through caspase-1. NLRP3 Inflammasome promotes oxidative DNA damage. Inflammation and DNA damage culminates in pyroptosis releasing contents from the damaged cell. This in turn promotes a vicious cycle of further Inflammasome mediated pathogenic process

Harijith A, Ebenezer DL, Natarajan V. Reactive oxygen species at the crossroads of inflammasome and inflammation. Front Physiol. 2014;5:352.

Mort cellulaire, inflammation et flux ioniques



Lucia Celkova [1], Sarah L. Doyle [2] and Matthew Campbell [1,*]

J. Clin. Med. **2015**, *4*, 172-192; doi:10.3390/jcm4010172

Gérard Lizard,

Cell. Mol. Life Sci. (2016) 73:2387–2403
DOI 10.1007/s00018-016-2208-z

Cellular and Molecular Life Sciences

MULTI-AUTHOR REVIEW

Ion channels in regulated cell death

Karl Kunzelmann[1]

Abstract Activation of ion channels and pores are essential steps during regulated cell death. Channels and pores participate in execution of apoptosis, necroptosis and other forms of caspase-independent cell death. Within the program of regulated cell death, these channels are strategically located. Ion channels can shrink cells and drive them towards apoptosis, resulting in silent, i.e. immunologically unrecognized cell death. Alternatively, activation of channels can induce cell swelling, disintegration of the cell membrane, and highly immunogenic necrotic cell death. The underlying cell death pathways are not strictly separated as identical stimuli may induce cell shrinkage and apoptosis when applied at low strength, but may also cause cell swelling at pronounced stimulation, resulting in regulated necrosis. Nevertheless, the precise role of ion channels during regulated cell death is far from being understood, as identical channels may support regulated death in some cell types, but may cause cell proliferation, cancer development, and metastasis in others. Along this line,

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