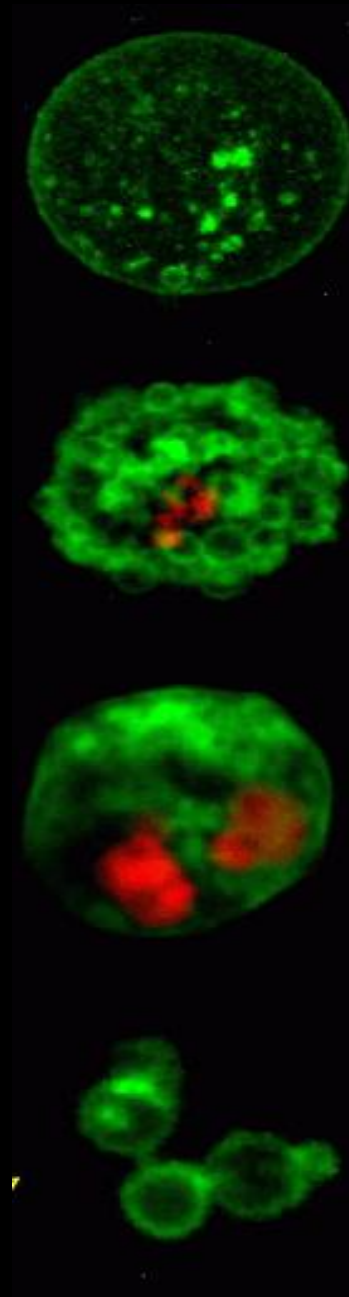


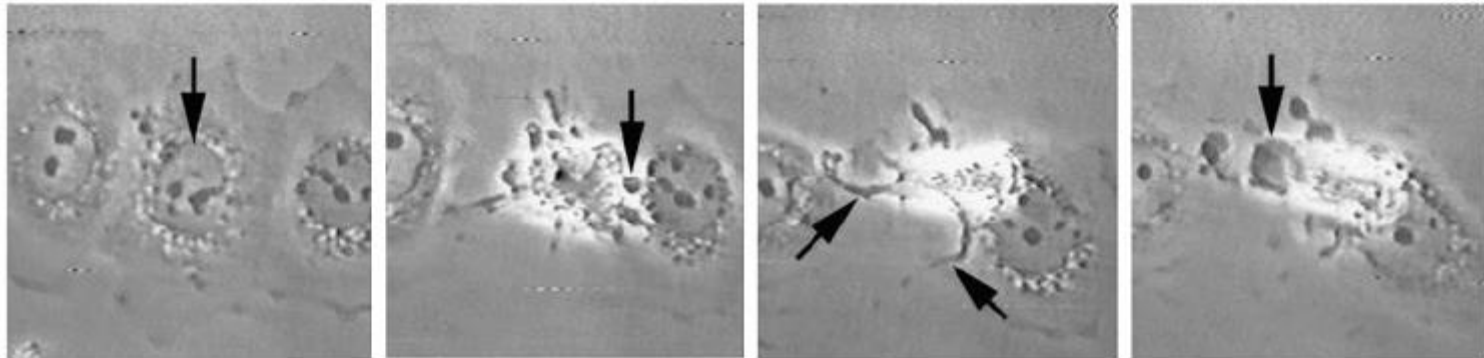
MORTE CELULAR

Nathalie Cella
ncella@usp.br

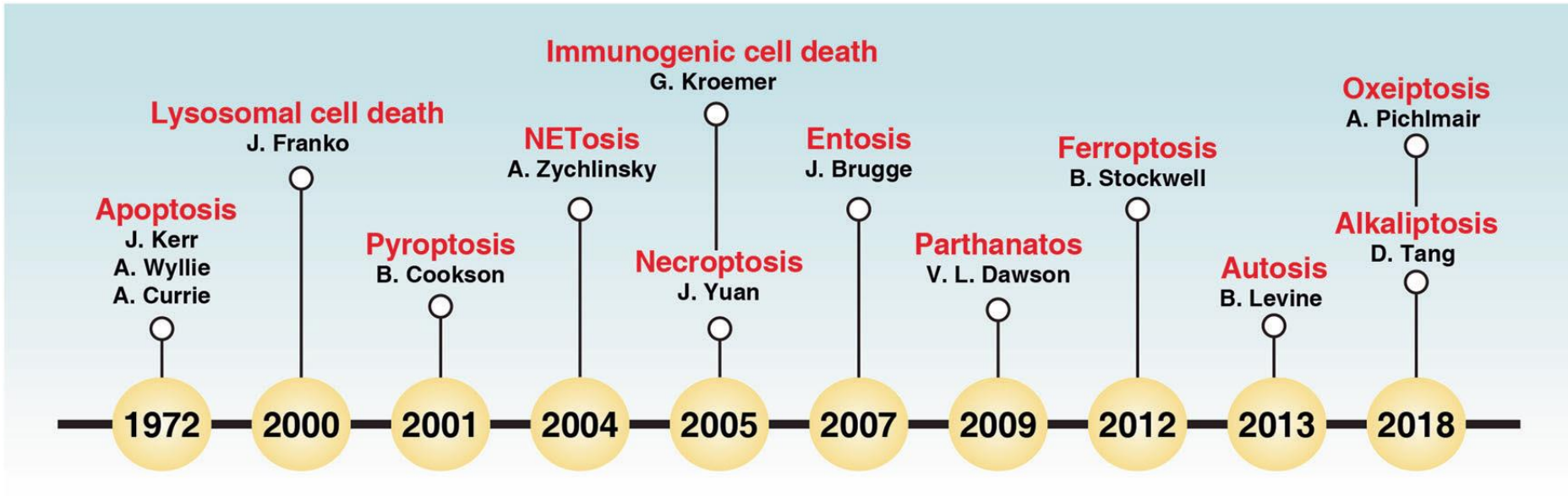


Morte Celular

- ✓ Carl Vogt em 1842
- ✓ 1972: Kerr, Wyllie e Currie – apoptose
Kerr et al. Apoptosis: a basic phenomenon with wide-ranging implications in tissue kinetics. Br. J. Cancer 26: 239-257, 1972.
- ✓ apoptose = *falling off* (folhas caindo de uma árvore)



Diferentes modos de morrer



2005 - Nomenclature Committee on Cell Death - NCCD

2005

Cell Death and Differentiation (2005) 12, 1463–1467
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www.nature.com/cdd

News and Commentary

Classification of cell death: recommendations of the Nomenclature Committee on Cell Death

G Kroemer^{*,1}, WS El-Deiry², P Golstein³, ME Peter⁴, D Vaux⁵, P Vandenabeele⁶, B Zhivotovsky⁷, MV Blagosklonny⁸, W Malorni⁹, RA Knight¹⁰, M Piacentini¹¹, S Nagata¹² and G Melino^{10,13}

with or without, caspase activation and that 'autophagic cell death' represents a type of cell death with (but not necessarily through) autophagic vacuolization. This article details the 2005 recommendations of NCCD. Over time, molecular definitions are expected to emerge for those forms of cell death that remain descriptive.

2009

Cell Death and Differentiation (2009) 16, 3–11
© 2009 Macmillan Publishers Limited All rights reserved 1350-9047/09 \$32.00
www.nature.com/cdd

Review

Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009

G Kroemer^{*,1,2,3}, L Galluzzi^{1,2,3}, P Vandenabeele^{4,5}, J Abrams⁶, ES Alnemri⁷, EH Baehrecke⁸, MV Blagosklonny⁹, WS El-Deiry¹⁰, P Golstein^{11,12,13}, DR Green¹⁴, M Hengartner¹⁵, RA Knight¹⁶, S Kumar¹⁷, SA Lipton^{18,19,20}, W Malorni²¹, G Nuñez²², ME Peter²³, J Tschopp²⁴, J Yuan²⁵, M Piacentini^{26,27}, B Zhivotovsky²⁸ and G Melino^{29,30}

2012

Cell Death and Differentiation (2012) 19, 107–120
© 2012 Macmillan Publishers Limited All rights reserved 1350-9047/12
www.nature.com/cdd

Review

Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012

L Galluzzi^{1,2,3}, I Vitale^{1,2,3}, JM Abrams⁴, ES Alnemri⁵, EH Baehrecke⁶, MV Blagosklonny⁷, TM Dawson⁸, VL Dawson⁸, WS El-Deiry⁹, S Fulda¹⁰, E Gottlieb¹¹, DR Green¹², MO Hengartner¹³, O Kepp^{1,2,3}, RA Knight¹⁴, S Kumar^{15,16}, SA Lipton^{17,18,19,20}, X Lu²¹, F Madeo²², W Malorni^{23,24}, P Mehlen^{25,26,27,28}, G Nuñez²⁹, ME Peter³⁰, M Piacentini^{31,32}, DC Rubinsztein³³, Y Shi³⁴, H-U Simon³⁵, P Vandenabeele^{36,37}, E White³⁸, J Yuan³⁹, B Zhivotovsky⁴⁰, G Melino^{41,42} and G Kroemer^{*,1,43,44,45,46}



Review

2015

Essential *versus* accessory aspects of cell death: recommendations of the NCCD 2015

L Galluzzi^{1,2,3,126}, JM Bravo-San Pedro^{1,2,4}, I Vitale⁵, SA Aaronson⁶, JM Abrams⁷, D Adam⁸, ES Alnemri⁹, L Altucci¹⁰, D Andrews¹¹, M Annicchiarico-Petruzzelli¹², EH Baehrecke¹³, NG Bazan¹⁴, MJ Bertrand^{15,16}, K Bianchi^{17,18}, MV Blagosklonny¹⁹, K Blomgren²⁰, C Borner²¹, DE Bredesen^{22,23}, C Brenner^{24,25,26}, M Campanella²⁷, E Candi²⁸, F Cecconi^{29,30,31}, FK Chan³², NS Chandel³³, EH Cheng³⁴, JE Chipuk⁵, JA Cidlowski³⁵, A Ciechanover³⁶, TM Dawson^{37,38}, VL Dawson^{37,38}, V De Laurenzi³⁹, R De Maria⁵, K-M Debatin⁴⁰, N Di Daniele⁴¹, VM Dixit⁴², BD Dynlacht⁴³, WS El-Deiry⁴⁴, GM Fimia^{45,46}, RA Flavell⁴⁷, S Fulda⁴⁸, C Garrido^{49,50}, M-L Gougeon⁵¹, DR Green⁵², H Gronemeyer⁵³, G Hajnoczky⁵⁴, JM Hardwick⁵⁵, MO Hengartner⁵⁶, H Ichijo⁵⁷, B Joseph⁵⁸, PJ Jost⁵⁹, T Kaufmann⁶⁰, O Kepp^{2,4,61}, DJ Klionsky⁶², RA Knight^{63,64}, S Kumar^{65,66}, JJ Lemasters⁶⁷, B Levine^{68,69}, A Linkermann⁷⁰, SA Lipton^{71,72,73,74}, RA Lockshin⁷⁵, C López-Otin⁷⁶, E Lugli⁷⁷, F Madeo⁷⁸, W Malorni^{79,80}, J-C Marine^{81,82}, SJ Martin⁸³, J-C Martinou⁸⁴, JP Medema⁸⁵, P Meier⁸⁶, S Melino⁸⁷, N Mizushima⁸⁸, U Moll⁸⁹, C Muñoz-Pinedo⁹⁰, G Nuñez⁹¹, A Oberst⁹², T Panaretakis⁵⁸, JM Penninger⁹³, ME Peter⁹⁴, M Piacentini^{30,46}, P Pinton⁹⁵, JH Prehn⁹⁶, H Puthalakath⁹⁷, GA Rabinovich⁹⁸, KS Ravichandran⁹⁹, R Rizzuto¹⁰⁰, CM Rodrigues¹⁰¹, DC Rubinsztein¹⁰², T Rudel¹⁰³, Y Shi¹⁰⁴, H-U Simon¹⁰⁵, BR Stockwell^{106,106}, G Szabadkai^{100,107}, SW Tait^{108,109}, HL Tang⁵⁵, N Tavernarakis^{110,111}, Y Tsujimoto¹¹², T Vanden Berghe^{15,16}, P Vandennebeele^{15,16,113}, A Villunger¹¹⁴, EF Wagner¹¹⁵, H Walczak¹¹⁶, E White¹¹⁷, WG Wood^{118,119}, J Yuan¹²⁰, Z Zakeri^{121,122}, B Zhivotovskiy^{123,124}, G Melino^{28,64} and G Kroemer^{1,2,3,4,61,125,126}

Cell Death & Differentiation
<https://doi.org/10.1038/s41418-017-0012-4>

Cell Death & Differentiation

REVIEW

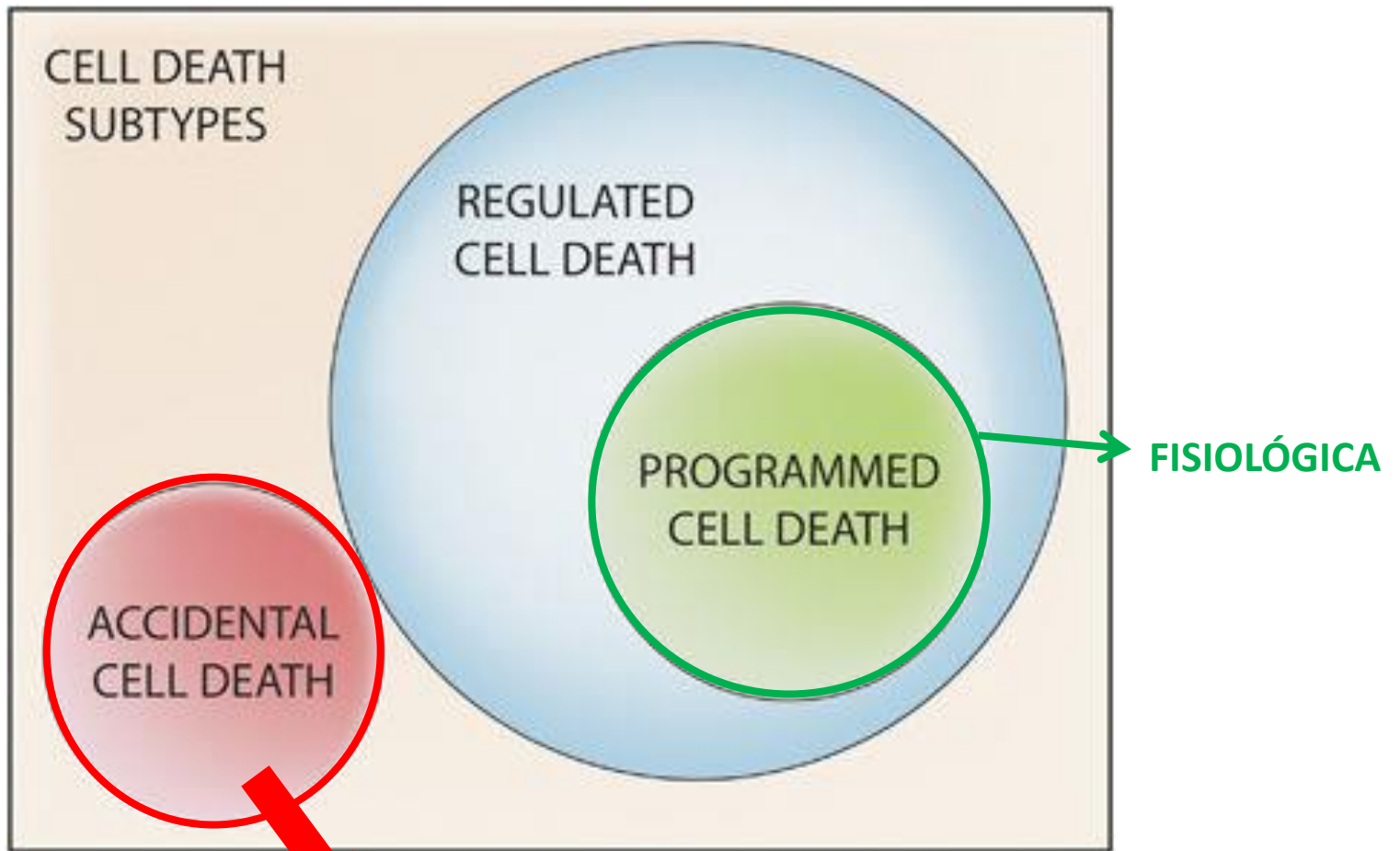


2018

Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

Lorenzo Galluzzi^{1,2,3} · Ilio Vitale^{4,5} et al.

Received: 11 October 2017 / Accepted: 13 October 2017
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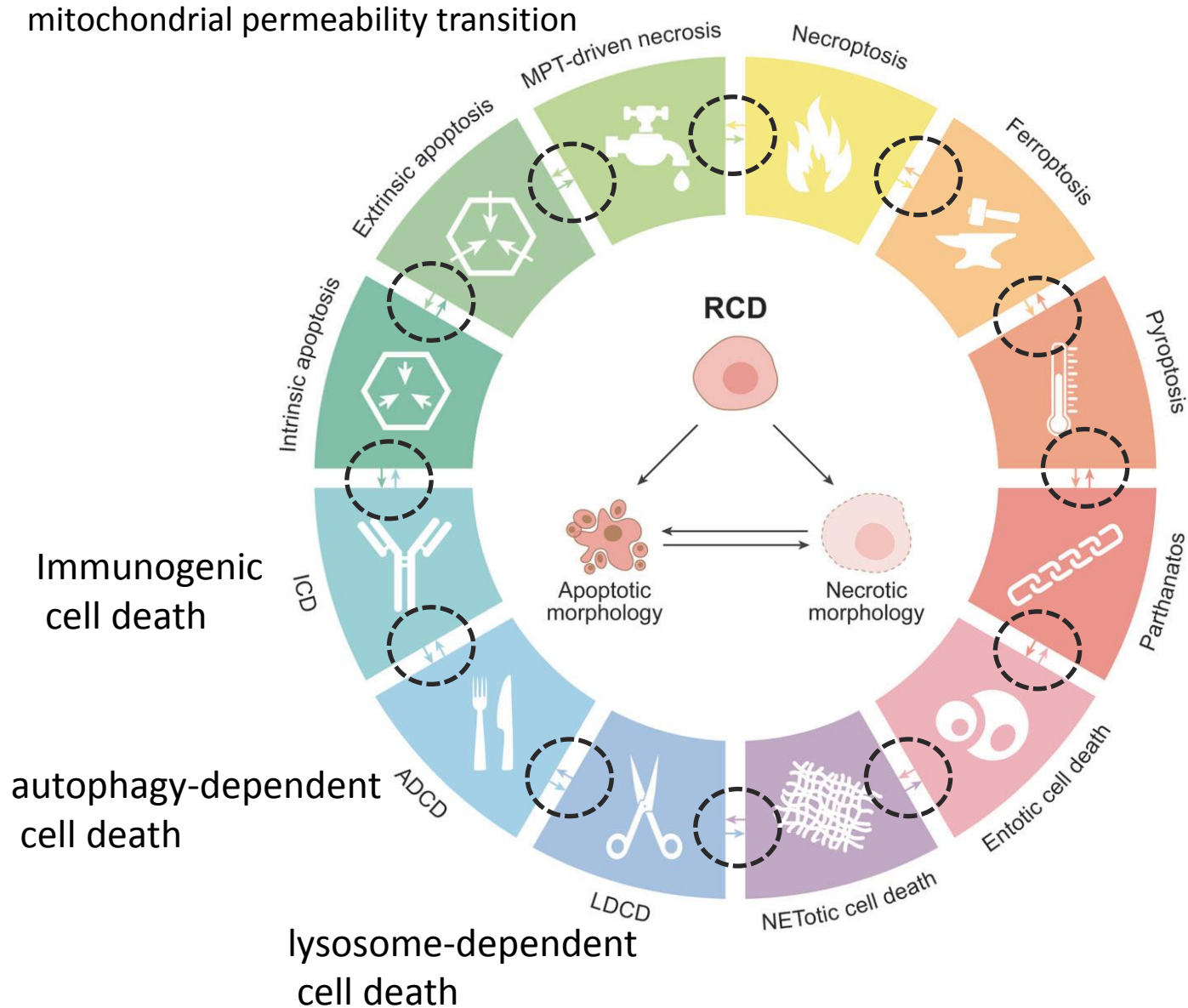


INSULTO EXTREMO { **mecânico, térmico, químico**
Inevitável e irreversível
Não depende de uma 'maquinaria' molecular

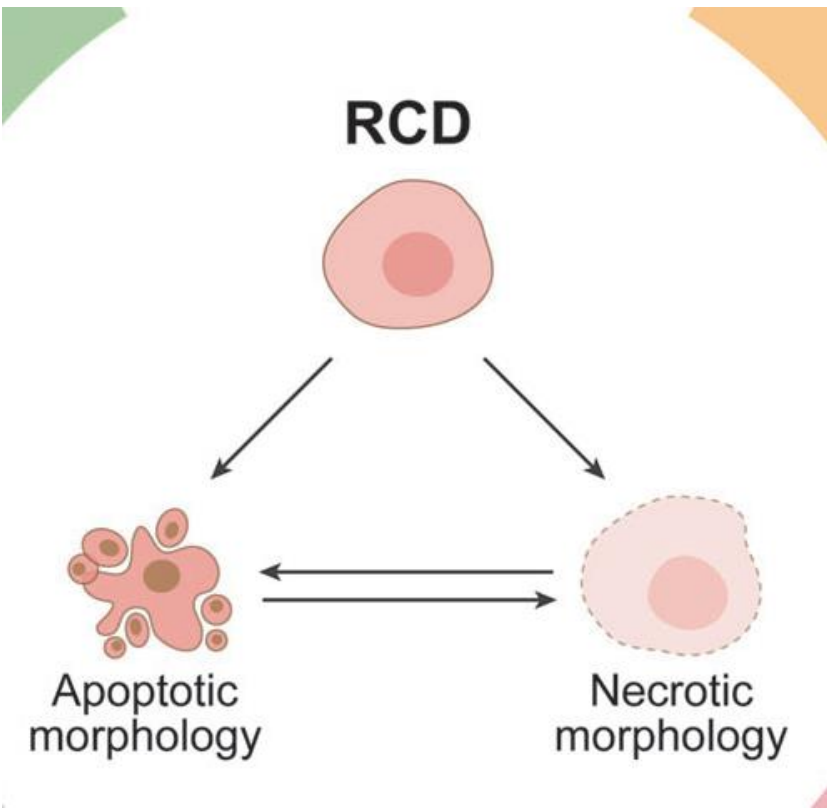
Essential *versus* accessory aspects of cell death: recommendations of the NCCD 2015

<http://www.nature.com/cdd/journal/v22/n1/full/cdd2014137a.html?foxtrotcallback=true>

“Subrotinas” de morte celular, de acordo com o NCCD 2018 :



Morfologia de células mortas por RCD



Morfología de células mortas por RCD

Morfología apoptótica



(A)

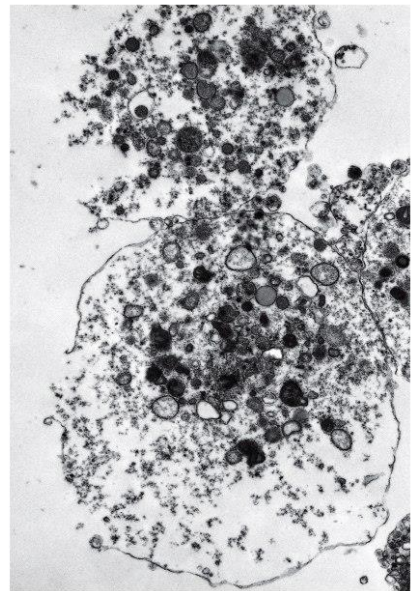
10 μ m



(B)

engulfed dead cell
phagocytic cell

Morfología necrótica



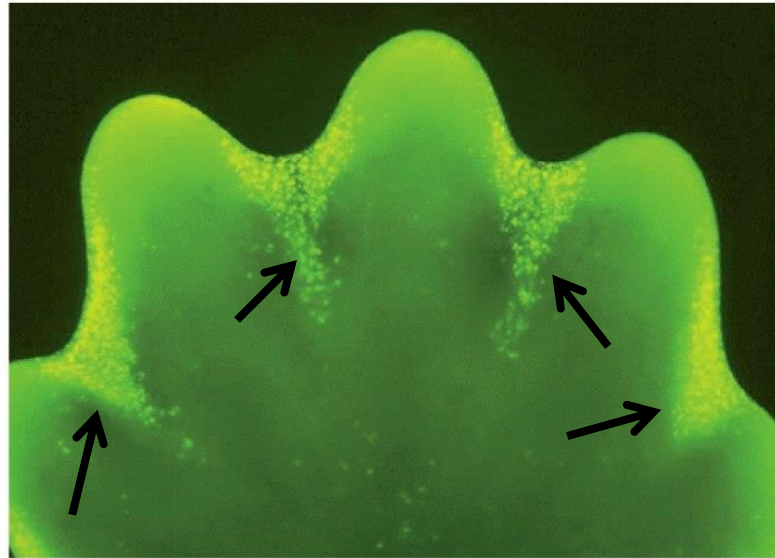
(C)

Figure 18-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

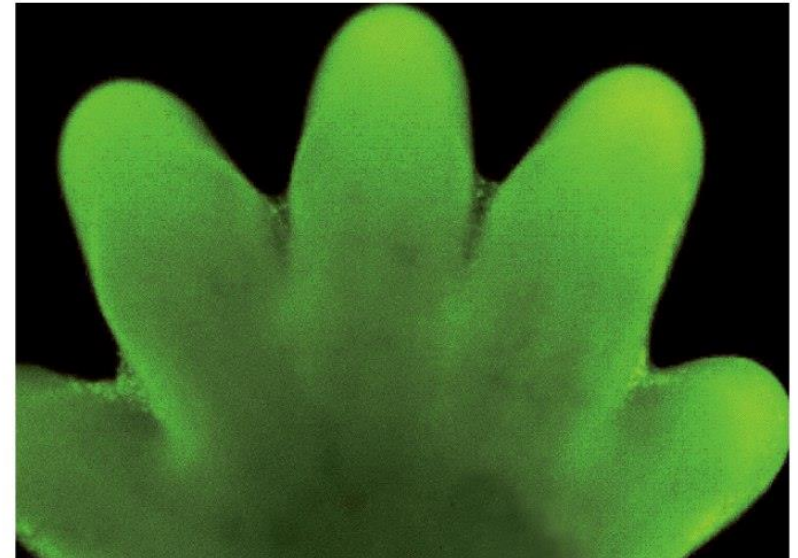
Morte Celular Programada (*PCD*)

- Forma particular de morte celular regulada que ocorre em situações fisiológicas.
- **NÃO** ocorre em decorrência de perturbações da homeostase.

Morte celular no desenvolvimento

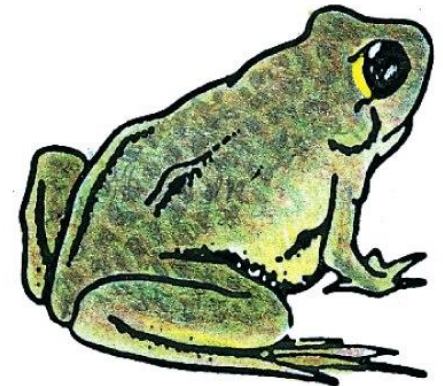
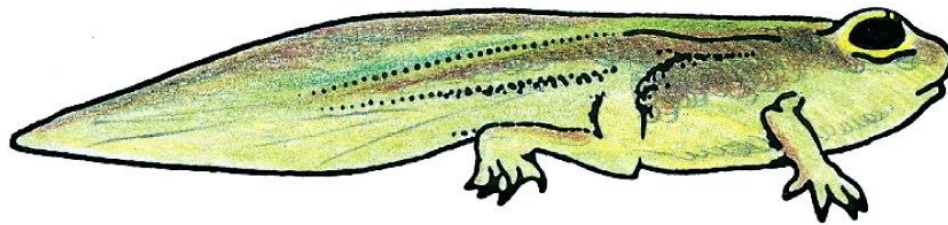


(A)

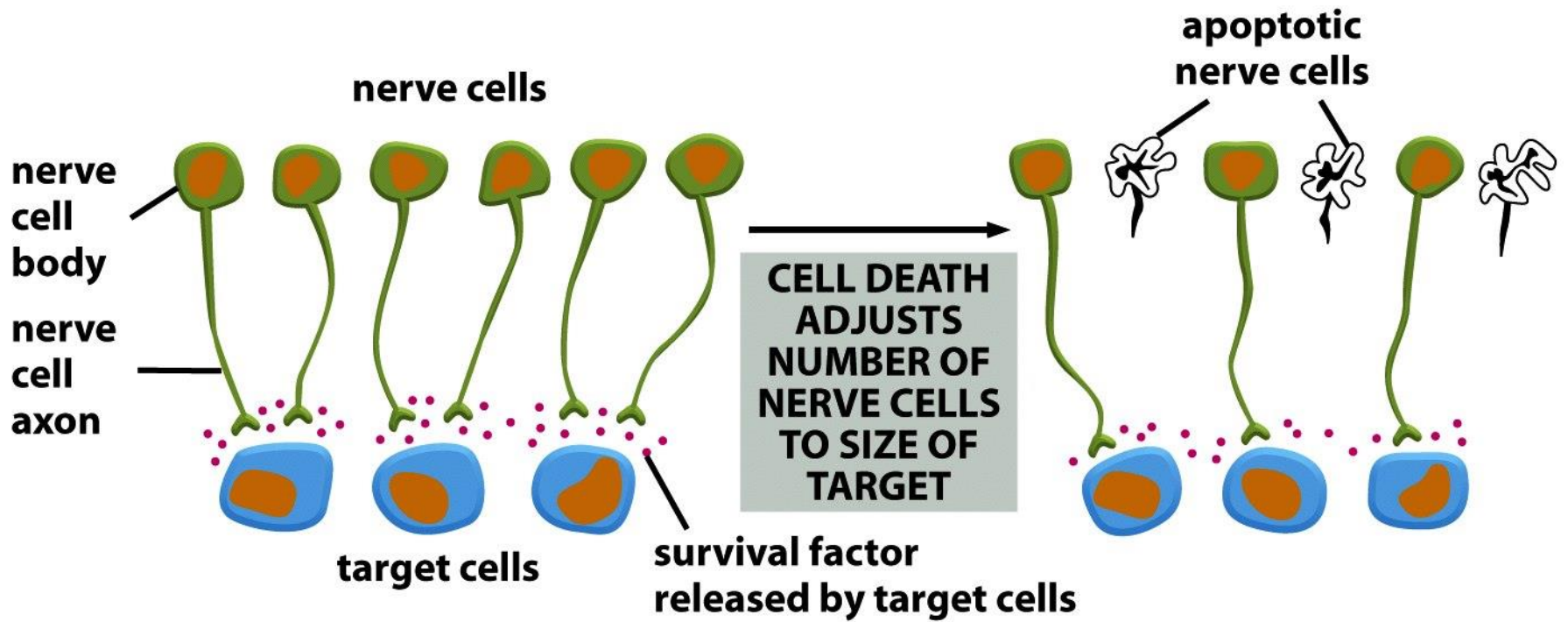


(B)

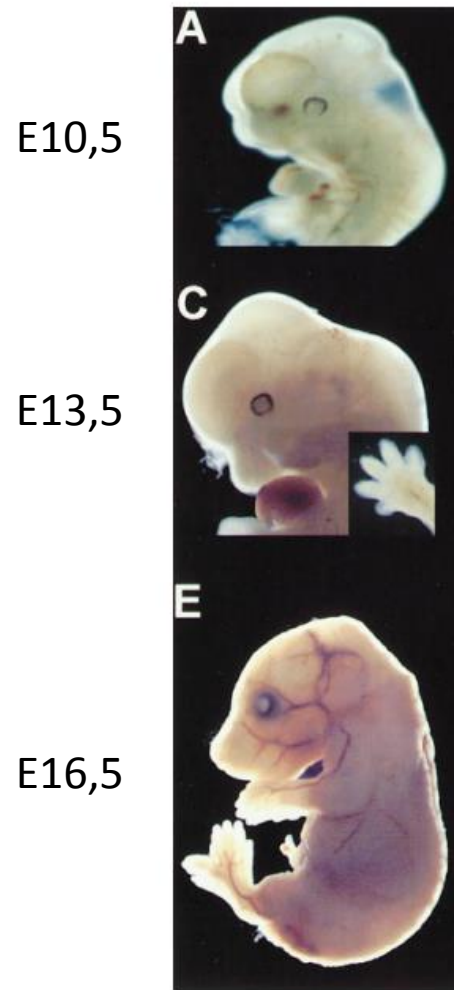
1 mm



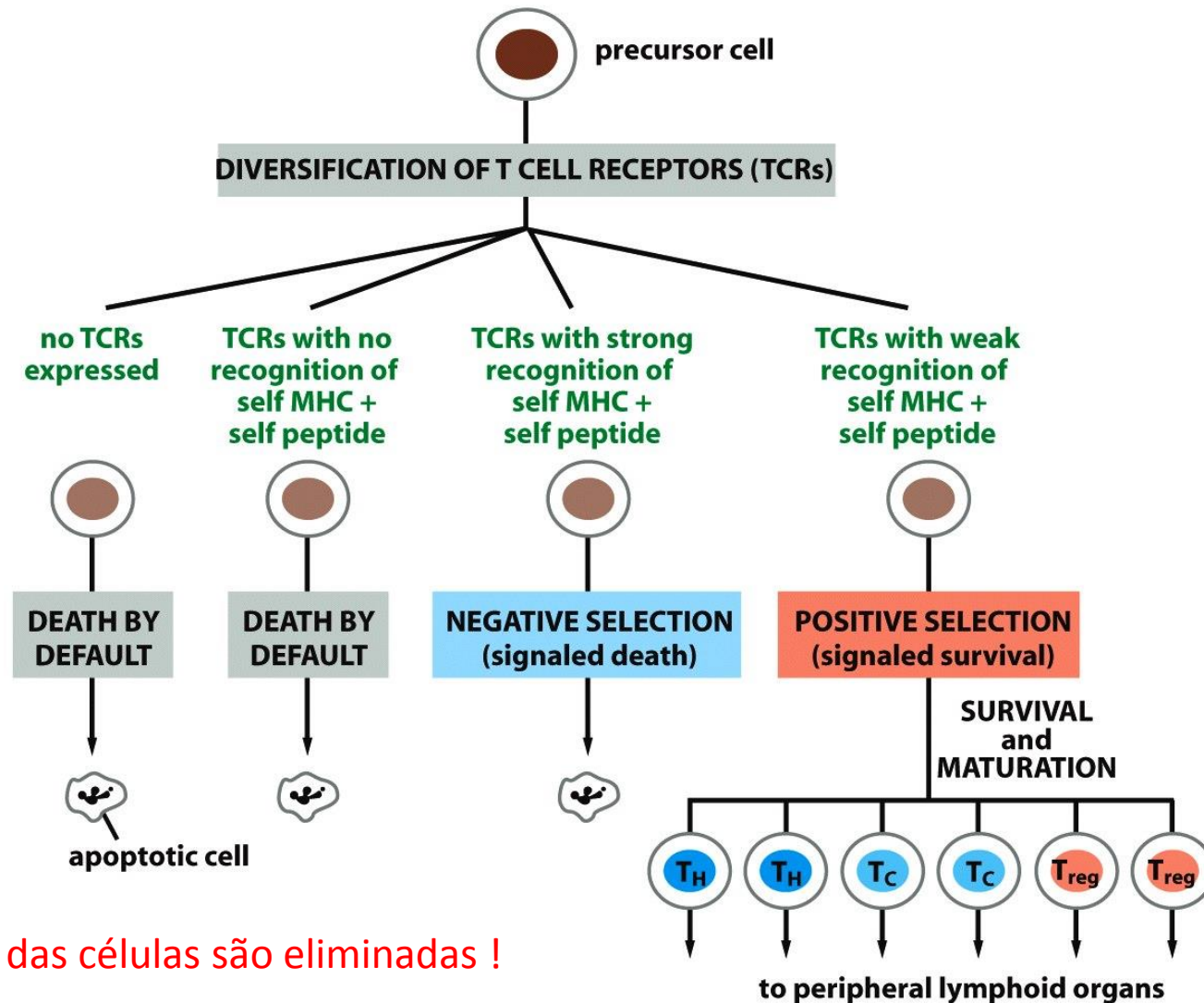
Morte celular no desenvolvimento



camundongos
selvagens

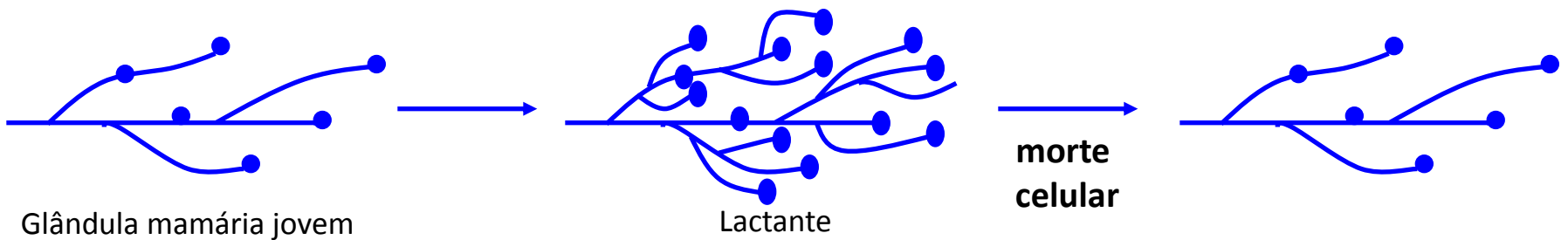
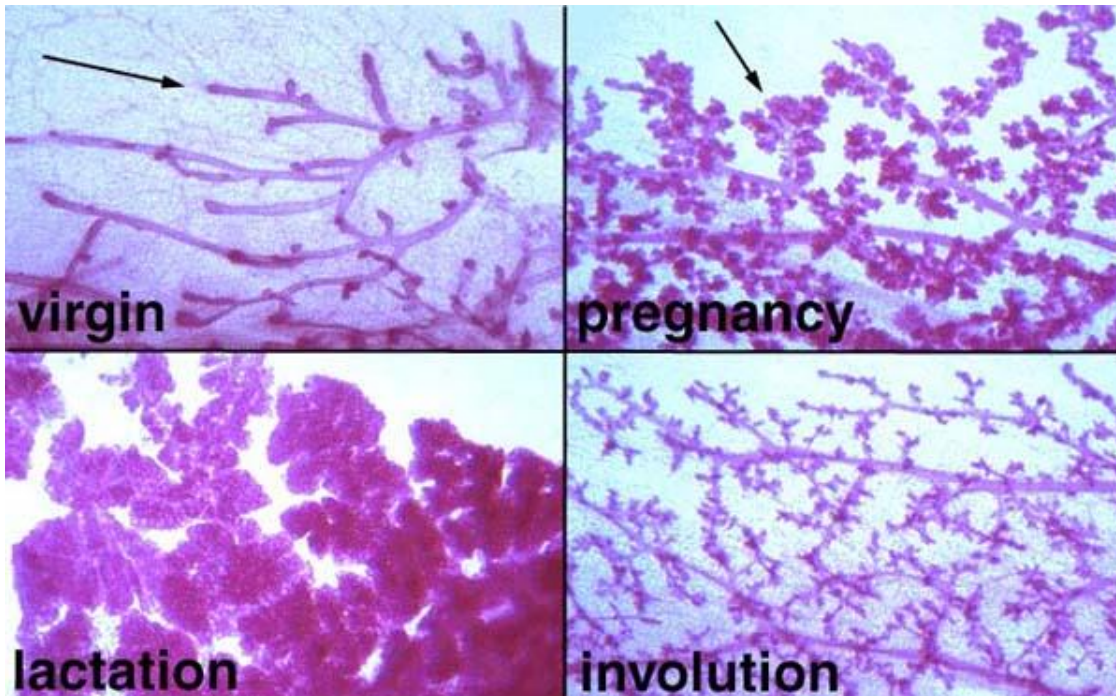


Morte celular no “controle de qualidade” de células do sistema imune (eliminação de células T autoreativas)



95% das células são eliminadas !

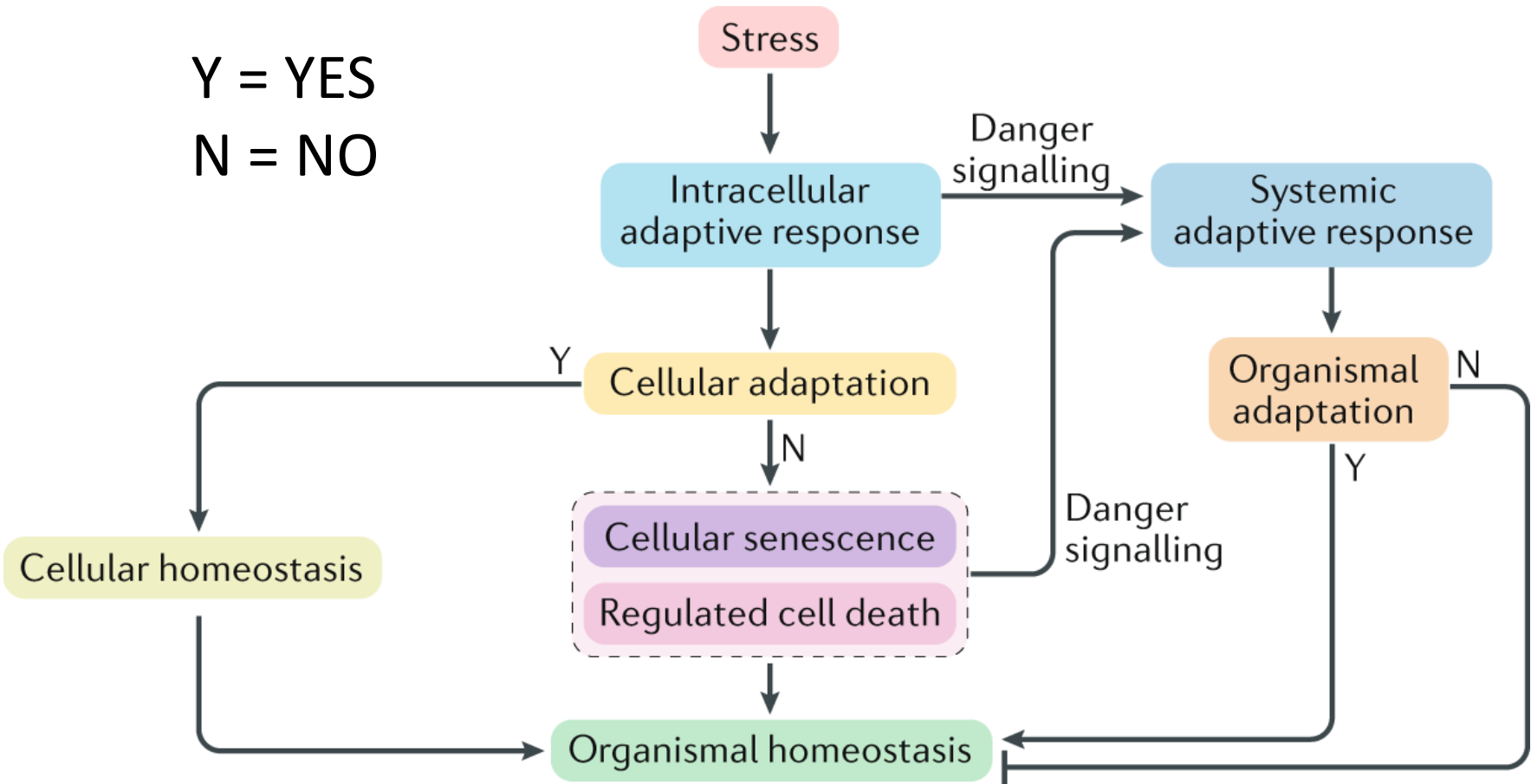
Controle do tamanho dos órgãos e eliminação de células que não são mais necessárias:



Nessa aula

- Apoptose
- Autofagia
- Necroptose

Y = YES
N = NO



apoptose

Células encolhem

Colapso do citoesqueleto

Rompimento do envelope nuclear

Fragmentação da cromatina

Formação dos corpos apoptóticos

Células apoptóticas são fagocitadas (B)

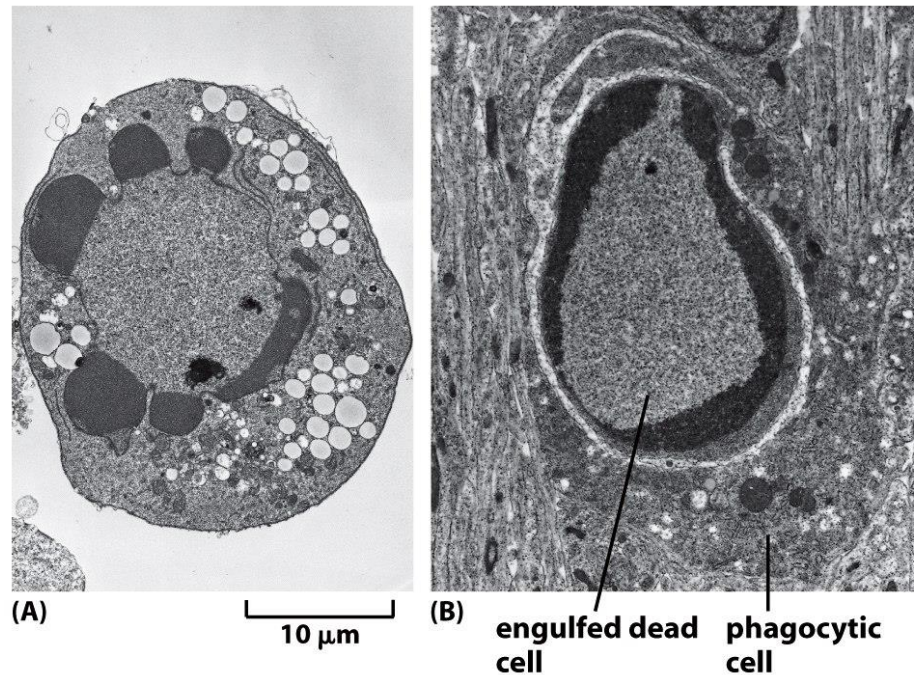


Figure 18-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

linfócito

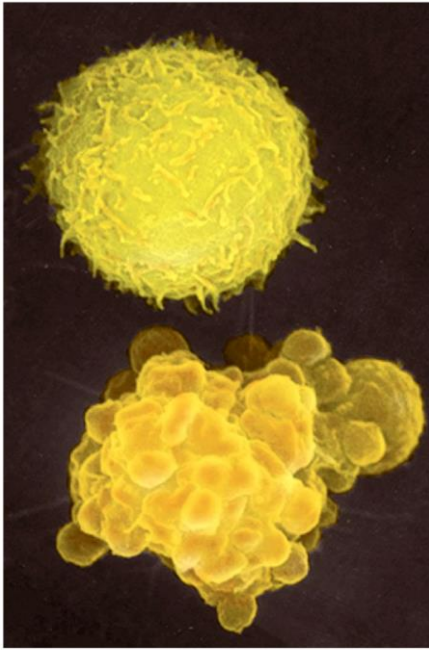


Figure 9-18a The Biology of Cancer (© Garland Science 2007)

Células HeLa

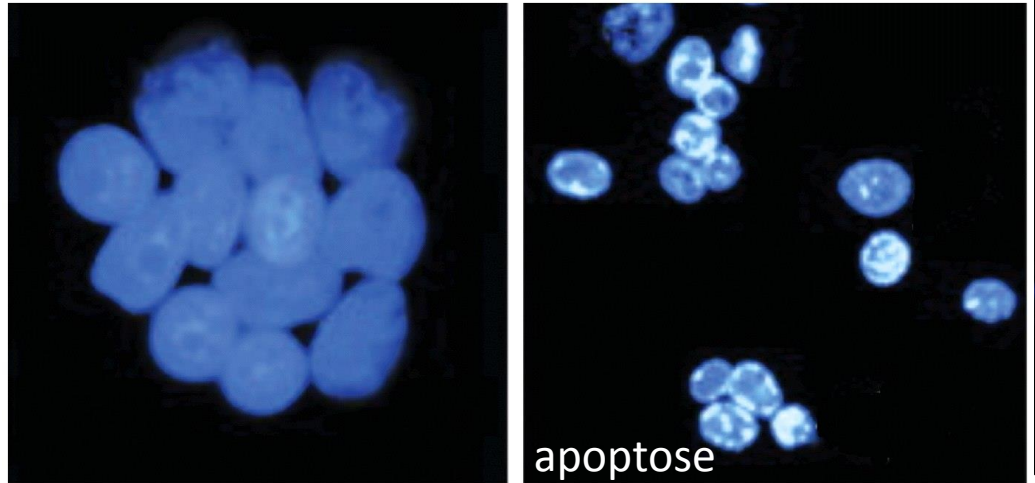


Figure 9-18b The Biology of Cancer (© Garland Science 2007)

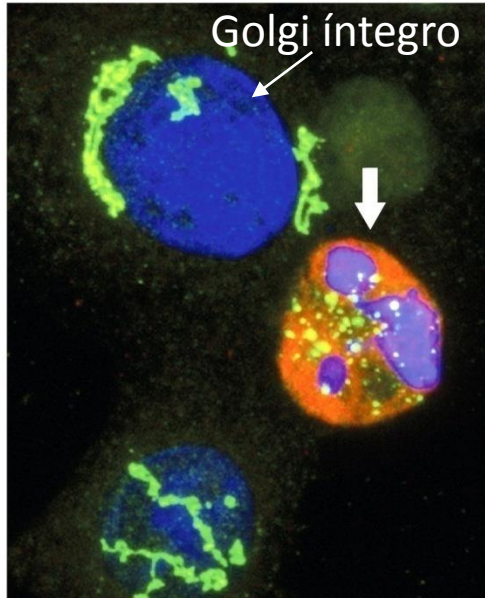


Figure 9-18d The Biology of Cancer (© Garland Science 2007)

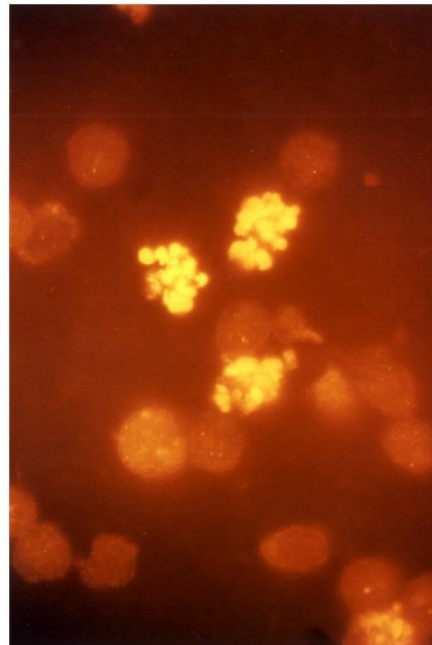


Figure 9-18e The Biology of Cancer (© Garland Science 2007)

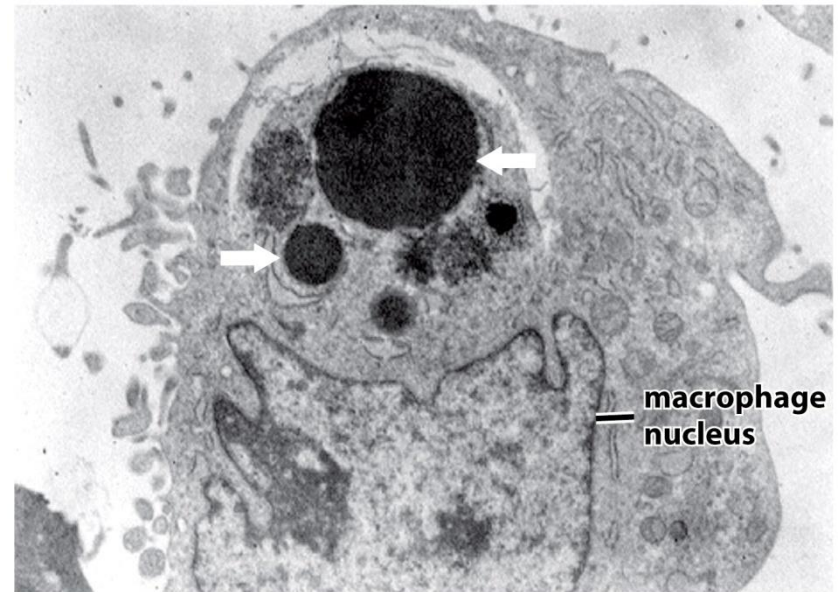
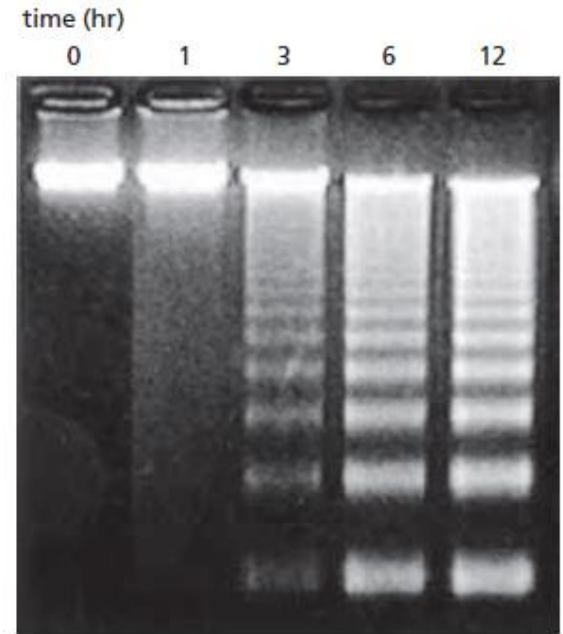
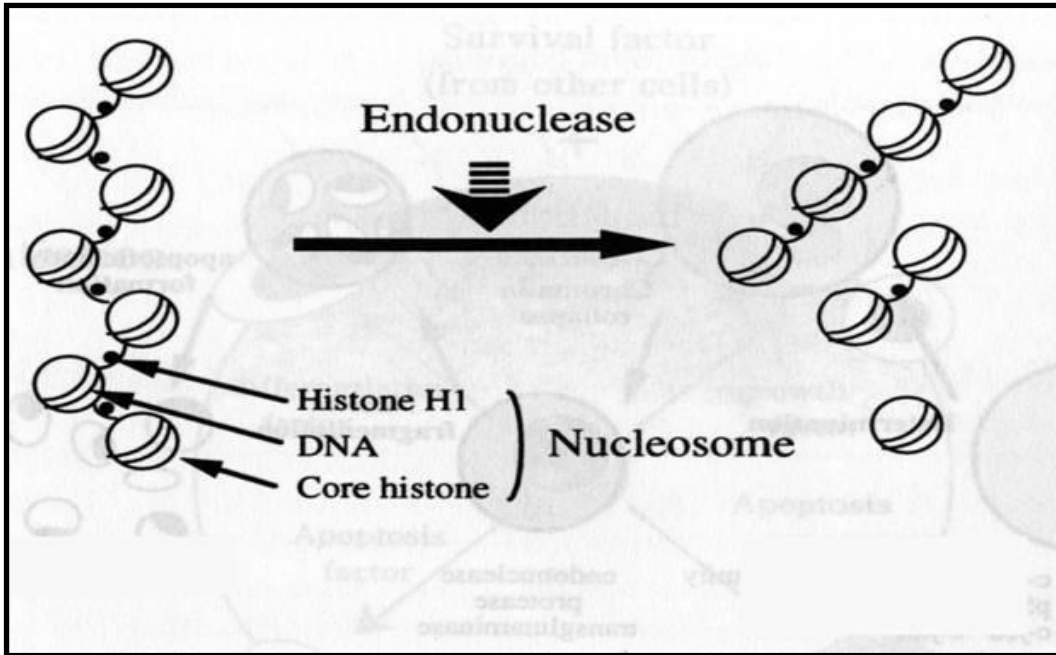


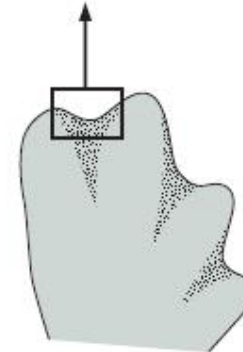
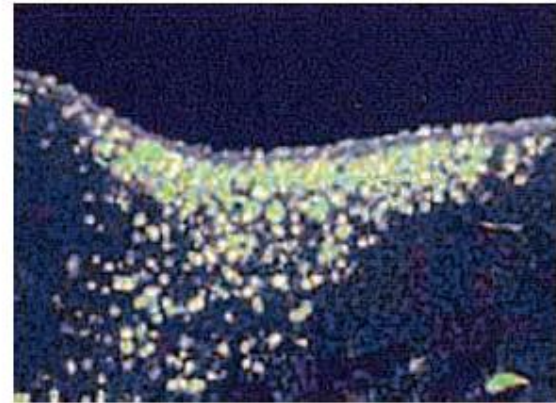
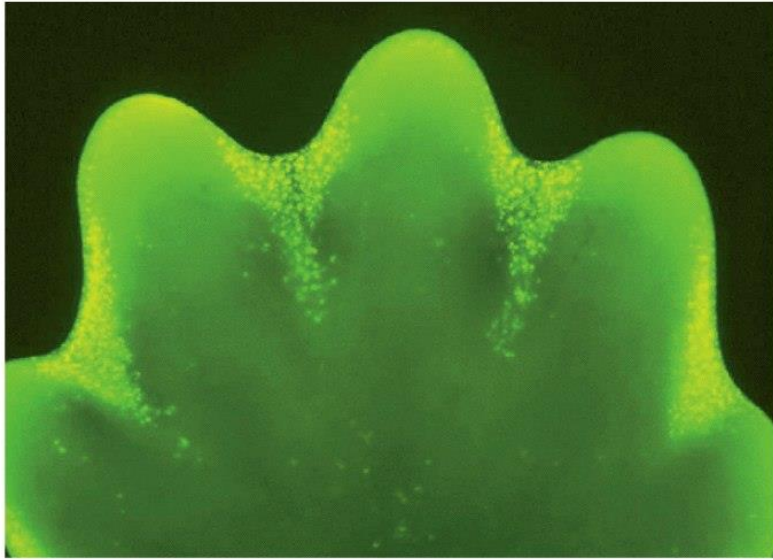
Figure 9-18f The Biology of Cancer (© Garland Science 2007)

Como as células apoptóticas são experimentalmente detectadas?

“escada” de DNA em gel de eletroforese



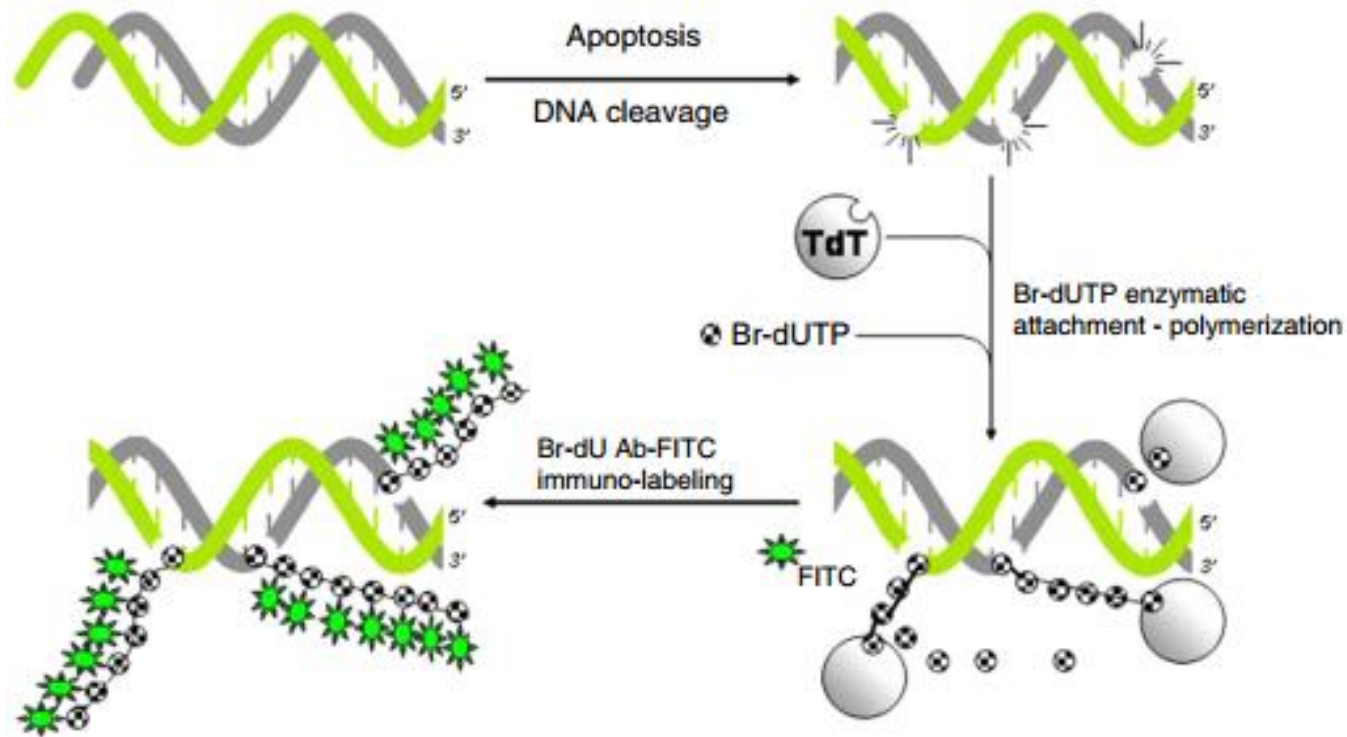
TdT-mediated dUTP nick end labeling (TUNEL)



(c)

TdT-mediated dUTP nick end labeling (TUNEL)

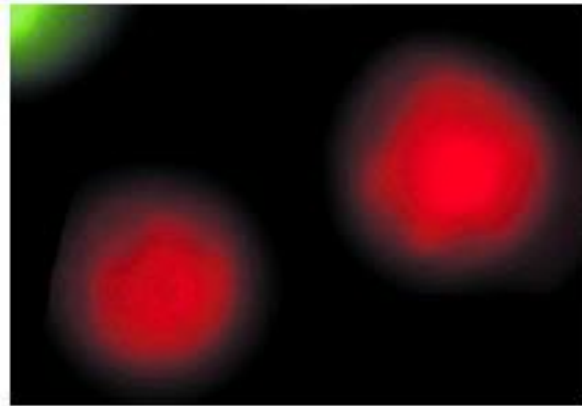
TdT = terminal desoxinucleotidil transferase



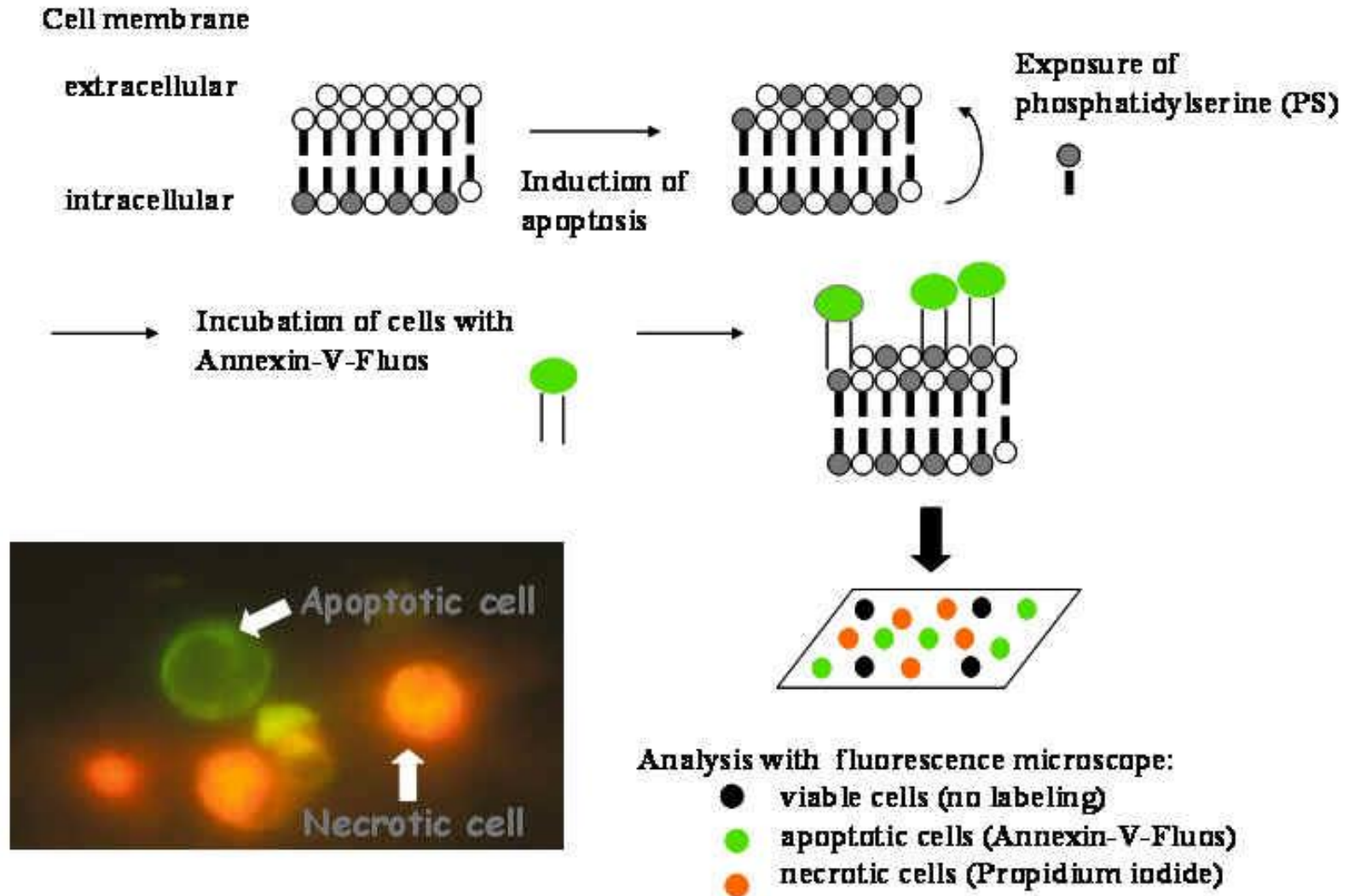
Br-dUTP = 5-Bromo-2'-Deoxyuridine 5'-Triphosphate

Ab-FITC = anticorpo anti-Br-dU conjugado à fluoresceína

Permeabilidade da membrana



Exposição de fosfatidilserina na superfície da célula (detecção precoce da apoptose)



A EXPOSIÇÃO DA PS É CONSEQUÊNCIA DA MORTE CELULAR, NÃO CAUSA

Caspases

(Cysteine-Aspartate-Specific ProteASES)

- Enzimas responsáveis pela proteólise intracelular da apoptose
- Milhares de substratos, a maioria é desconhecido

procaspase activation by cleavage

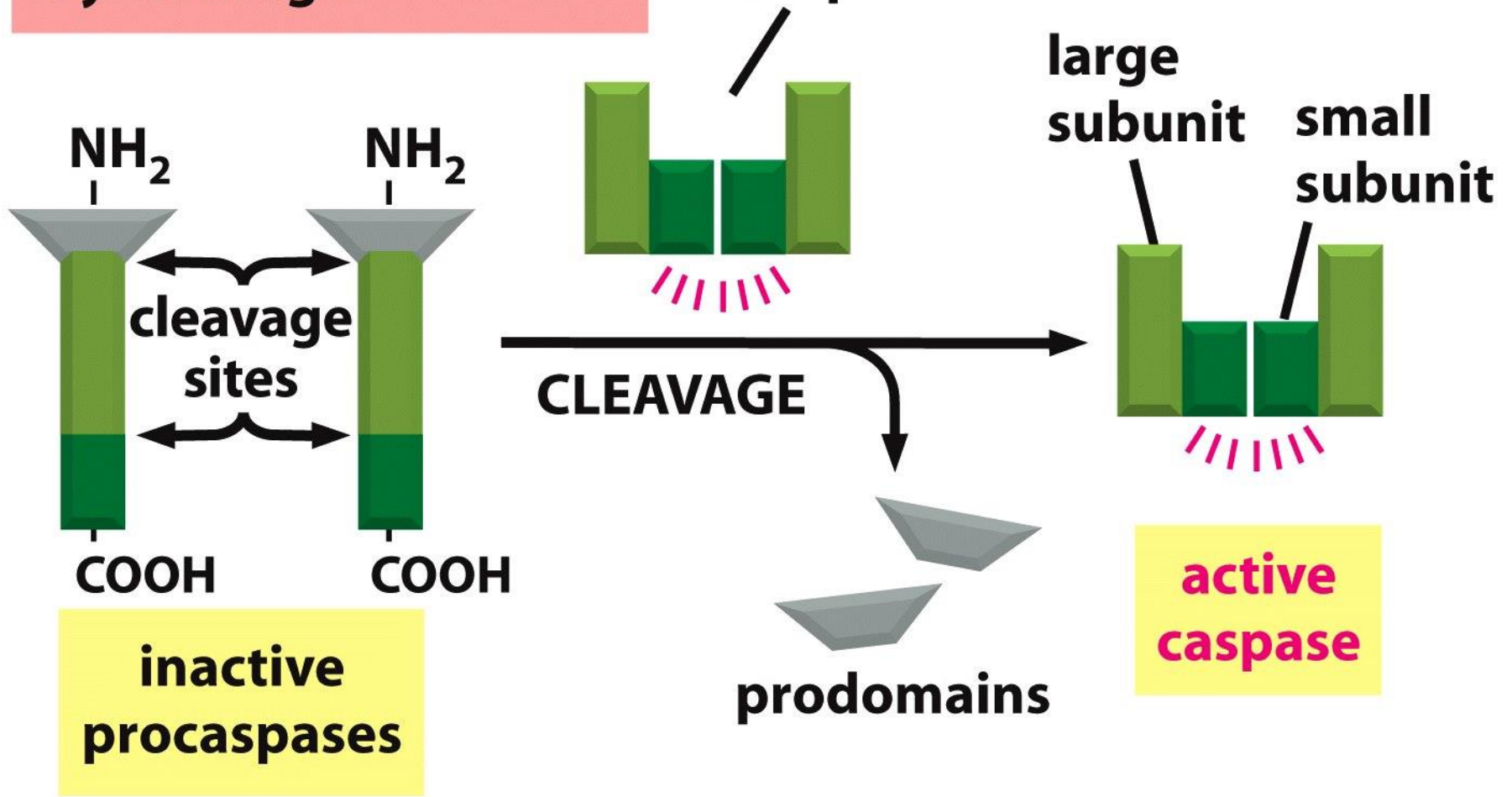
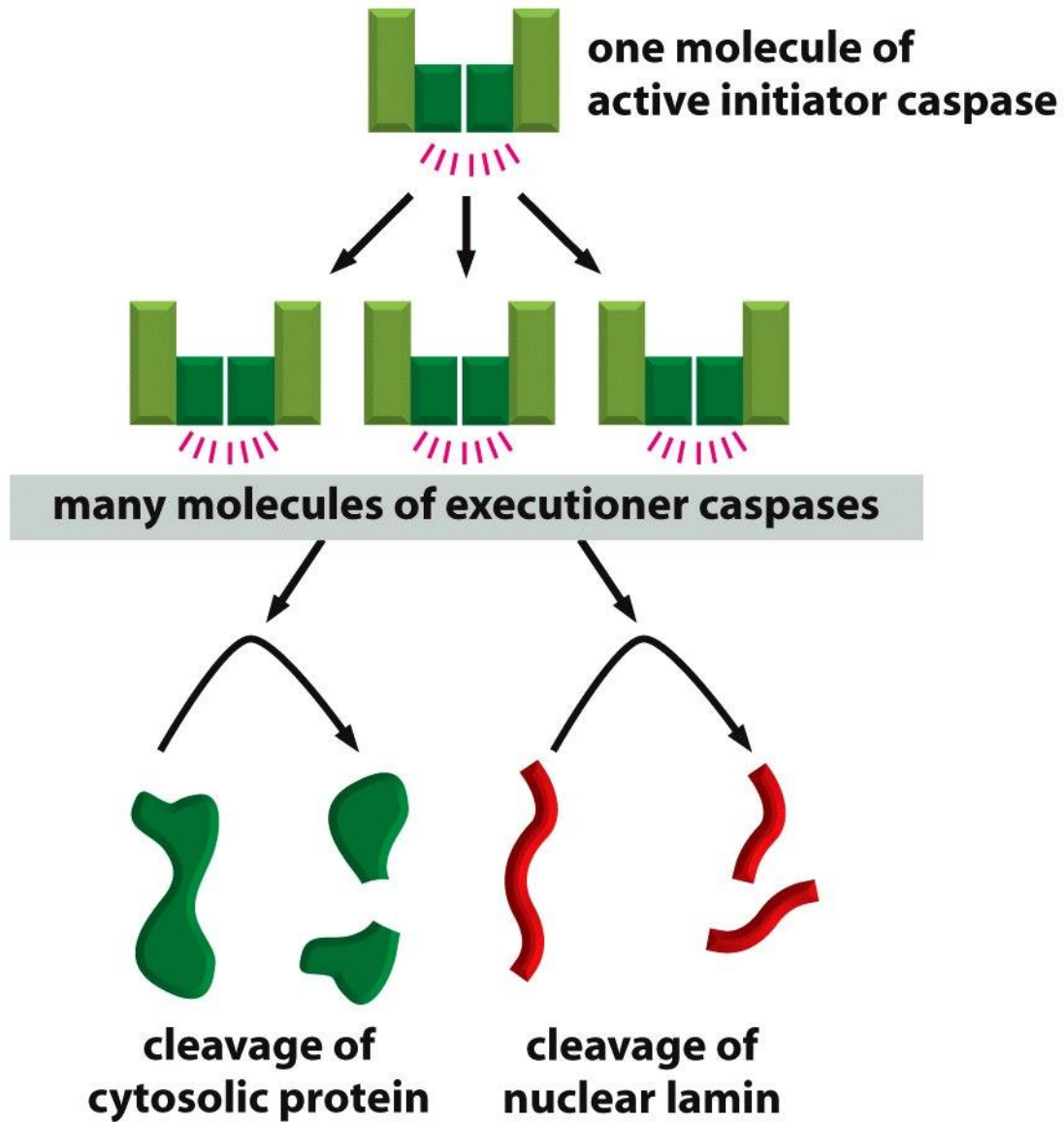


Figure 18-5a Molecular Biology of the Cell 5/e (© Garland Science 2008)

caspase cascade



DOIS TIPOS DE CASPASES:

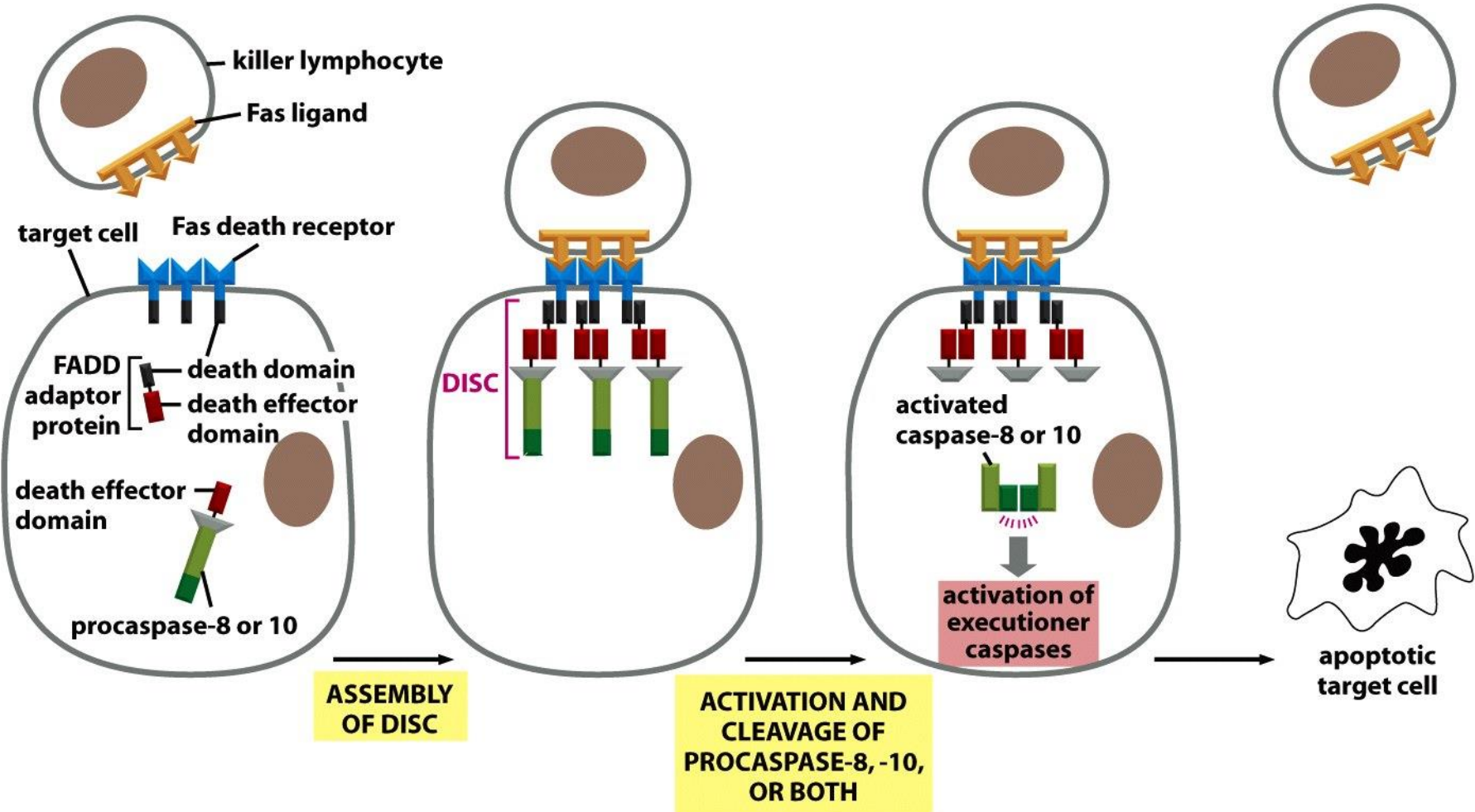
Iniciadoras: caspases 1, 2, 8, 9, 10

Executores: caspases 3, 4, 5, 6, 7, 11 a 17

Há 2 vias de sinalização que ativam as caspases

- Via extrínica
- Via intrínica

Via extrínscica



FADD = Fas-associated death domain

DISC = death-induced signaling complex

Exemplo típico de indução de apoptose pela via extrínica

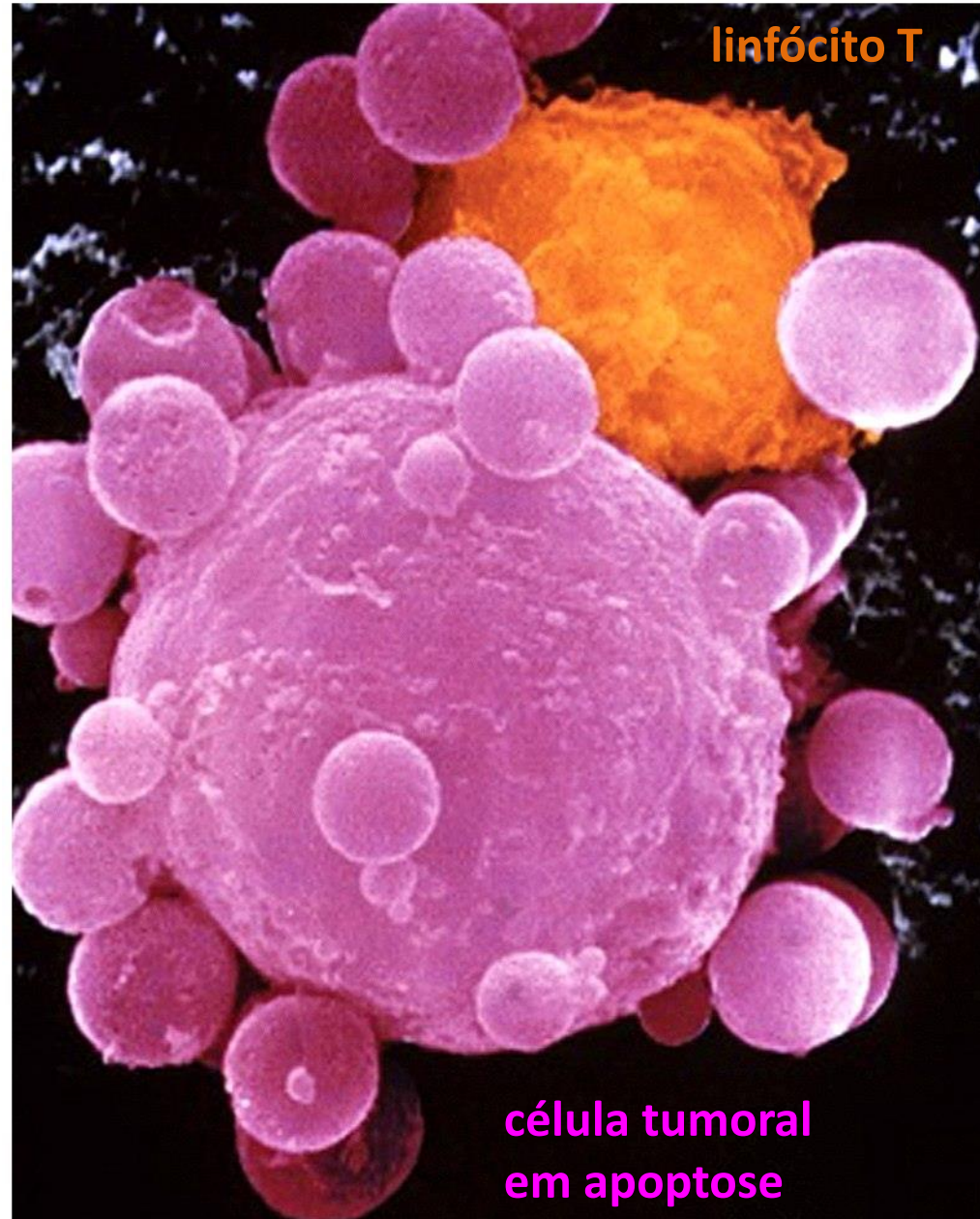
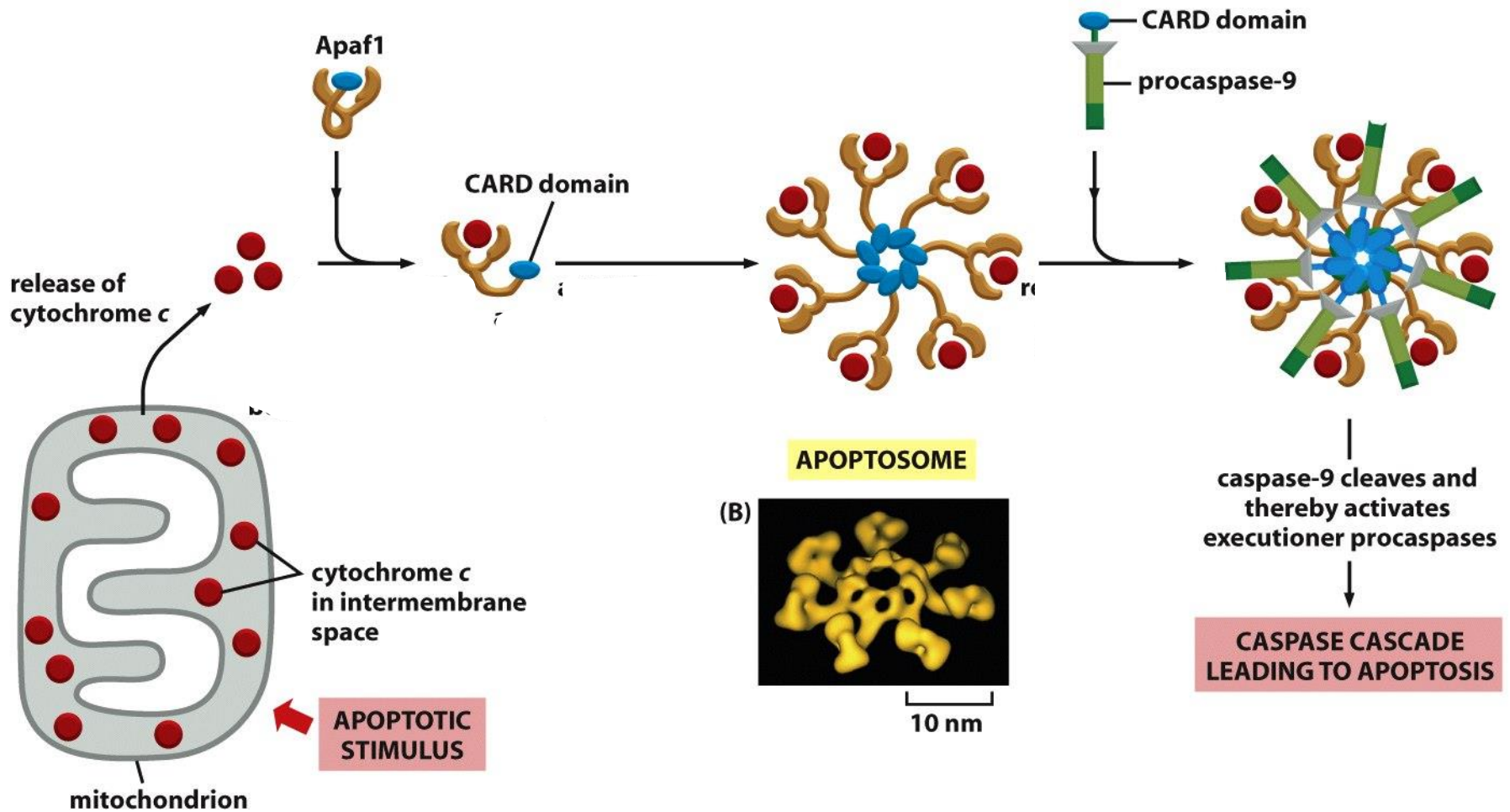


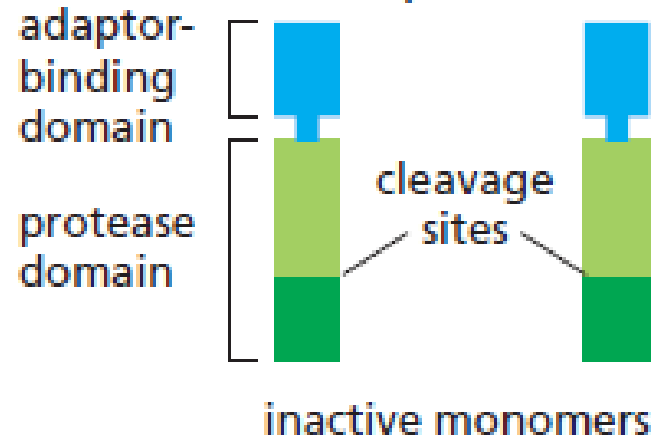
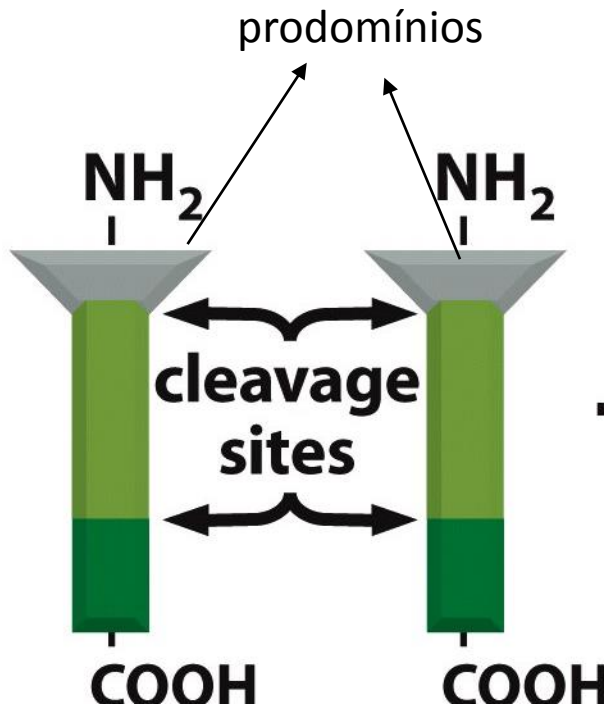
Figure 9-31c The Biology of Cancer (© Garland Science 2007)

Via intrínstica



Apaf1 = *apoptotic protease activating factor-1*
CARD = *caspase recruitment domain*

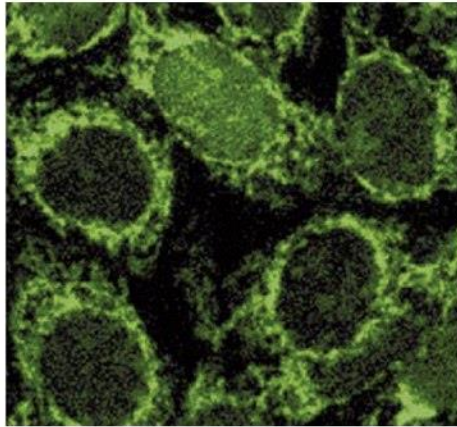
Caspases iniciadoras (recapitulando..)



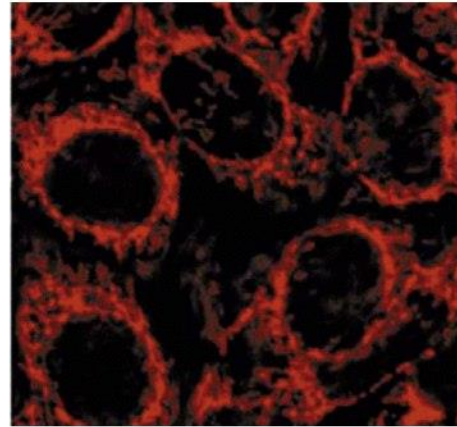
CARD=caspase recruitment domain

(A) CONTROL

cytochrome-c-GFP



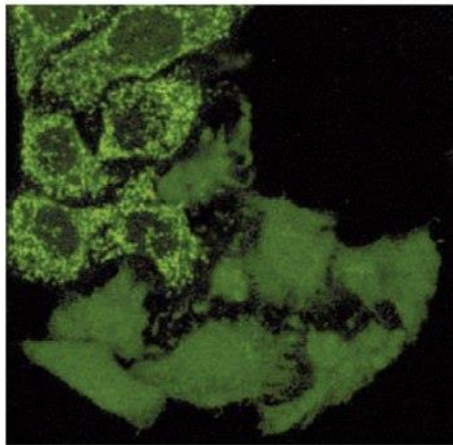
mitochondrial dye



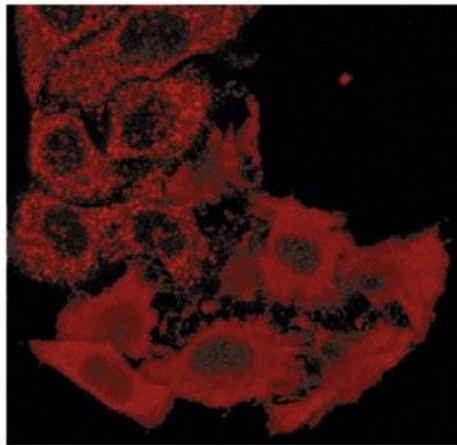
10 μm

(B) UV TREATED

cytochrome-c-GFP



anti-cytochrome c



25 μm



+/-

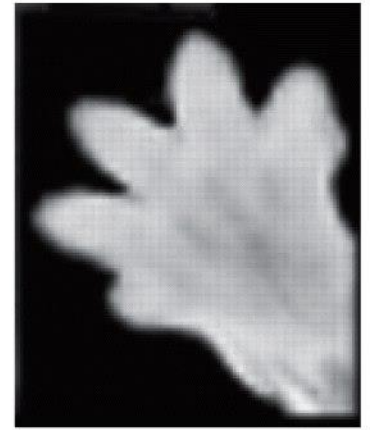


-/-

Apaf1



+/+

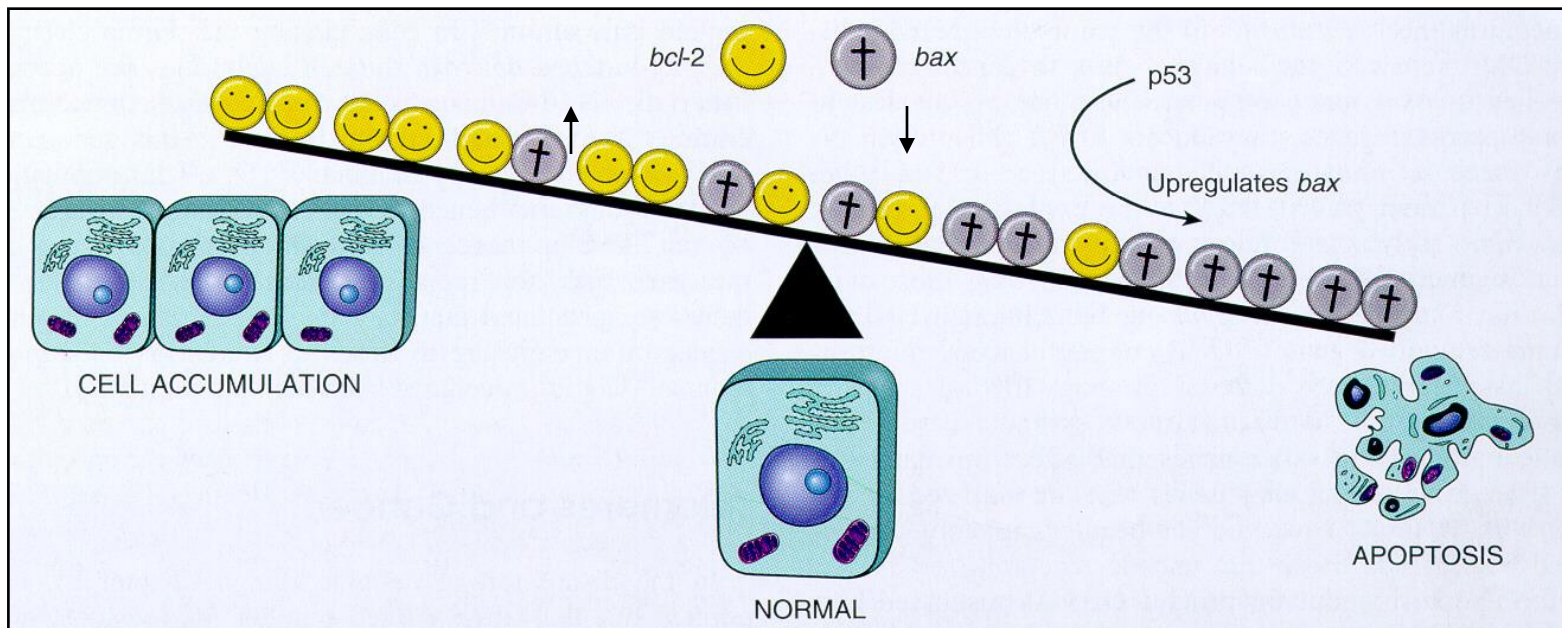


-/-

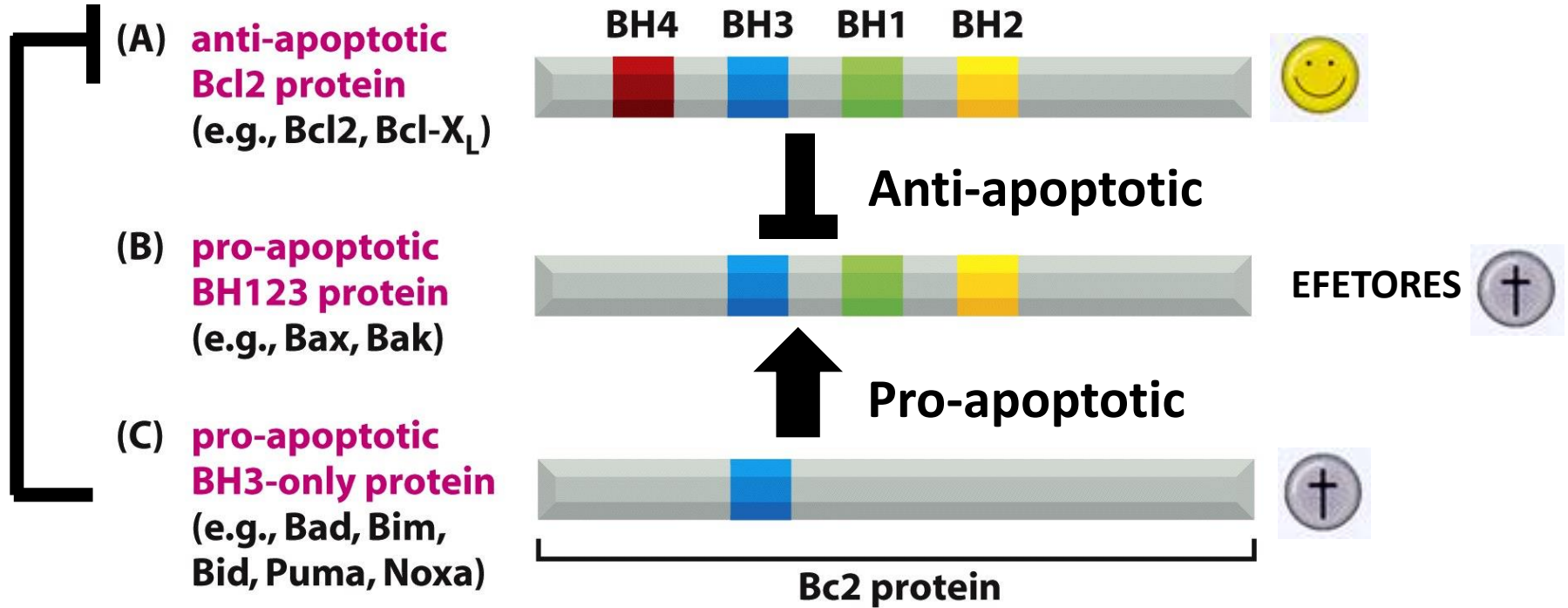
Casp9

A família Bcl-2

- Originalmente detectadas em linfoma folicular de células B (*B-cell lymphoma*)
- controlam a liberação de citocromo C
- anti-apoptóticos – bloqueiam a liberação de cyt C
- pró-apoptóticos – estimulam a liberação de cyt C



Membros da família Bcl2

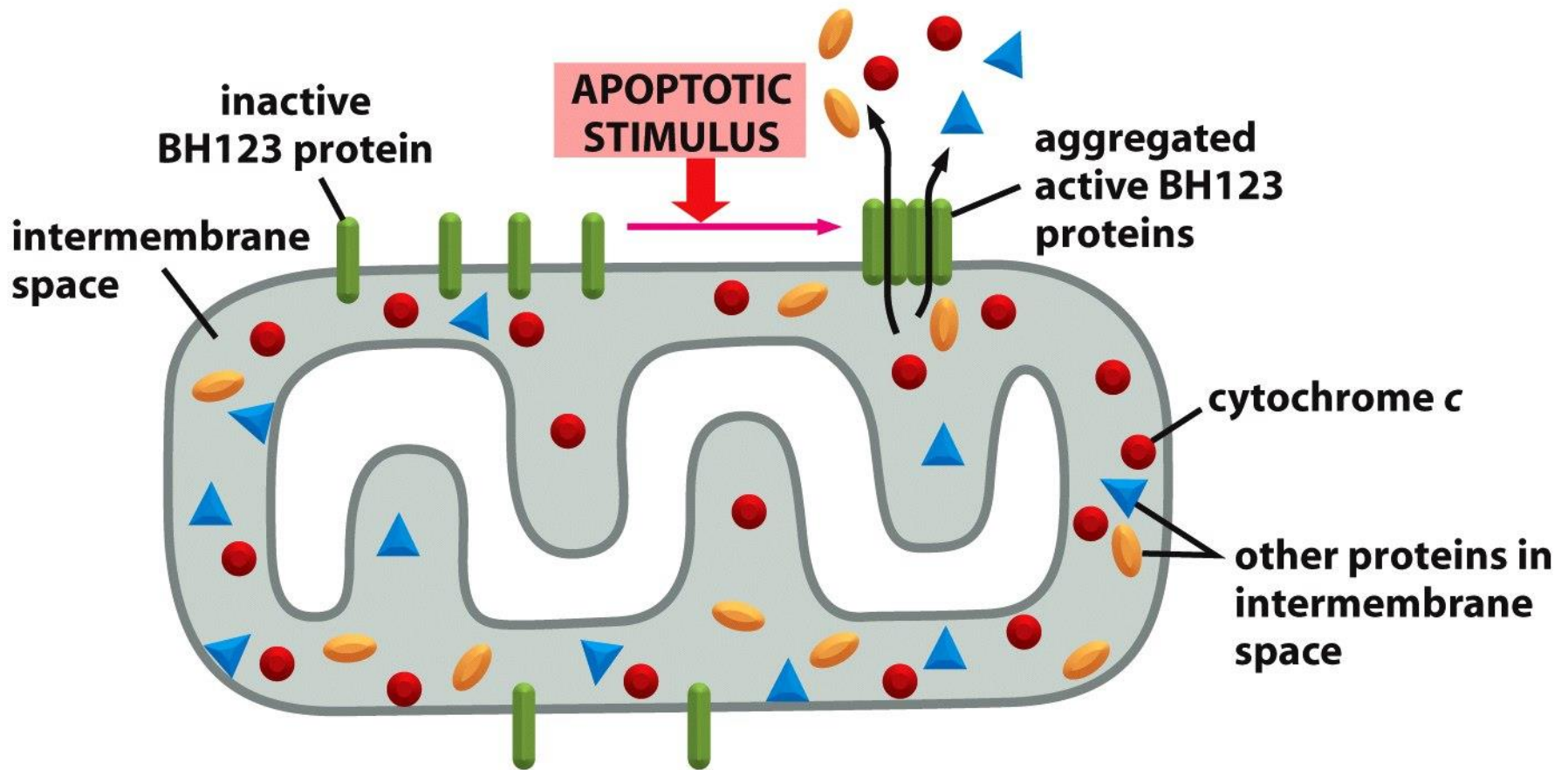


atenção!

anti-apoptotic = pro-survival

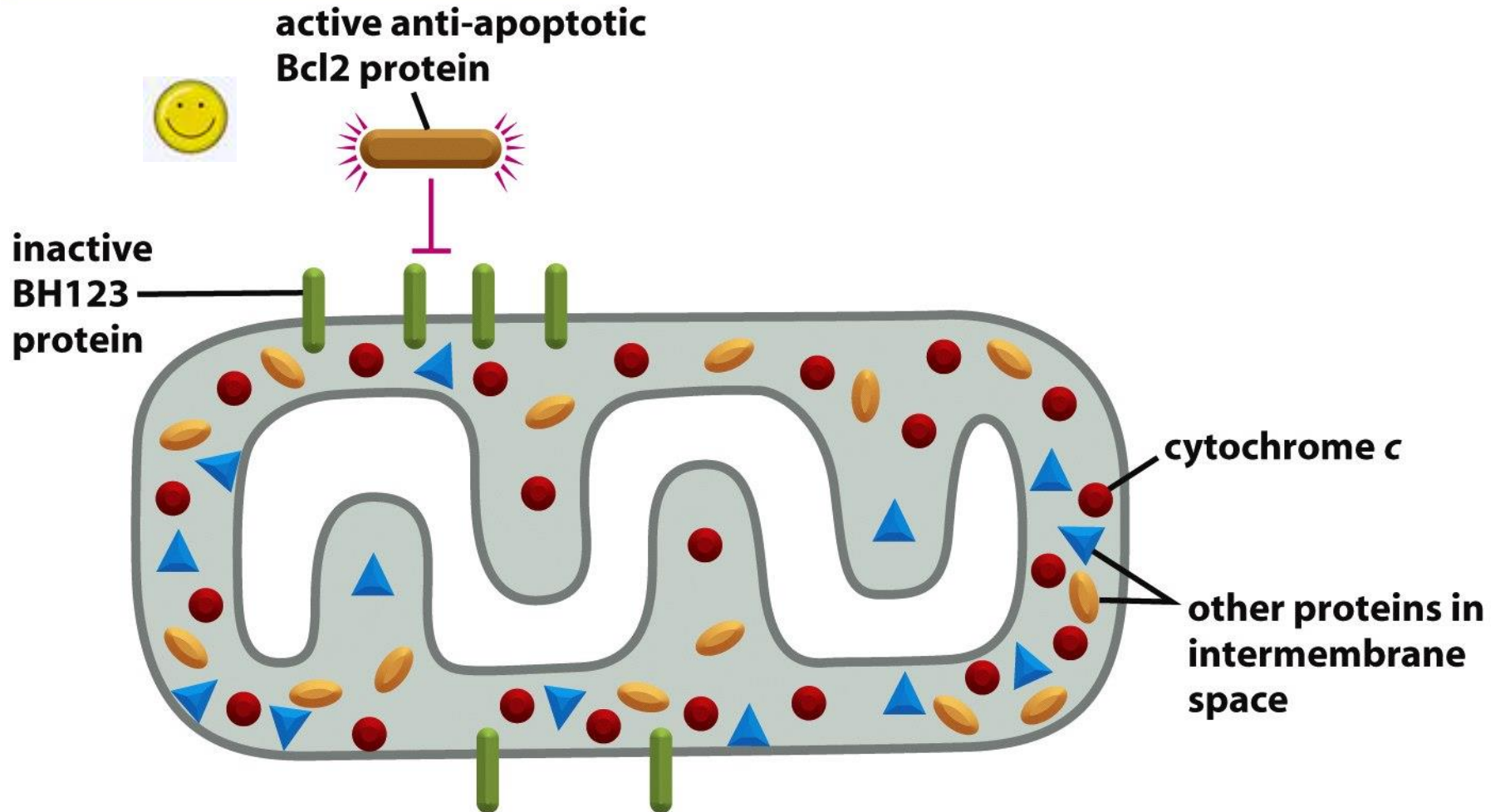
pro-apoptotic = pro-death = anti-survival

Como os pró-apoptóticos BH123 atuam?

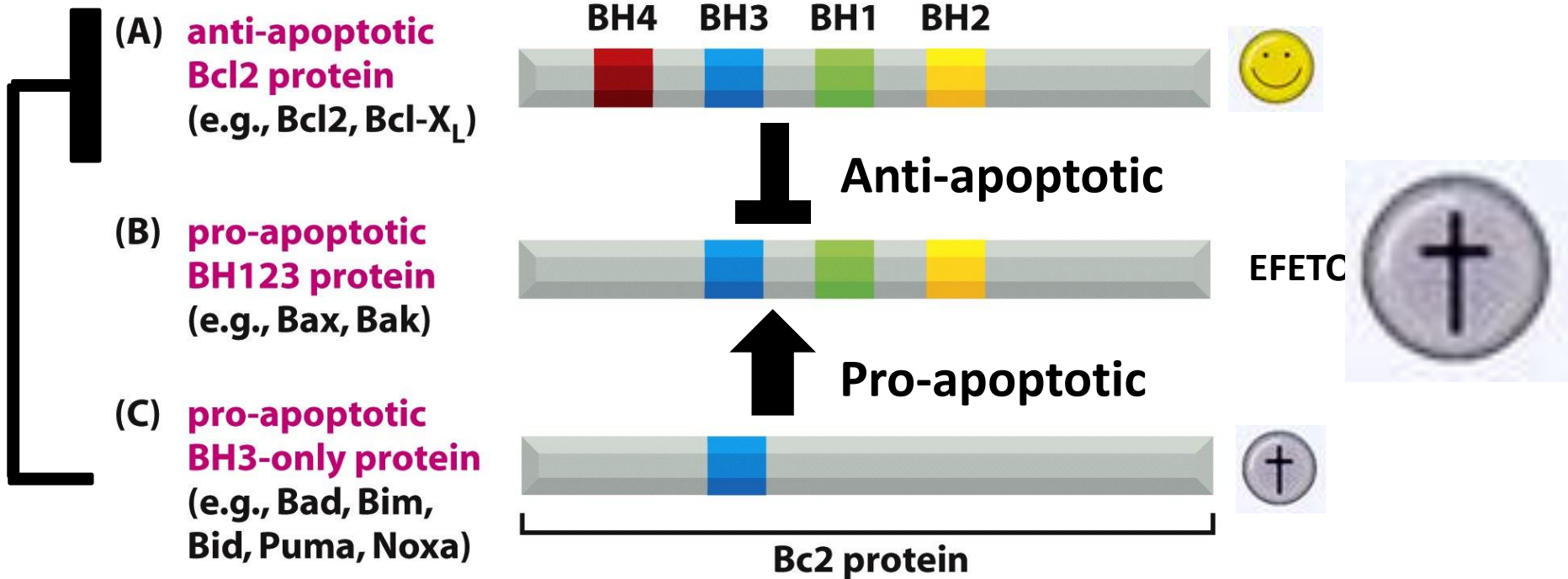


Como os anti-apoptóticos Bcl2 atuam?

INACTIVE INTRINSIC PATHWAY

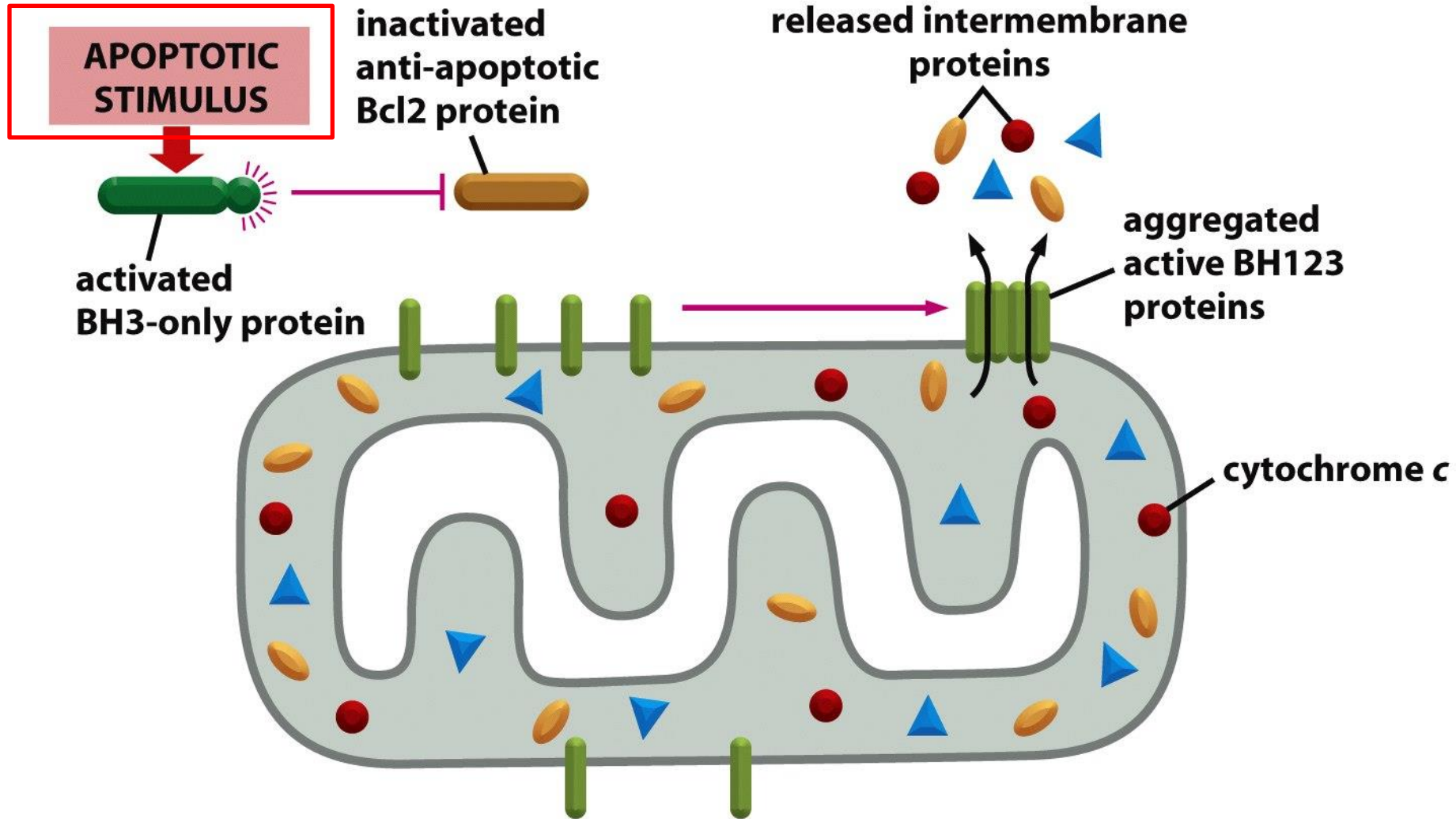


Membros da família Bcl2



Os BH3 RECEBEM OS ESTÍMULOS APOPTÓTICOS

ACTIVATION OF INTRINSIC PATHWAY



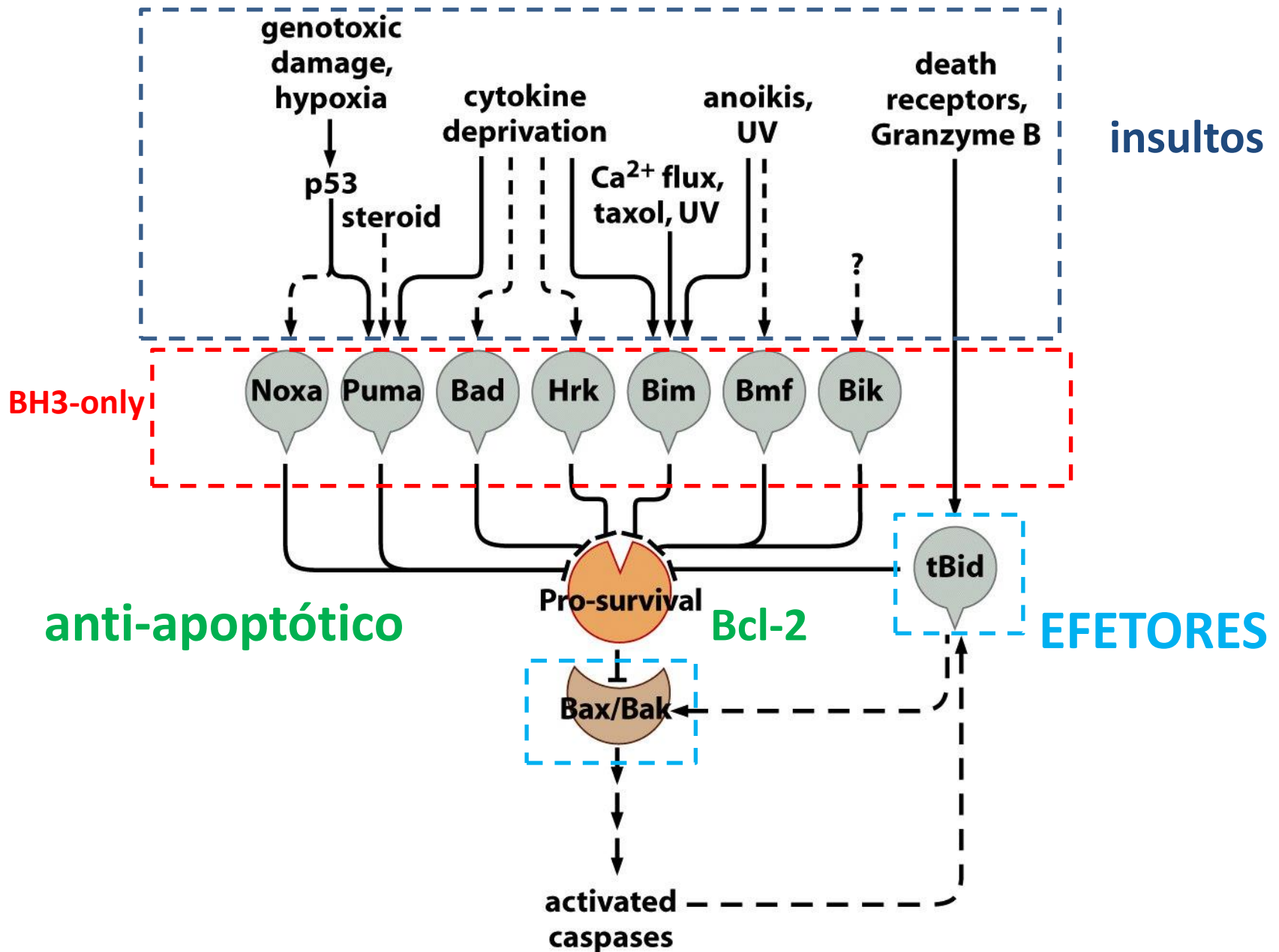
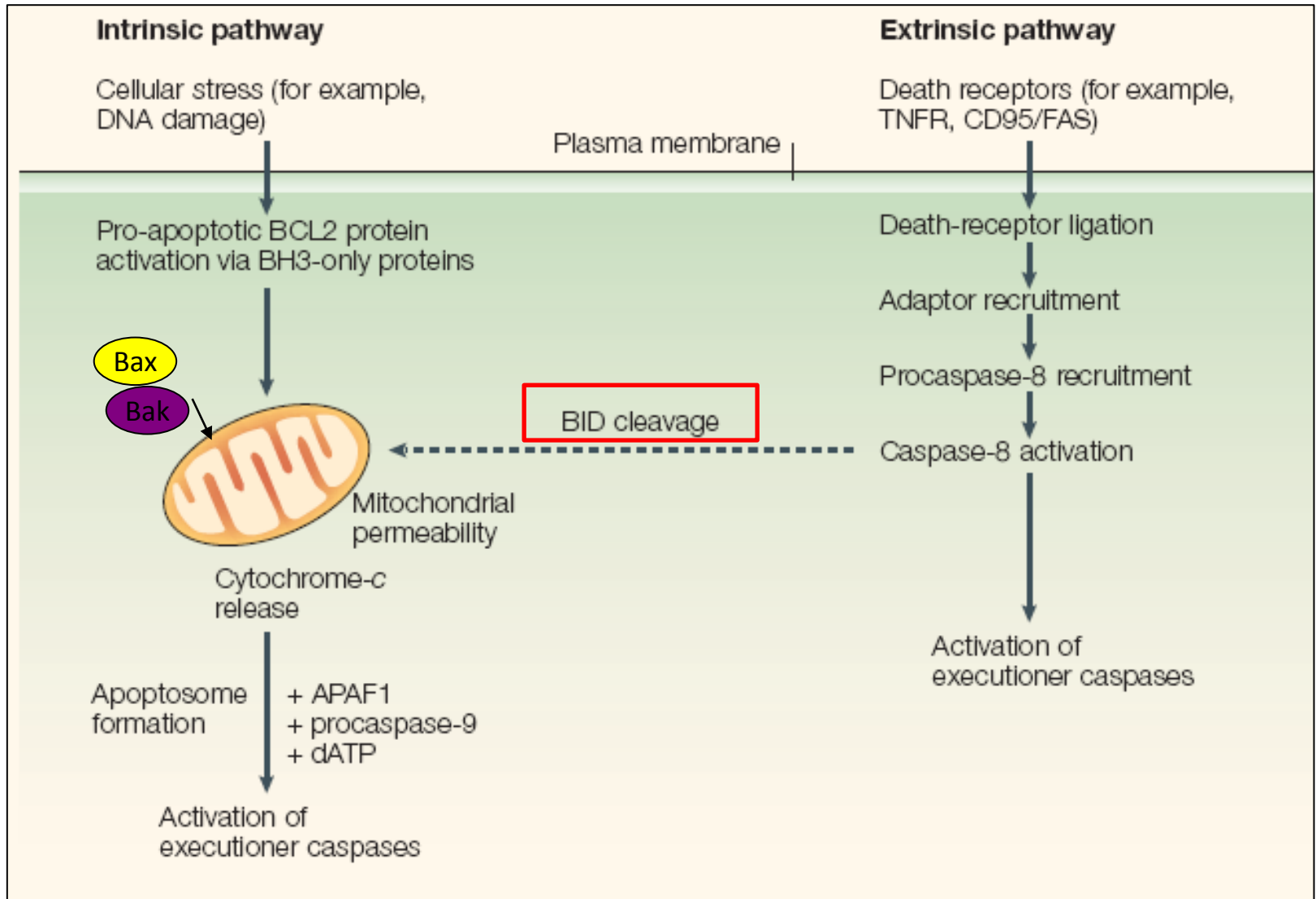


Figure 9-27a The Biology of Cancer (© Garland Science 2007)

A via intríntrica 'ajuda' a extríntrica



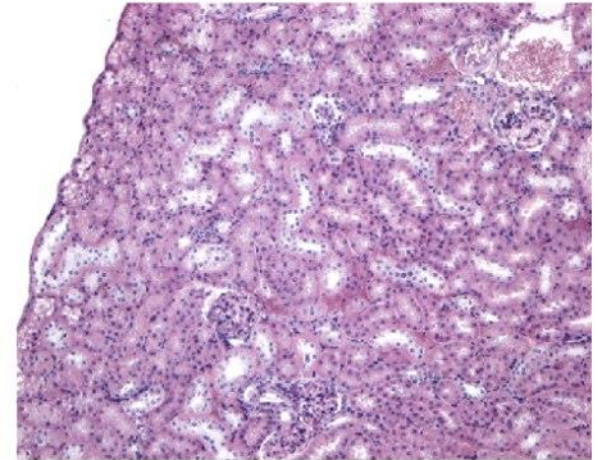
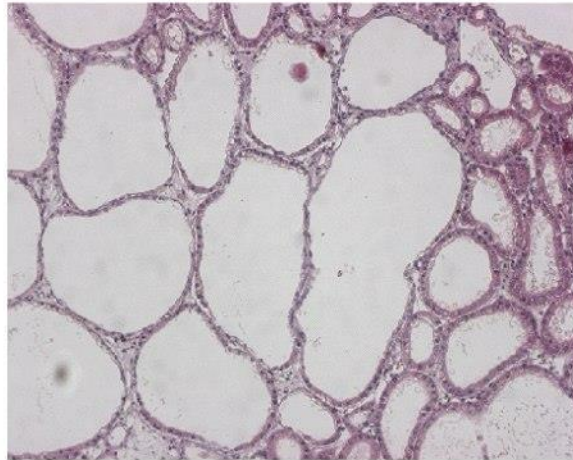
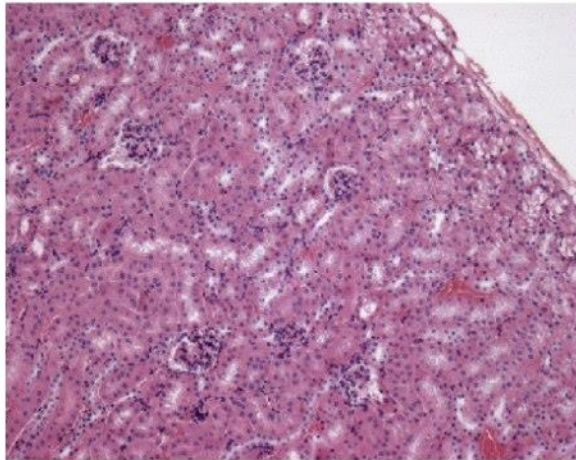
Estudos *in vivo* indicam que esse Equilíbrio é complexo...

Deleção de UM alelo de *bim-2* (pró-apoptose) basta para reverter o fenótipo

Rim normal
wt, 5 wk

Anti-apoptose
bcl-2^{-/-}, 5 wk

bcl-2^{-/-} *bim-2*^{+/-}, 5 wk



(A)

(B)

(C)

Figure 9-26 The Biology of Cancer (© Garland Science 2007)

Apoptose

Visualização simultânea de **citocromo**, **fosfatidilserina** e **DNA**



<https://www.youtube.com/watch?v=rs1Je-8Y3Po>

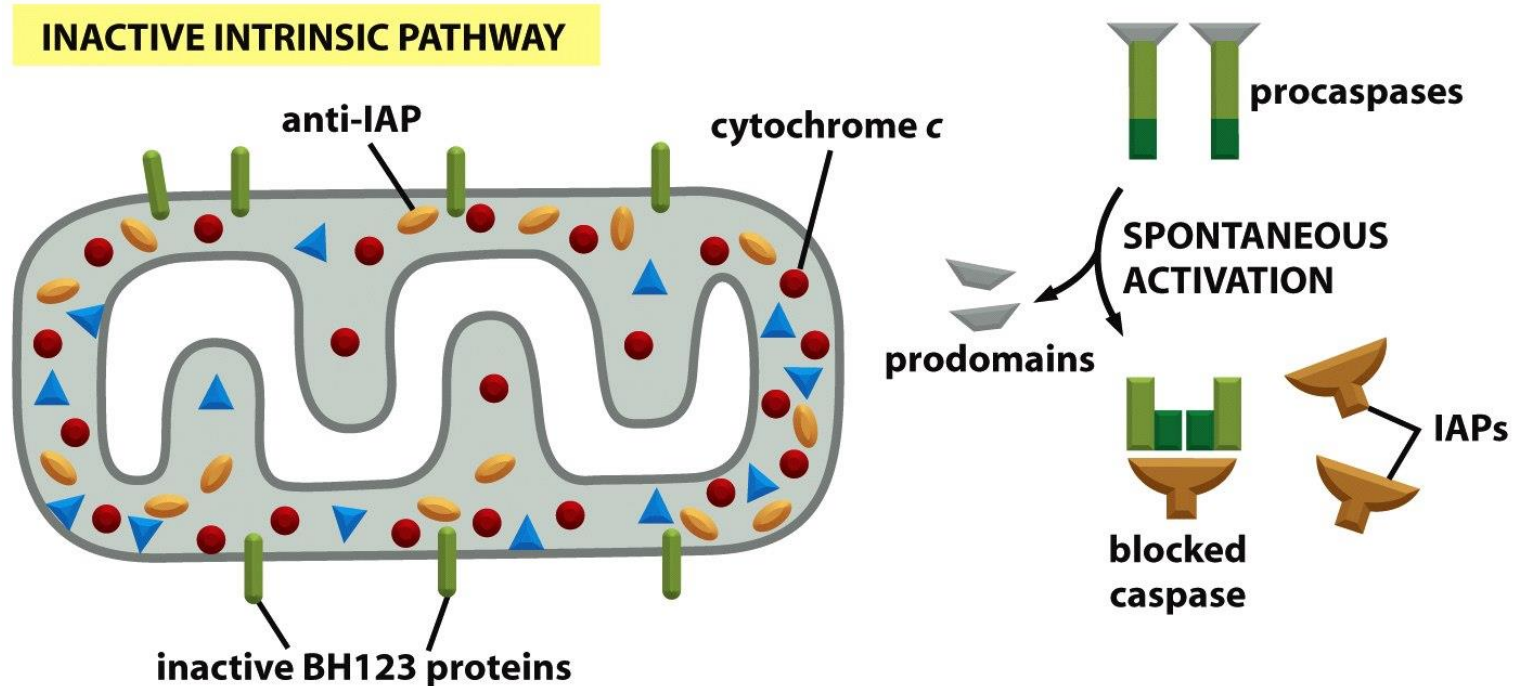
Resumo..

- A via extríntrica pode ativar a intríntrica para amplificar a cascata de caspases. Isso é feito através da BH3 Bid
- Caspase 8 → clivagem de Bid → tBid transloca para a mitocôndria e induz agregação dos BH123
- Bim, Bid e Puma (entre outros) são capazes de inibir TODOS os membros ANTI-apoptóticos

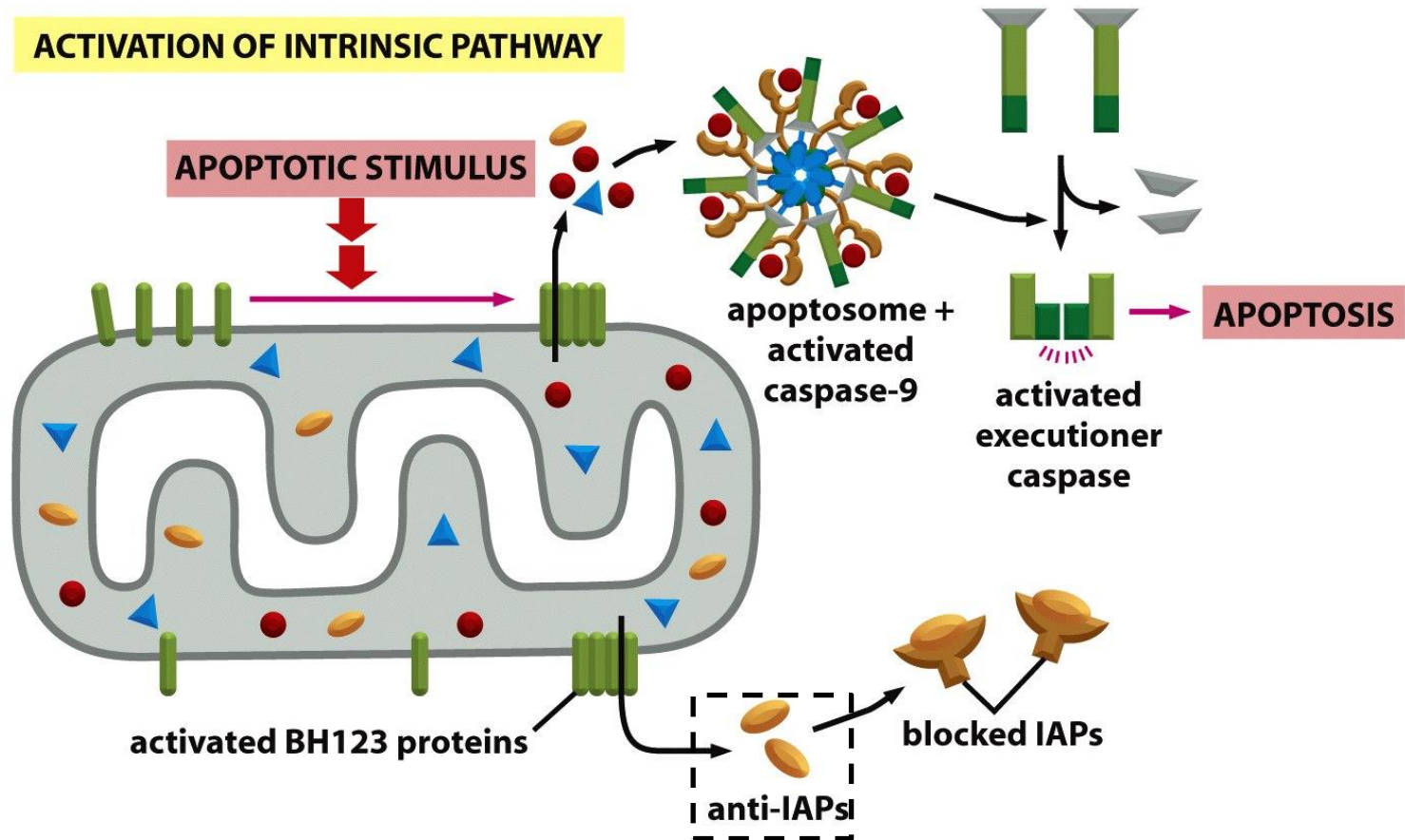
IAPs e anti-IAPs



- *IAP* = inhibitors of apoptosis
- “Equivalentes” às proteínas Bcl2 em mamíferos



Na presença de um estímulo apoptótico a mitocôndria libera ANTI-IAPs



p53



GENOME

GUARDIAN



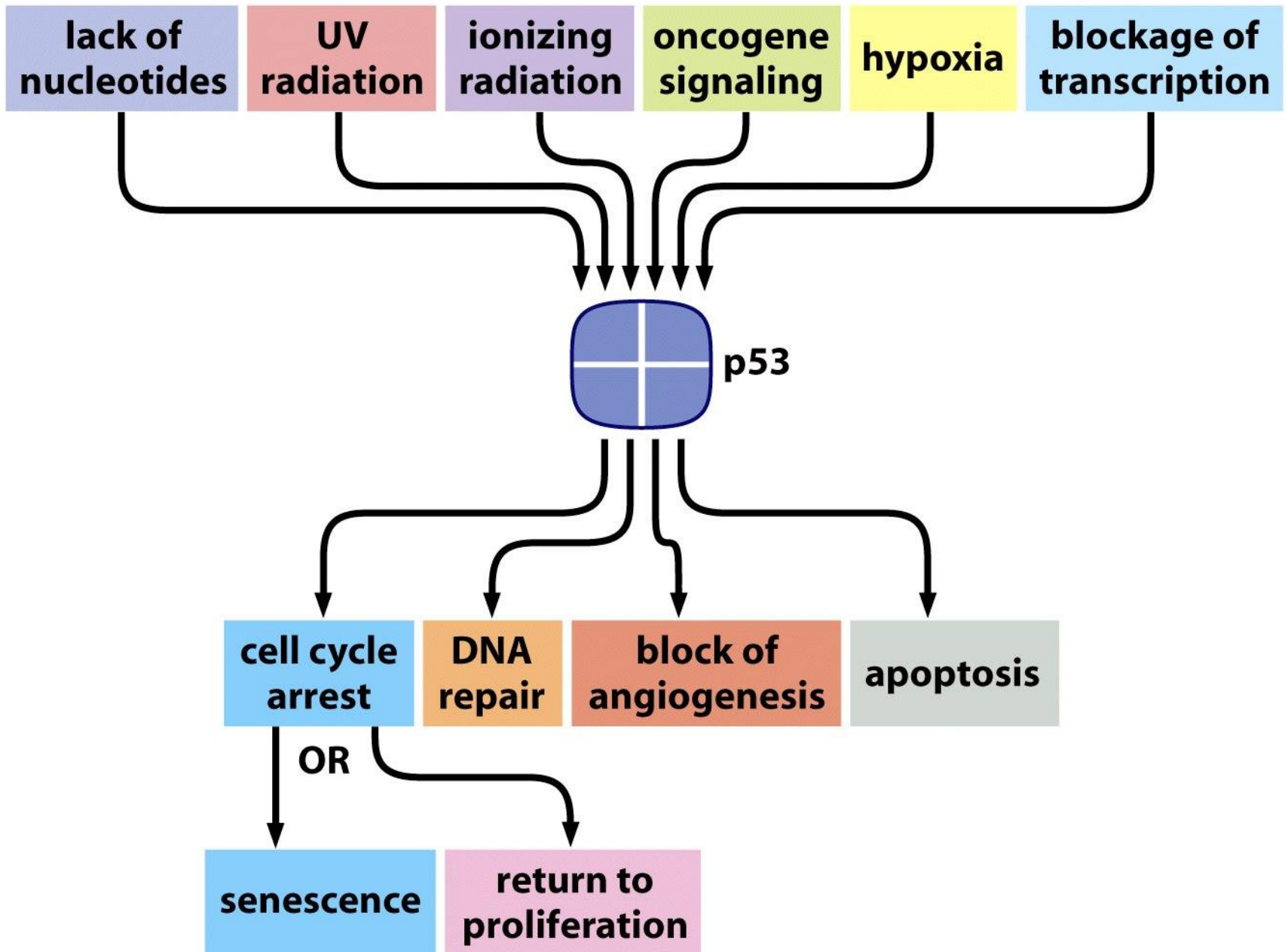
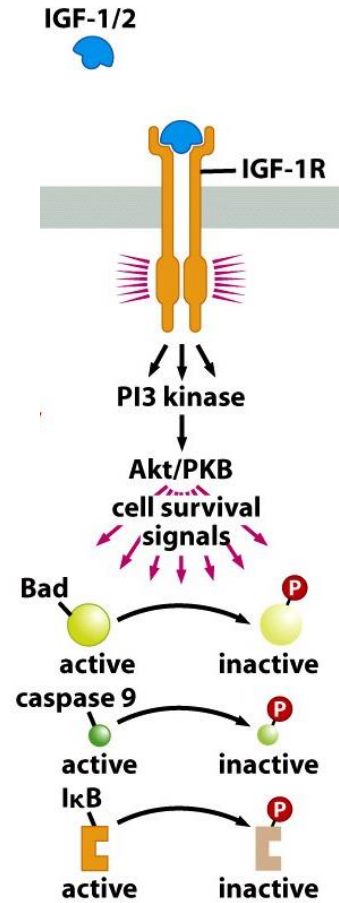


Figure 9-8 The Biology of Cancer (© Garland Science 2007)

Como p53 promove a apoptose?



Como p53 promove a apoptose?

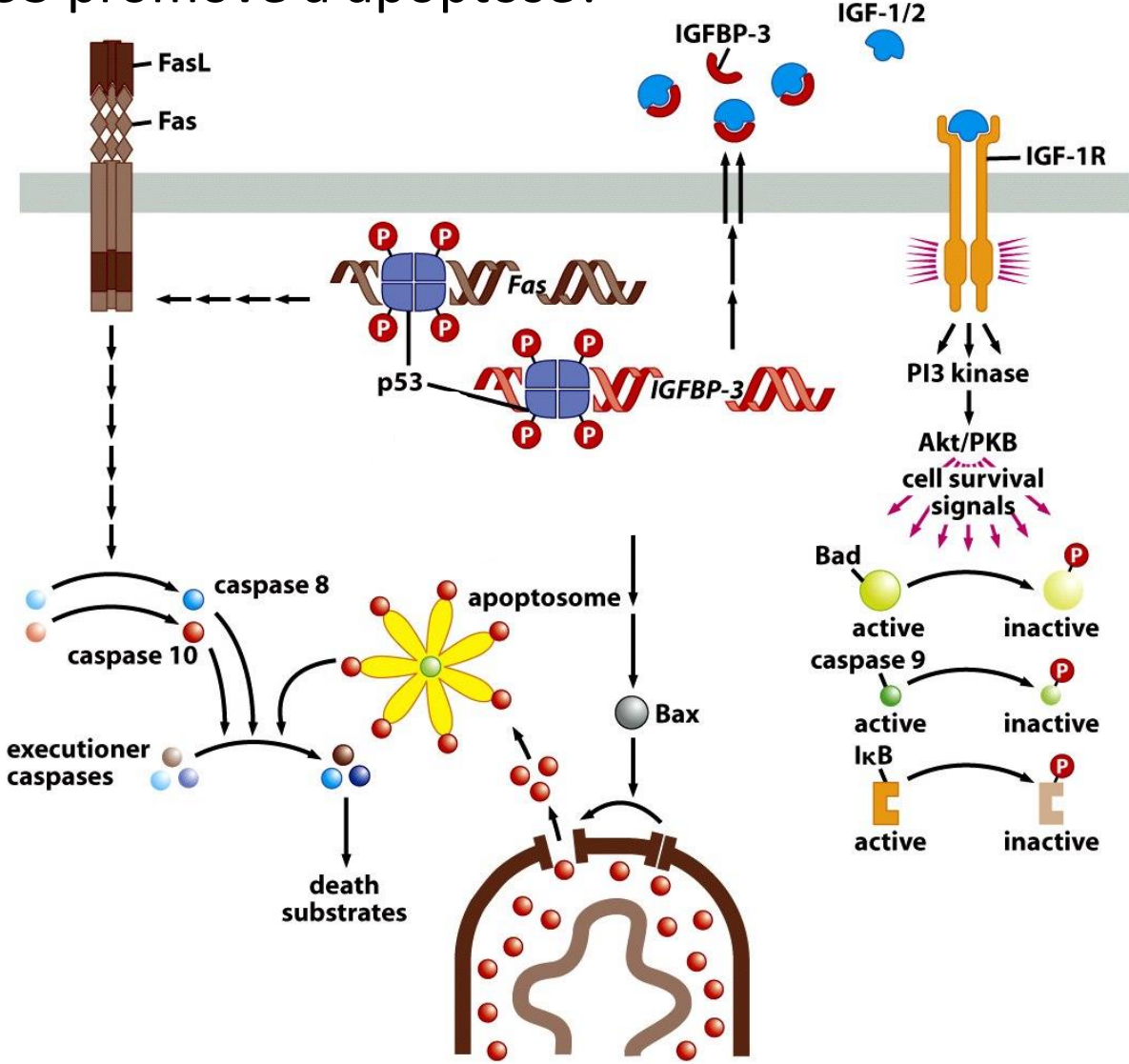
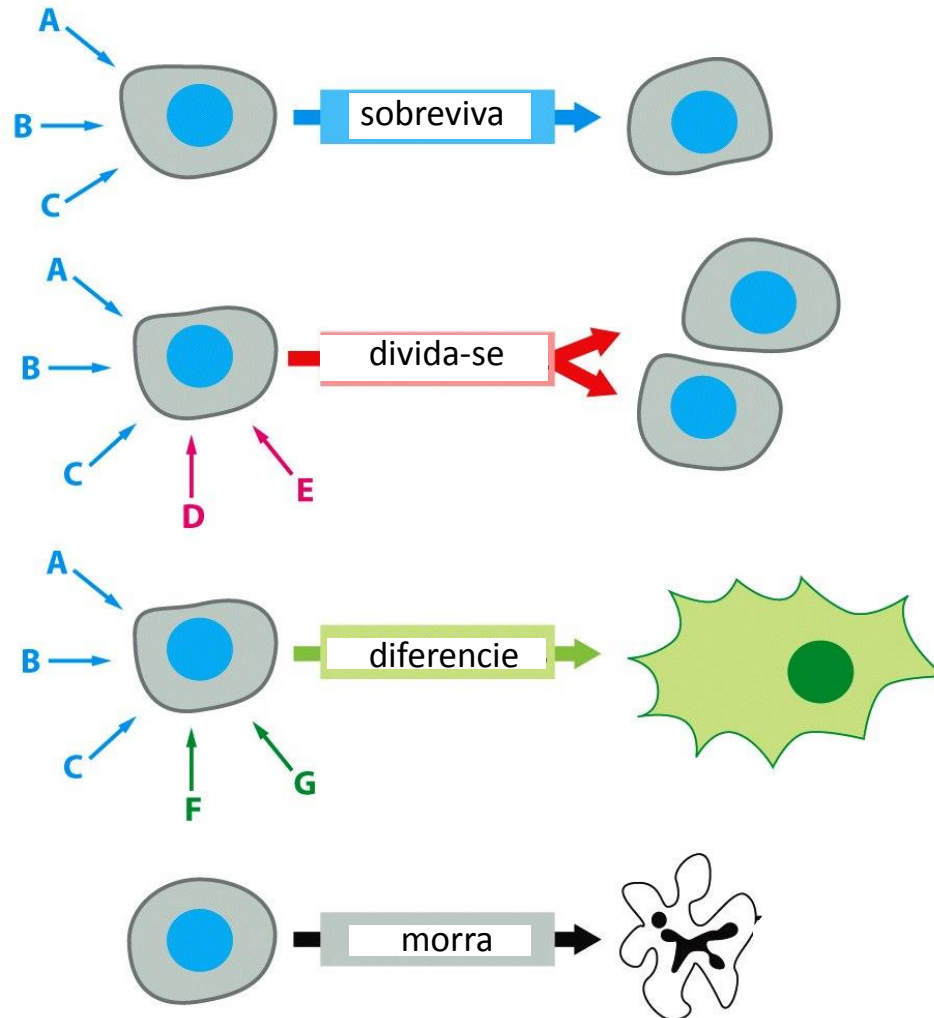


Figure 9-33 The Biology of Cancer (© Garland Science 2007)

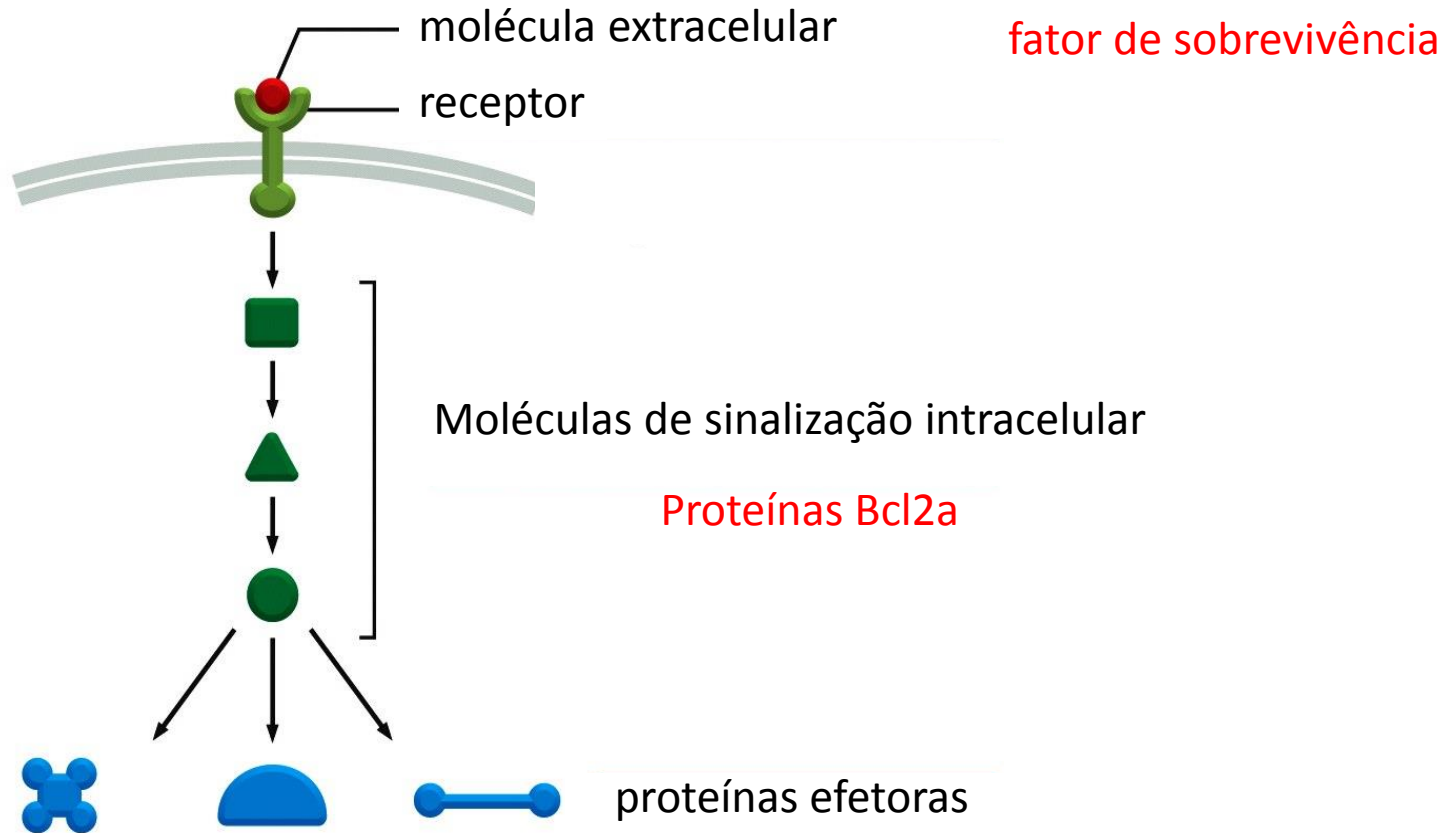
IGFBP-3- insulin-like growth fator binding protein

Fatores de Sobrevivência

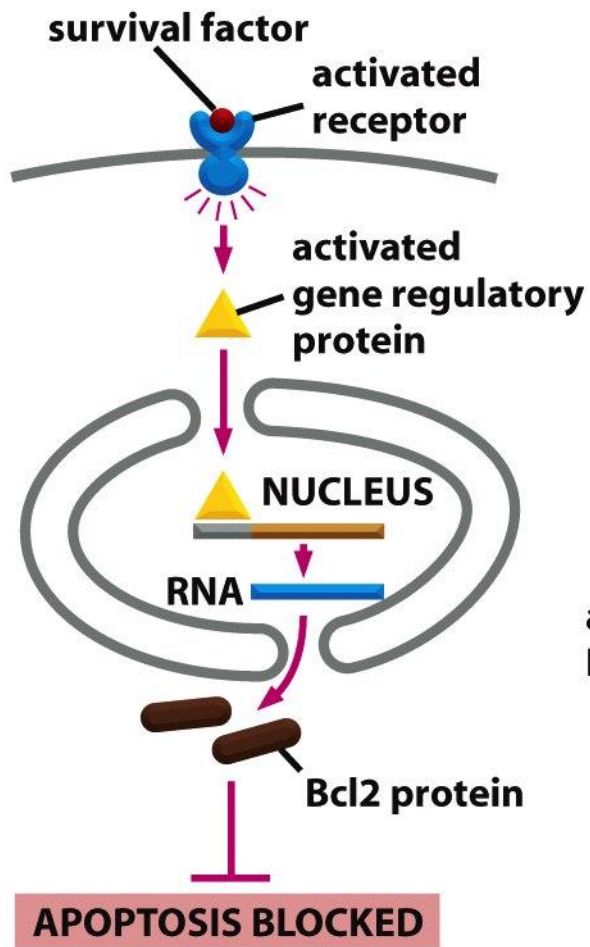
Lembrando da aula de sinalização..



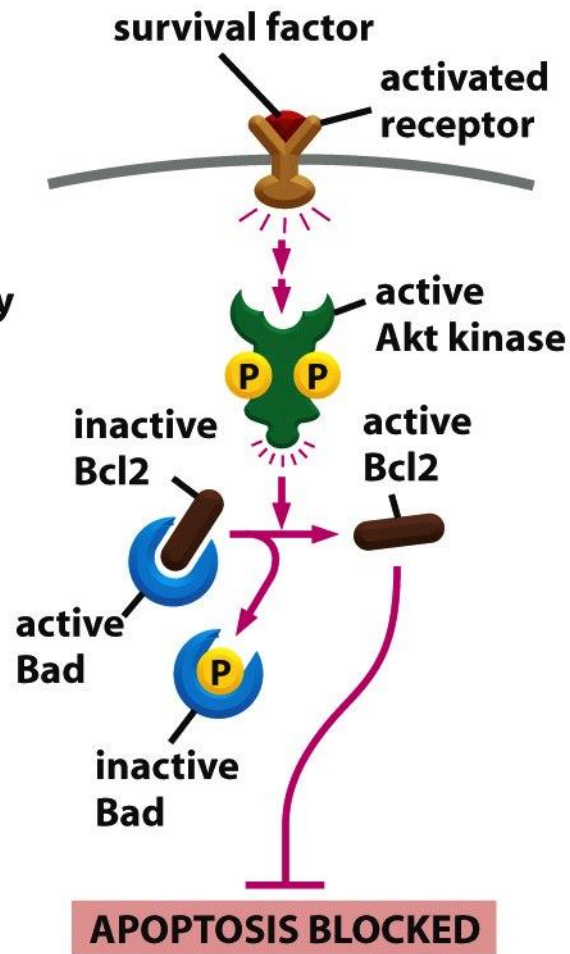
Sinalização dos fatores de sobrevivência segue a mesma regra



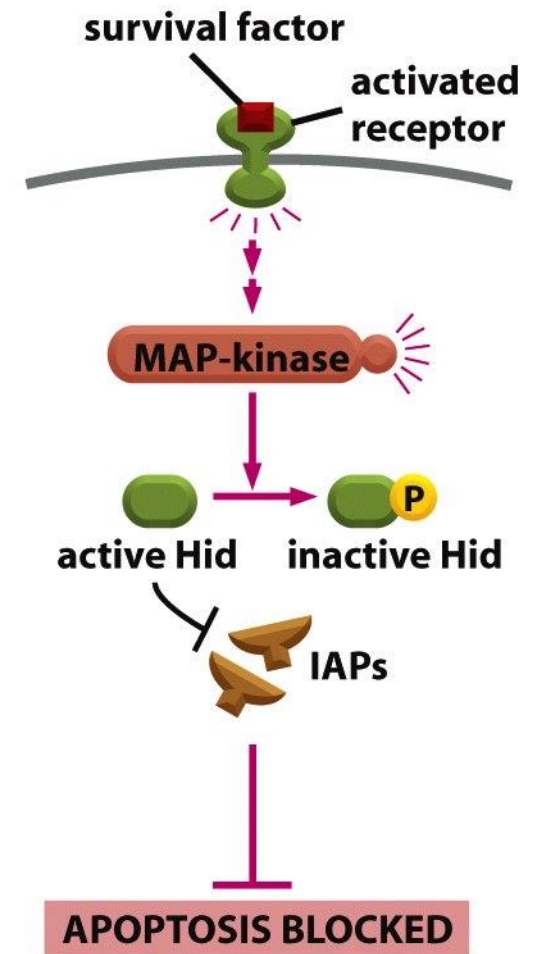
(A) increased production of anti-apoptotic Bcl2 protein



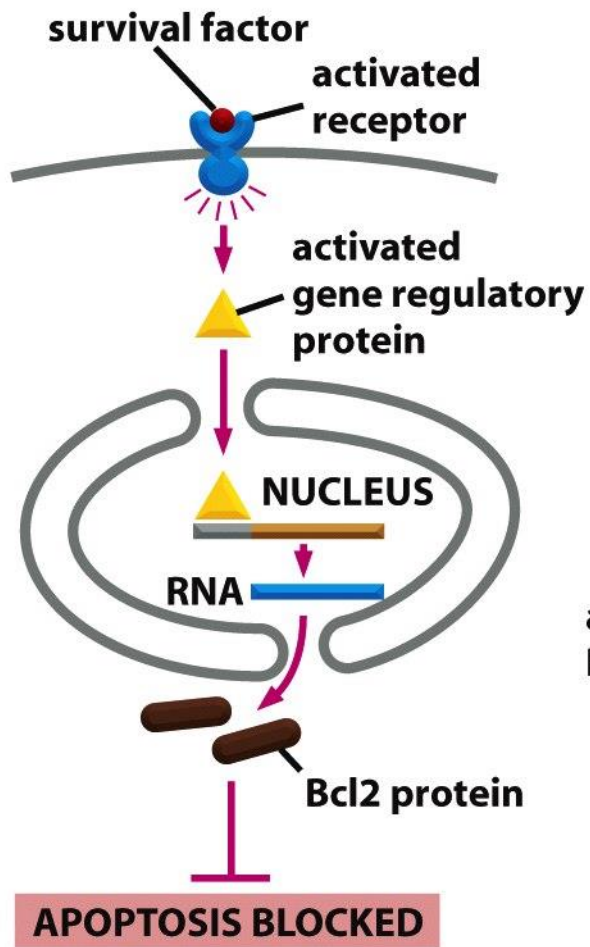
(B) inactivation of pro-apoptotic BH3-only Bcl2 protein



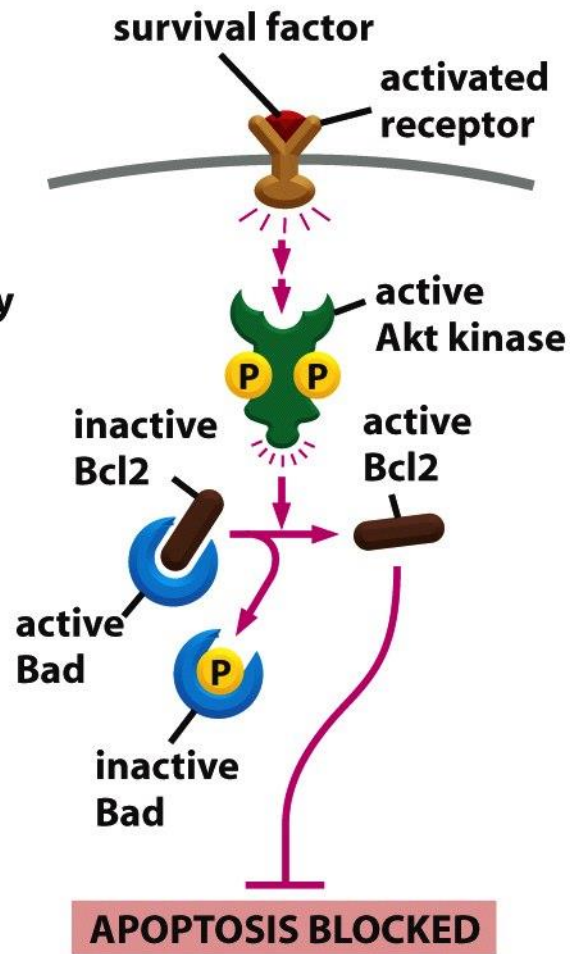
(C) inactivation of anti-IAPs



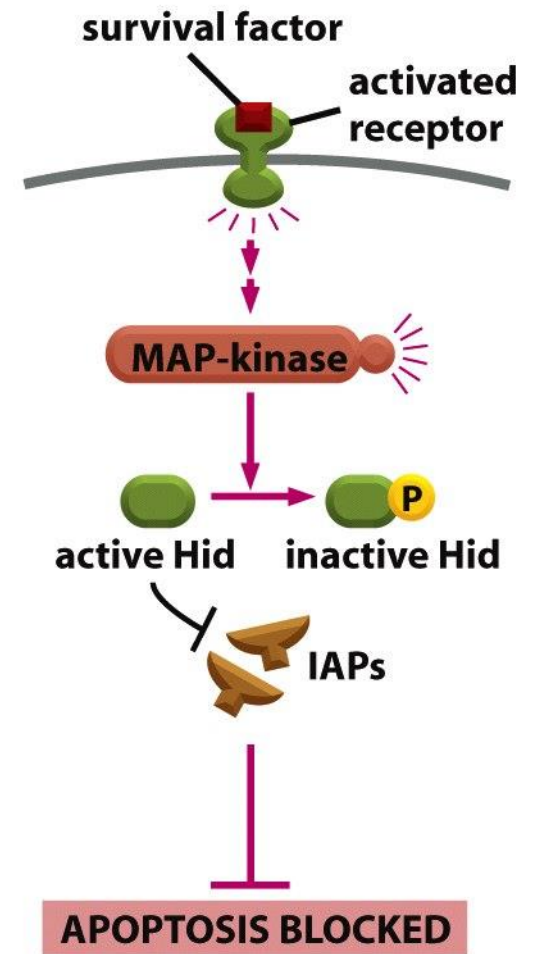
(A) increased production of anti-apoptotic Bcl2 protein



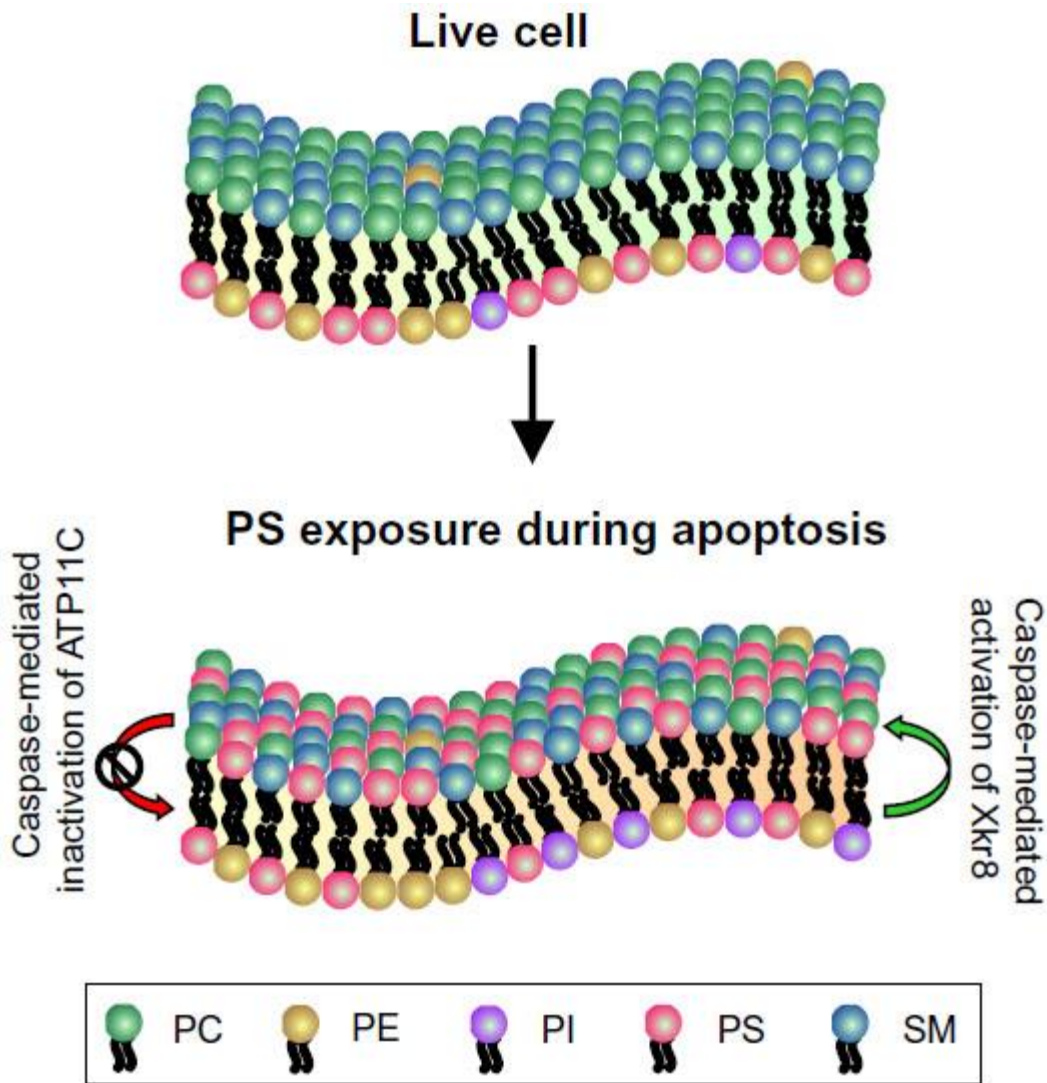
(B) inactivation of pro-apoptotic BH3-only Bcl2 protein



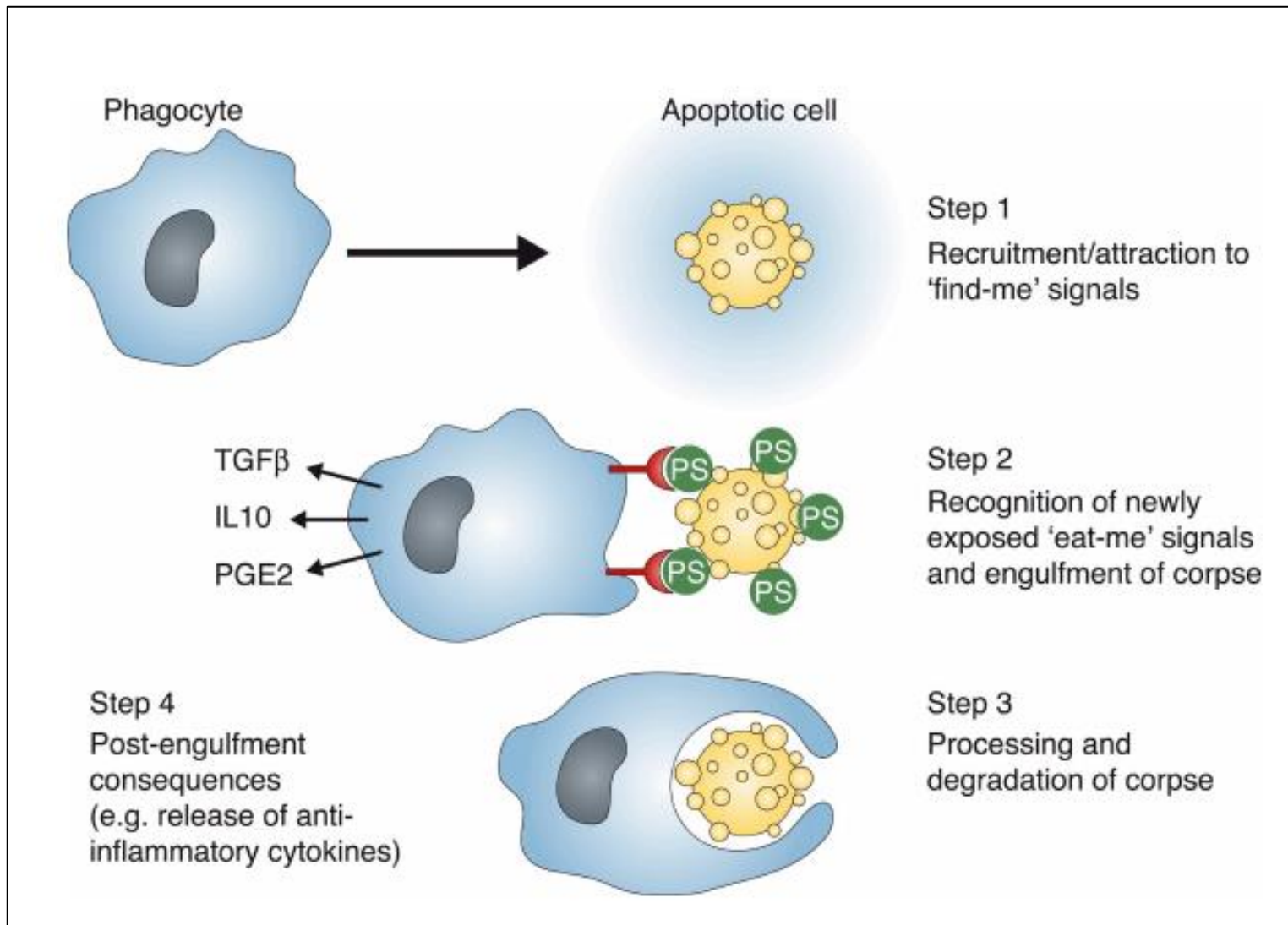
(C) inactivation of anti-IAPs



Como as células mortas são eliminadas?



PC – fosfatidilcolina; PE – fosfatidiletanolamina; PI – fosfatidilinositol
PS – fosfatidilserina; SM - esfingomielina



Doenças associadas à morte celular

- Huntington
- Alzheimer
- Parkinson
- Câncer
- Doenças auto-imunes
- Infartos e derrames

Table 9.5 Examples of anti-apoptotic alterations found in human tumor cells

Alteration	Mechanism of anti-apoptotic action	Types of tumors
<i>CASP8</i> promoter methylation	inactivation of extrinsic cascade	SCLC, pediatric tumors
<i>CASP3</i> repression	inactivation of executioner caspase	breast carcinomas
Survivin overexpression ^a	caspase inhibitor	mesotheliomas, melanomas, many carcinomas
ERK activation	repression of caspase-8 expression	many types
ERK activation	protection of Bcl-2 from degradation	many types
Raf activation	sequestration of Bad by 14-3-3 proteins	many types
<i>PI3K</i> mutation/activation	activation of Akt/PKB	gastrointestinal
NF-κB constitutive activation ^b	induction of anti-apoptotic genes	many types
<i>p53</i> mutation	loss of ability to induce pro-apoptotic genes	many types
<i>p14^{ARF}</i> gene inactivation	suppression of <i>p53</i> levels	many types
<i>Mdm2</i> overexpression	suppression of <i>p53</i> levels	sarcomas
<i>IAP-1</i> gene amplification	antagonist of caspases-3 and 7	esophageal, cervical
<i>APAF1</i> methylation	loss of caspase-9 activation by cytochrome <i>c</i>	melanomas
<i>BAX</i> mutation	loss of pro-apoptotic protein	colon carcinomas
<i>Bcl-2</i> overexpression	closes mitochondrial channel	~ of human tumors
<i>PTEN</i> inactivation	hyperactivity of Akt/PKB kinase	glioblastoma, prostate carcinoma, endometrial carcinoma
IGF-1/2 overexpression	activates PI3K	many types
<i>IGFBP</i> repression	loss of anti-apoptotic IGF-1/2 antagonist	many types
<i>Casein kinase II</i>	activation of NF-κB	many types
<i>TNFR1</i> methylation	repressed expression of death receptor	Wilms tumor
FLIP overexpression	inhibition of caspase-8 activation by death receptors	melanomas, many others
Akt/PKB activation	phosphorylation and inactivation of pro-apoptotic Bcl-2-like proteins	many types
Stat3 activation	induces expression of Bcl-X _L	several types
<i>TRAIL-R1</i> repression	loss of responsiveness to death ligand	small-cell lung carcinoma
FAP-1 overexpression	inhibition of Fas receptor signaling	pancreatic carcinoma
<i>XAF1</i> methylation ^c	loss of inhibition of anti-apoptotic XIAP	gastric carcinoma
Wip1 overexpression ^d	suppression of <i>p53</i> activation	breast and ovarian carcinomas, neuroblastoma

^aSurvivin is an inhibitor of apoptosis (IAP) in gastric, lung, and bladder cancer and melanoma in addition to the mesotheliomas indicated here. The expression of a number of IAP genes is directly induced by the NF-κB TFs.

^bInduces synthesis of c-IAPs, XIAP, Bcl-X_L, and other anti-apoptotic proteins.

^cXAF1 (XIAP-associated factor 1) normally binds and blocks the anti-apoptotic actions of XIAP, the most potent of the IAPs.

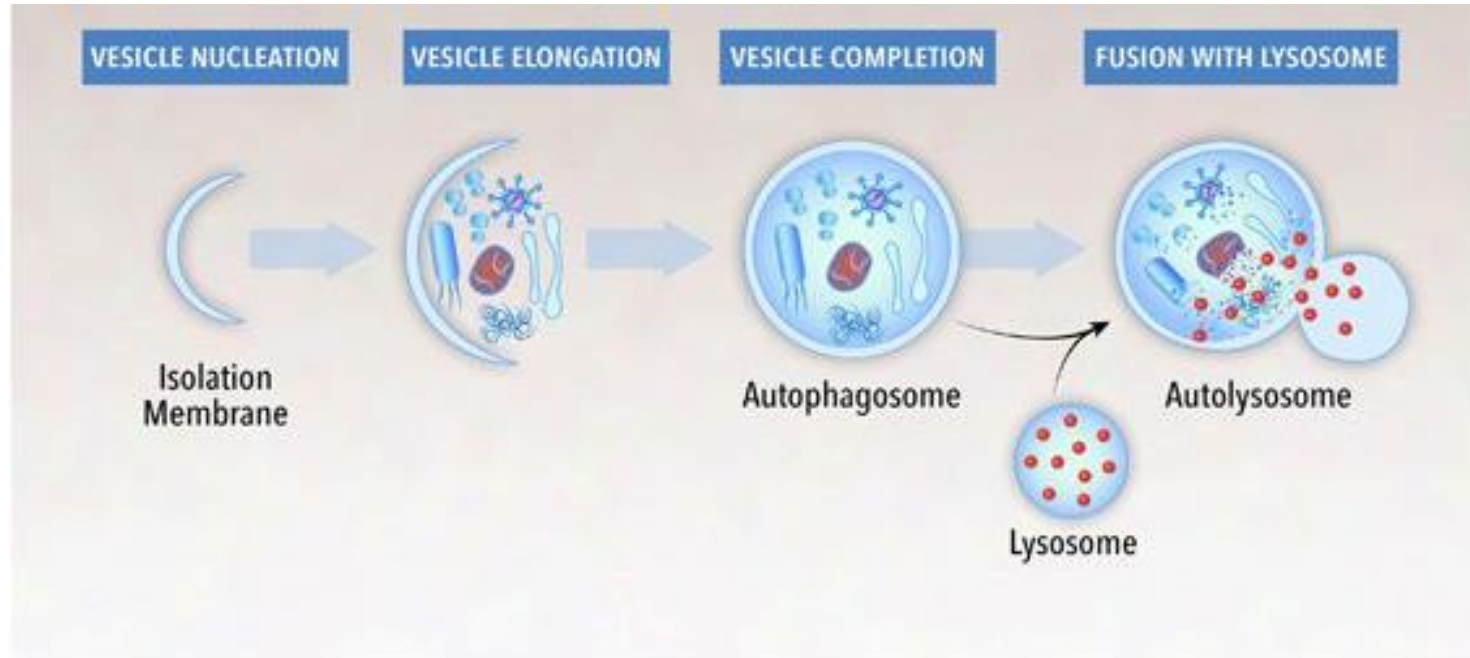
^dWip1 is a phosphatase that inactivates p38 MAPK, which otherwise would phosphorylate and stimulate the pro-apoptotic actions of p53.

- Autofagia / morte dependente de autofagia
- Necroptose

Autofagia

- Processo através do qual macromoléculas e organelas são degradadas e recicladas
- A autofagia é ativada para proteger a células de alguns tipos de estresse: falta de nutrientes, de hormônios, de fatores de crescimento, estresse oxidativo, infecções, alta demanda energética
- **PORTANTO, a autofagia é um mecanismo de sobrevivência**

Autofagia



mitochondrion peroxisome



1 μm

Figure 13-42b Molecular Biology of the Cell 5/e (© Garland Science 2008)



Fibroblasto de embrião carenciado de nutrientes

e – retículo endoplasmático
m – mitocôndria

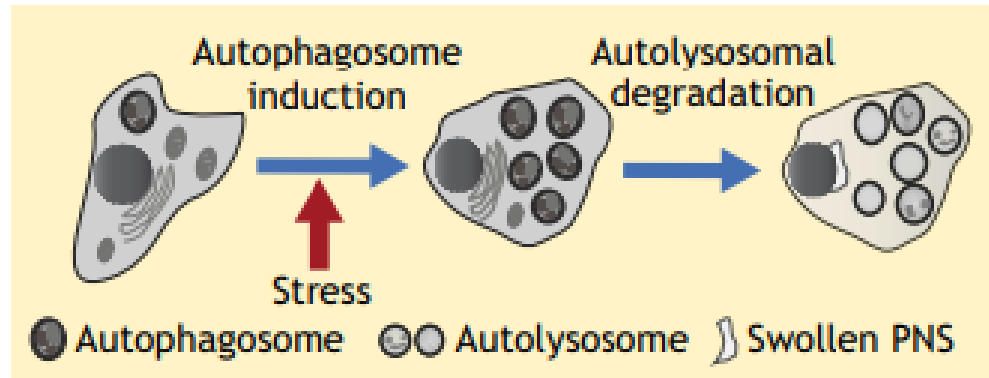
Morte dependente de autofagia

(ADCD - *autophagy-dependent cell death*)

- morte celular que do ponto de vista mecânico DEPENDE da maquinaria de autofagia

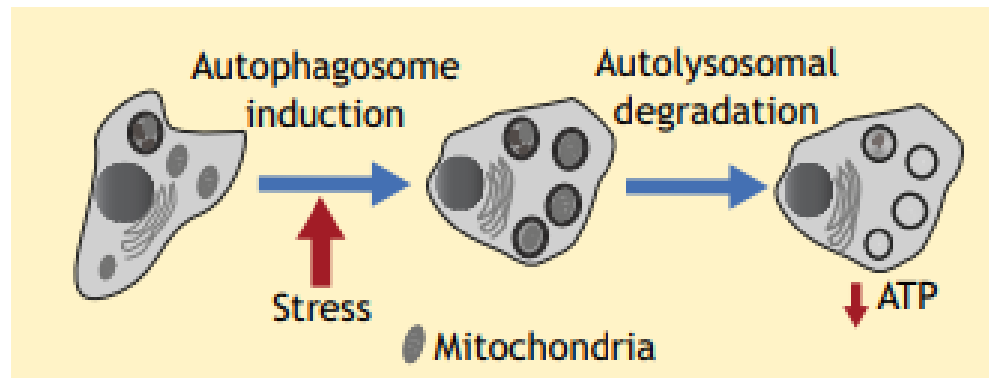
Morte celular dependente de autofagia

A Excessive autophagy

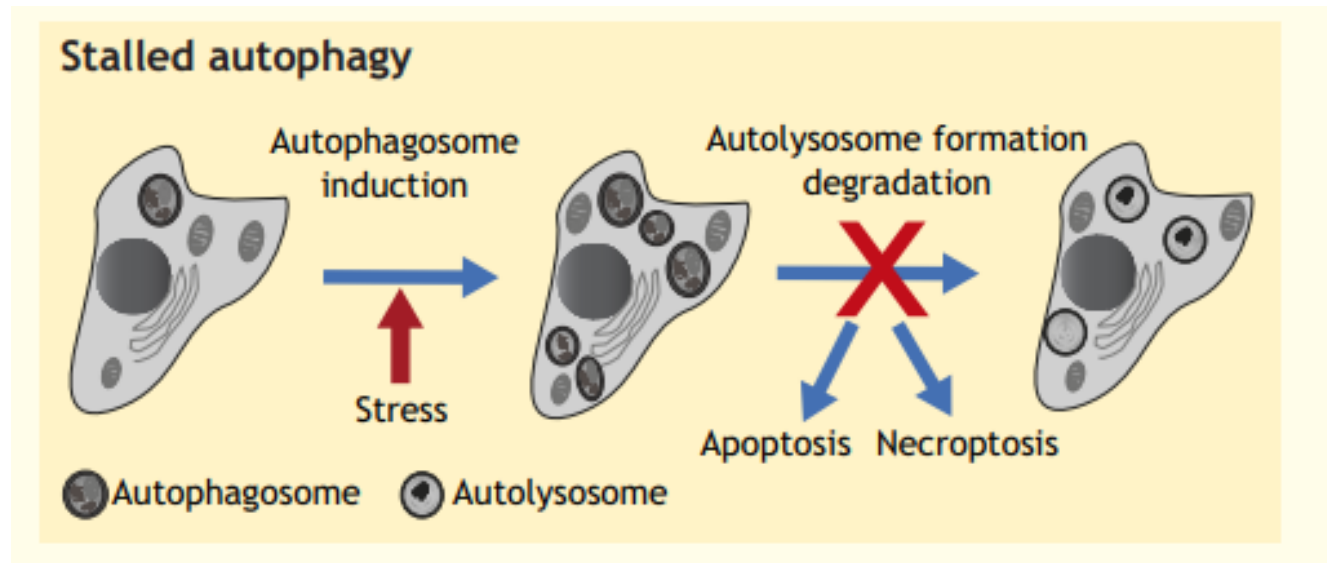


EXCESSO !!

B Excessive mitophagy

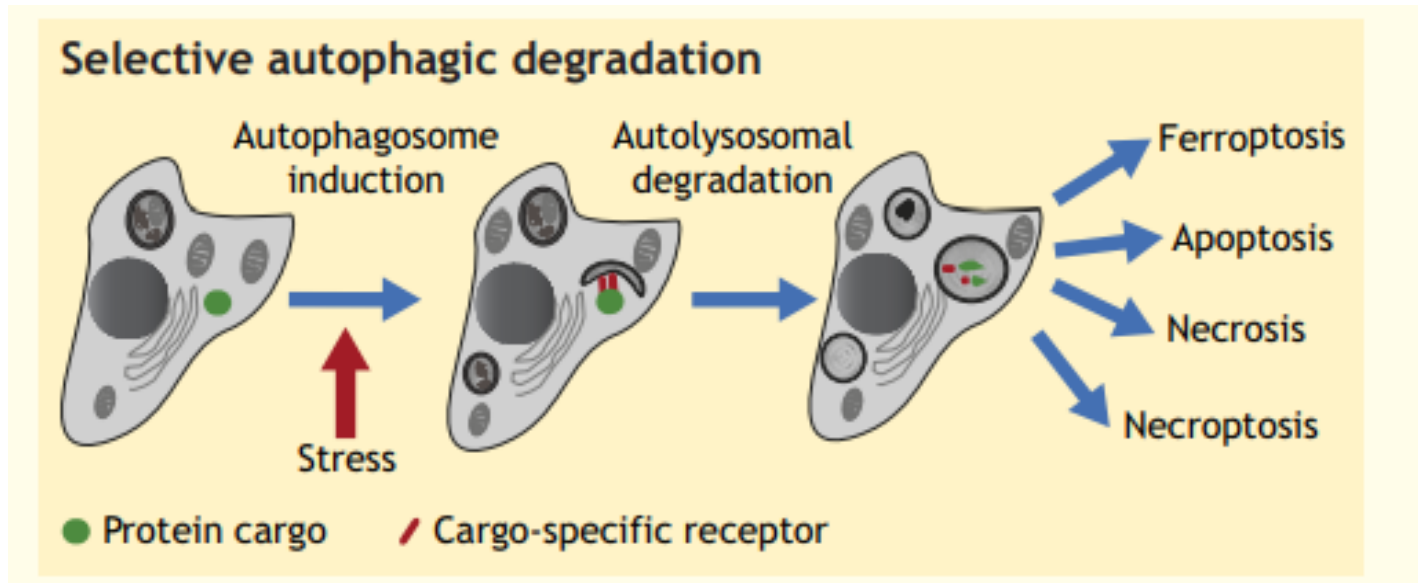


Morte celular dependente de autofagia

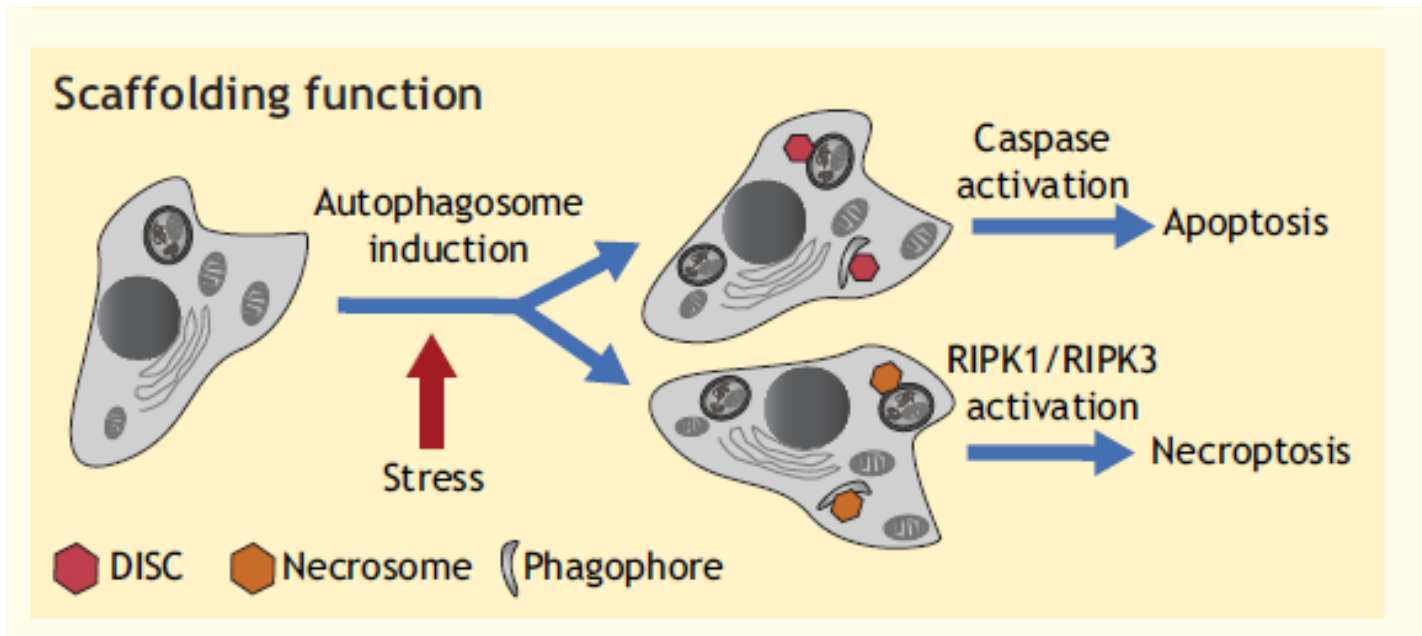


Ao impedir que a célula faça autofagia (ou seja, que tente sobreviver) as vias de apoptose ou necrose são ativadas, resultando em morte

Morte celular dependente de autofagia



Morte celular dependente de autofagia



Necroptose

- Termo genérico para definir morte celular independente de caspases
- Ganho de volume da célula e 'inchaço' das organelas
- Não há clivagem do DNA e sim descondensação da cromatina
- Lise celular e extravasamento do seu conteúdo
- Reação inflamatória
- Quando ocorre: infarto, AVC, aterosclerose, infecção viral

apoptose

~~necrose~~ **necroptose**

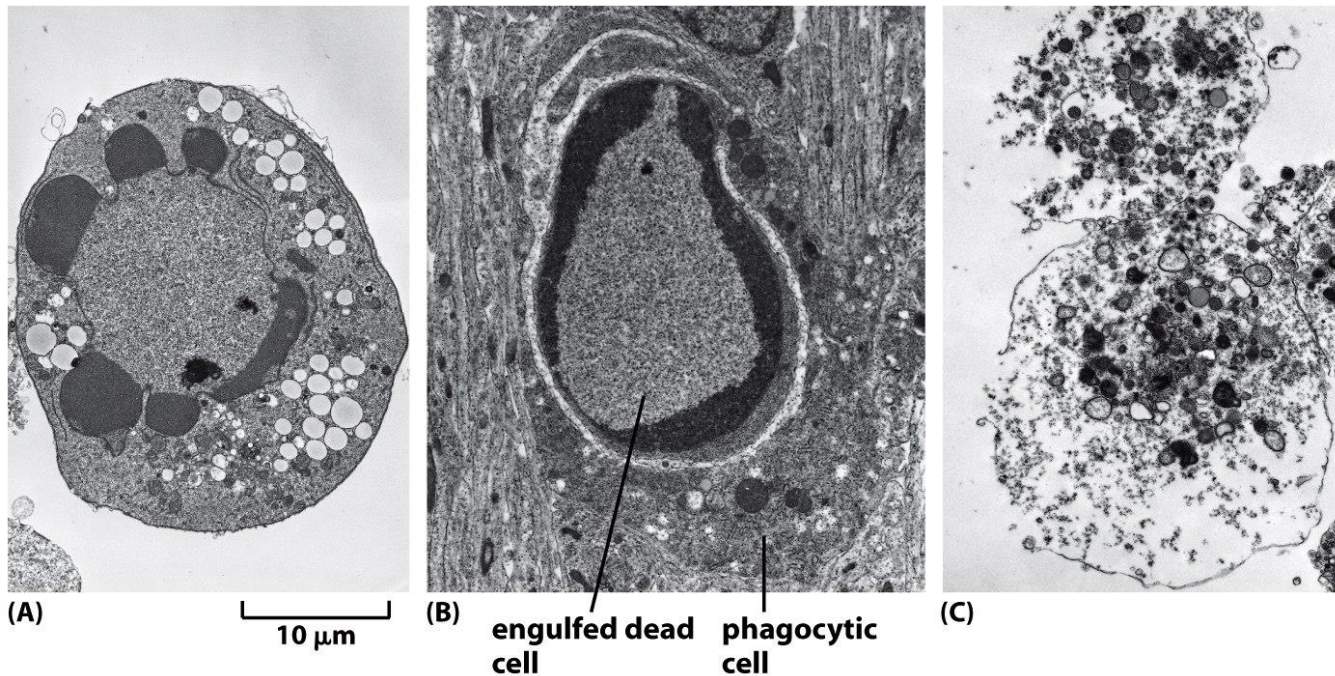


Figure 18-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

APOPTOSE

- Células encolhem
- Colapso do citoesqueleto
- Rompimento do envelope nuclear
- Fragmentação da cromatina
- Formação dos corpos apoptóticos
- Células apoptóticas são fagocitadas (B)

~~NECROSE~~ **necroptose**

- rompimento da membranas plasmática
- Extravasamento do conteúdo celular
- Resposta inflamatória

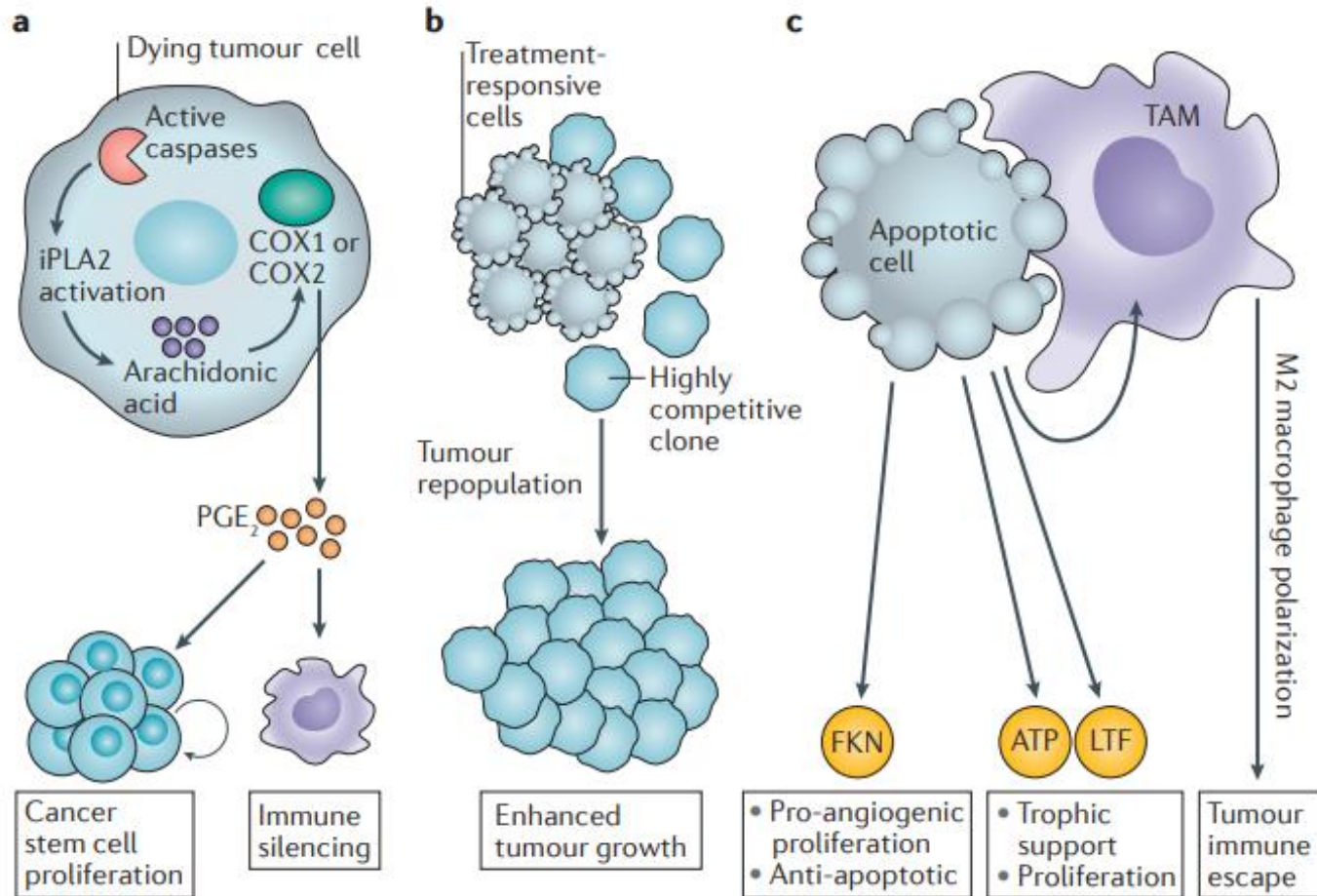
OPINION

A fate worse than death: apoptosis as an oncogenic process

Gabriel Ichim and Stephen W. G. Tait

Abstract | Apoptotic cell death is widely considered a positive process that both prevents and treats cancer. Although undoubtedly having a beneficial role, paradoxically, apoptosis can also cause unwanted effects that may even promote cancer. In this Opinion article we highlight some of the ways by which apoptosis can exert oncogenic functions. We argue that fully understanding this dark side will be required to optimally engage apoptosis, thereby maximizing tumour cell kill while minimizing unwanted pro-tumorigenic effects.

A fate worse than death: apoptosis as an oncogenic process

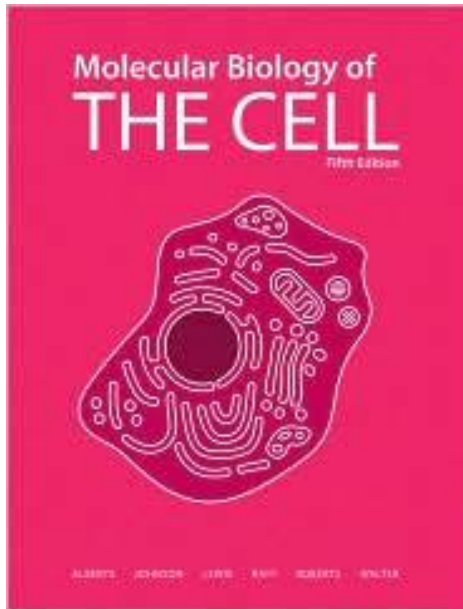


WHAT WE DON'T KNOW

- How many forms of programmed cell death exist? What are the underlying mechanisms and benefits of each?
- Thousands of caspase substrates have been identified. Which ones are the critical proteins that must be cleaved to trigger the major cell remodeling events underlying apoptosis?
- How did the intrinsic pathway of apoptosis evolve, and what is the advantage of having mitochondria play such a central role in regulating apoptosis?
- How are “don’t eat me” signals eliminated or inactivated during apoptosis to allow the cells to be phagocytosed?

Bibliografia

Capítulos 18



Cell Death & Differentiation
<https://doi.org/10.1038/s41418-017-0012-4>

Cell Death &
Differentiation

REVIEW



Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

Lorenzo Galluzzi^{1,2,3} · Ilio Vitale^{4,5} et al.

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Abstract

Over the past decade, the Nomenclature Committee on Cell Death (NCCD) has formulated guidelines for the definition and interpretation of cell death from morphological, biochemical, and functional perspectives. Since the field continues to expand and novel mechanisms that orchestrate multiple cell death pathways are unveiled, we propose an updated classification of cell death subroutines focusing on mechanistic and essential (as opposed to correlative and dispensable) aspects of the process. As we provide molecularly oriented definitions of terms including intrinsic apoptosis, extrinsic apoptosis, mitochondrial permeability transition (MPT)-driven necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic cell death, NETotic cell death, lysosome-dependent cell death, autophagy-dependent cell death, immunogenic cell death, cellular senescence, and mitotic catastrophe, we discuss the utility of neologisms that refer to highly specialized instances of these processes. The mission of the NCCD is to provide a widely accepted nomenclature on cell death in support of the continued development of the field.

<https://www.nature.com/articles/s41418-017-0012-4>

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