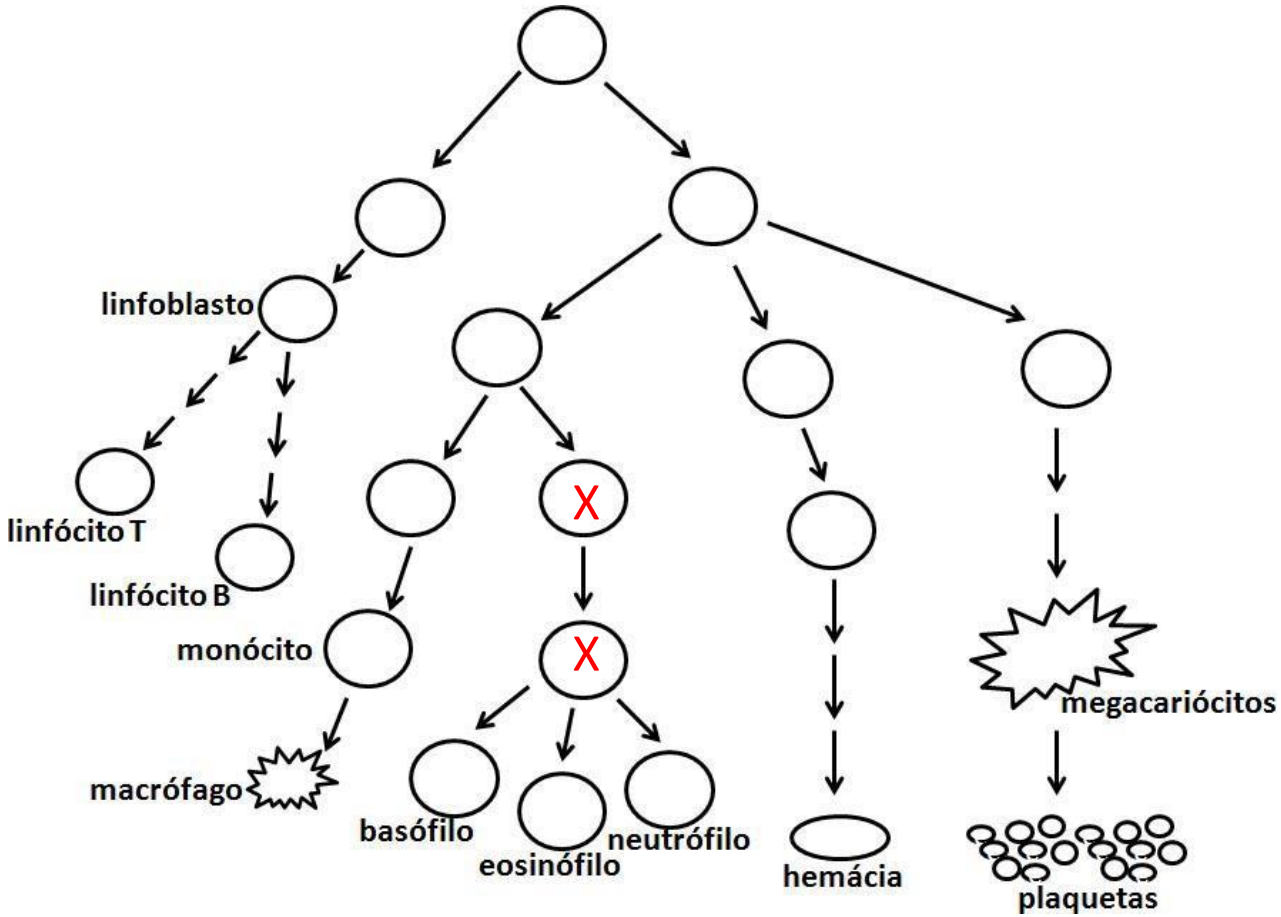
Correção dos exercícios da aula de células-tronco e diferenciação

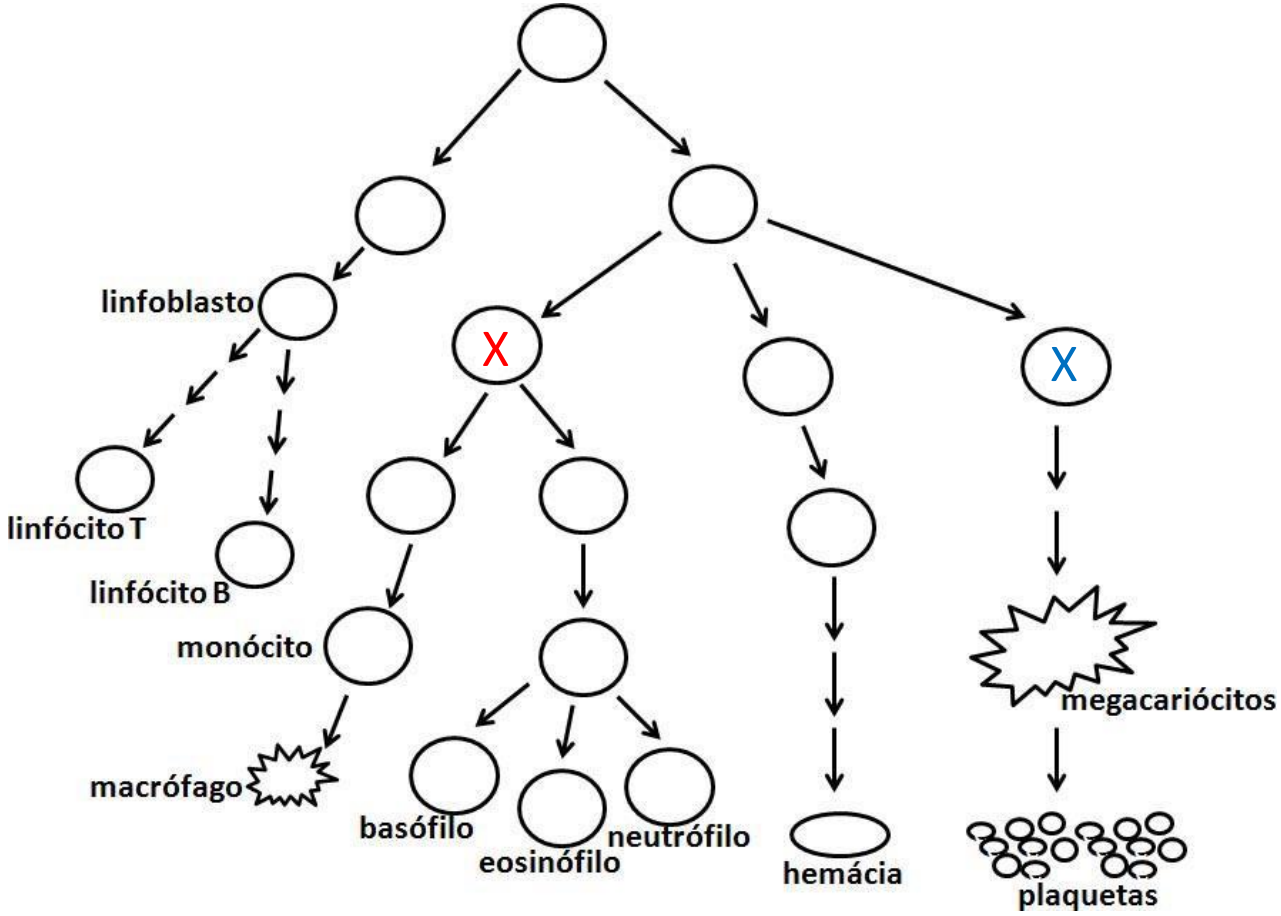
1.O sistema hematopoiético de mamíferos é um modelo para estudo de células-tronco. Se um camundongo for irradiado todas as células da sua medula óssea morrerão. Esse animal, no entanto, pode se recuperar se receber uma injeção de um pequeno número de células da medula óssea de um animal doador. Explique como esse ensaio prova que existem células-tronco na medula óssea.

2. Uma população de células-tronco pluripotentes foi irradiada com uma dada dose de raio-X. Essa dose não mata as células, mas gera quebras e rearranjos aleatórios nos cromossomos que podem ser detectados ao microscópio. Consequentemente, cada uma dessas células terá uma pequena anomalia cromossômica que servirá para distingui-las entre si (como uma MARCA). Essas células foram usadas para salvar a vida de um animal que foi irradiado.

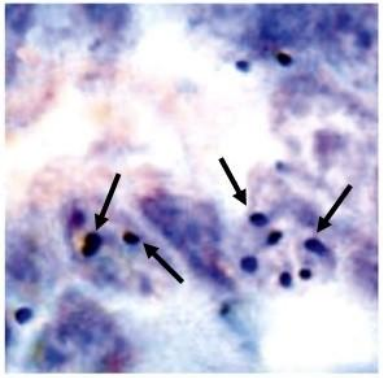
2.1 Analisando o sangue do animal recuperado, você verifica que todos os basófilos, neutrófilos e eosinófilos têm a mesma MARCA. Marque no diagrama abaixo qual/quais é/são a/as célula(s) que primeiro sofreu(ram) o rearranjo



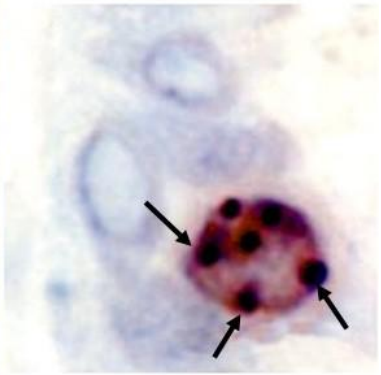
2.2 Analisando o sangue de um segundo animal recuperado, você verifica que todos os basófilos, neutrófilos, eosinófilos e monócitos têm a mesma MARCA, enquanto que os megacariócitos têm uma MARCA diferente. Quantas tipos de células-tronco da população doadora sofreram o rearranjo cromossômico? Explique



3.A glândula mamária só começa a proliferar e se desenvolver na puberdade, por isso é um modelo onde a proliferação e morfogênese podem ser estudadas. Camundongos no início da puberdade foram submetidos a uma injeção única de ^{3}H-timidina - timidina marcada radioativamente com ^{3}H (um isótopo do hidrogênio). Cinco semanas após a injeção verificou-se que 2% das células retiveram a ^{3}H-timidina (painel da esquerda, setas). Nessa 5ª semana após a injeção de ^{3}H-timidina os animais receberam uma nova injeção de um análogo da timidina, o BrdU. Dois dias depois os animais foram sacrificados e as células que incorporaram BrdU foram identificadas através de imunohistoquímica com anti-BrdU (painel da direita). Nesse ensaio, verificaram que a maioria das células que havia retido ^{3}H-timidina estavam avermelhadas (isto é, haviam incorporado BrdU). Como esse fenômeno pode ser explicado, baseado no que discutimos em aula sobre auto-renovação de células-tronco adultas/teciduais?



Células marcadas
com ^{3}H-timidina (setas)



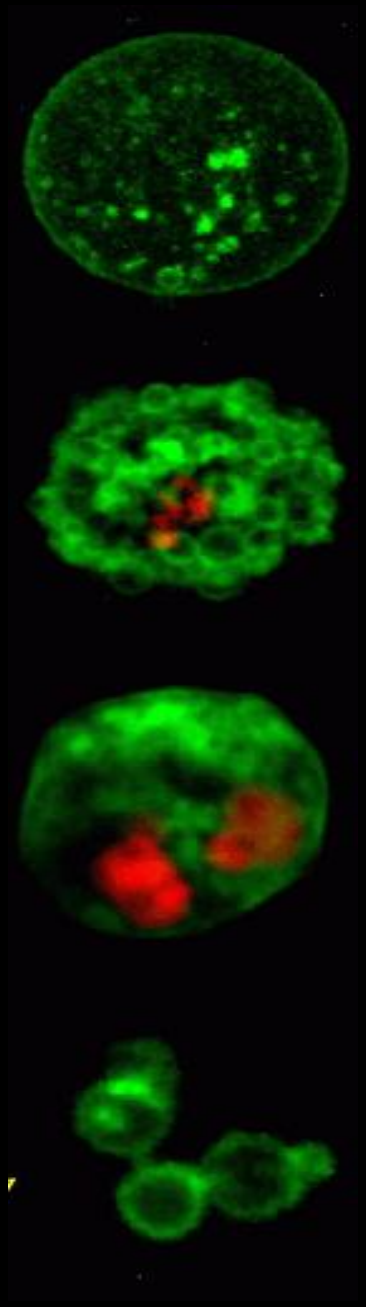
células marcadas
com ^{3}H-timidina (seta)
e anti-BrdU (avermelhado)

No início da puberdade a glândula está se formando, por isso céls-tronco estão se dividindo simetricamente para gerar mais células-tronco. Essas mais tarde se dividirão assimetricamente, gerando células progenitoras que se dividirão e diferenciarão. Ao injetar BrdU é possível então rastrear as células que proliferaram na glândula a aprtir da 5ª semana Enquanto muitas células certamente estavam marcadas só com BrdU, a maioria das que tinha retido 3H-timidina também estavam marcadas, indicando que retiveram a fita original gerada 5 semanas antes.

2.3 Você então analisa o sangue de um terceiro animal recuperado. Nesse animal você descobre que há células-tronco de medula óssea pluripotentes. Como é/são a/s MARCA(s) resultante(s) do(s) rearranjo(s) cromossômicos nesse animal?

Nesse animal TODAS as células do diagrama têm a mesma marca

MORTE CELULAR
06/06/2019

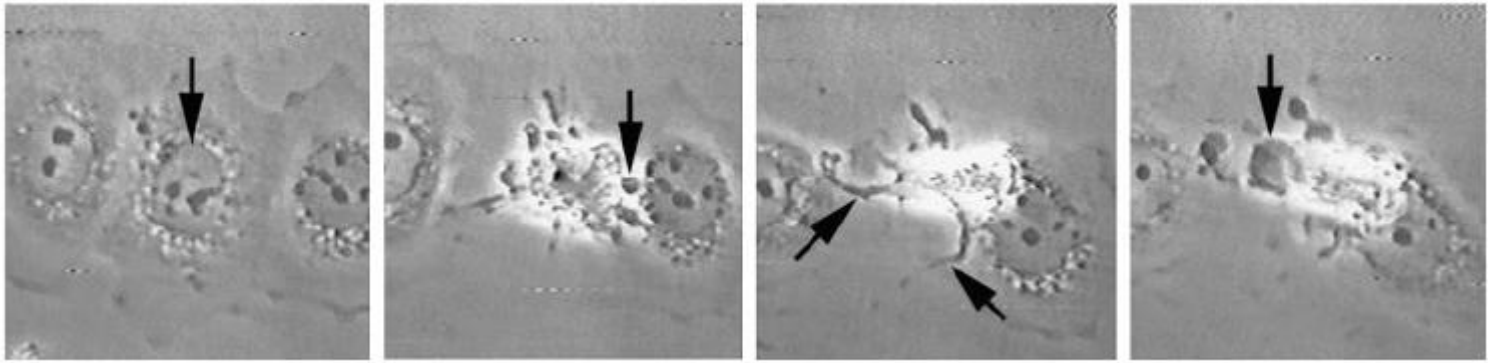


Morte Celular

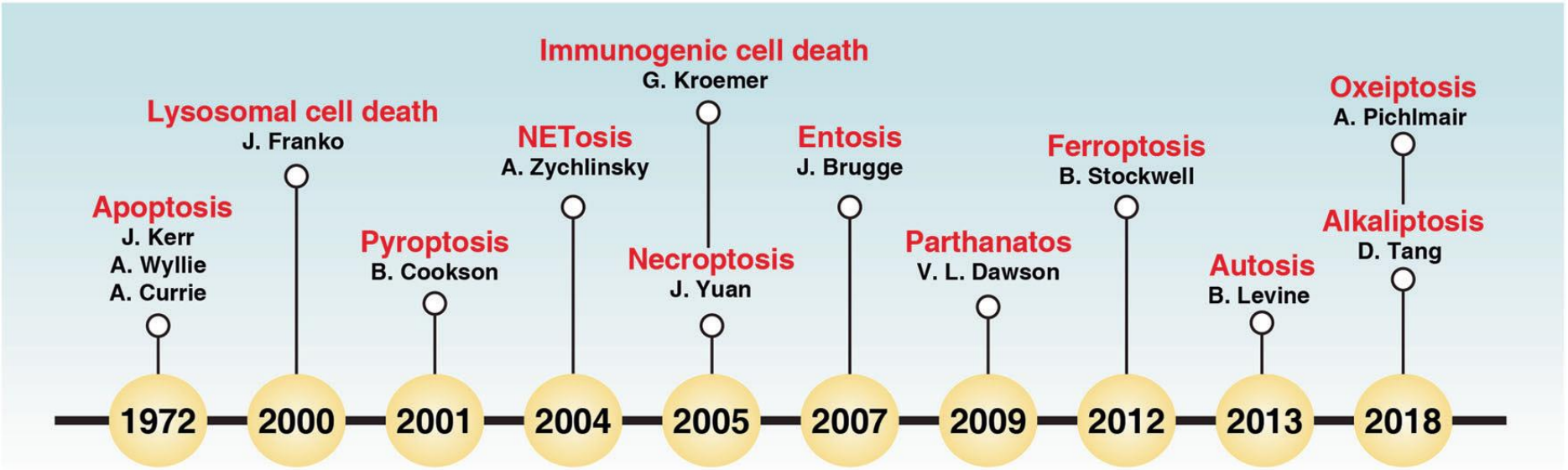
- ✓ Carl Vogt em 1842
- ✓ 1972: Kerr, Wyllie e Currie – apoptose

Kerr et al. Apoptosis: a basic phenomenon with wide-ranging implications in tissue kinetics. Br. J. Cancer 26: 239-257, 1972.

- ✓ Grego: *falling off* (folhas caindo de uma árvore)



Diferentes nomes para morte celular



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-Deiry[2], P Golstein[3], ME Peter[4], D Vaux[5], P Vandenabeele[6], B Zhivotovsky[7], MV Blagosklonny[8], W Malorni[9], RA Knight[10], M Piacentini[11], S Nagata[12] 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 Abrams[6], ES Alnemri[7], EH Baehrecke[8], MV Blagosklonny[9], WS El-Deiry[10], P Golstein[11,12,13], DR Green[14], M Hengartner[15], RA Knight[16], S Kumar[17], SA Lipton[18,19,20], W Malorni[21], G Nuñez[22], ME Peter[23], J Tschopp[24], J Yuan[25], M Piacentini[26,27], B Zhivotovsky[28] and G Melino[29,30]

2012

Cell Death and Differentiation (2012) 19, 107–120
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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 Abrams[4], ES Alnemri[5], EH Baehrecke[6], MV Blagosklonny[7], TM Dawson[8], VL Dawson[8], WS El-Deiry[9], S Fulda[10], E Gottlieb[11], DR Green[12], MO Hengartner[13], O Kepp[1,2,3], RA Knight[14], S Kumar[15,16], SA Lipton[17,18,19,20], X Lu[21], F Madeo[22], W Malorni[23,24], P Mehlen[25,26,27,28], G Nuñez[29], ME Peter[30], M Piacentini[31,32], DC Rubinsztein[33], Y Shi[34], H-U Simon[35], P Vandenabeele[36,37], E White[38], J Yuan[39], B Zhivotovsky[40], G Melino[41,42] and G Kroemer*,[1,43,44,45,46]

2015

Cell Death and Differentiation (2015) 22, 58–73
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www.nature.com/cdd

OPEN

Review

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 Vitale[5], SA Aaronson[6], JM Abrams[7], D Adam[8], ES Alnemri[9], L Altucci[10], D Andrews[11], M Annicchiarico-Petruzzelli[12], EH Baehrecke[13], NG Bazan[14], MJ Bertrand[15,16], K Bianchi[17,18], MV Blagosklonny[19], K Blomgren[20], C Borner[21], DE Bredesen[22,23], C Brenner[24,25,26], M Campanella[27], E Candi[28], F Cecconi[29,30,31], FK Chan[32], NS Chandel[33], EH Cheng[34], JE Chipuk[6], JA Cidlowski[35], A Ciechanover[36], TM Dawson[37,38], VL Dawson[37,38], V De Laurenzi[39], R De Maria[5], K-M Debatin[40], N Di Daniele[41], VM Dixit[42], BD Dynlacht[43], WS El-Deiry[44], GM Fimia[45,46], RA Flavell[47], S Fulda[48], C Garrido[49,50], M-L Gougeon[51], DR Green[52], H Gronemeyer[53], G Hajnoczky[54], JM Hardwick[55], MO Hengartner[56], H Ichijo[57], B Joseph[58], PJ Jost[59], T Kaufmann[60], O Kepp[2,4,61], DJ Klionsky[62], RA Knight[63,64], S Kumar[65,66], JJ Lemasters[67], B Levine[68,69], A Linkermann[70], SA Lipton[71,72,73,74], RA Lockshin[75], C López-Otín[76], E Lugli[77], F Madeo[78], W Malorni[79,80], J-C Marine[81,82], SJ Martin[83], J-C Martinou[84], JP Medema[85], P Meier[86], S Melino[87], N Mizushima[88], U Moll[89], C Muñoz-Pinedo[90], G Nuñez[91], A Oberst[92], T Panaretakis[58], JM Penninger[93], ME Peter[94], M Piacentini[30,46], P Pinton[95], JH Prehn[96], H Puthalakath[97], GA Rabinovich[98], KS Ravichandran[99], R Rizzuto[100], CM Rodrigues[101], DC Rubinsztein[102], T Rudel[103], Y Shi[104], H-U Simon[105], BR Stockwell[69,106], G Szabadkai[100,107], SW Tait[108,109], HL Tang[55], N Tavernarakis[110,111], Y Tsujimoto[112], T Vanden Berghe[15,16], P Vandenabeele[15,16,113], A Villunger[114], EF Wagner[115], H Walczak[116], E White[117], WG Wood[118,119], J Yuan[120], Z Zakeri[121,122], B Zhivotovsky[123,124], G Melino[28,64] and G Kroemer*[,2,3,4,61,125,126]

2018

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

Cell Death & Differentiation

REVIEW

Check for updates

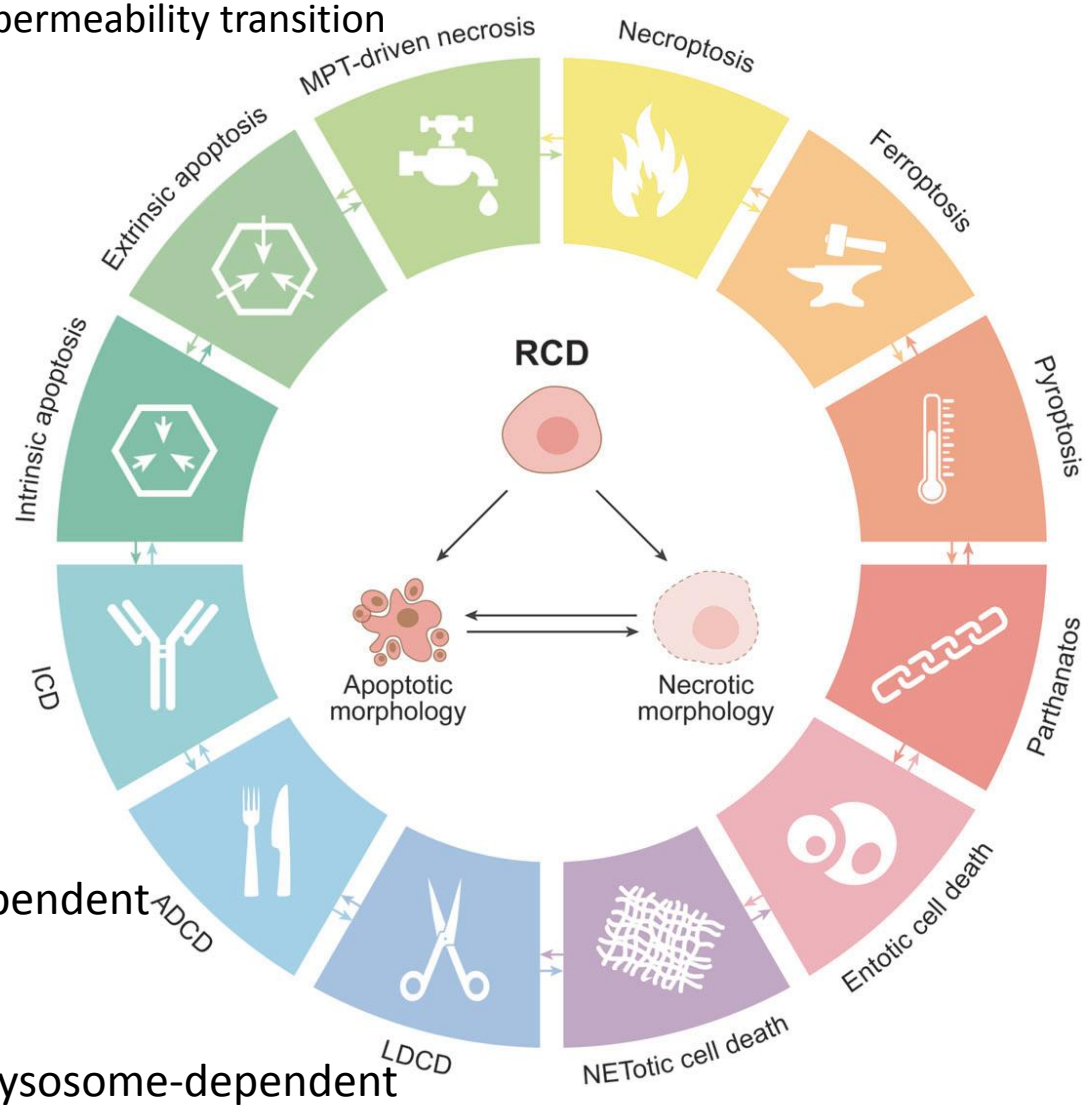
Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

Lorenzo Galluzzi[1,2,3] · Ilio Vitale[4,5] et al.

Received: 11 October 2017 / Accepted: 13 October 2017
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Principais tipos de morte celular, de acordo com o NCCD 2018 :

mitochondrial permeability transition

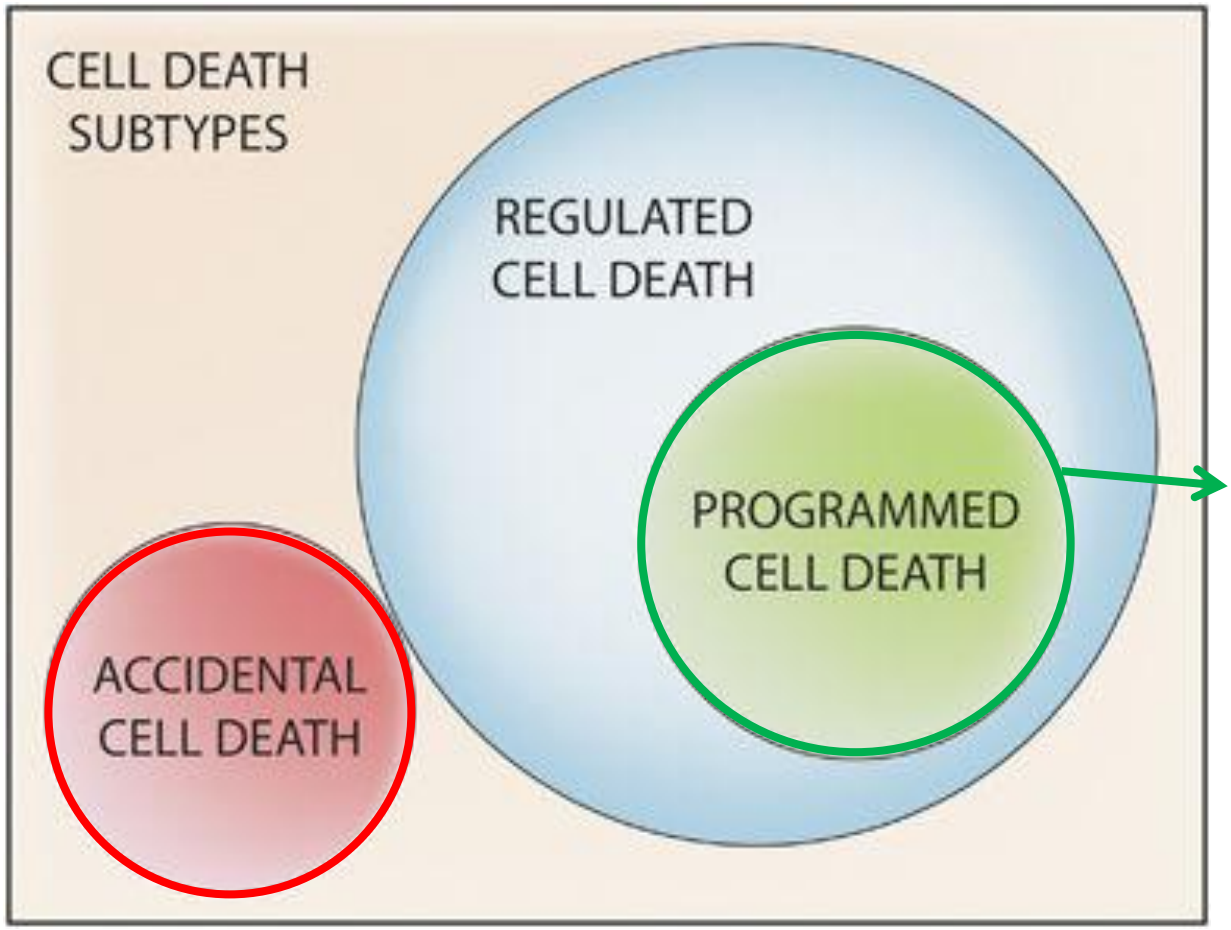


Immunogenic cell death

autophagy-dependent cell death

lysosome-dependent cell death

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



FISIOLÓGICA

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

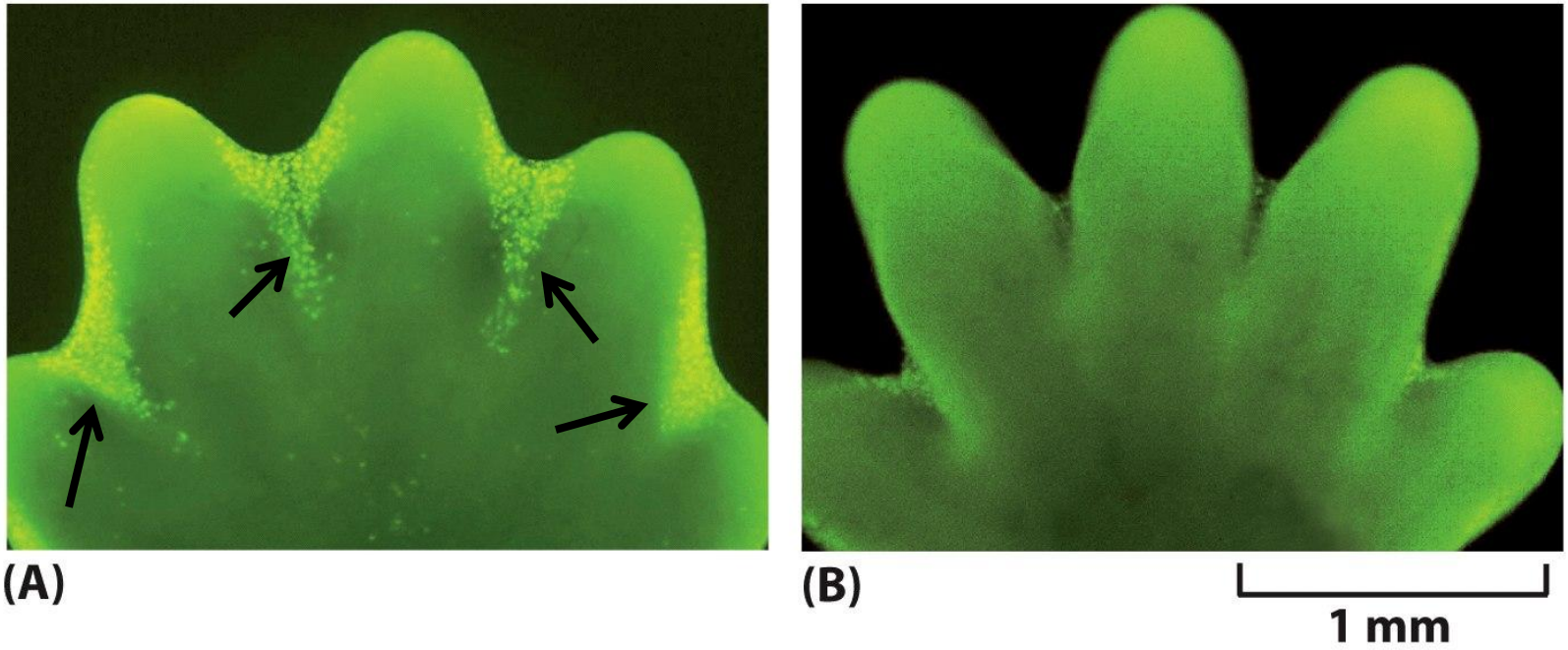
Essential *versus* accessory aspects of cell death: recommendations of the NCCD 2015

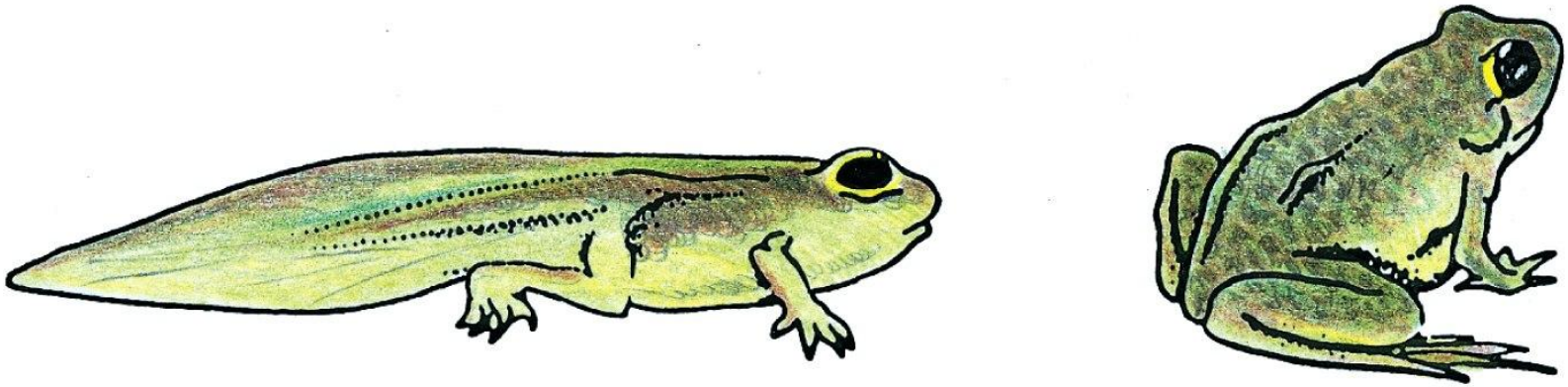
http://www.nature.com/cdd/journal/v22/n1/full/cdd2014137a.html?foxtrotcallback=true

Morte Celular Programada (*PCD*)

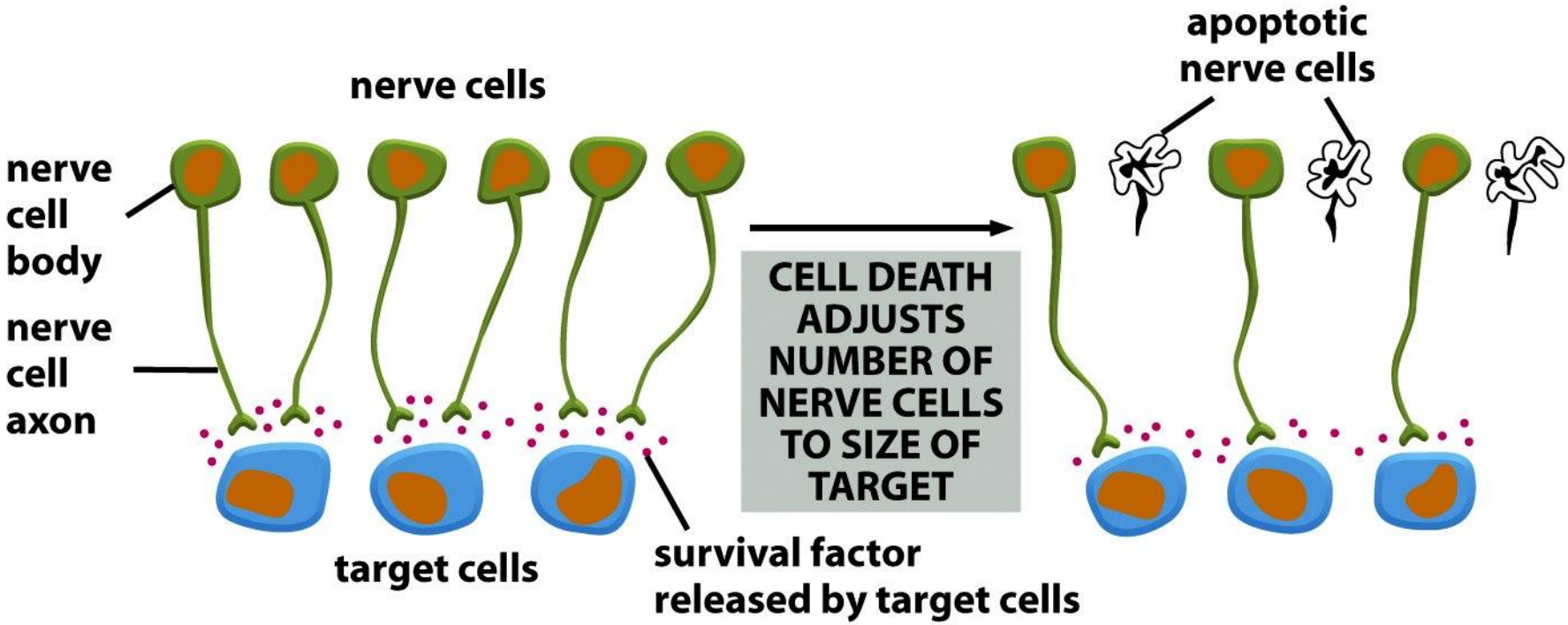
- Forma particular de morte celular regulada que ocorre em situações fisiológicas.
- NÃO ocorre em decorrência de perturbações da homeostase

Morte celular no desenvolvimento





Morte celular no desenvolvimento



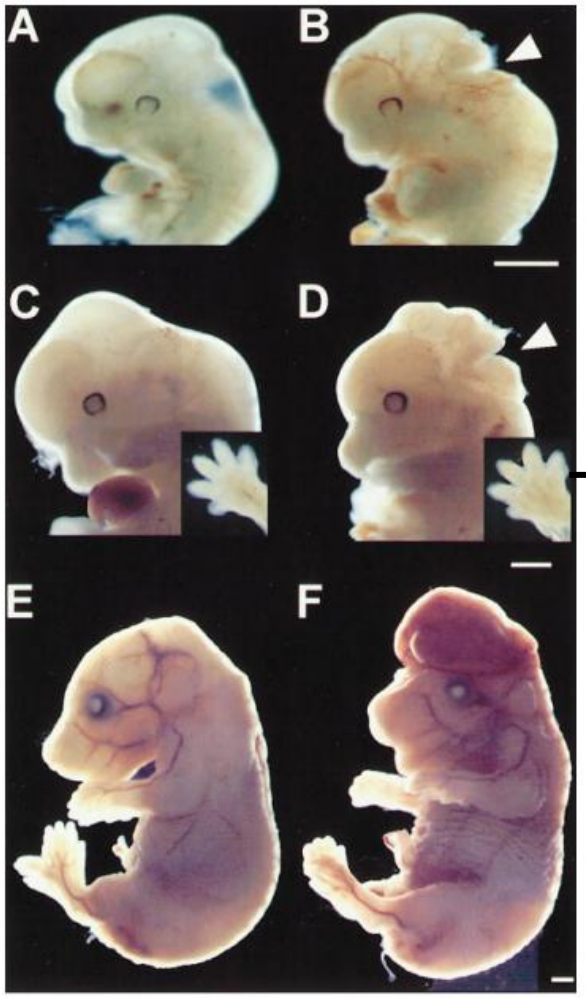
camundongos selvagens

camundongos deficientes em caspase-9

E10,5

E13,5

E16,5

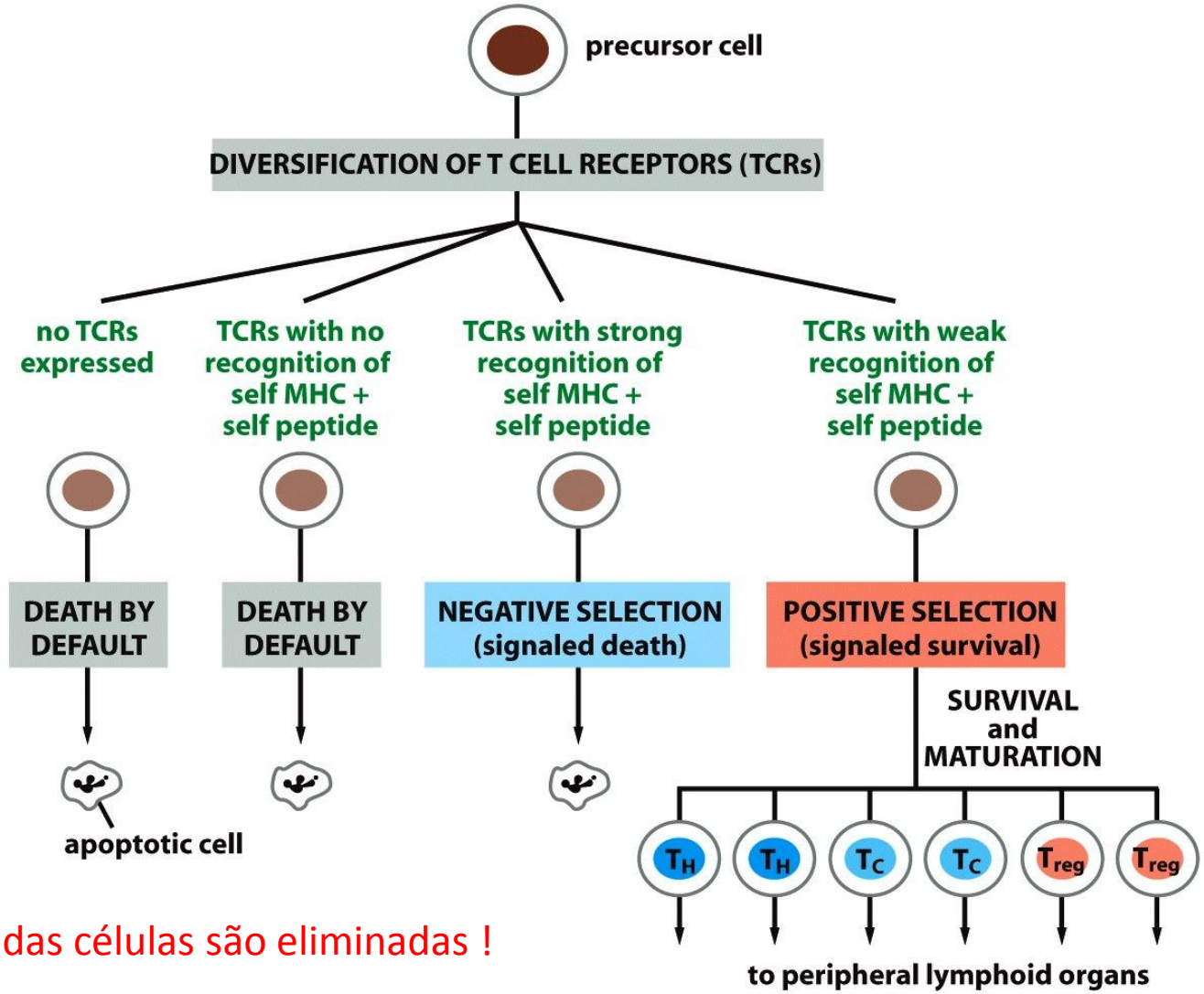


membranas interdigitais não diferem

Kuida K et al, 1998. Reduced Apoptosis and Cytochrome c–Mediated Caspase Activation in Mice Lacking Caspase 9.Cell, 94: 325–337

Morte celular no “controle de qualidade” de células do sistema imune

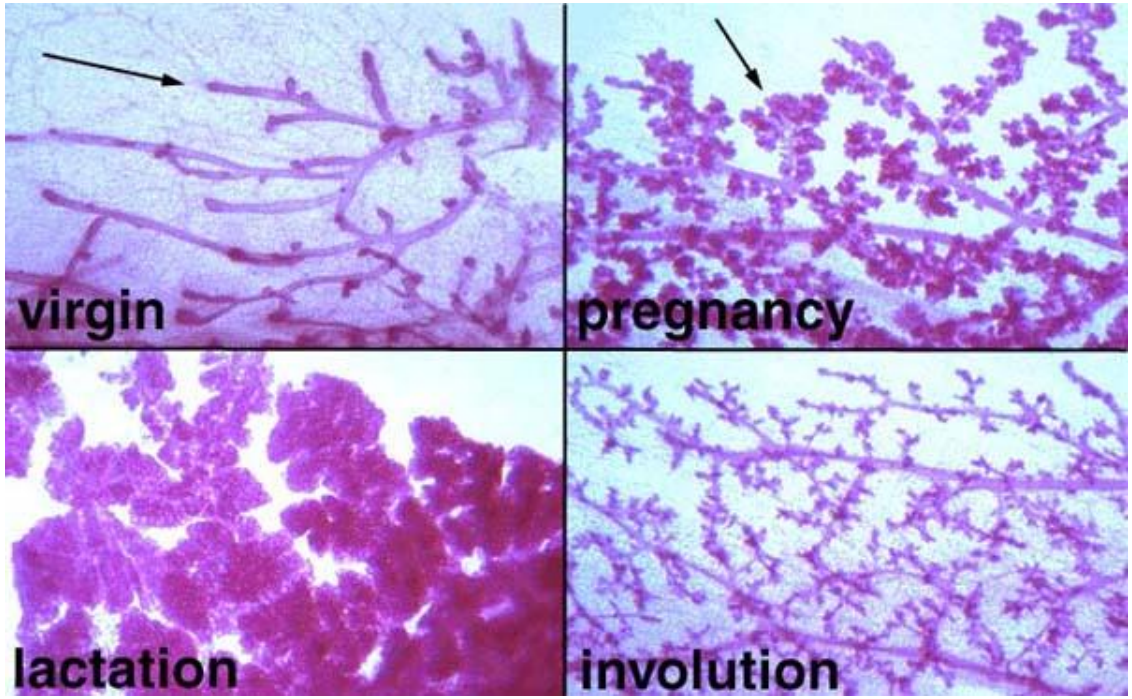
(eliminação de células T autoreativas)



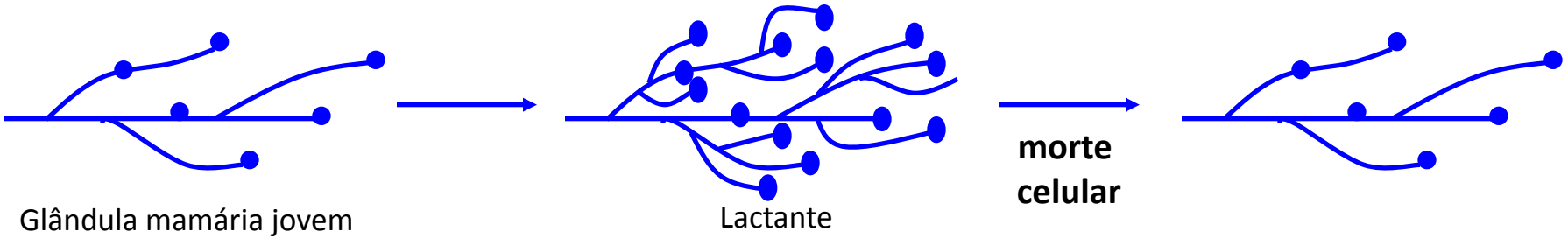
95% das células são eliminadas !

Figure 25-64 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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







Glândula mamária jovem

Lactante

Nessa aula

- Apoptose
- Autofagia
- Necroptose

apoptose

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

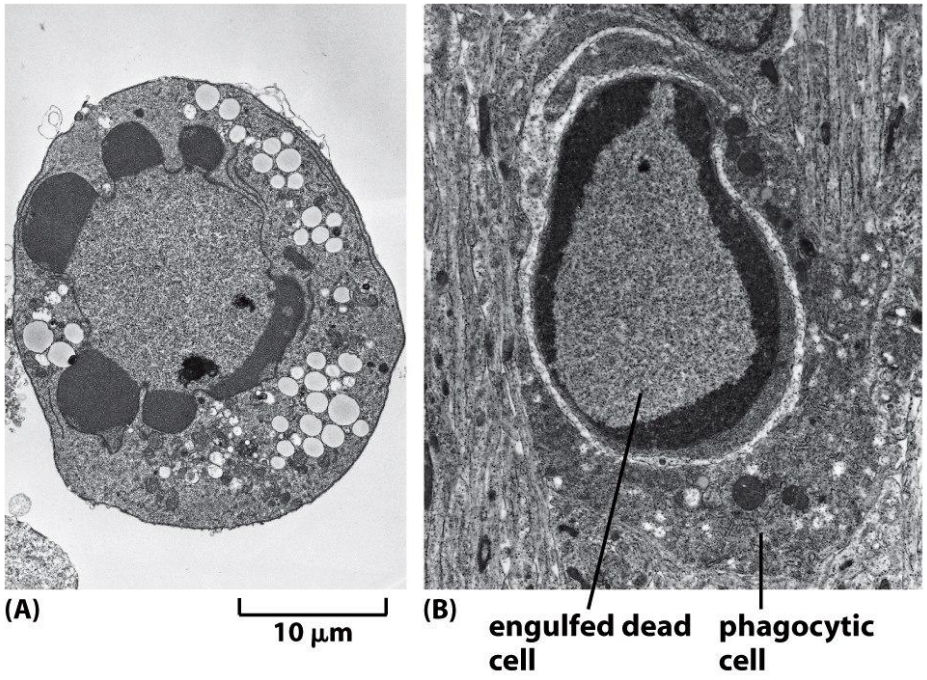


Figure 18-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

linfócito

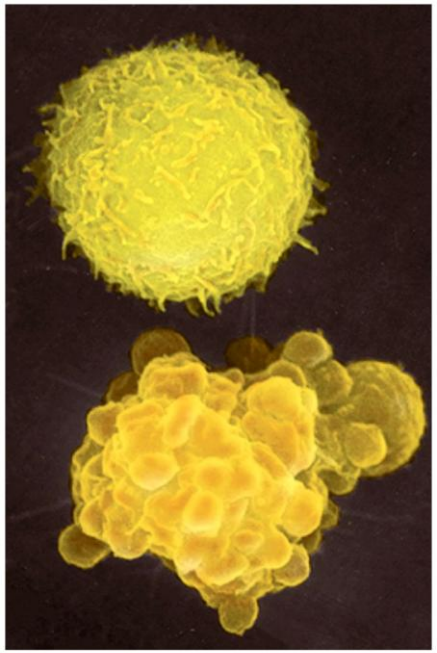


Figure 9-18a The Biology of Cancer (© Garland Science 2007)

Células HeLa

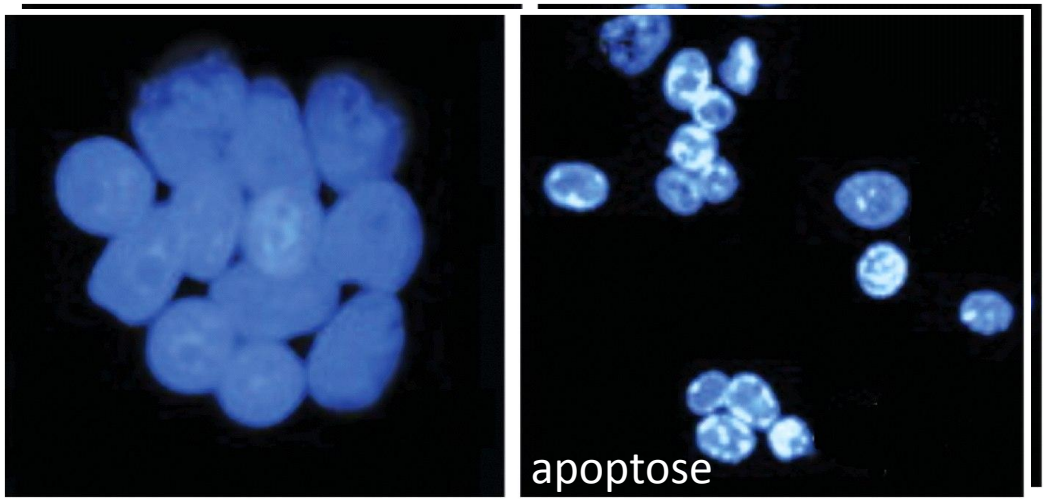


Figure 9-18b The Biology of Cancer (© Garland Science 2007)

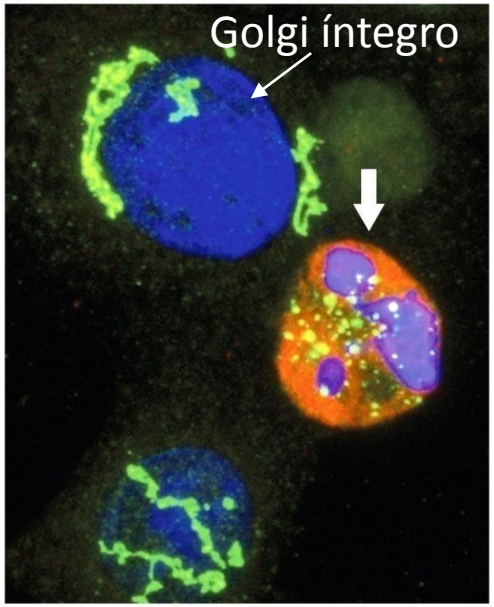


Figure 9-18d The Biology of Cancer (© Garland Science 2007)

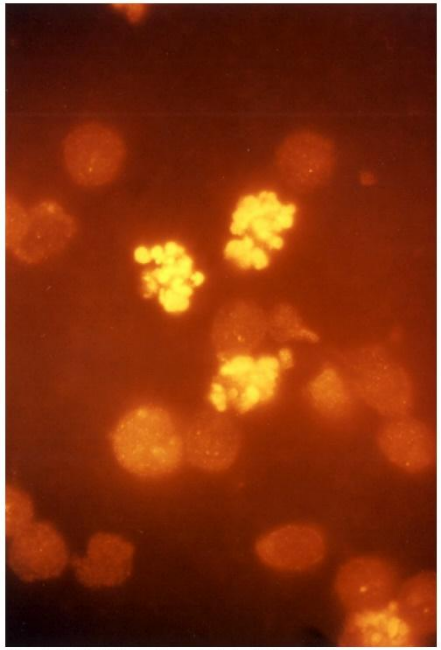


Figure 9-18e The Biology of Cancer (© Garland Science 2007)

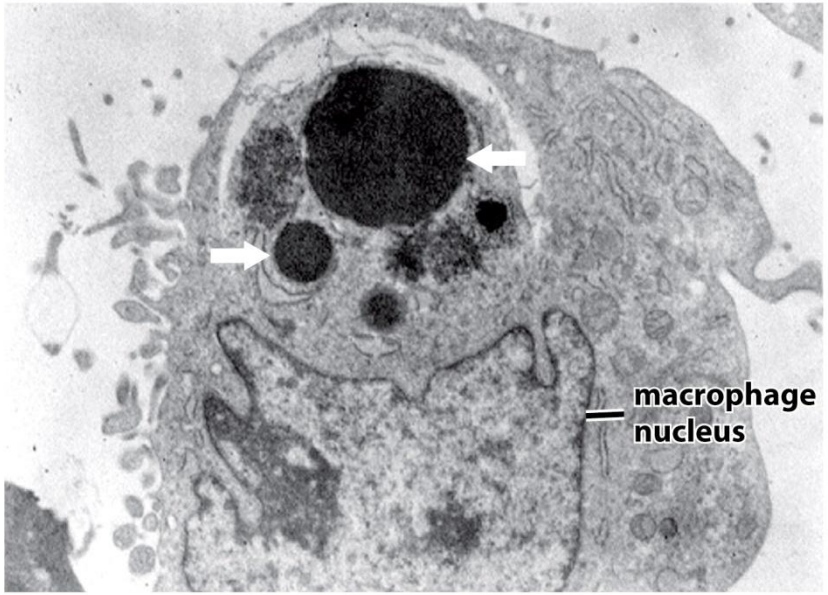
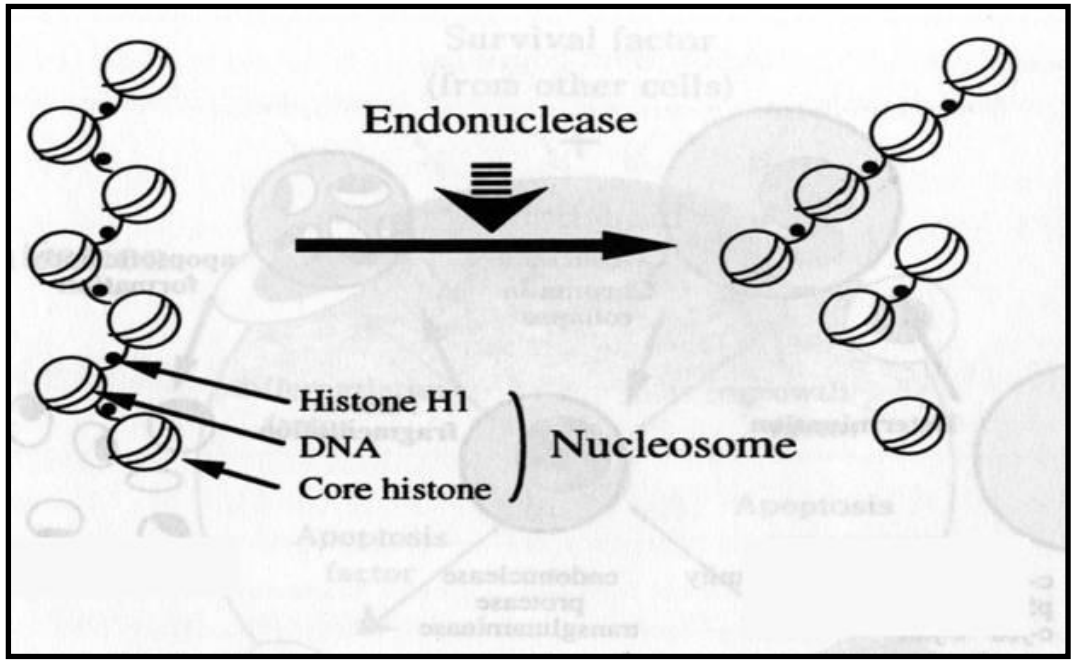
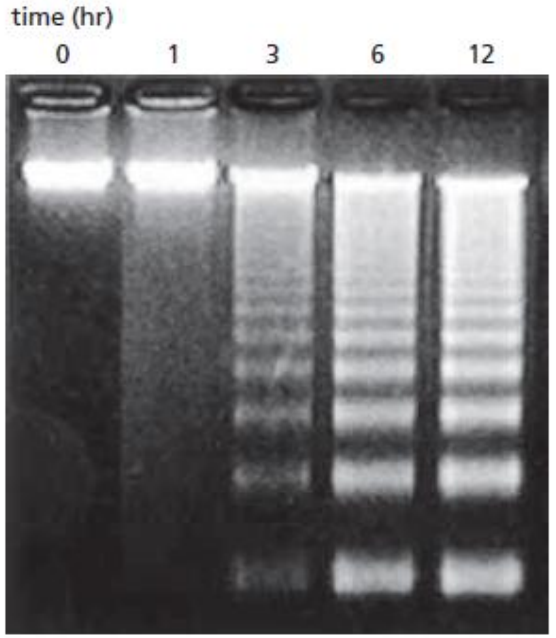


Figure 9-18f The Biology of Cancer (© Garland Science 2007)

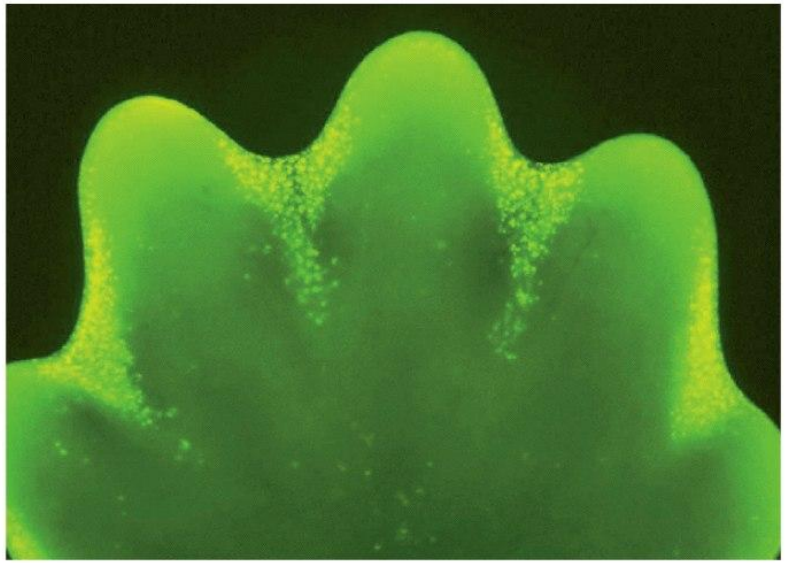
Como as células apoptóticas são experimentalmente detectas?

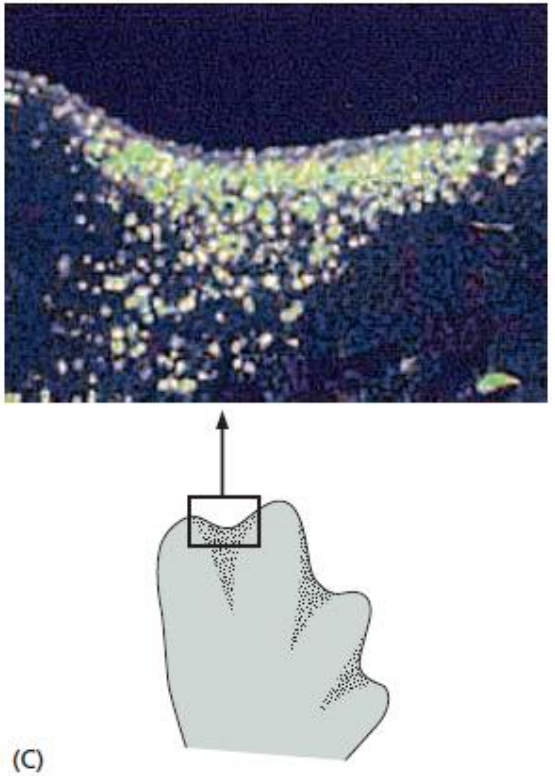
“escada” de DNA em gel de eletroforese





TdT-mediated dUTP nick end labeling (TUNEL)

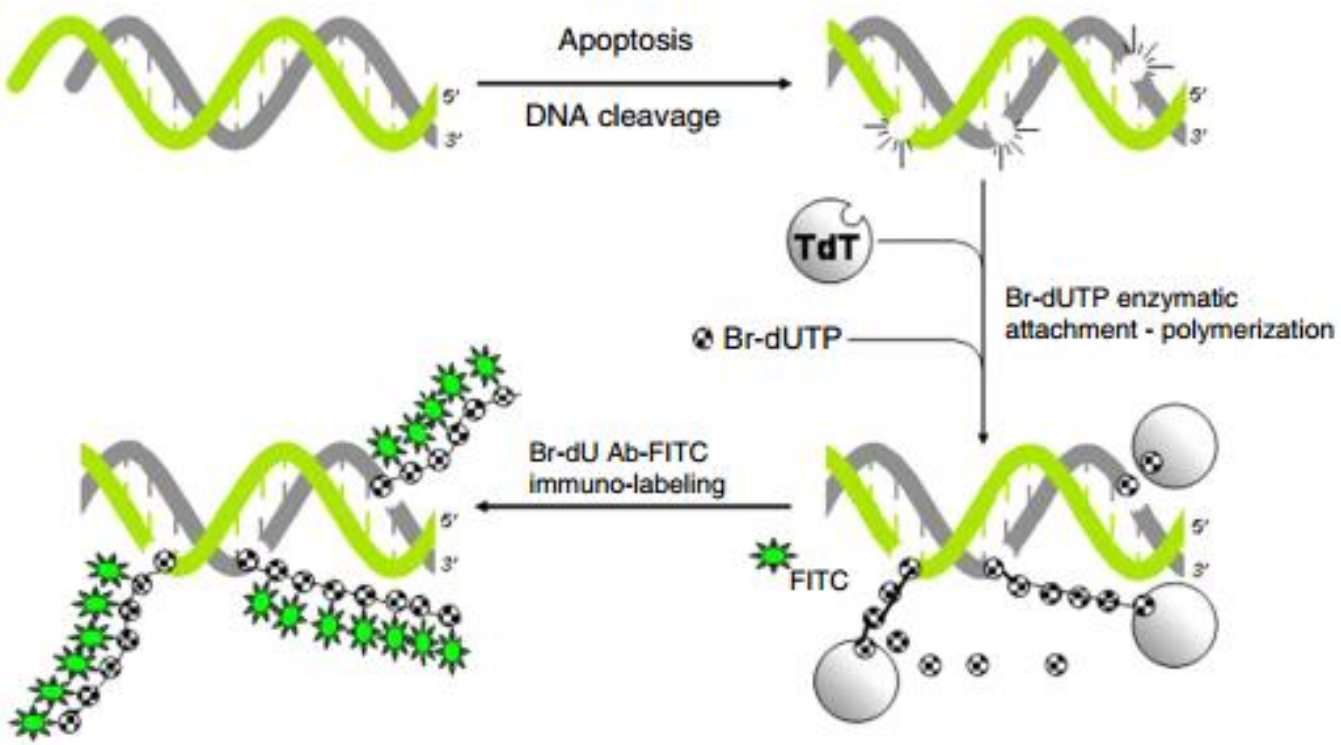




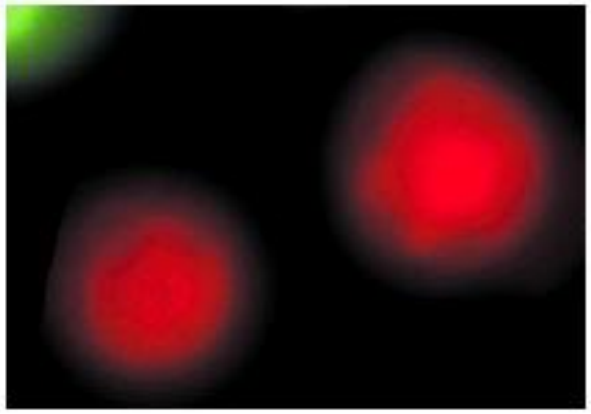
(C)

TdT-mediated dUTP nick end labeling (TUNEL)

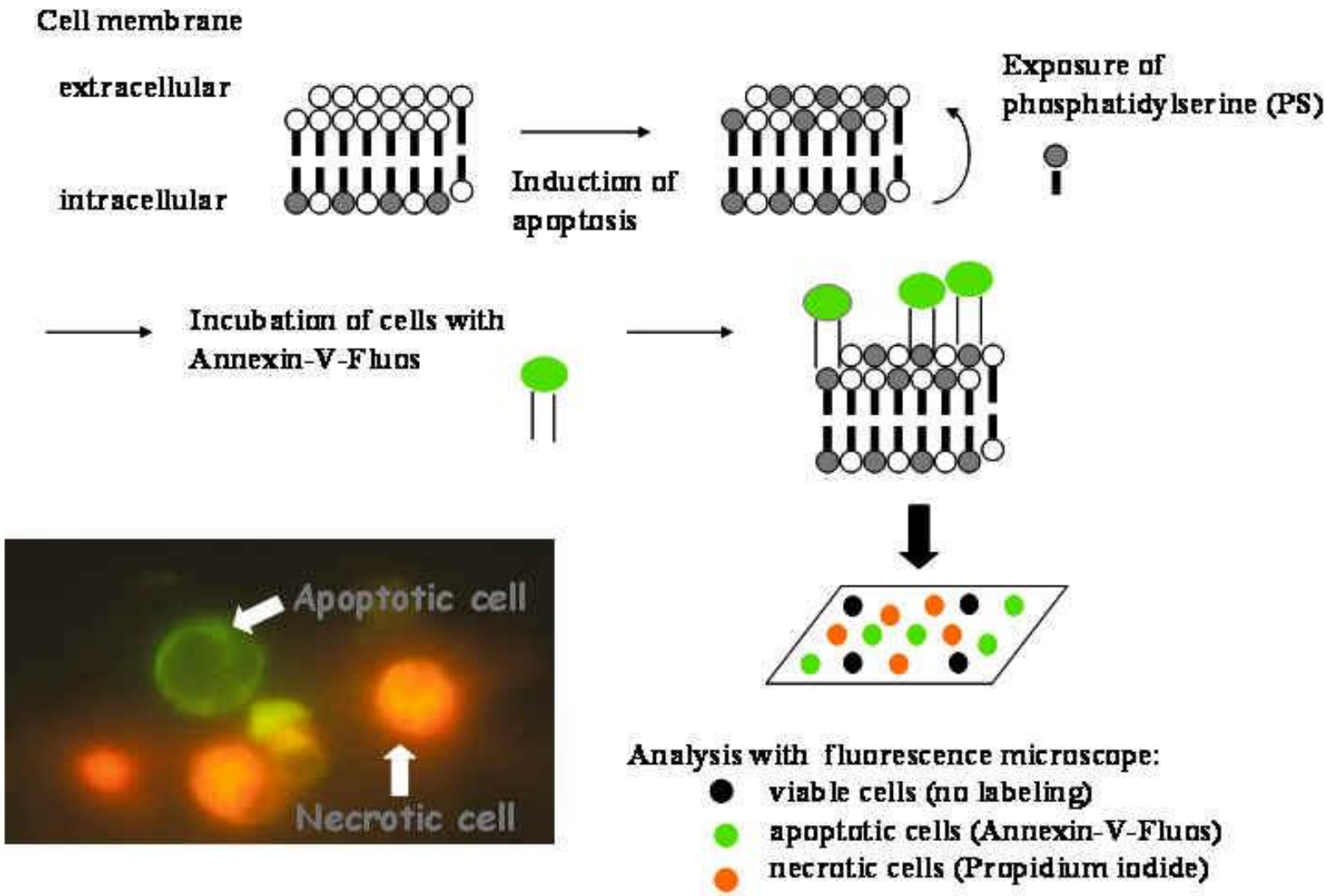
TdT = desoxinucleotidil transferase

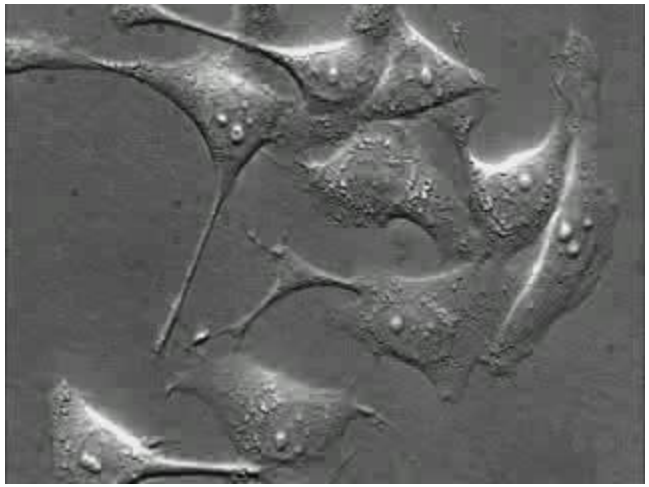


Permeabilidade da membrana



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





Caspases

(**C**ysteine-**A**spartate-**S**pecific **P**rote**ASES)**

- Enzimas responsáveis pela proteólise intracelular da apoptose

- Milhares de substratos, a maioria é desconhecido

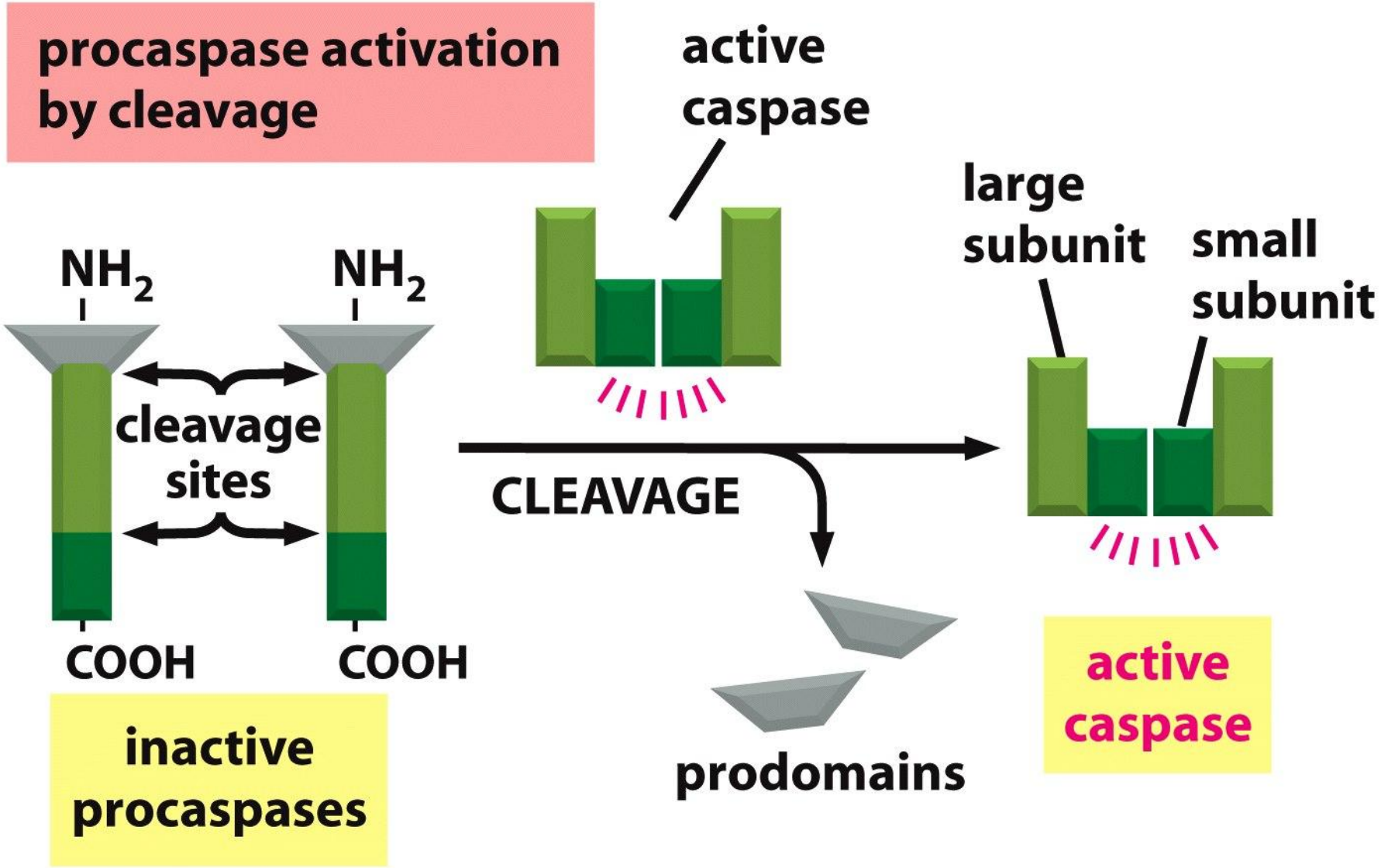


Figure 18-5a Molecular Biology of the Cell 5/e (© Garland Science 2008)

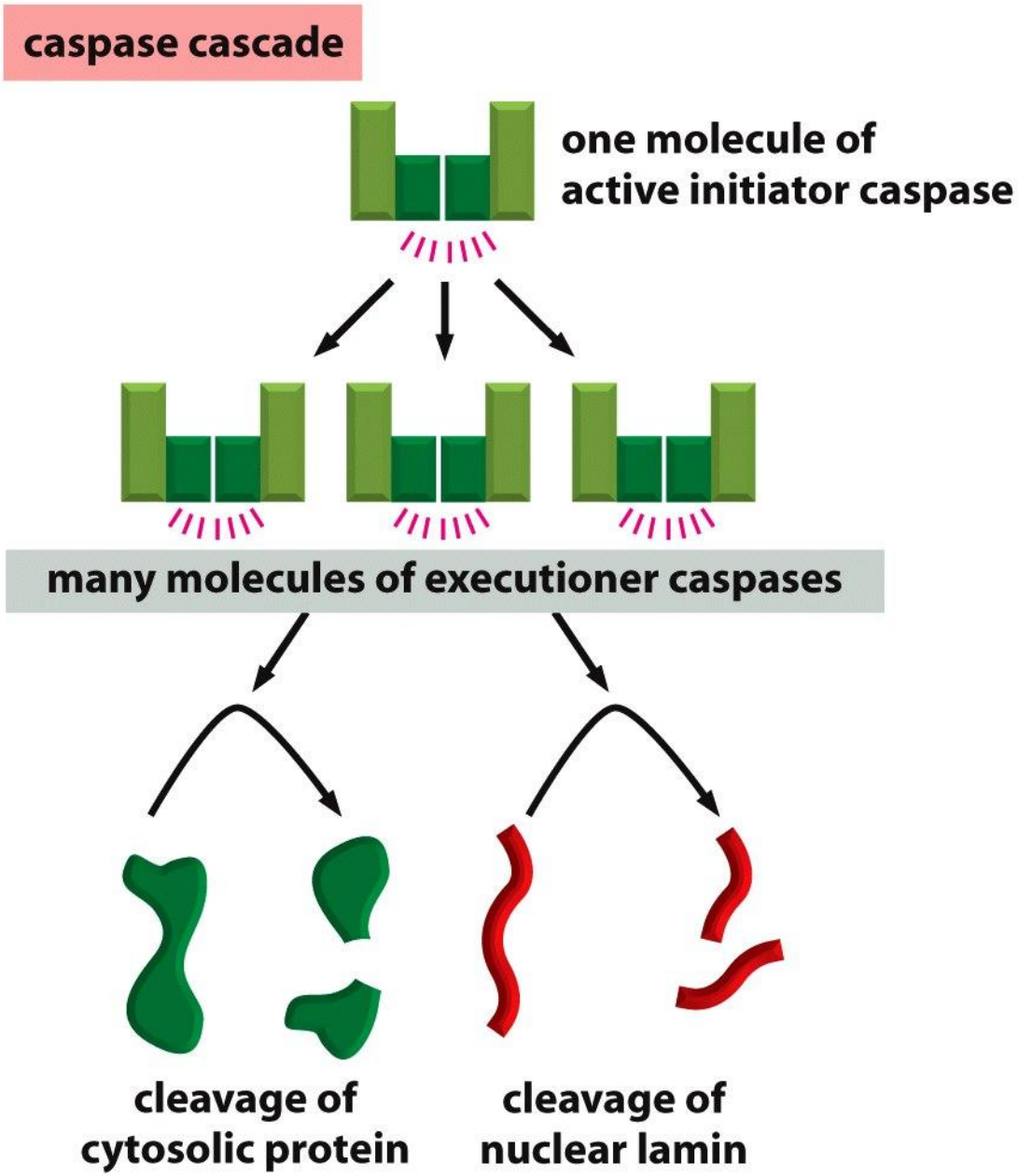


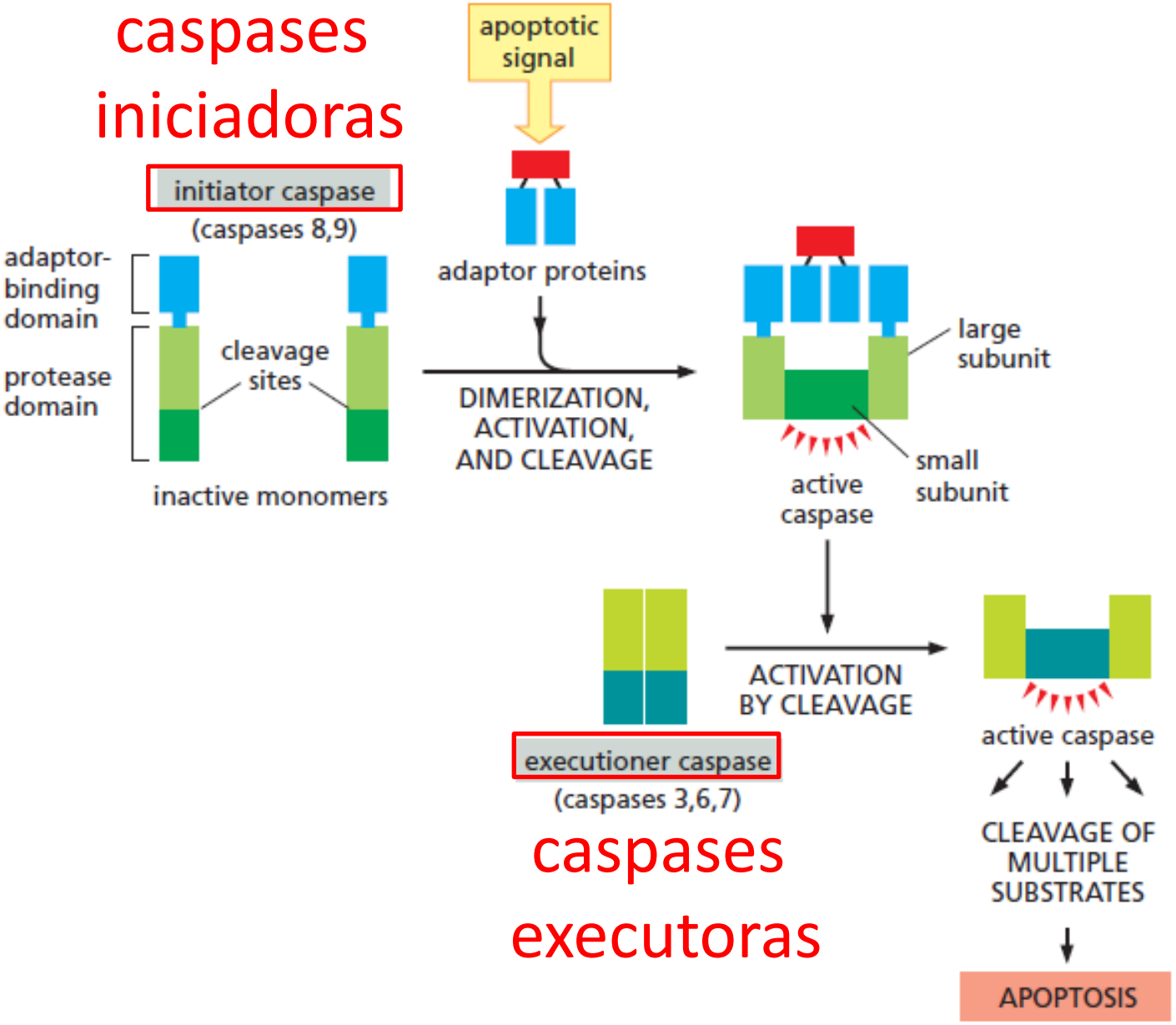
Figure 18-5b *Molecular Biology of the Cell* (© Garland Science 2008)

DOIS TIPOS DE CASPASES:

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

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

caspases iniciadoras

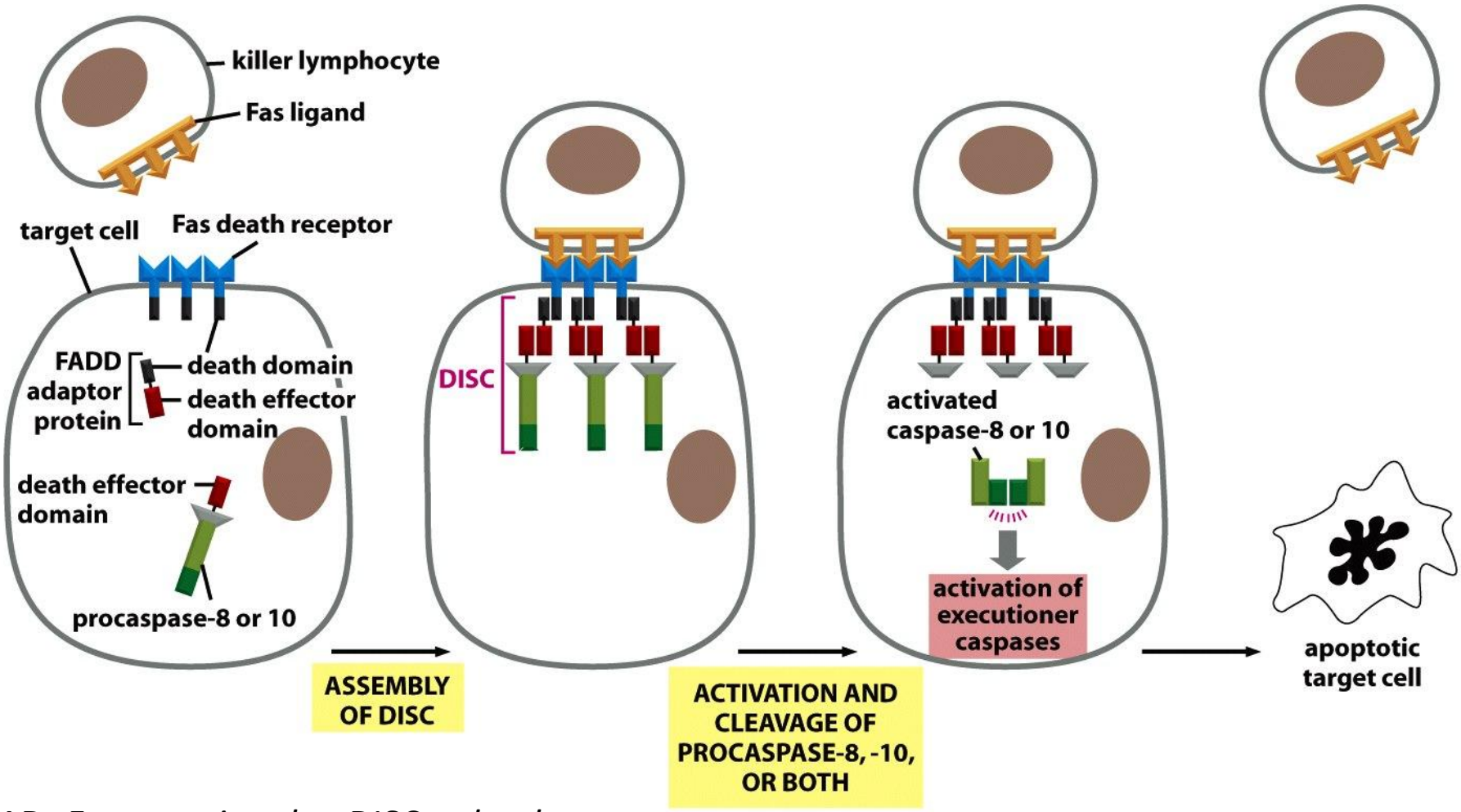


caspases executoras

Há 2 vias de sinalização que ativam as caspases

- Via extrínsica
- Via intrínsica

Via extrínsica



FAAD=*Fas-associated death domain*

DISC = *death-induced signaling complex*

Exemplo típico de indução de apoptose pela via extrínsica

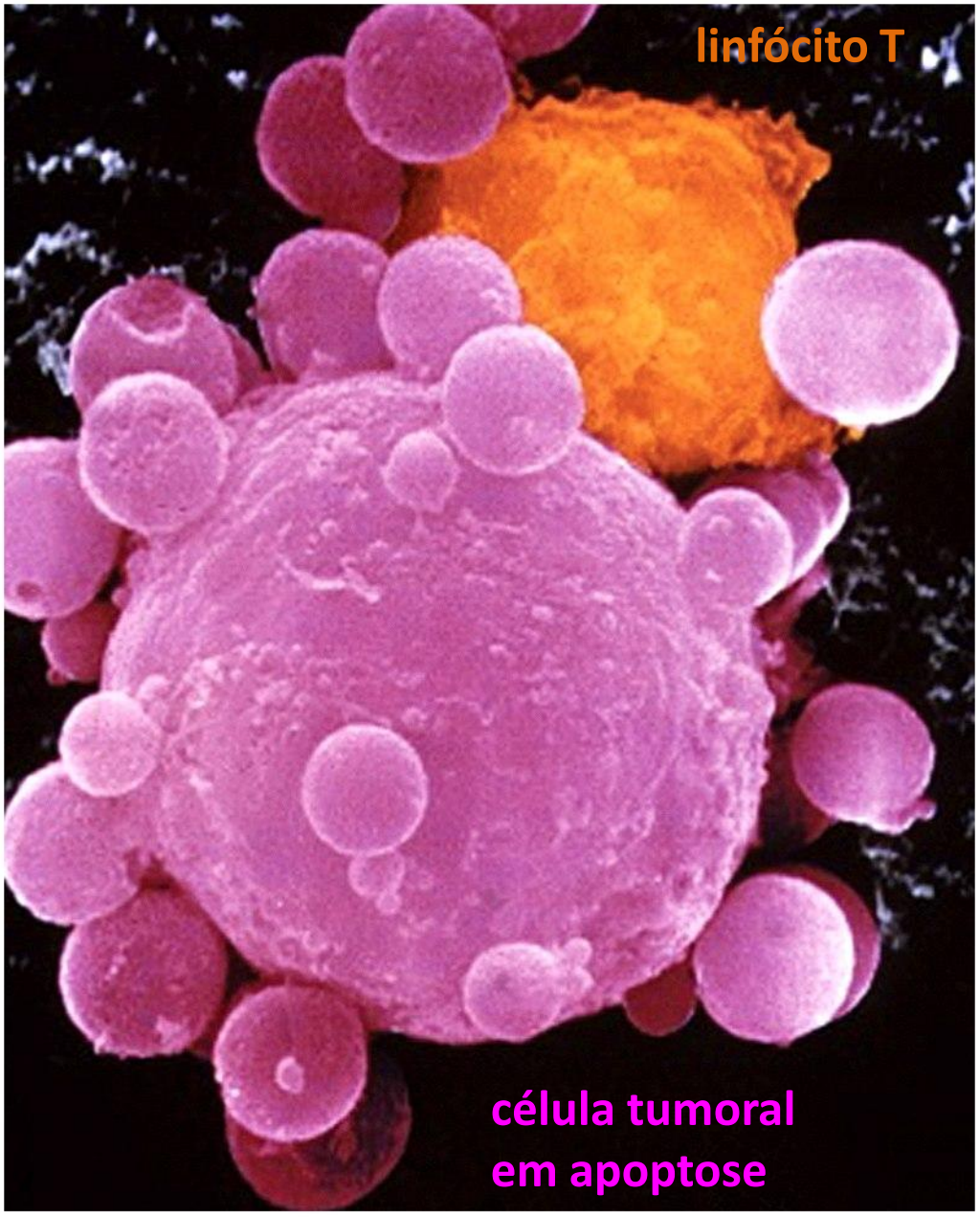
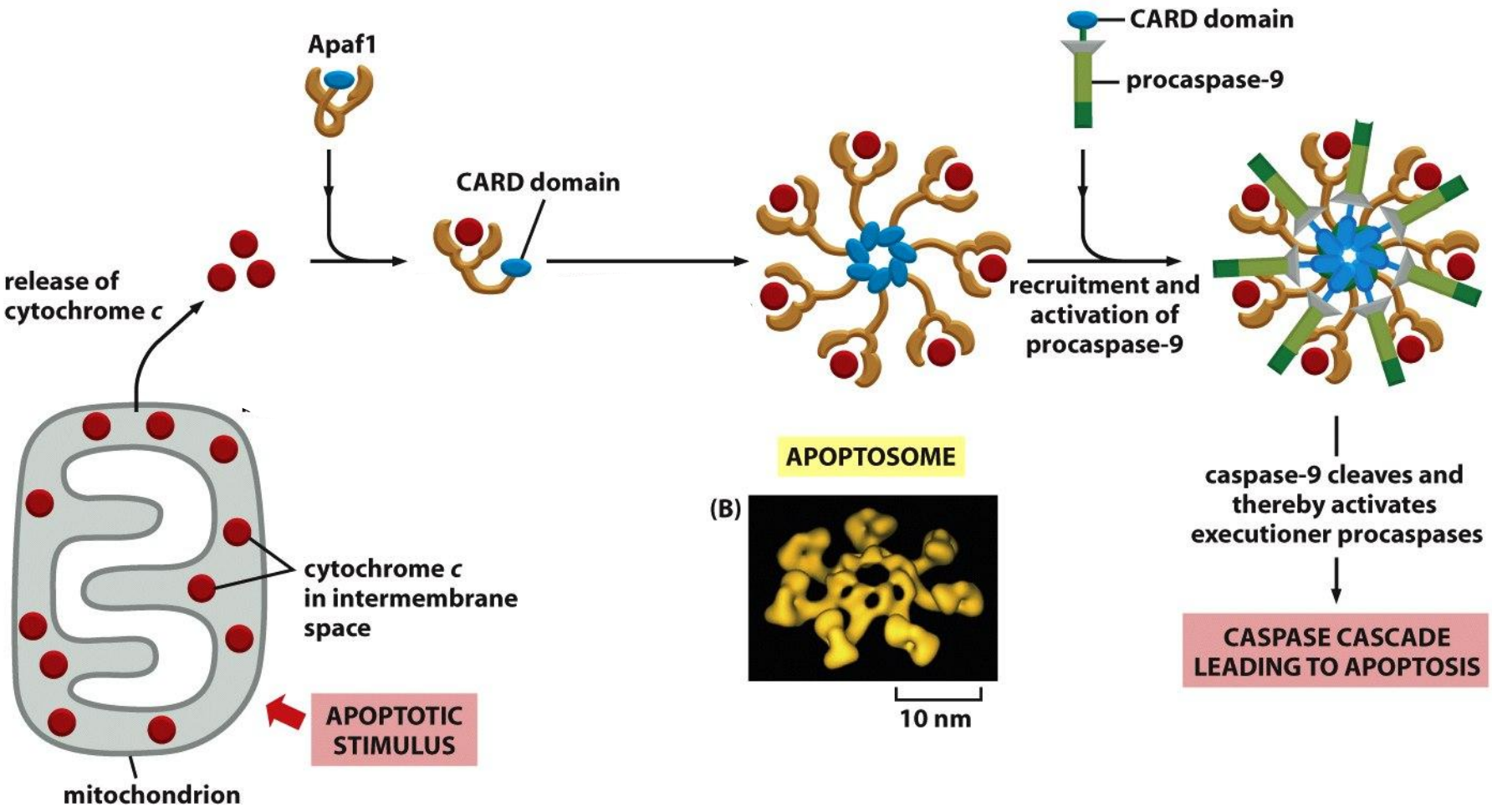


Figure 9-31c The Biology of Cancer (© Garland Science 2007)

Via intrínsica



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

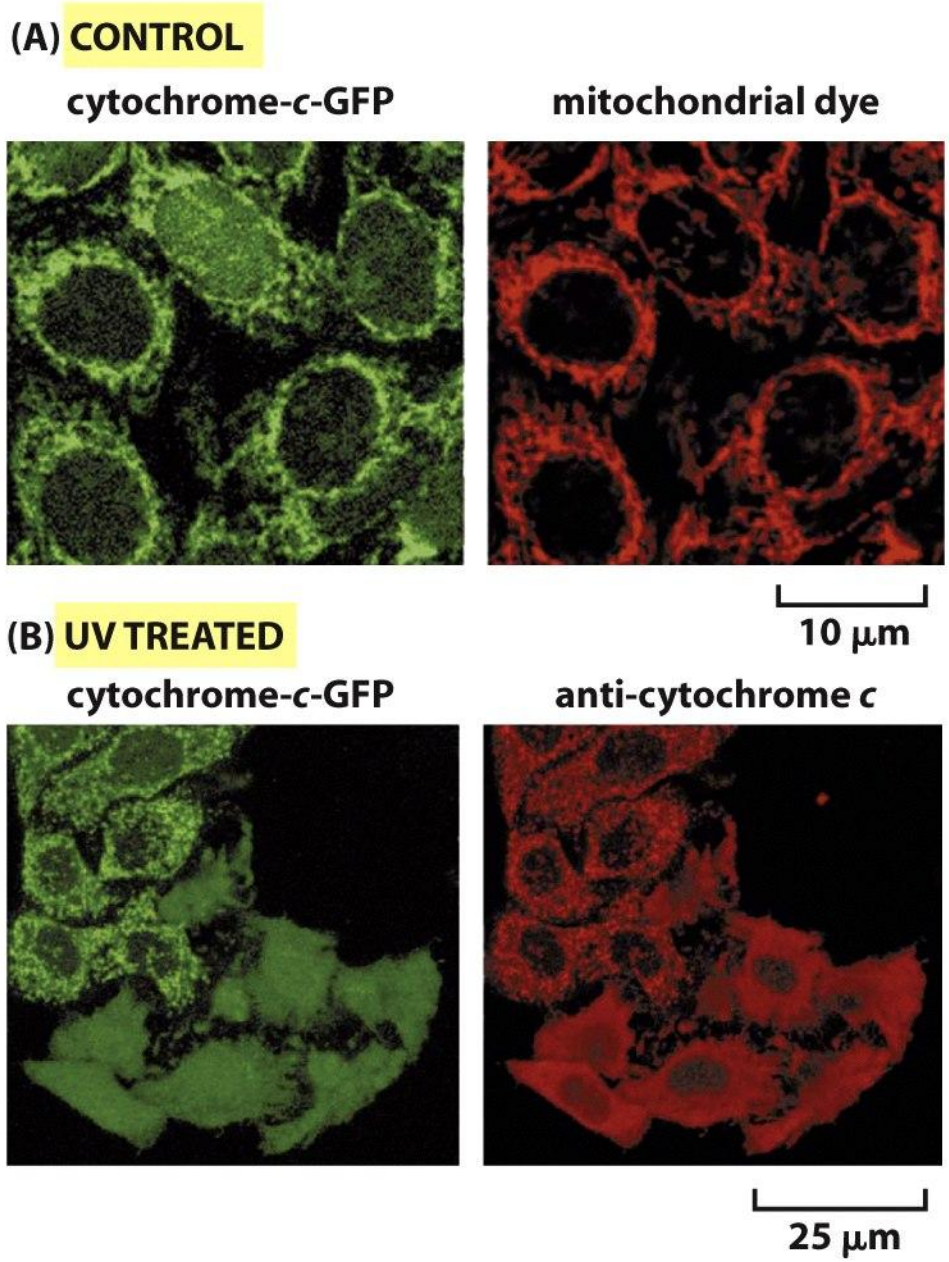
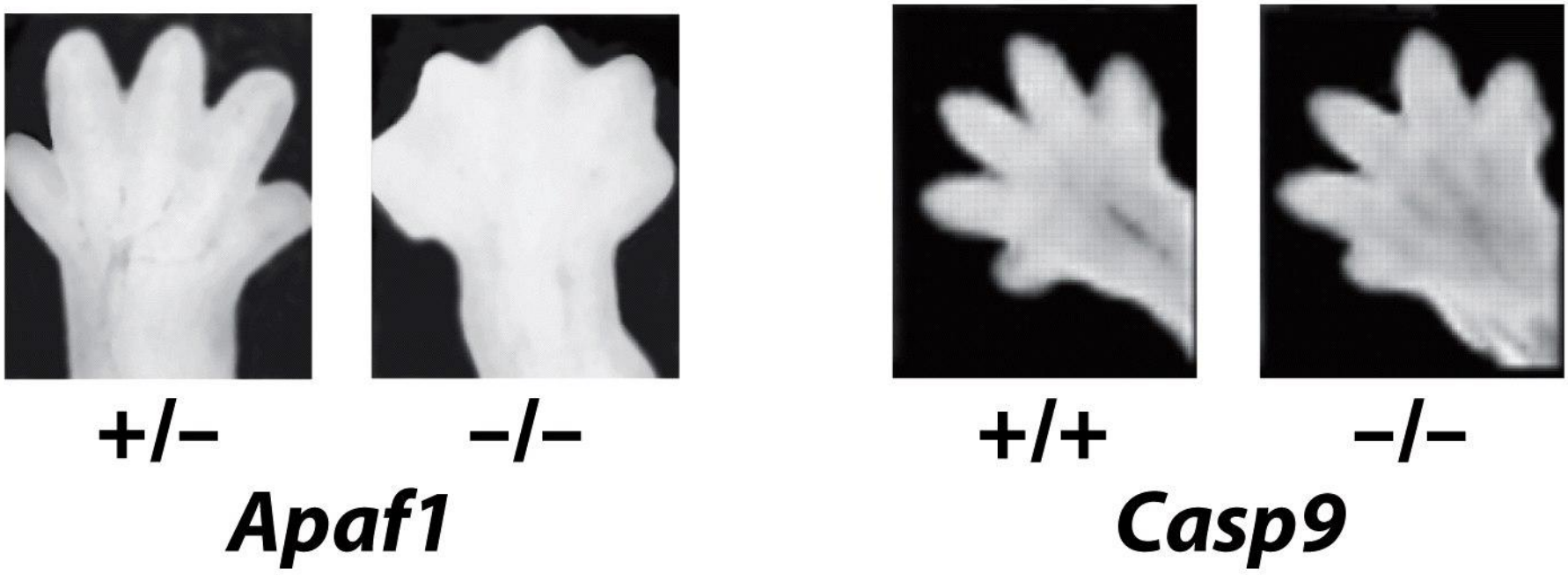


Figure 18-7 *Molecular Biology of the Cell* (© Garland Science 2008)



animais Casp9 -/- não diferem dos selvagens, sugerindo que nas células da membrana interdigital Apaf ativa uma OUTRA caspase

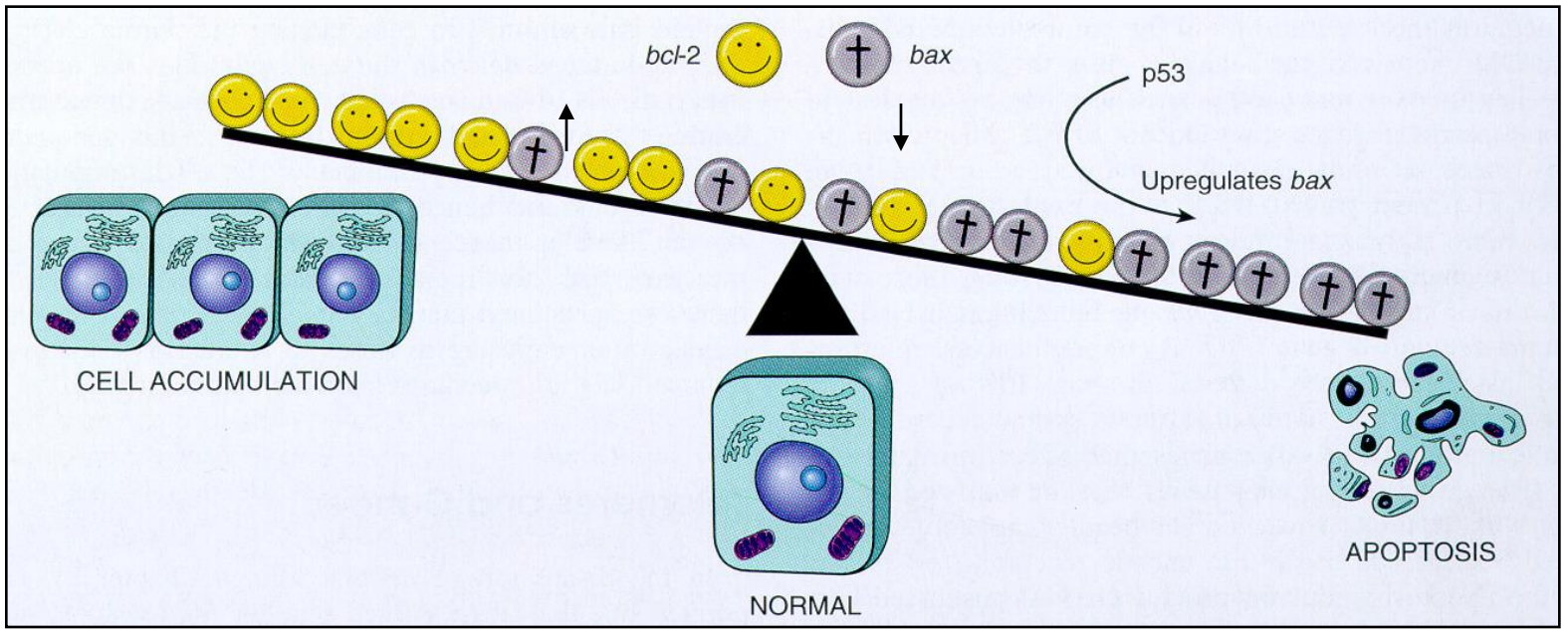
A família Bcl-2

• Originalmente detectadas em uma translocação de linfoma folicular de células B (***B*-*c*ell *l*ymphoma**)

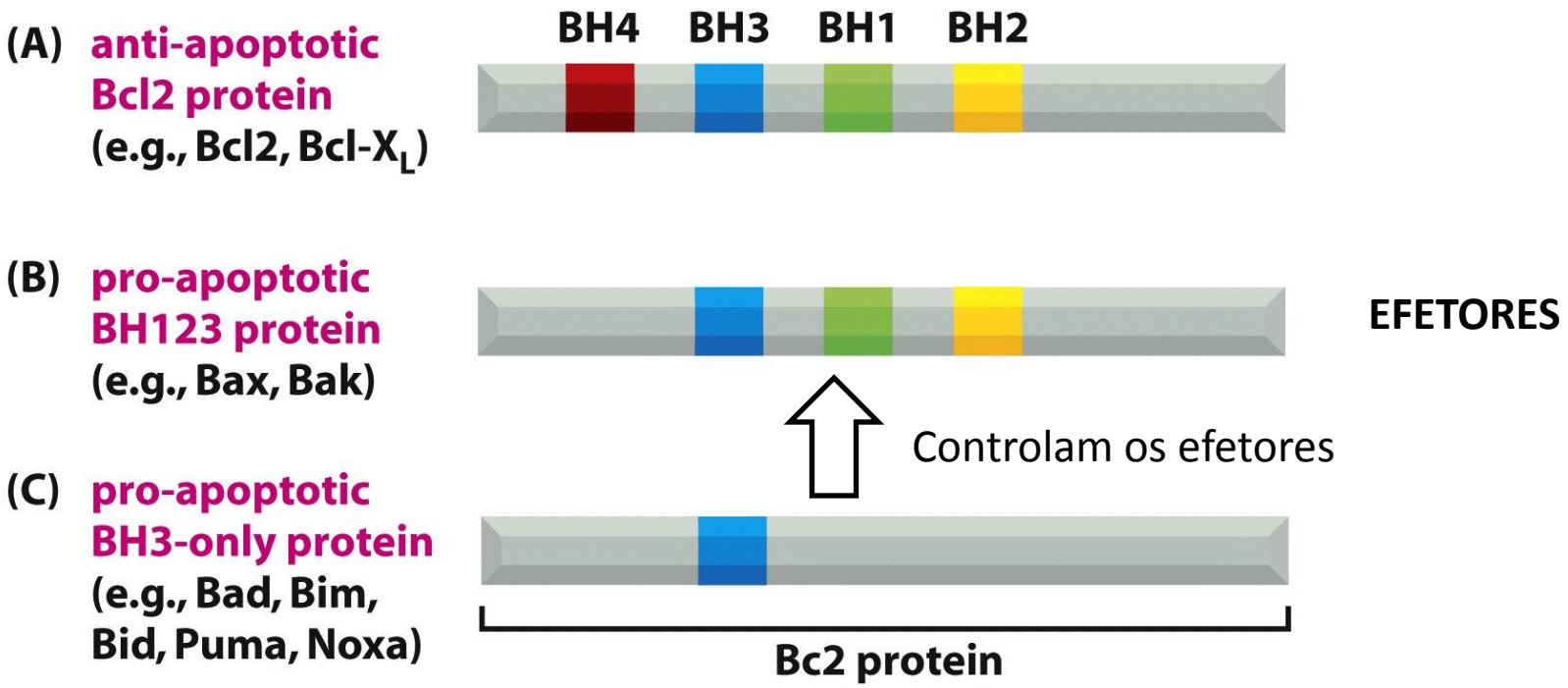
• controlam a liberação de citocromo C

•anti-apoptóticos – bloqueiam a liberação de cyt C

•pró-apoptóticos – estimulam a liberação de cyt C

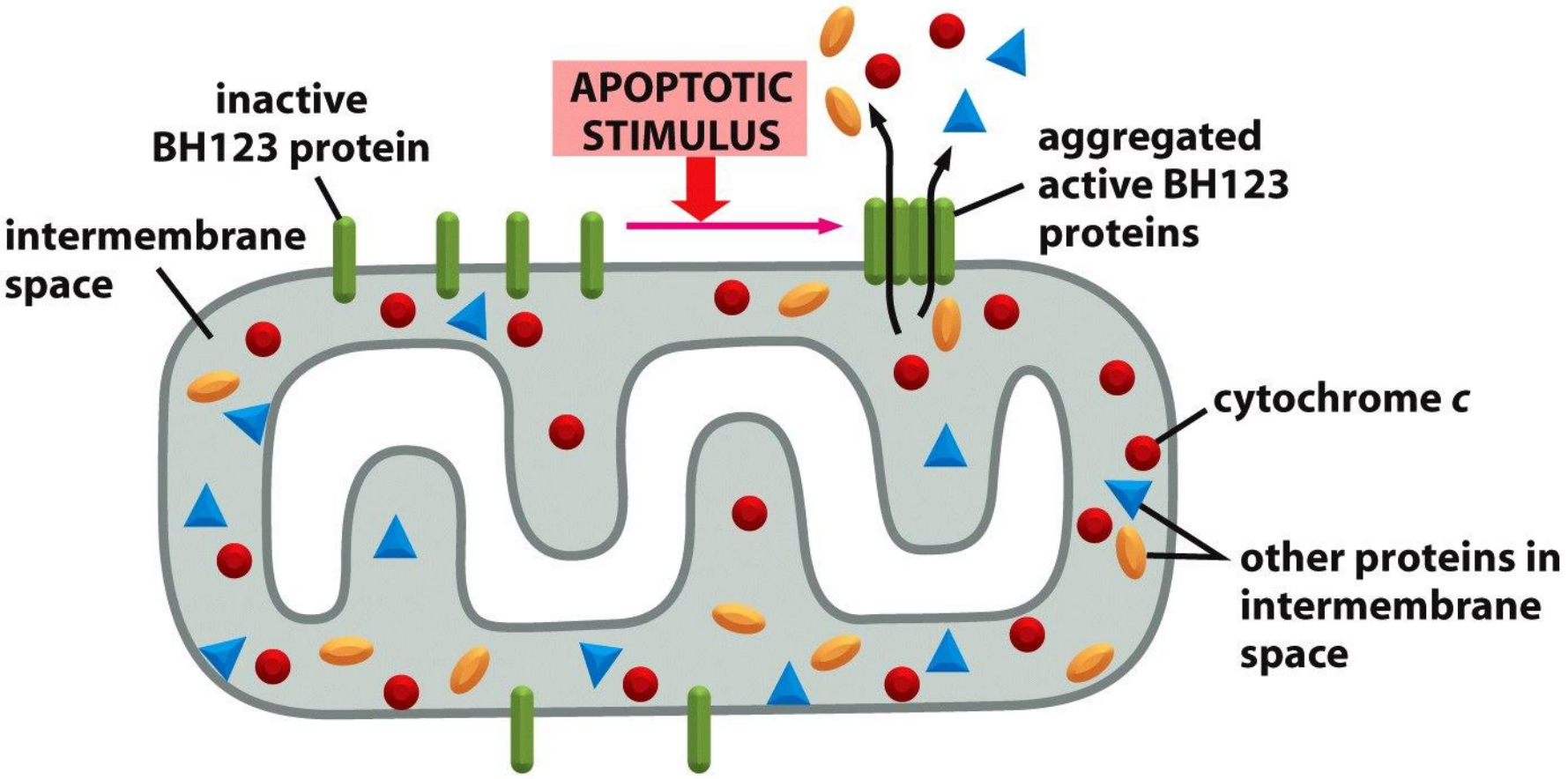


Membros da família Bcl2

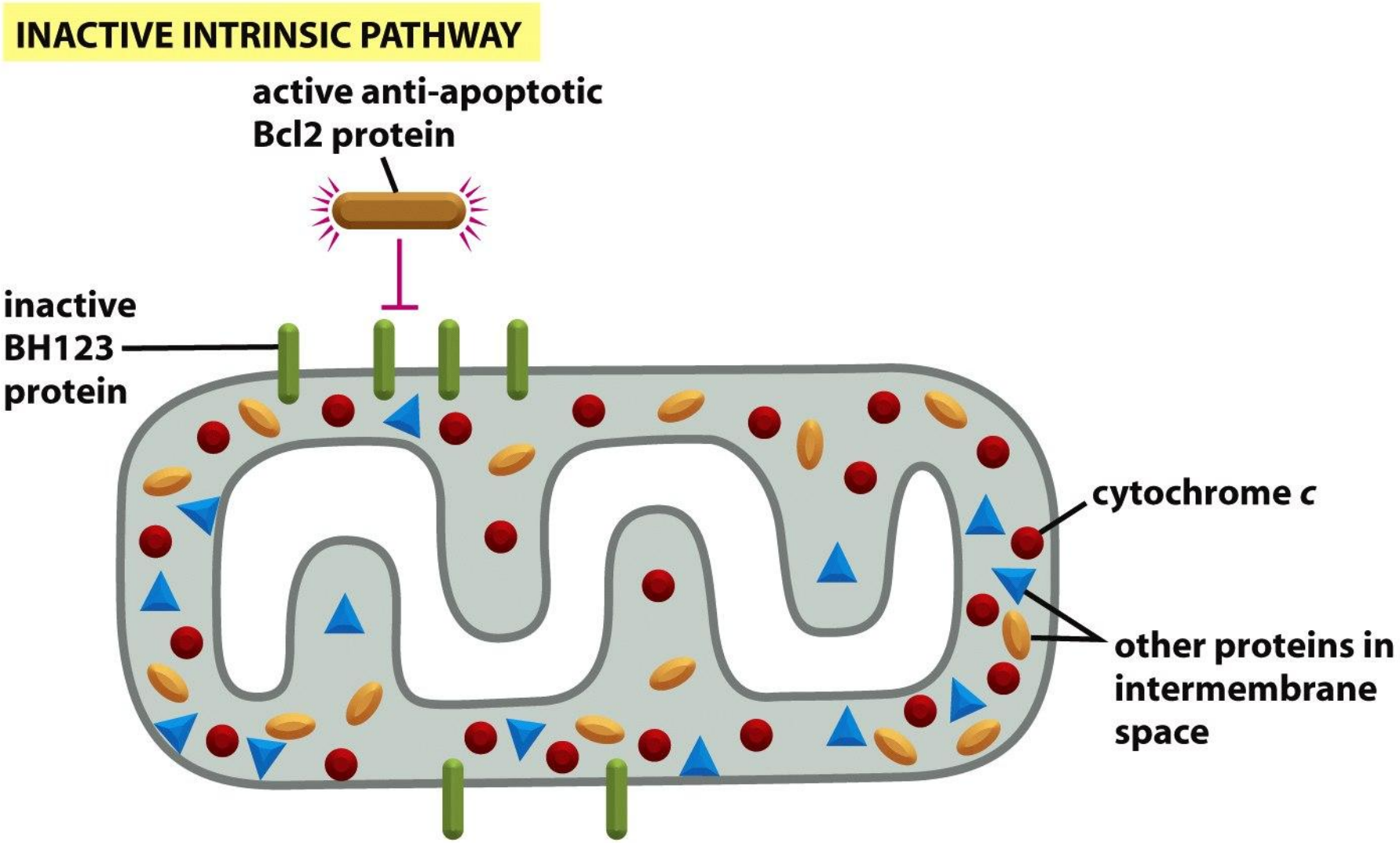


BH = *Bcl-2 homology*

Como os pró-apoptóticos atuam



Se um ANTI-apoptótico estiver ativo, esse inibe os PRÓ-apoptóticos



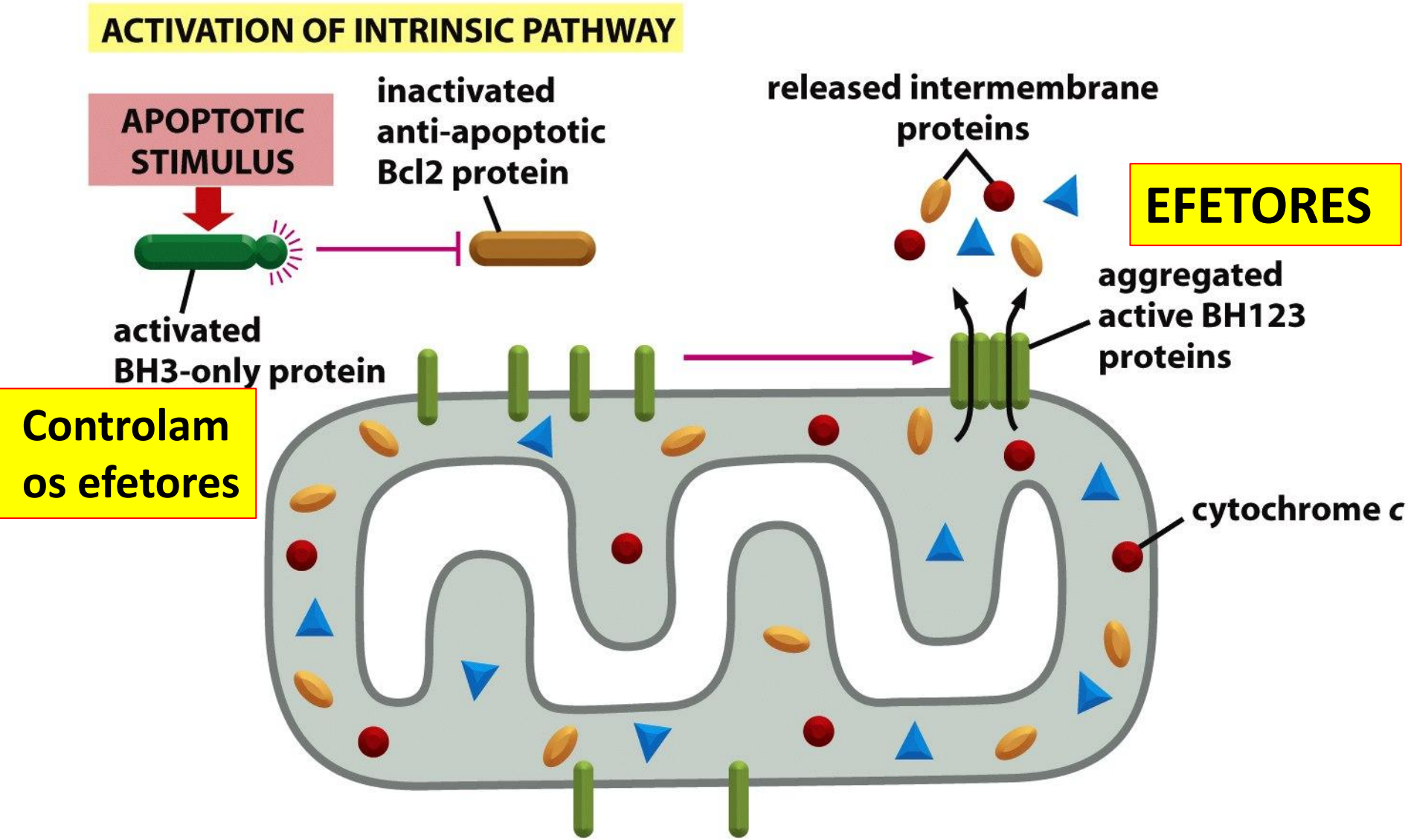


Figure 18-11b *Molecular Biology of the Cell* (© Garland Science 2008)

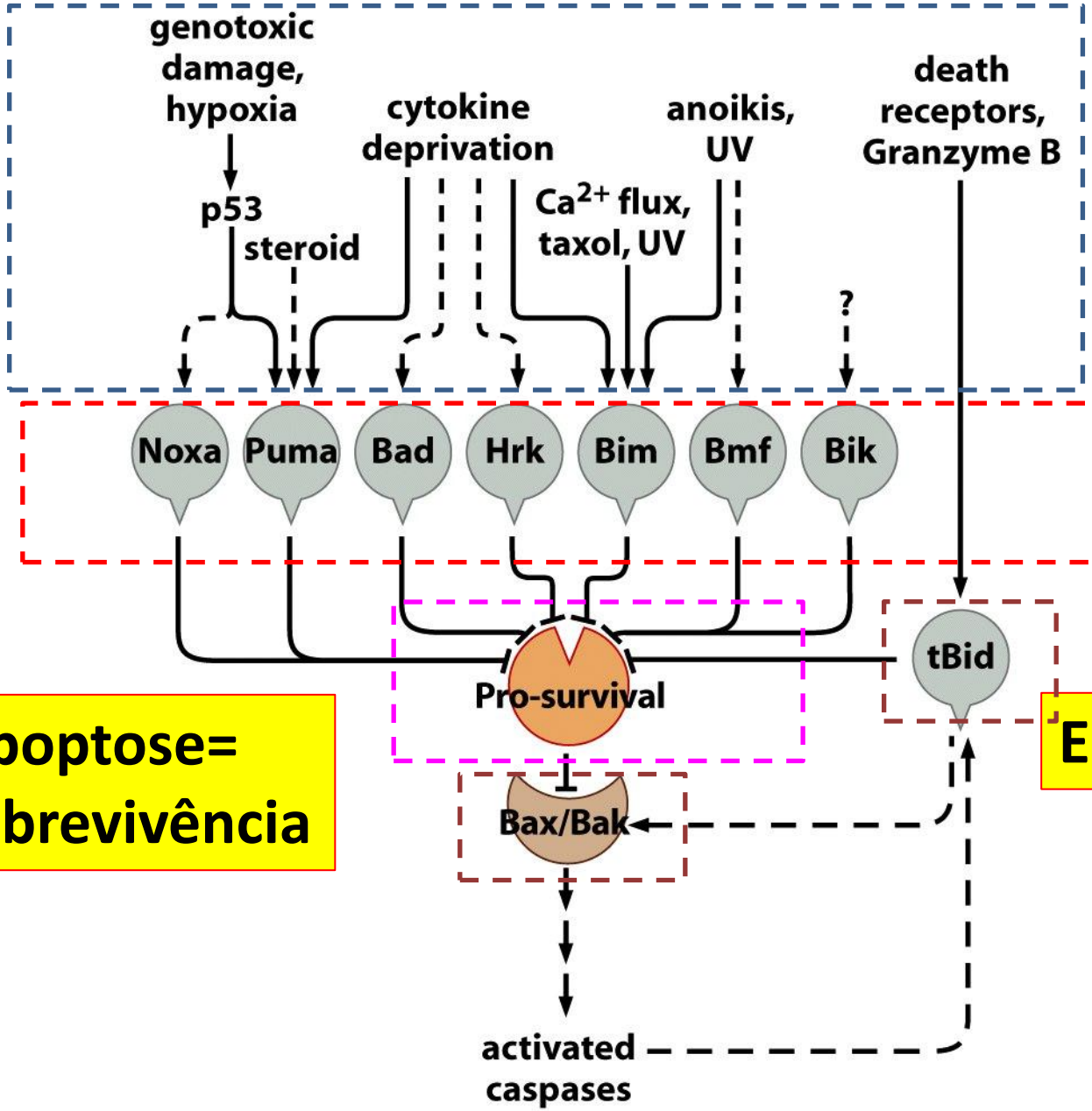


Figure 9-27a The Biology of Cancer (© Garland Science 2007)

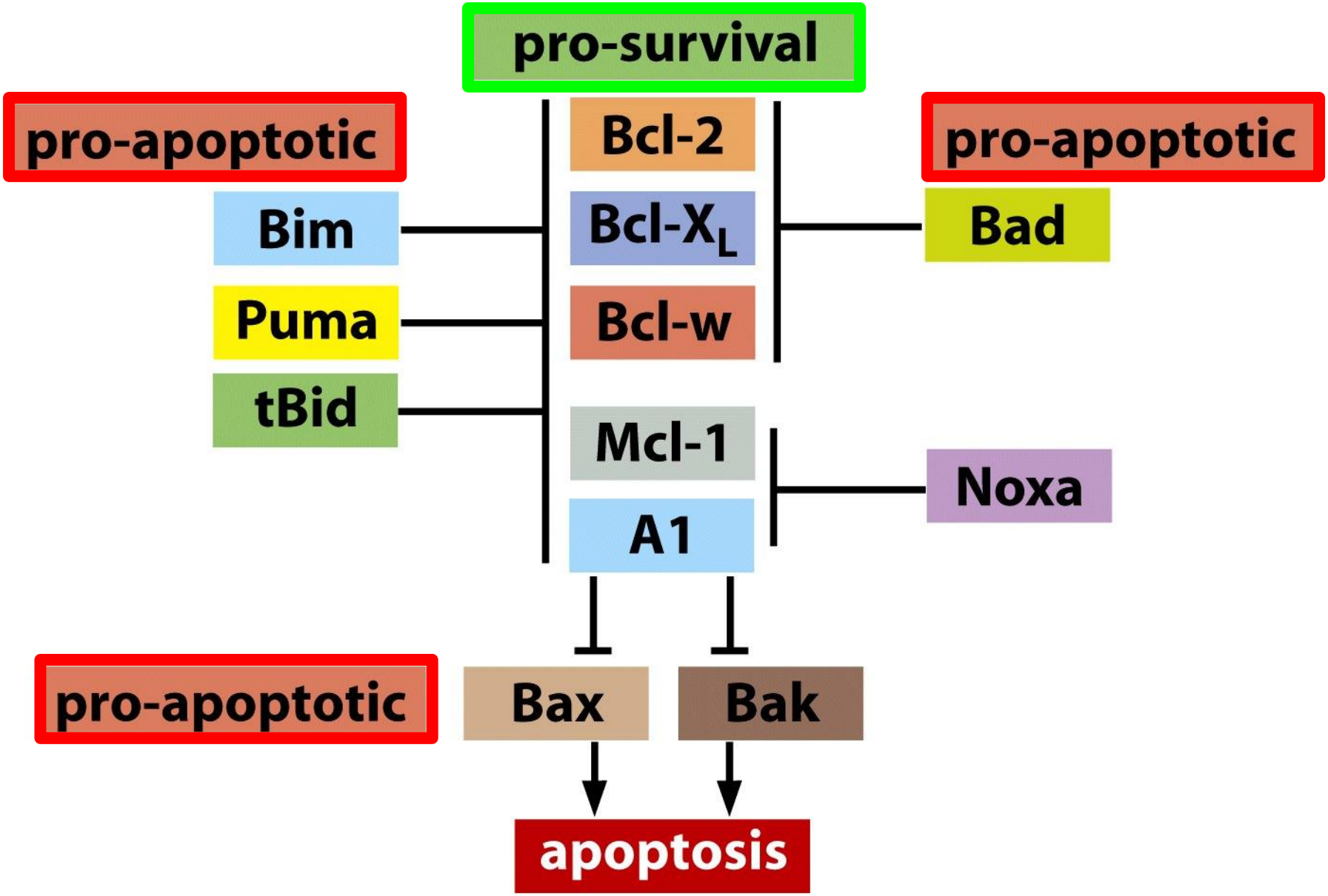
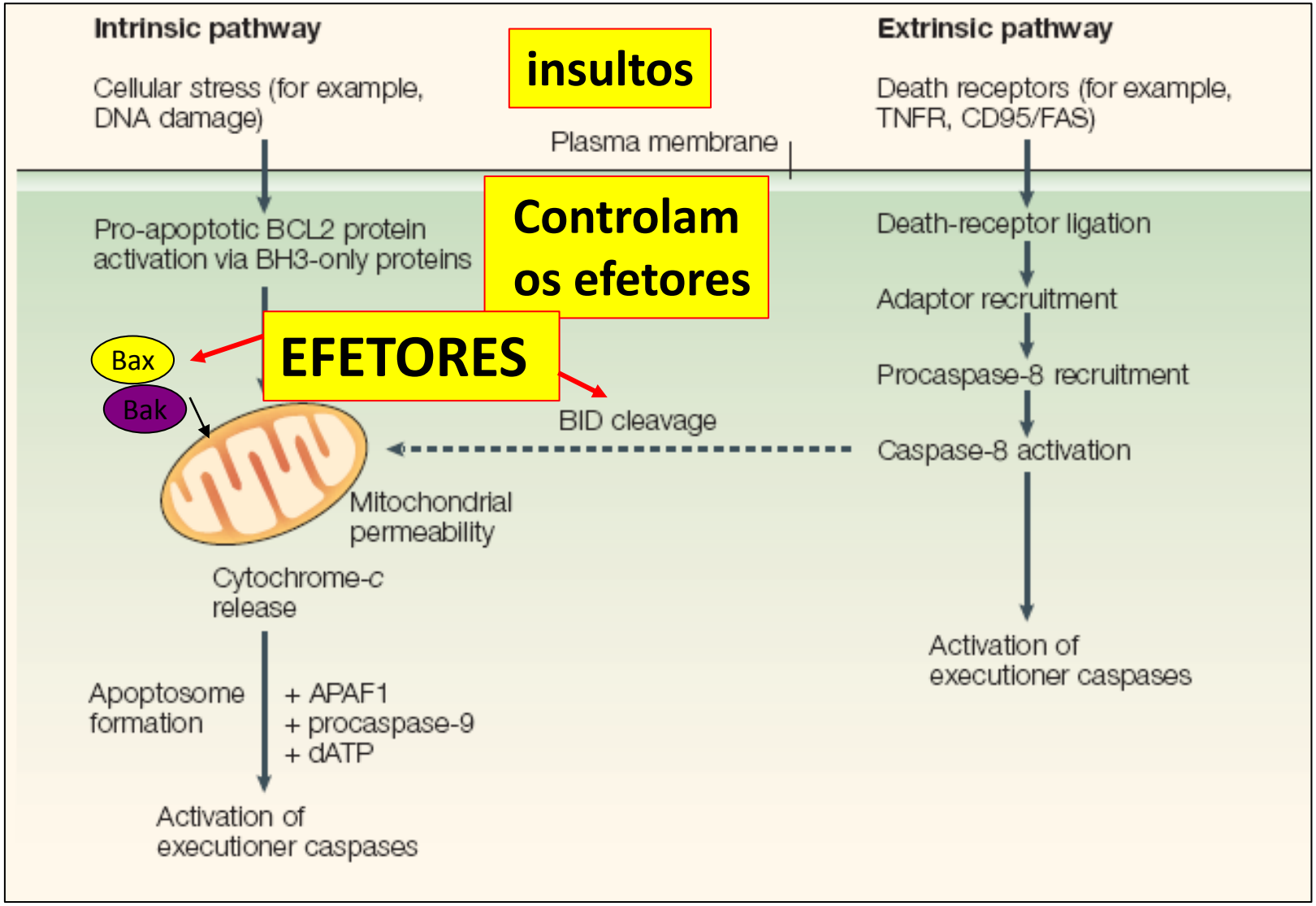
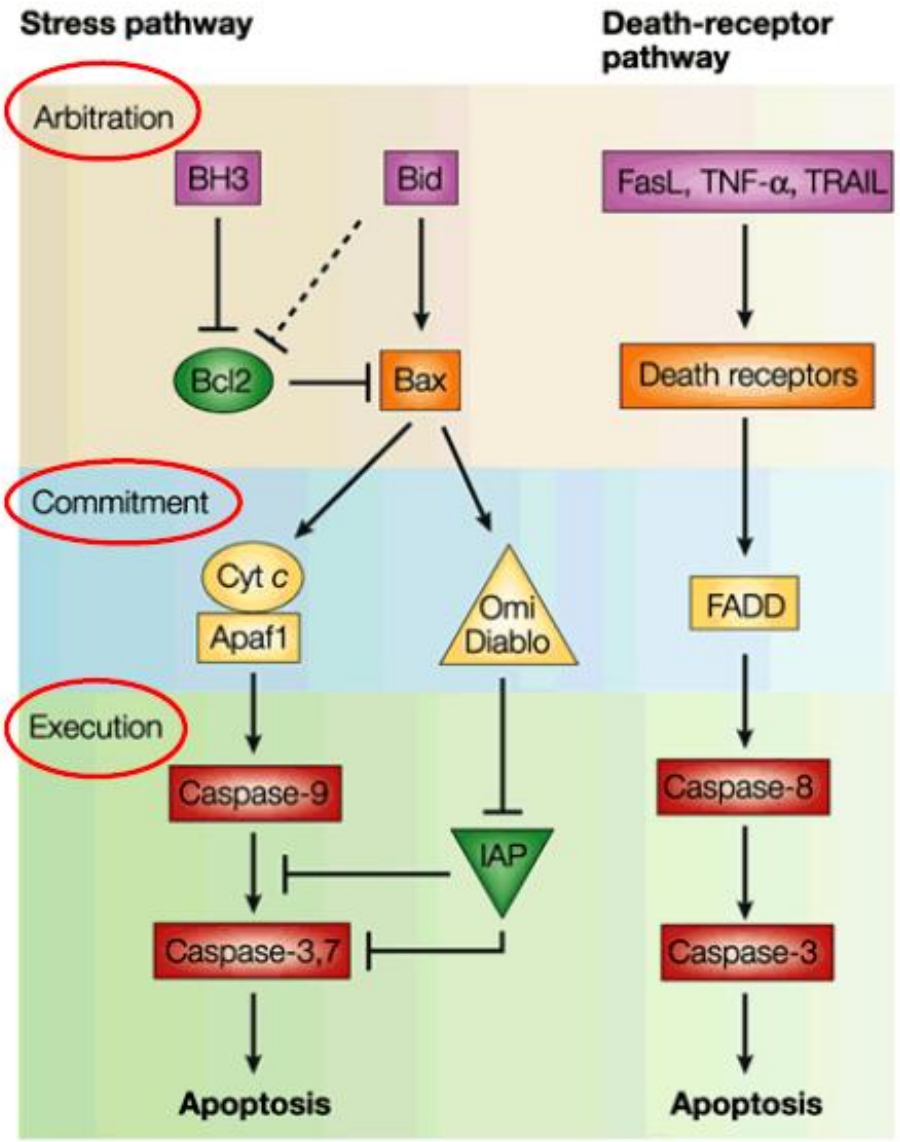


Figure 9-27c The Biology of Cancer (© Garland Science 2007)

A via intrínsica ‘ajuda’ a extrínsica

Chipuk & Green, Nat Rev Mol Cel Biol, 2005, 6:268-275





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

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

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

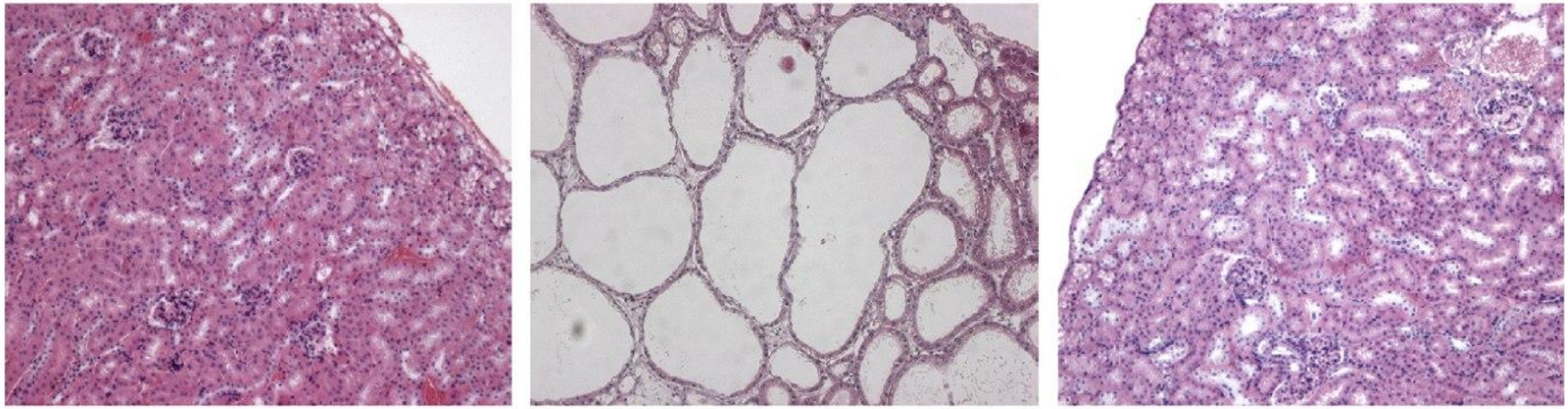
Rim normal

Anti-apoptose

***wt*, 5 wk**

***bcl–2*$^{-/-}$, 5 wk**

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



(A) **(B)** **(C)**

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

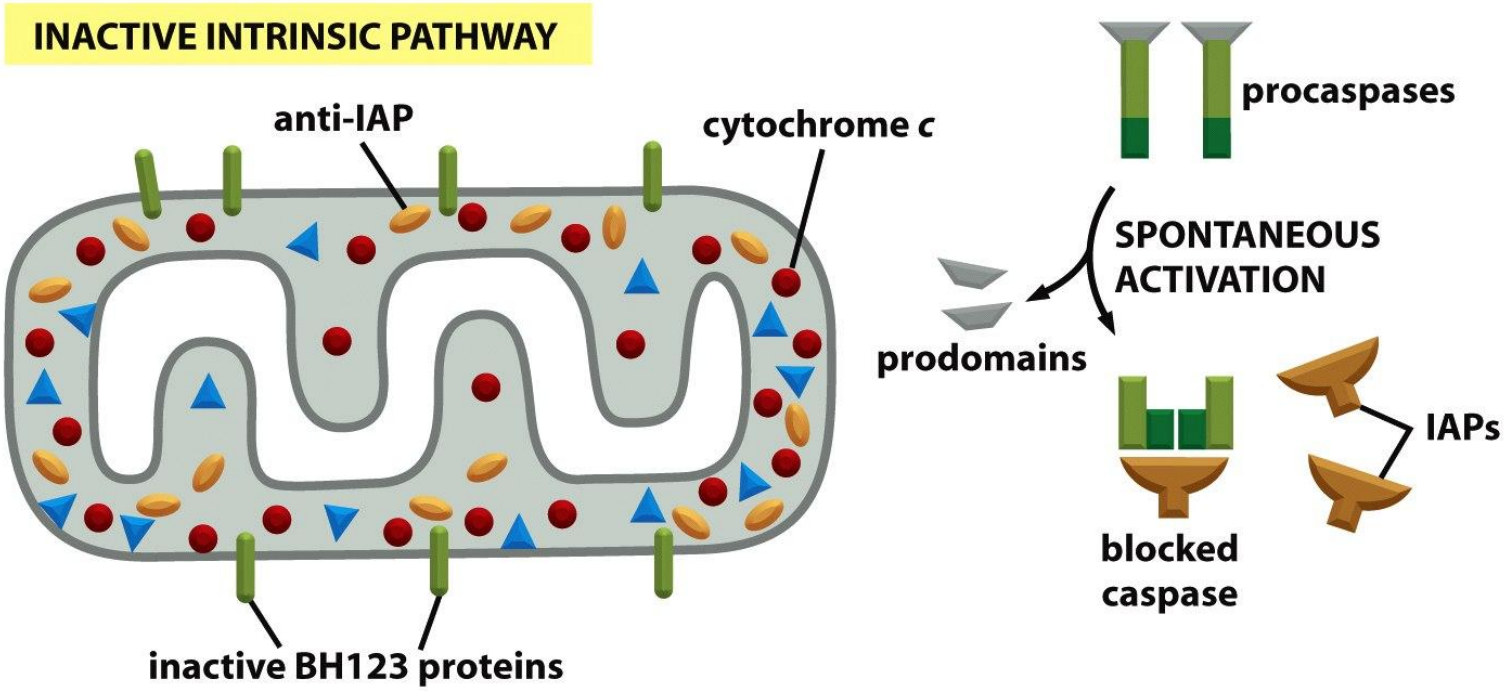
Resumo..

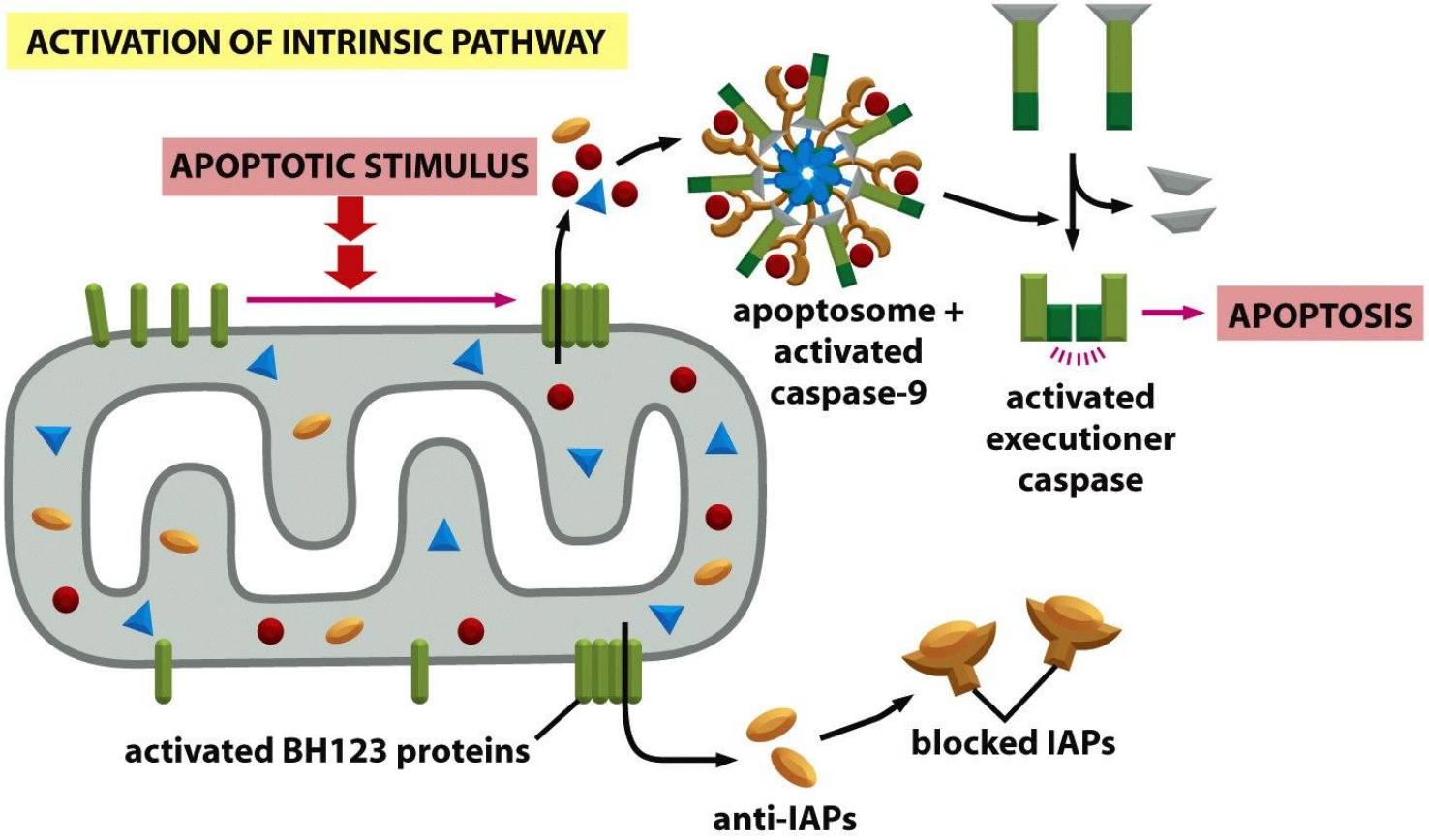
- A via extrínsica pode ativar a intrínsica para aamplificar a cascata de caspases. Isso é feito através da BH3 Bid
- Caspase 8 →clivagem de Bid →tBid transloca para a mitocôndria e induz agregação dos BH123
- Bim, Bid e Puma (entre outros) são capazes de inibir TODOS os membros ANTI-apoptóticos

IAPs e anti-IAPs



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




ACTIVATION OF INTRINSIC PATHWAY
APOPTOTIC STIMULUS
apoptosome +
activated
caspase-9
activated
executioner
caspase
APOPTOSIS
activated BH123 proteins
anti-IAPs
blocked IAPs


p53
GENOME GUARDIAN


American Association for the Advancement of Science
SCIENCE
24 December 1993
Vol. 262 • Pages 1945–2108
$6.00
p53
Molecule of the Year
A Genetic Key to Cancer

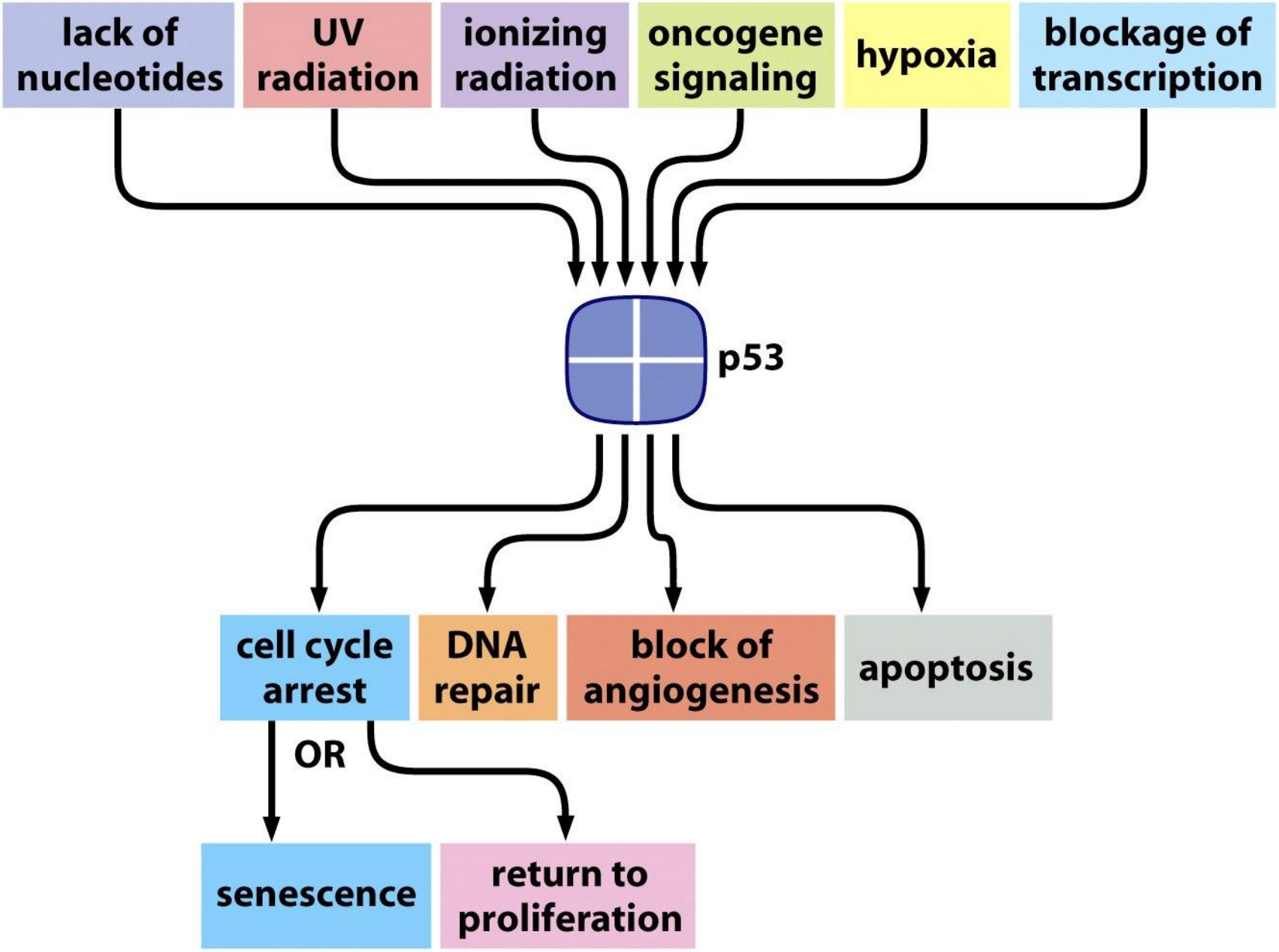


Figure 9-8 The Biology of Cancer (© Garland Science 2007)

P53 ativa apoptose de várias maneiras:

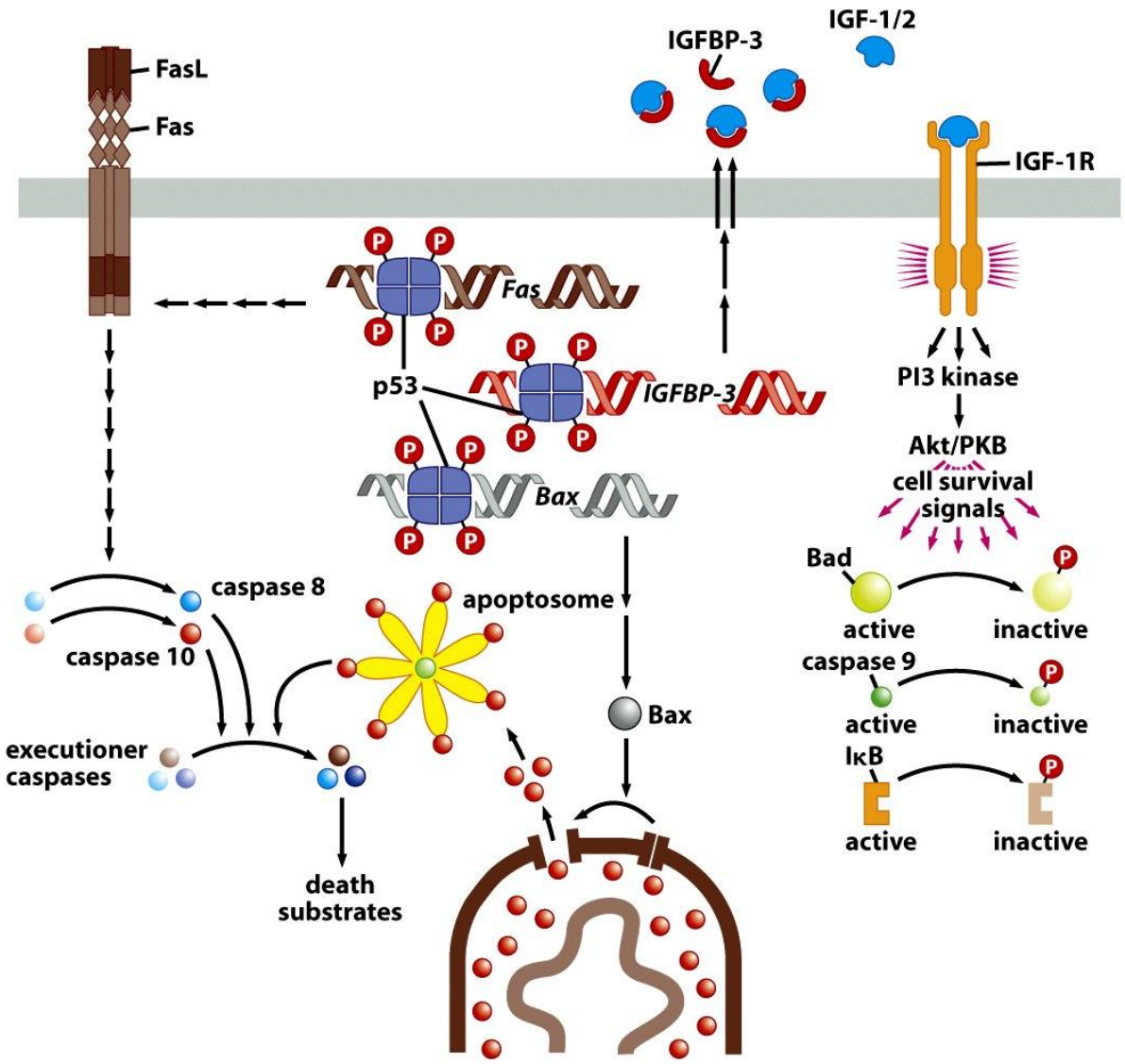
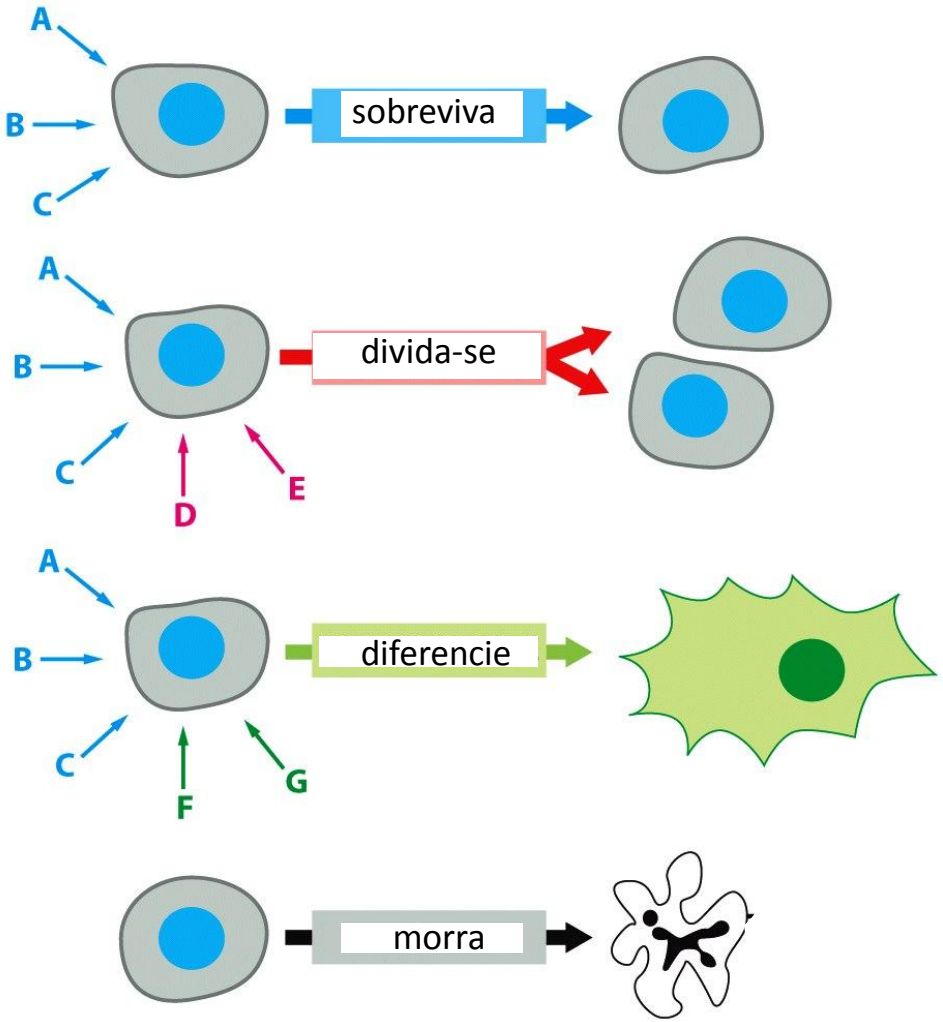


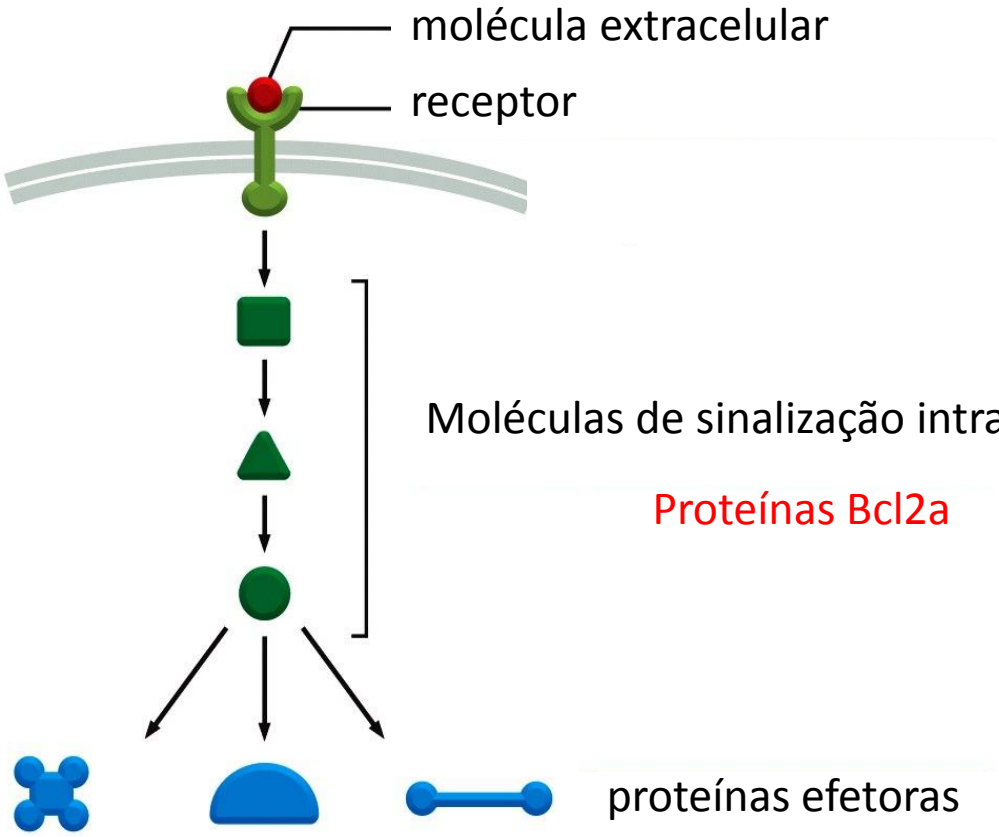
Figure 9-33 The Biology of Cancer (© Garland Science 2007)

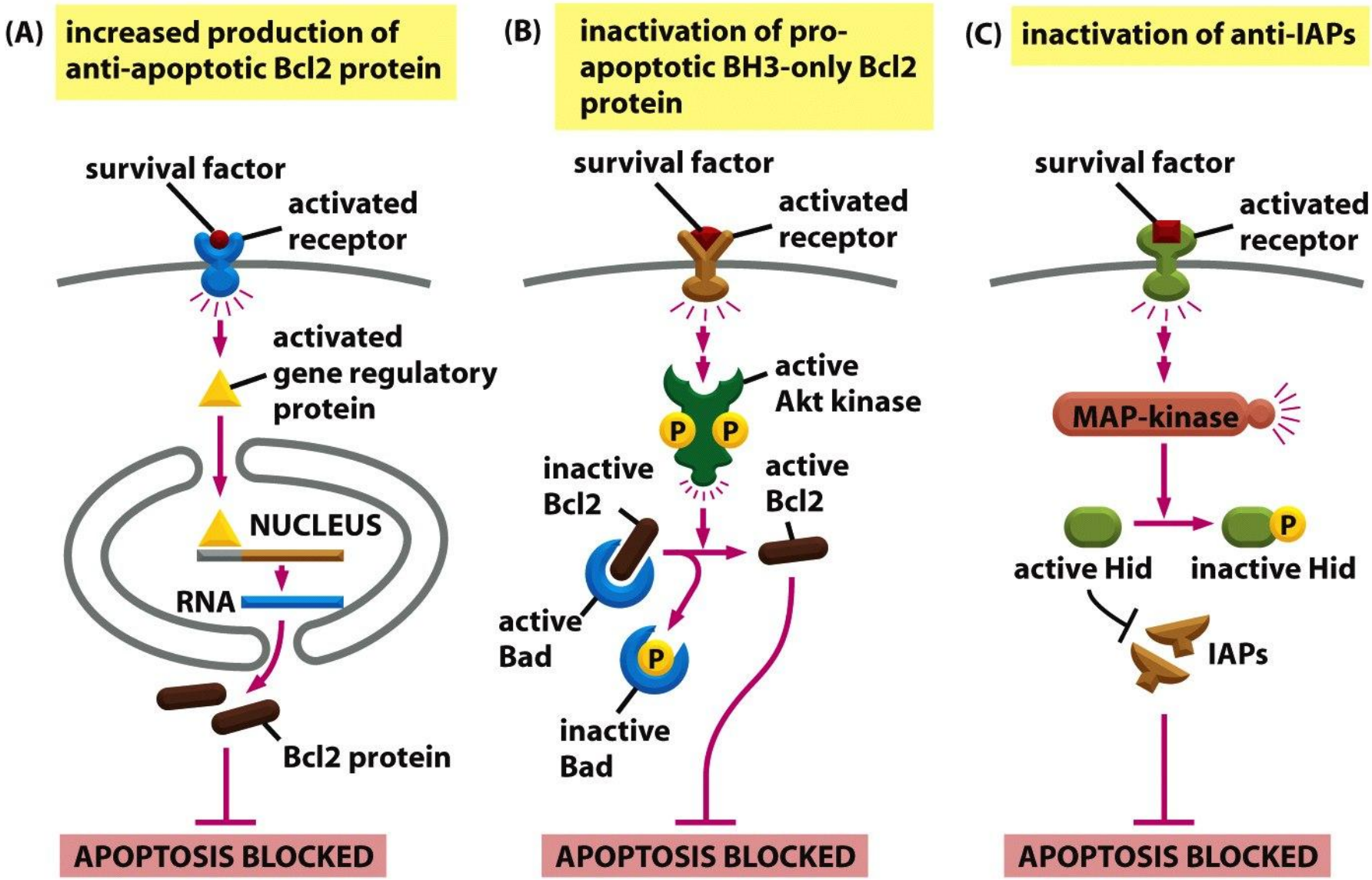
Fatores de Sobrevivência

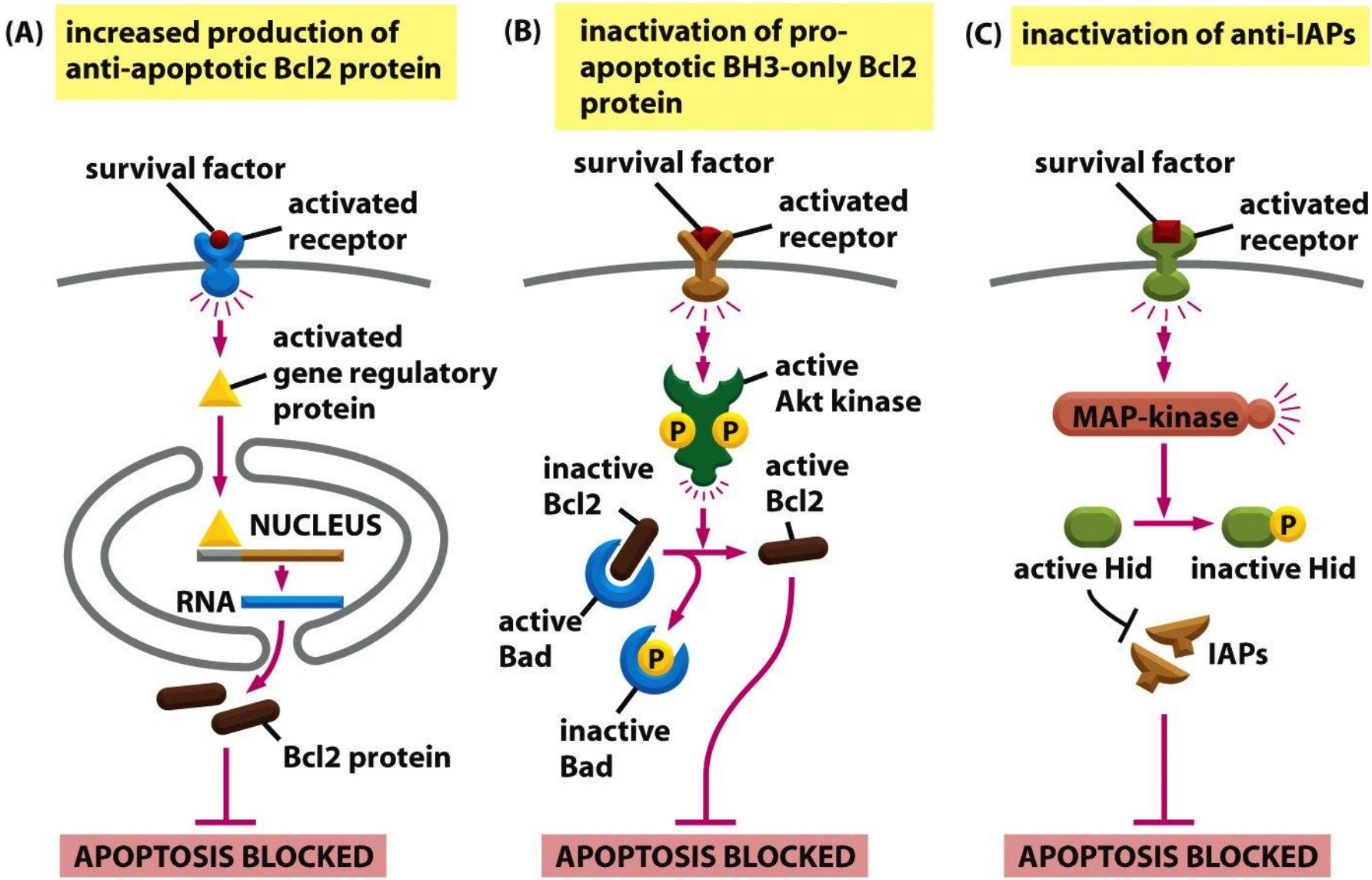
Lembrando da aula de sinalização..



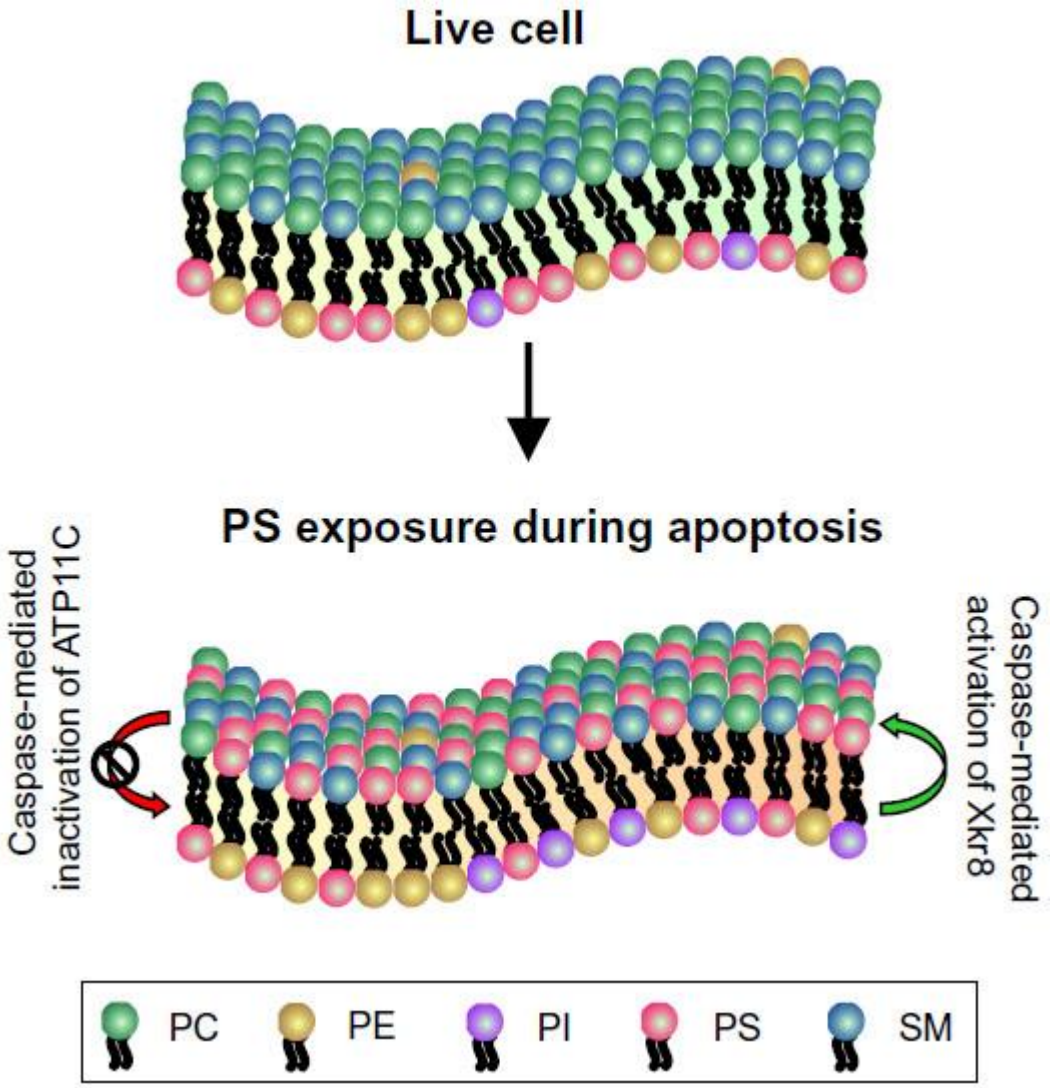
Sinalização dos fatores de sobrevivência segue a mesma regra ....




(A)
increased production of anti-apoptotic Bcl2 protein
survival factor
activated receptor
activated gene regulatory protein
NUCLEUS
RNA
Bcl2 protein
APOPTOSIS BLOCKED
(B)
inactivation of pro-apoptotic BH3-only Bcl2 protein
survival factor
activated receptor
active Akt kinase
P
P
inactive Bcl2
active Bcl2
active Bad
P
inactive Bad
APOPTOSIS BLOCKED
(C)
inactivation of anti-IAPs
survival factor
activated receptor
MAP-kinase
P
active Hid
inactive Hid
IAPs
APOPTOSIS BLOCKED

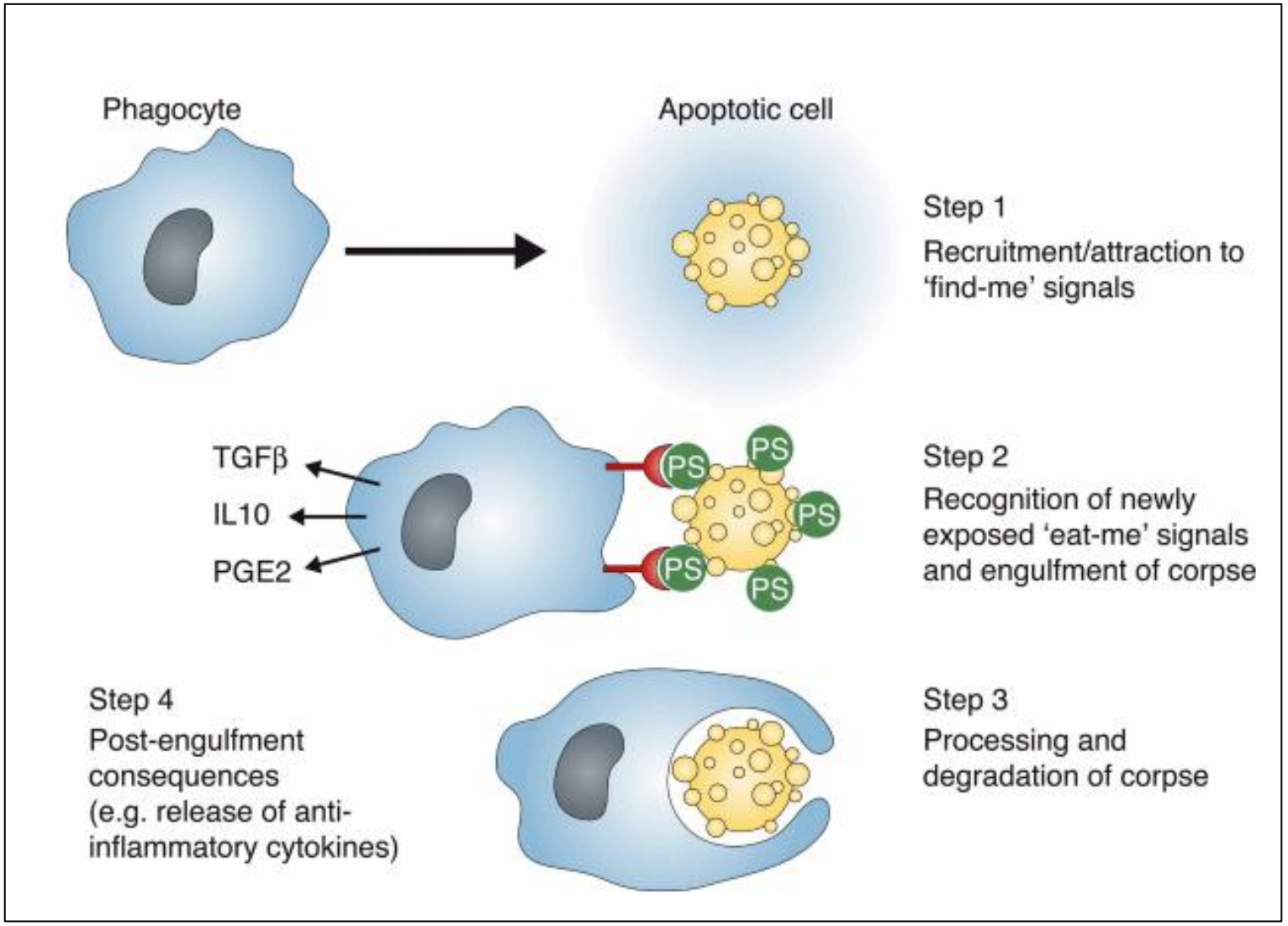

(A)
increased production of anti-apoptotic Bcl2 protein
survival factor
activated receptor
activated gene regulatory protein
NUCLEUS
RNA
Bcl2 protein
APOPTOSIS BLOCKED
(B)
inactivation of pro-apoptotic BH3-only Bcl2 protein
survival factor
activated receptor
active Akt kinase
P
P
inactive Bcl2
active Bcl2
active Bad
P
inactive Bad
APOPTOSIS BLOCKED
(C)
inactivation of anti-IAPs
survival factor
activated receptor
MAP-kinase
P
active Hid
inactive Hid
IAPs
APOPTOSIS BLOCKED

Como as células mortas são eliminadas?



Linda & Olson, 2015. Apoptotic membrane dynamics in health and disease. Cell Health and Cytoskeleton,7: 133–142

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



Ravichandran KS, 2010. Find-me and eat-me signals in apoptotic cell clearance: progress and conundrums. J. Exp. Med. Vol. 207 No. 9 1807-1817

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
CASP8 promoter methylation	inactivation of extrinsic cascade	SCLC, pediatric tumors
CASP3 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
PI3K mutation/activation	activation of Akt/PKB	gastrointestinal
NF-κB constitutive activation[b]	induction of anti-apoptotic genes	many types
p53 mutation	loss of ability to induce pro-apoptotic genes	many types
$p14^{ARF}$ gene inactivation	suppression of p53 levels	many types
Mdm2 overexpression	suppression of p53 levels	sarcomas
IAP-1 gene amplification	antagonist of caspases-3 and 7	esophageal, cervical
APAF1 methylation	loss of caspase-9 activation by cytochrome *c*	melanomas
BAX mutation	loss of pro-apoptotic protein	colon carcinomas
Bcl-2 overexpression	closes mitochondrial channel	~ of human tumors
PTEN inactivation	hyperactivity of Akt/PKB kinase	glioblastoma, prostate carcinoma, endometrial carcinoma
IGF-1/2 overexpression	activates PI3K	many types
IGFBP repression	loss of anti-apoptotic IGF-1/2 antagonist	many types
Casein kinase II	activation of NF-κB	many types
TNFR1 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 $Bcl\text{-}X_L$	several types
TRAIL-R1 repression	loss of responsiveness to death ligand	small-cell lung carcinoma
FAP-1 overexpression	inhibition of Fas receptor signaling	pancreatic carcinoma
XAF1 methylation[c]	loss of inhibition of anti-apoptotic XIAP	gastric carcinoma
Wip1 overexpression[d]	suppression of p53 activation	breast and ovarian carcinomas, neuroblastoma

[a]Survivin 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.
[b]Induces synthesis of c-IAPs, XIAP, $Bcl\text{-}X_L$, and other anti-apoptotic proteins.
[c]XAF1 (XIAP-associated factor 1) normally binds and blocks the anti-apoptotic actions of XIAP, the most potent of the IAPs.
[d]Wip1 is a phosphatase that inactivates p38 MAPK, which otherwise would phosphorylate and stimulate the pro-apoptotic actions of p53.

Table 9-5 The Biology of Cancer (© Garland Science 2007)

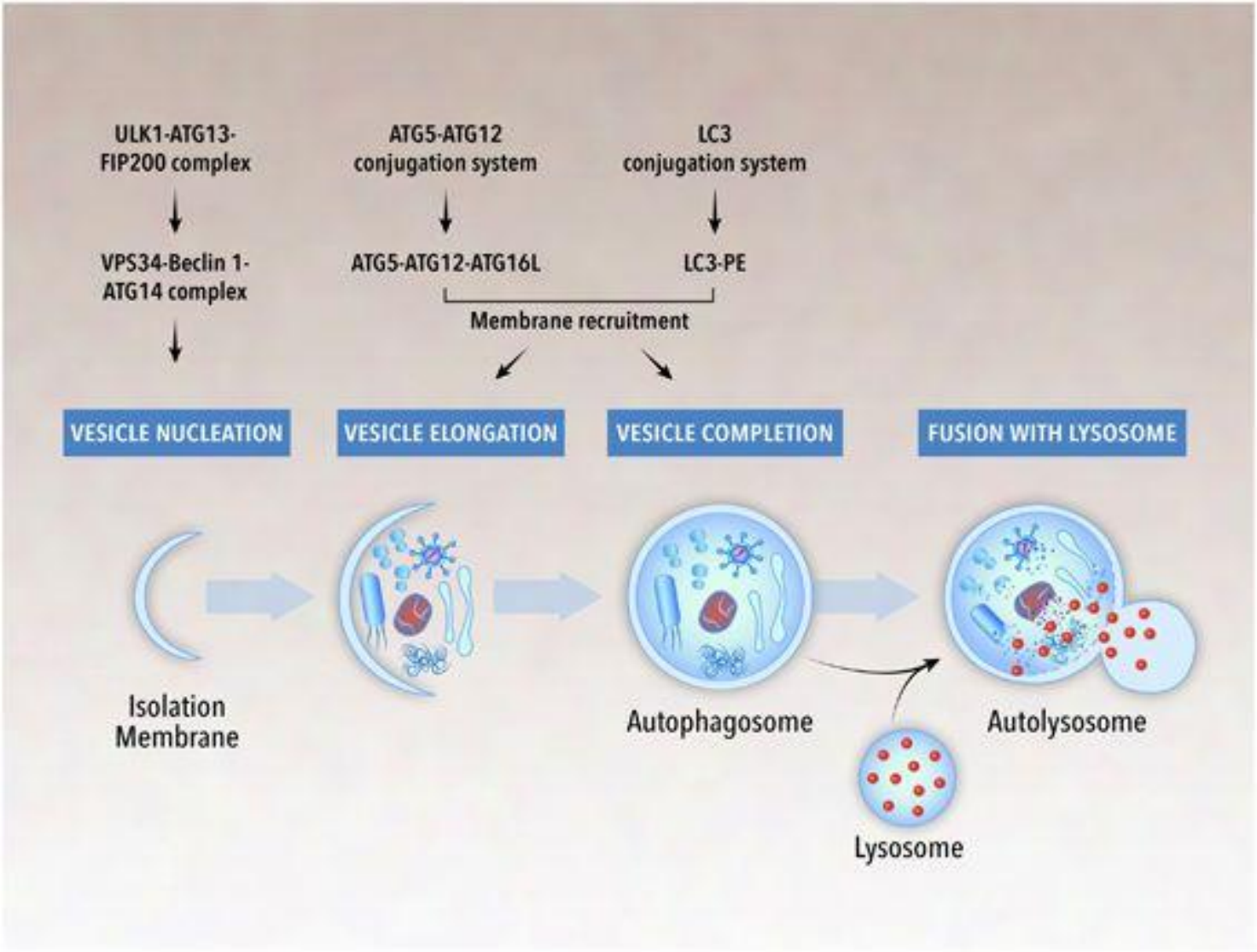
Nessa aula

- Apoptose
- Autofagia
- Necroptose

Autofagia

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

autophagy-related (Atg) proteins



Autofagossomo:

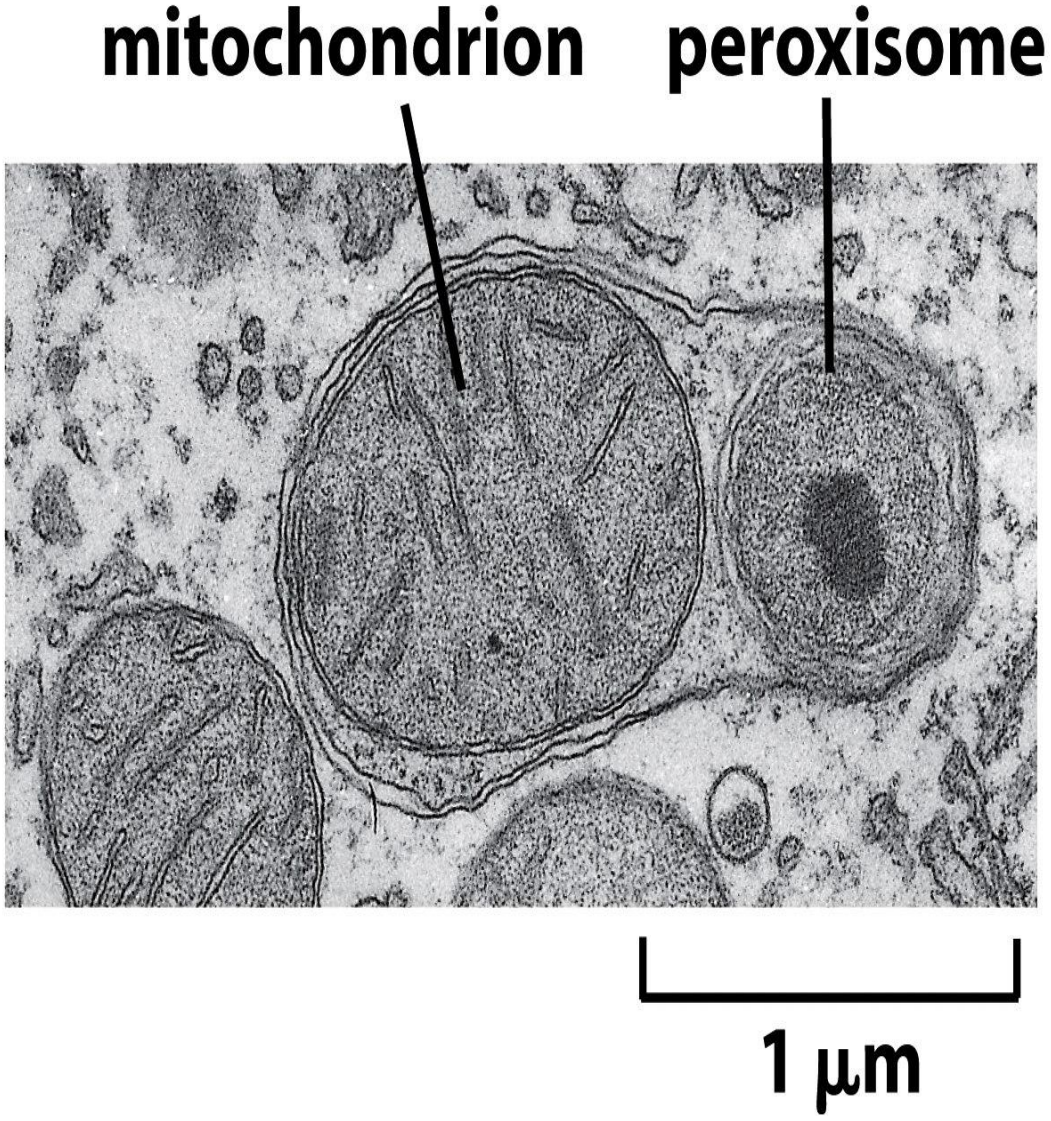
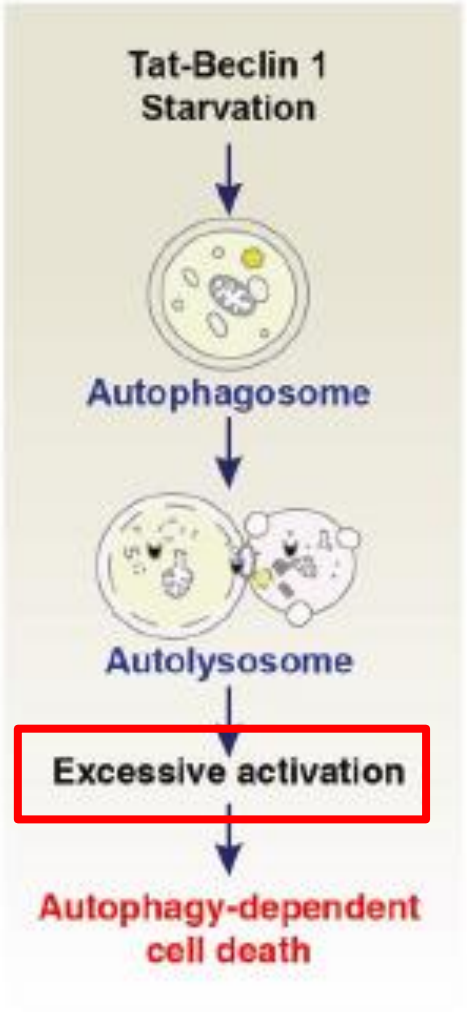
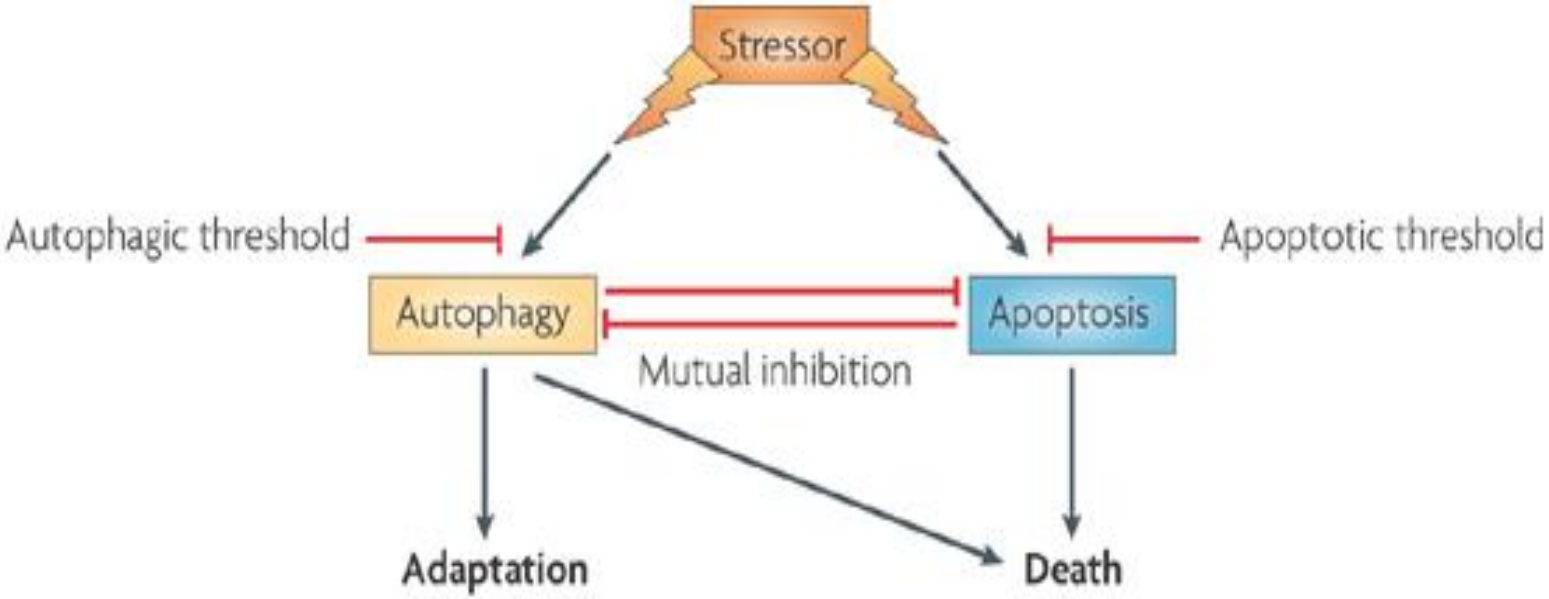


Figure 13-42b Molecular Biology of the Cell 5/e (© Garland Science 2008)


Tat-Beclin 1
Starvation
Autophagosome
Autolysosome
Excessive activation
Autophagy-dependent
cell death



Nature Reviews | Molecular Cell Biology

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

apoptose | necrose

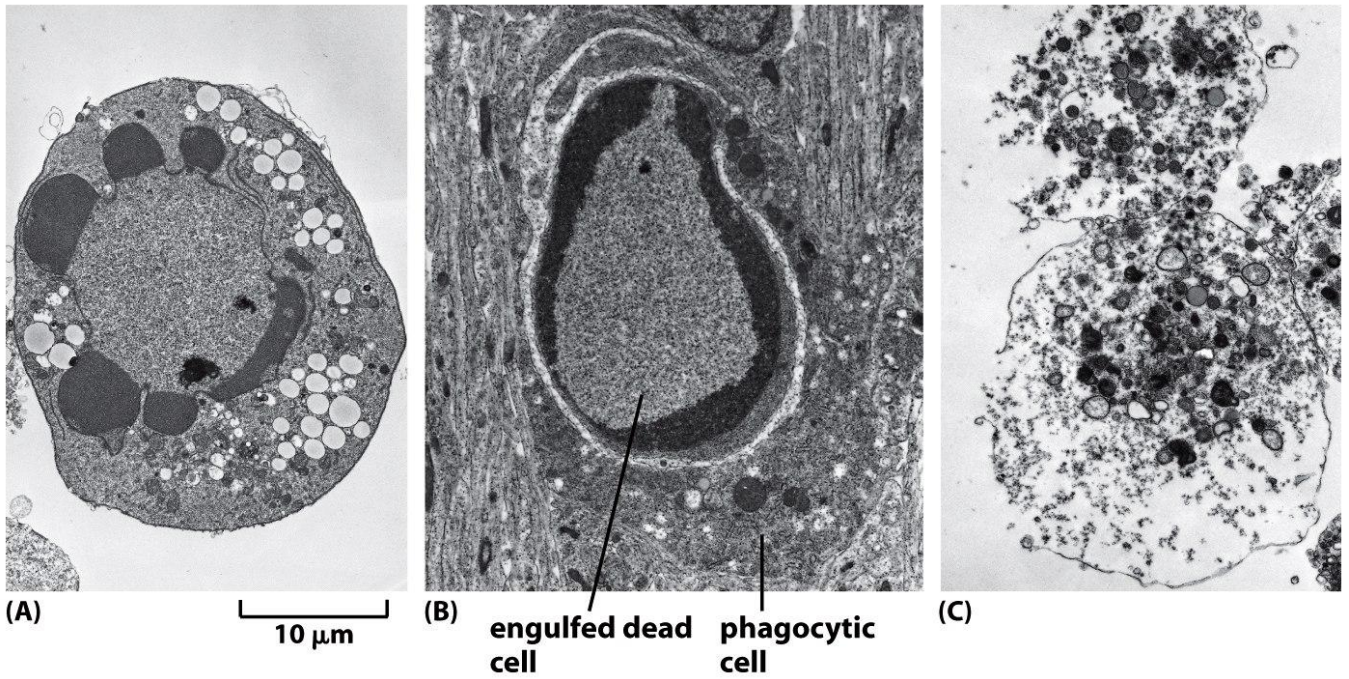


Figure 18-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

APOPTOSE

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

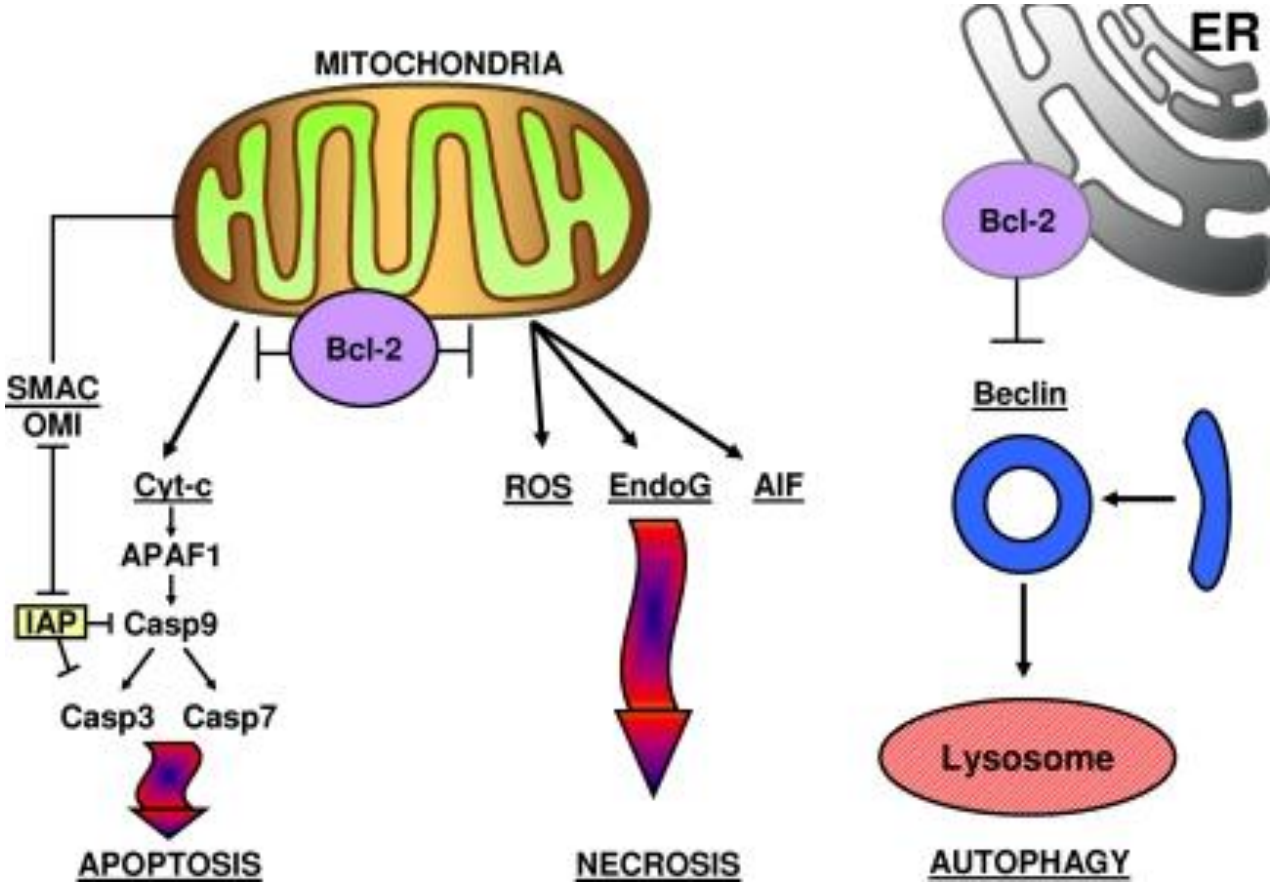
NECROSE

rompimento da membranas plasmática
Extravasamento do conteúdo celular
Resposta inflamatória

Table 9.3 Apoptosis versus necrosis

	Apoptosis	Necrosis
Provoking stimuli		
	programmed tissue remodeling	metabolic stresses
	maintenance of cell pool size	absence of nutrients
	genomic damage	changes in pH, temperature
	metabolic derangement	hypoxia, anoxia
	hypoxia	
	imbalances in signaling pathways	
Morphological changes		
Affected cells	individual cells	groups of cells
Cell volume	decreased	increased
Chromatin	condensed	fragmented
Lysosomes	unaffected	abnormal
Mitochondria	morphologically normal initially	morphologically aberrant
Inflammatory response	none	marked
Cell fate	apoptotic bodies consumed by neighboring cells	lysis
Molecular changes		
Gene activity	required for program	not needed
Chromosomal DNA	cleaved at specific sites	random cleavage
Intracellular calcium	increased	unaffected
Ion pumps	continue to function	lost

Adapted from R.J.B. King, Cancer Biology, 2nd ed. Harlow, UK: Pearson Education, 2000.



Reed JC et al 2008. Blood, 111: 3322–3330

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?

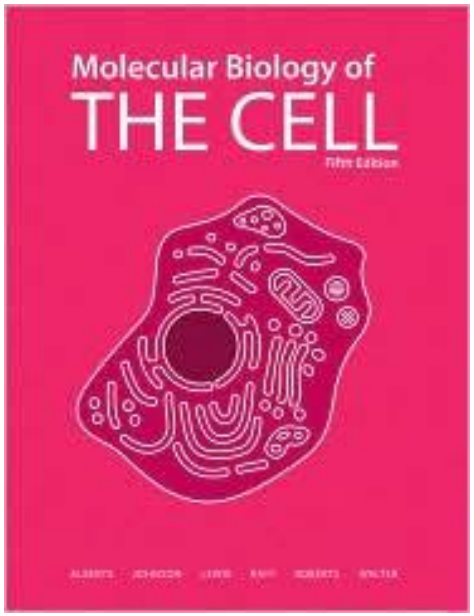
- How did the intrinsic pathway of apoptosis evolve, and what is the advantage of having mitochondria play such a central role in regulating apoptosis?

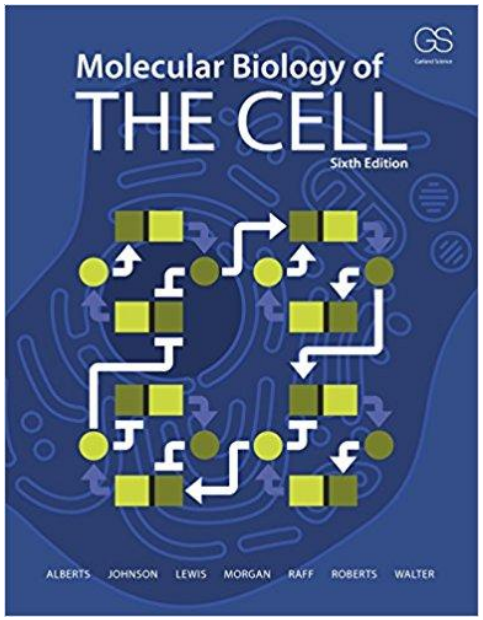
- How are "don't eat me" signals eliminated or inactivated during apoptosis to allow the cells to be phagocytosed?

Molecular Biology of the Cell, Bruce Alberts 6ª edição

Bibliografia

Capítulos 18





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