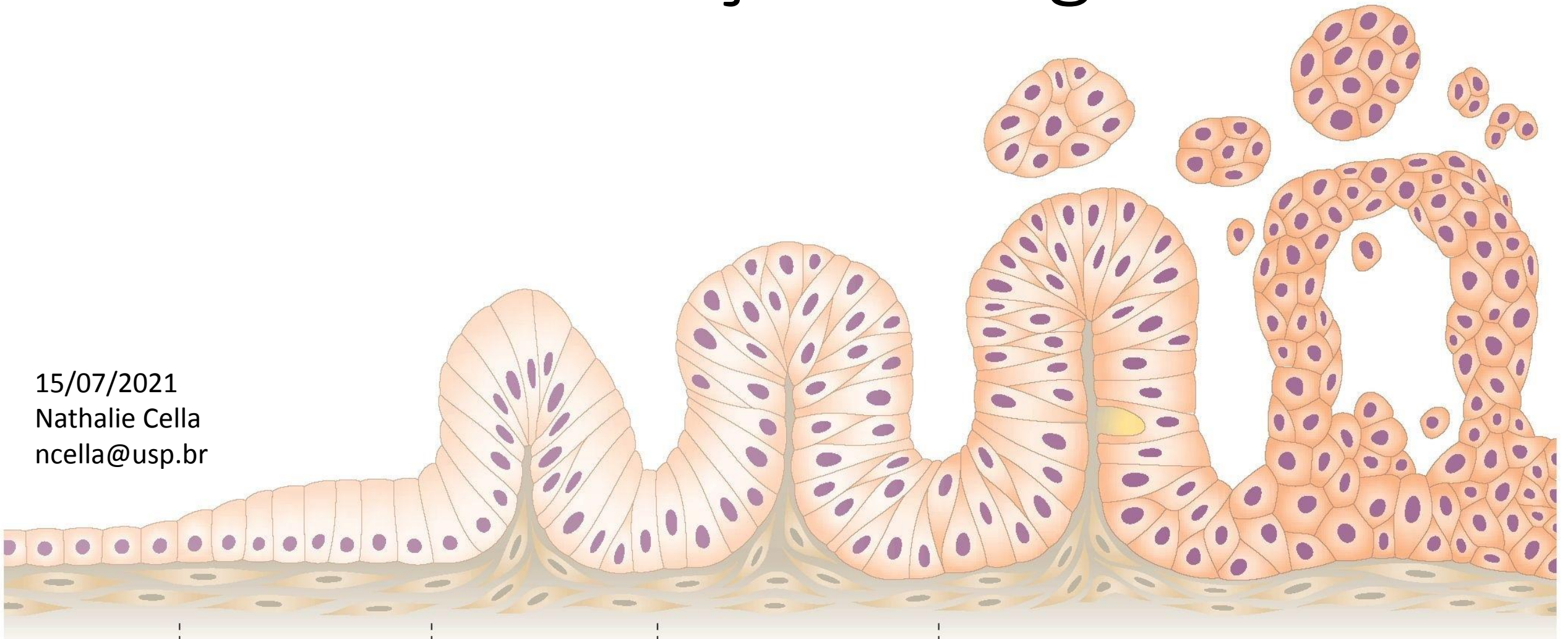
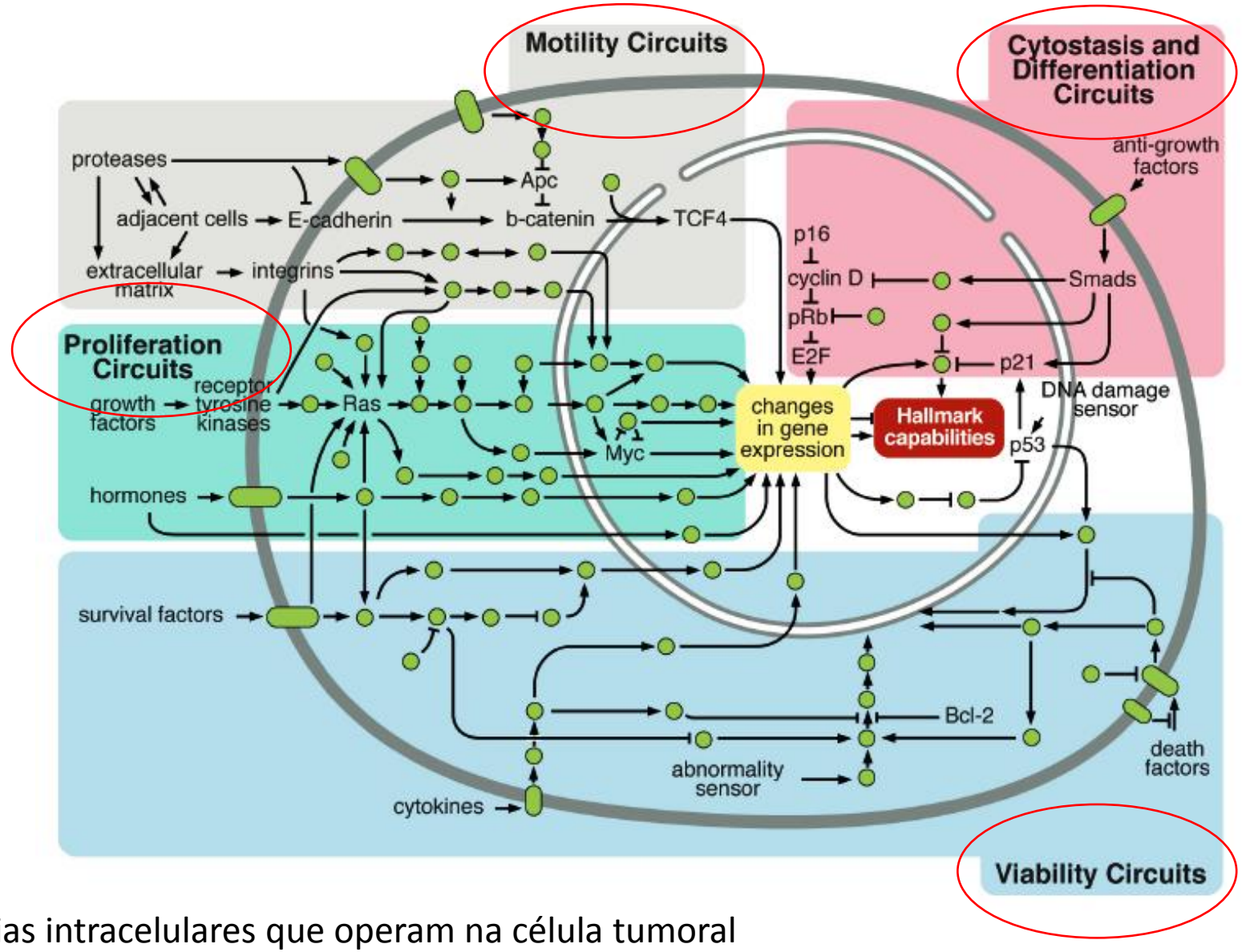
Transformação Maligna

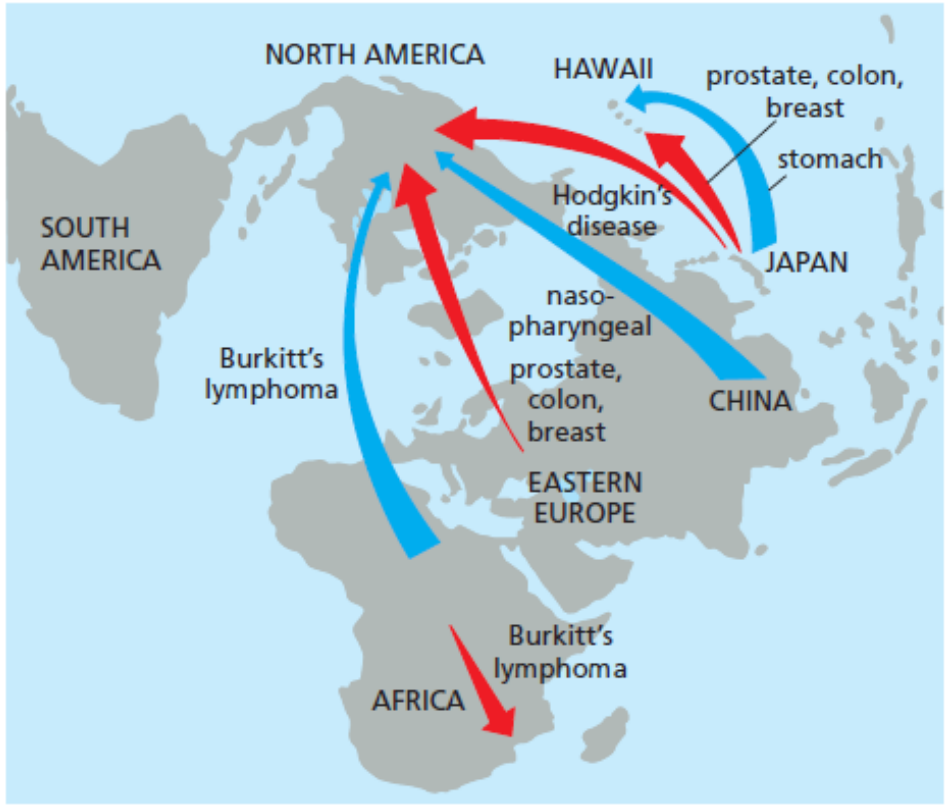


15/07/2021
Nathalie Cella
ncella@usp.br



Vias intracelulares que operam na célula tumoral

Hanahan & Weinberg **Cell** 2011



(A)

cause	cancers caused (percent of total)	number of deaths in US (annual)	magnitude of reduction possible (percent)
smoking	33	189,000	75
diet, overweight, and obesity	25	143,000	50
lack of exercise	5	28,600	85
viruses	5	28,600	100
alcohol	3	17,200	50
UV and ionizing radiation	2	11,400	50
occupational carcinogens	5	28,600	50

(B)

80-90% dos tumores poderiam ser evitados OU adiados

Câncer – definição

- Conjunto de doenças resultantes de alterações genéticas que levam ao descontrole da proliferação celular
- As alterações genéticas são principalmente em:
  - oncogenes
  - genes supressores de tumor
  - genes de reparo de DNA
- Alterações na linhagem germinativa – câncer hereditário
- Alterações na linhagem somática – câncer esporádico

✓ Enrique

classificação e nomenclatura baseado na morfologia dos tumores

- Primário: o primeiro que surge
- Metastático: tumor derivado do tumor primário encontrado em outro local do organismo
- Carcinoma: tumor que surge de células epiteliais (80% dos casos)
- Sarcoma: tumor que se origina de células do tecido conjuntivo (fibroblastos, adipócitos, osteócitos, miócitos)
- Leucemia: tumor de origem hematopoiética
- Hiperplasia: aumento do número de células
- Metaplasia: presença de um tipo celular diferente do que é usual em um dado tecido
- Displasia: alterações morfológicas das células
- Carcinoma *in situ* : a lesão permanece confinada a um local (“encapsulado”)
- Carcinoma invasivo: tumor avança além dos limites normais (primeiro passo para formação de metástase)

Tumores têm origem monoclonal

(isto é, têm origem em uma única célula)

Como sabemos disso?

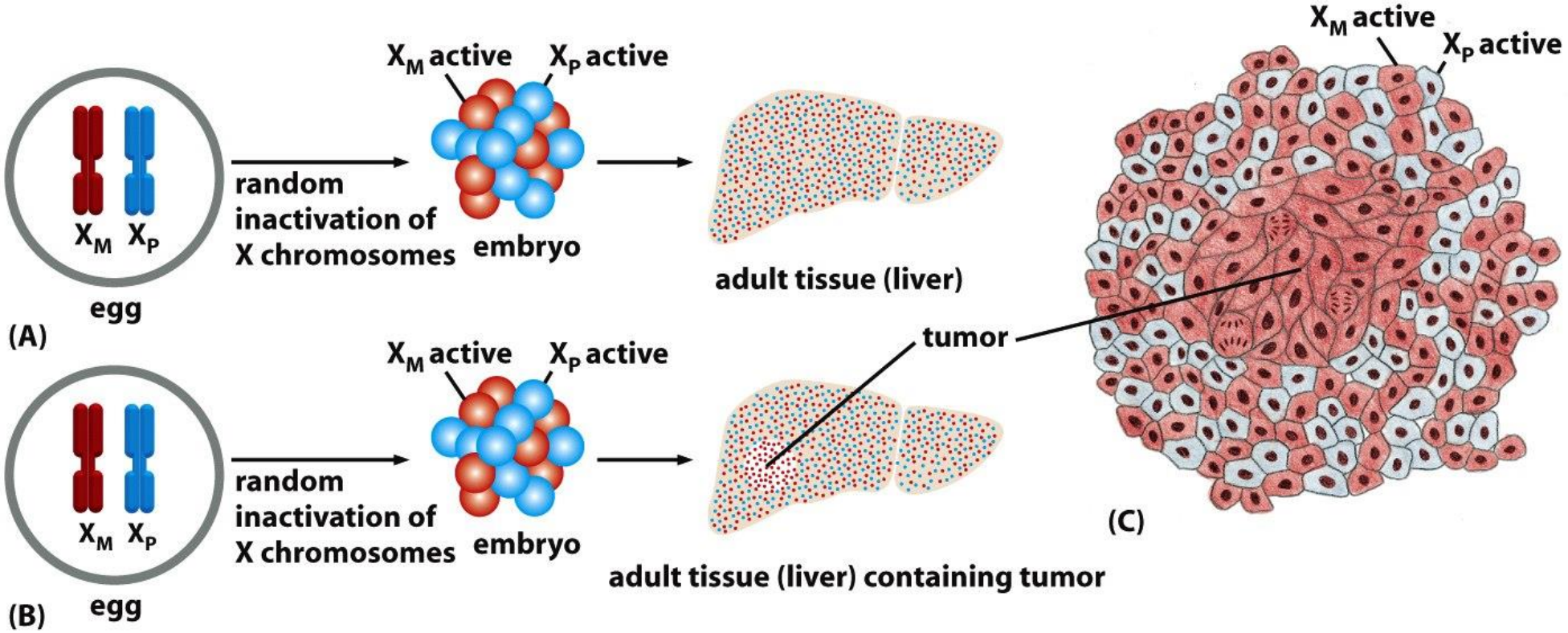


Figure 20-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Tumor benigno e maligno

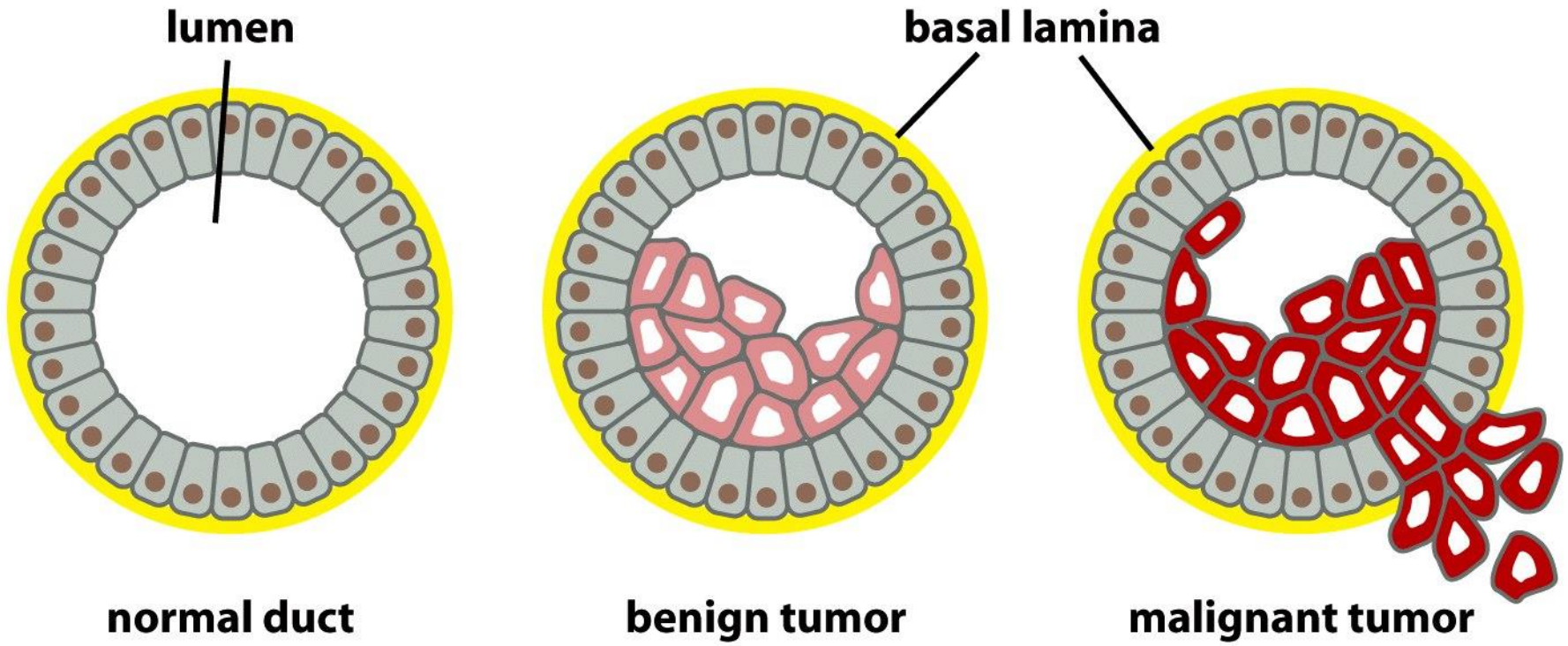


Figure 20-3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

NÃO INVADE

INVADE

O início – mutações somáticas

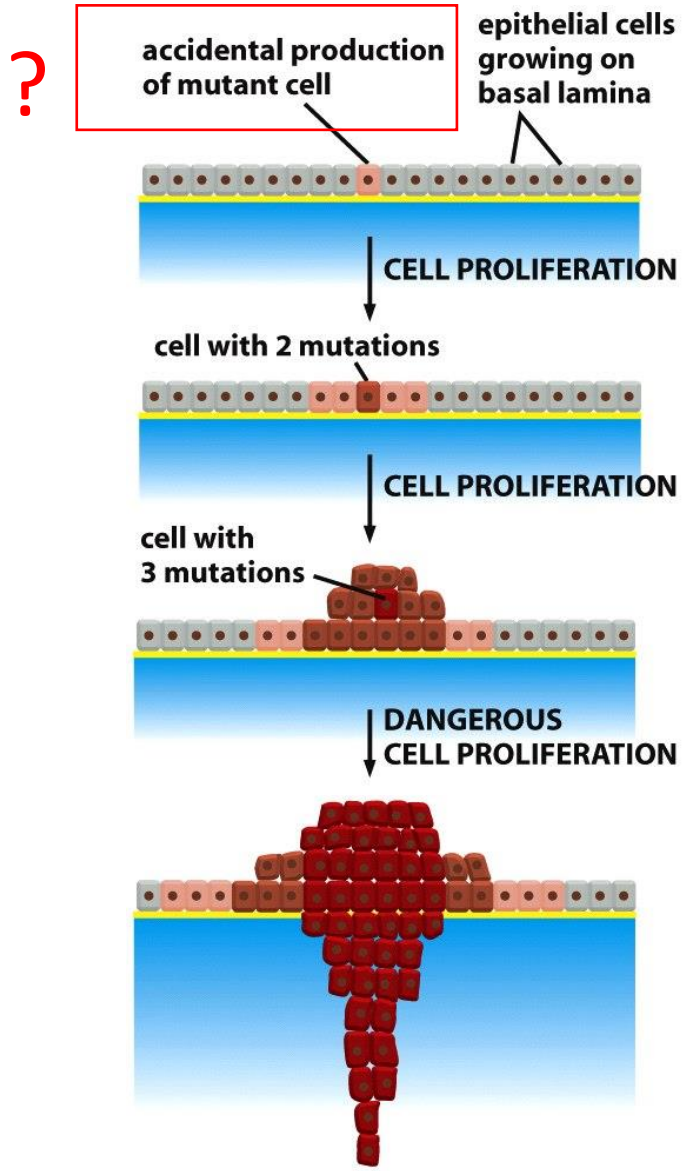


Figure 20-11 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Mutações OU alterações epigenéticas

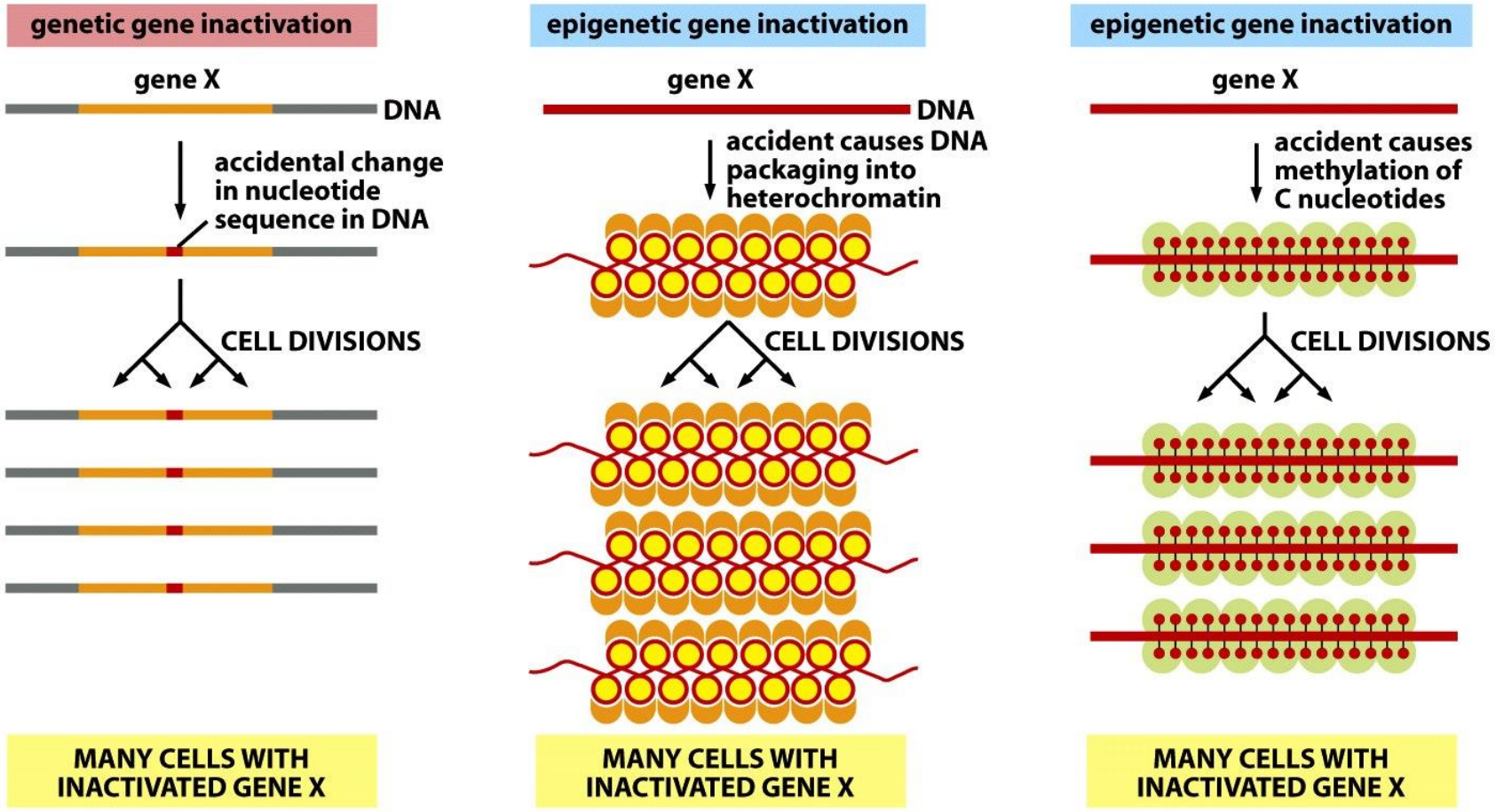


Figure 20-12 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Uma mutação não basta, por isso, na maioria dos casos, tumores demoram para aparecer

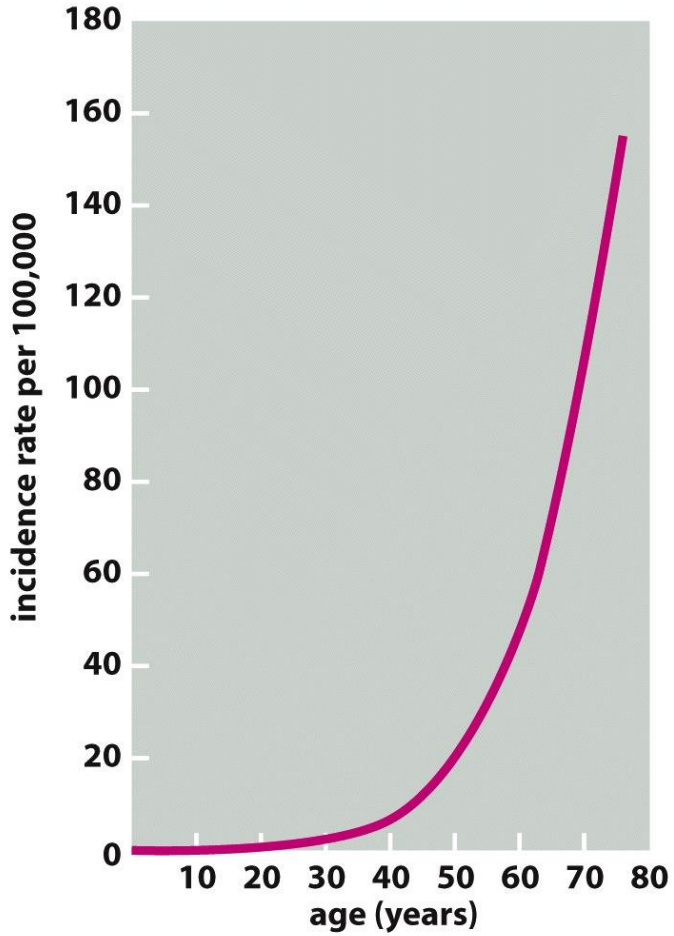
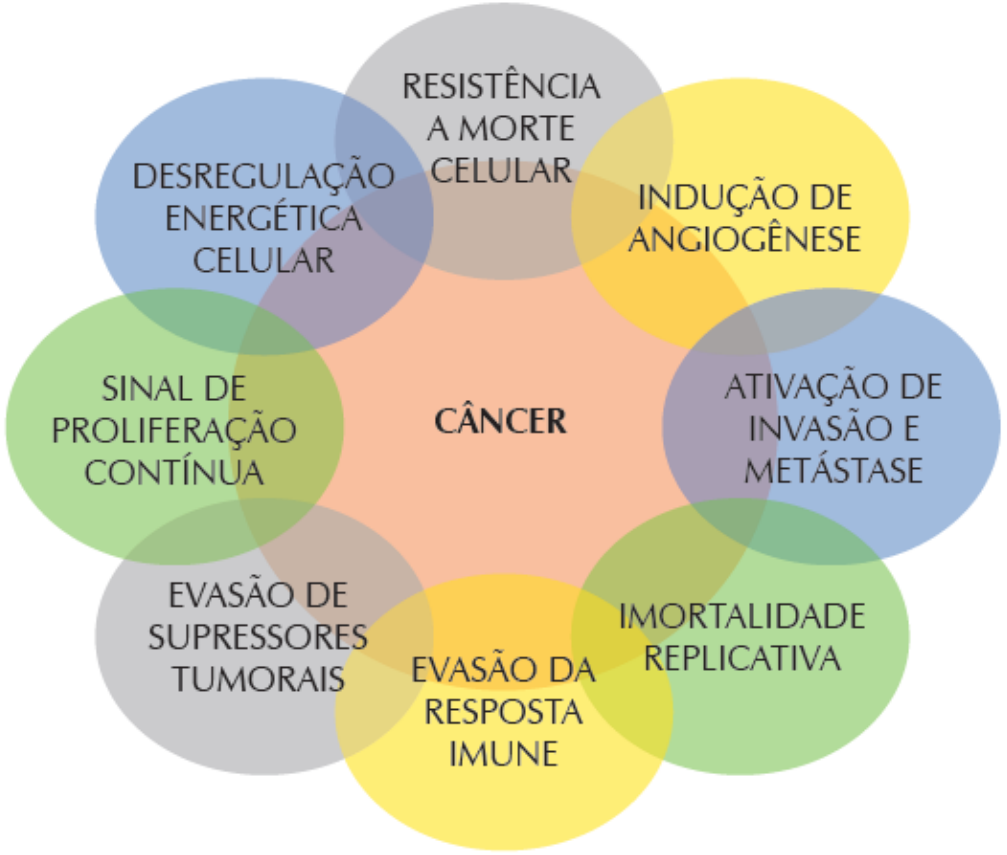


Figure 20-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

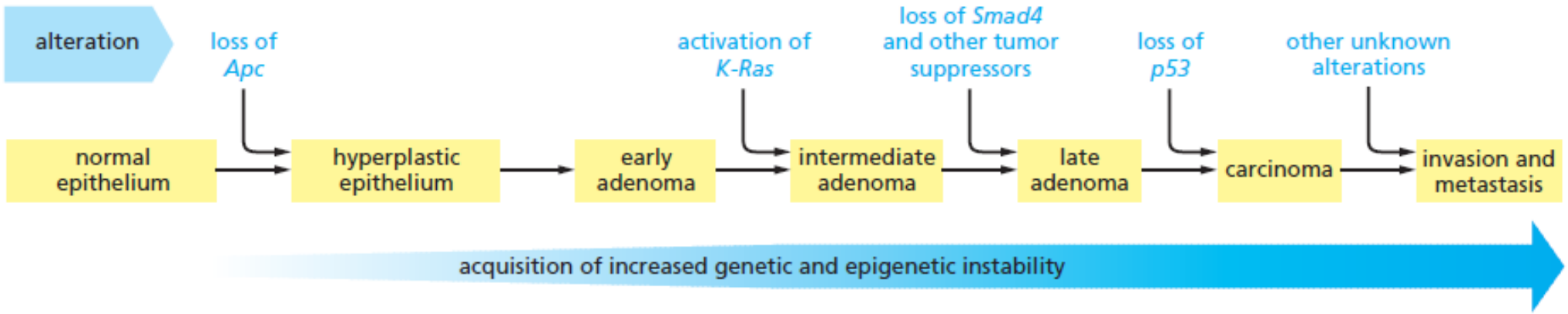
Para o tumor ‘vingar’ é preciso..



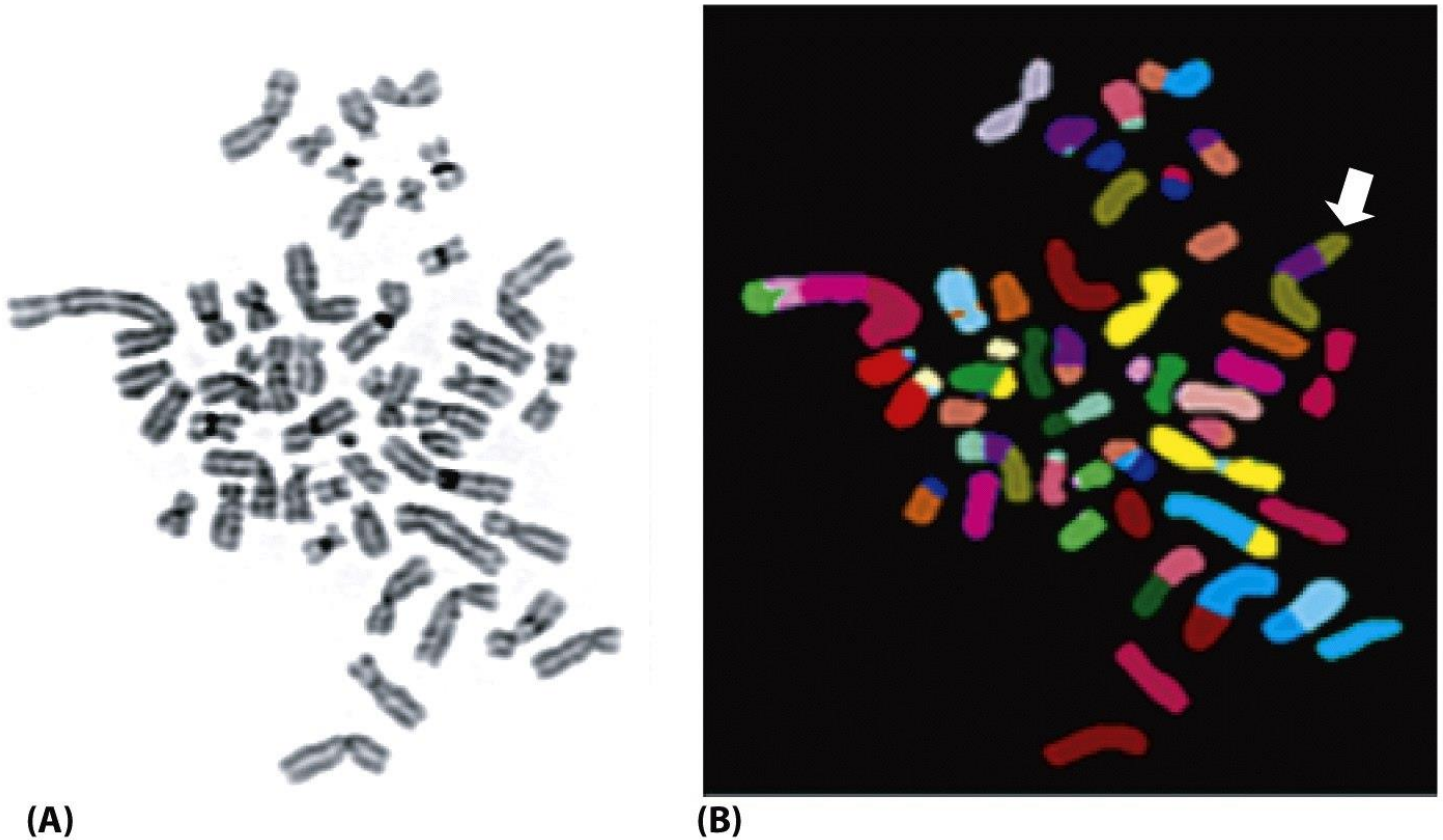
PRA REUNIR TODAS ESSAS PROPRIEDADES É PRECISO TEMPO !

Fundamentos de Oncologia Molecular, Saito RF, Lana MVG, Medrano, RFV, Chammas R
Editora Atheneu 2016

Sequência hipotética de alterações que levam ao desenvolvimento de um tumor



Muitas alterações se acumulam durante a progressão tumoral



(A) (B)

Figure 20-13 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Iniciadores e promotores tumorais

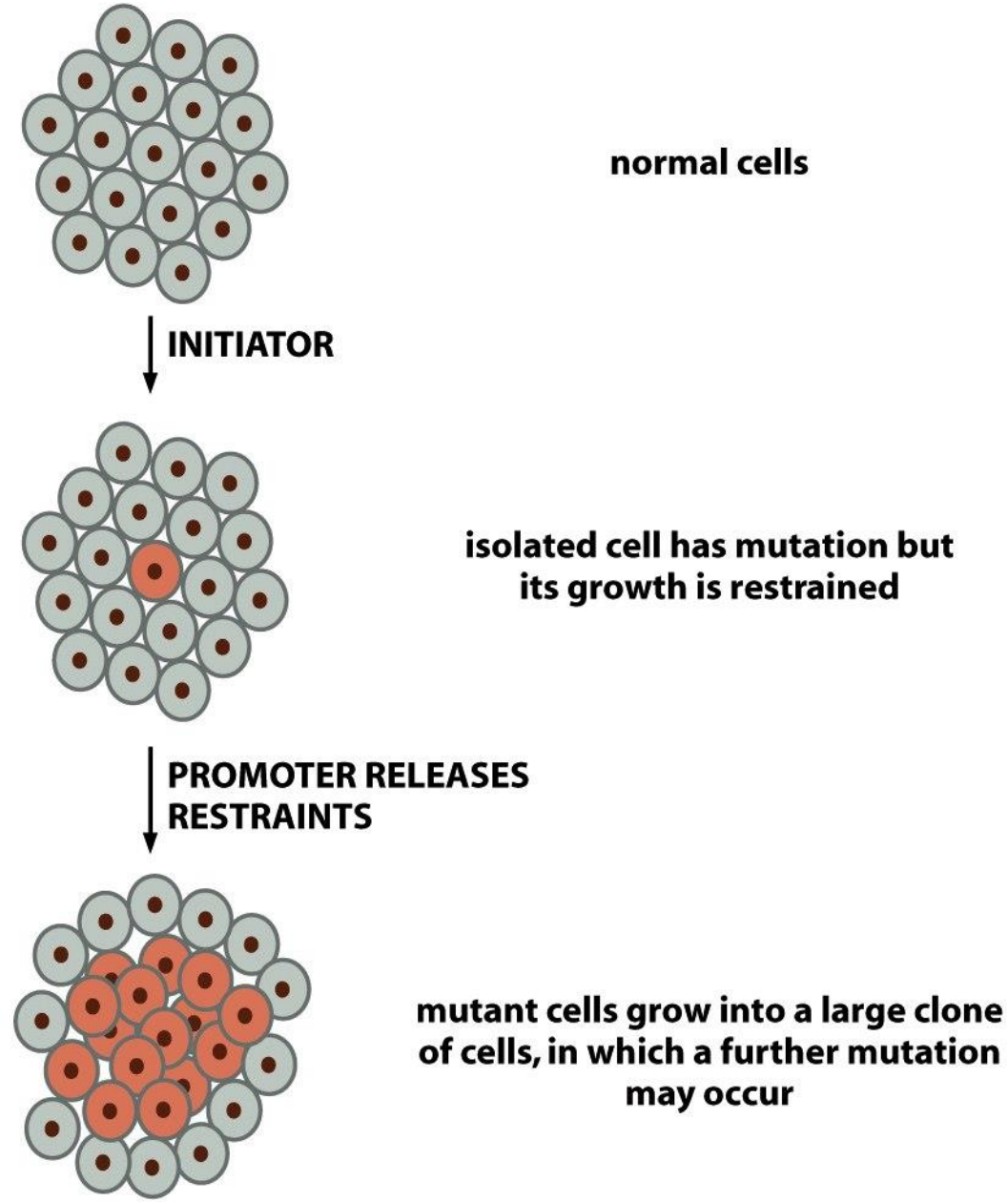


Figure 20-24 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Indução de tumor na pele de camundongos

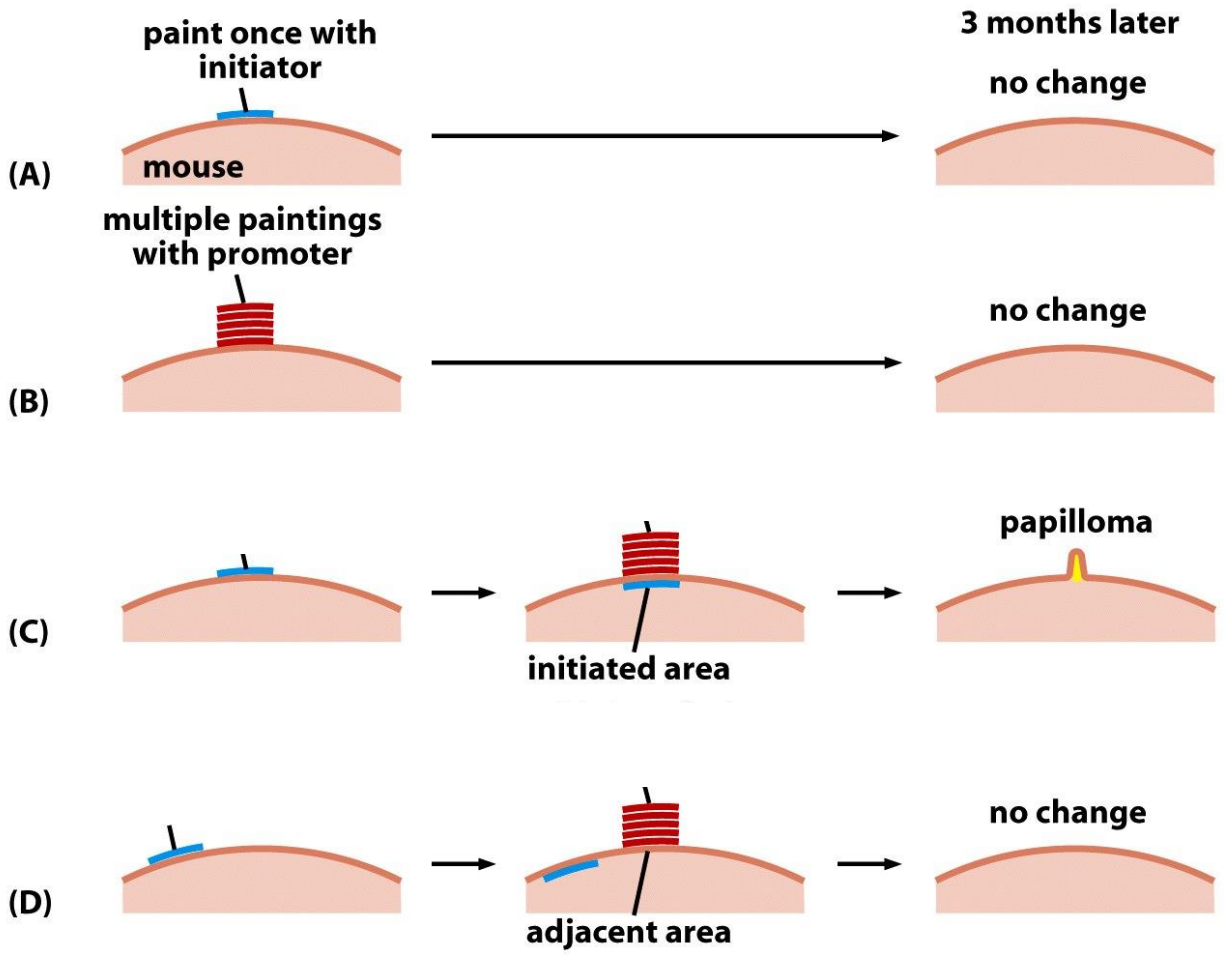


Figure 11-28 part 1 of 2 The Biology of Cancer (© Garland Science 2007)

Indução de tumor na pele de camundongos

DMBA – dimethylbenzanthraceno

TPA- tetraecanoylphorbol-13-acetate

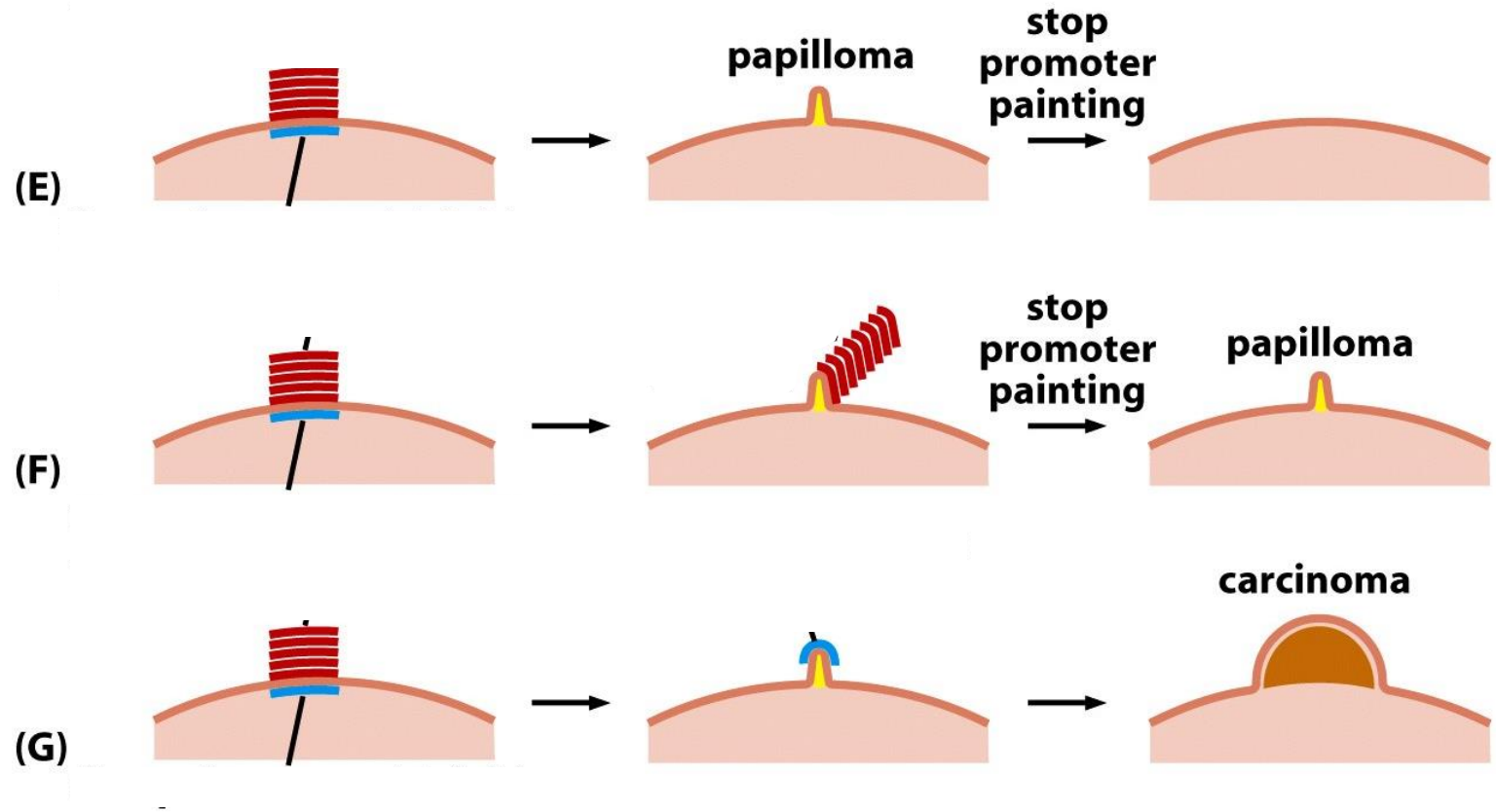


Figure 11-28 part 2 of 2 The Biology of Cancer (© Garland Science 2007)

PROGRESSÃO

Interpretação do ensaio:

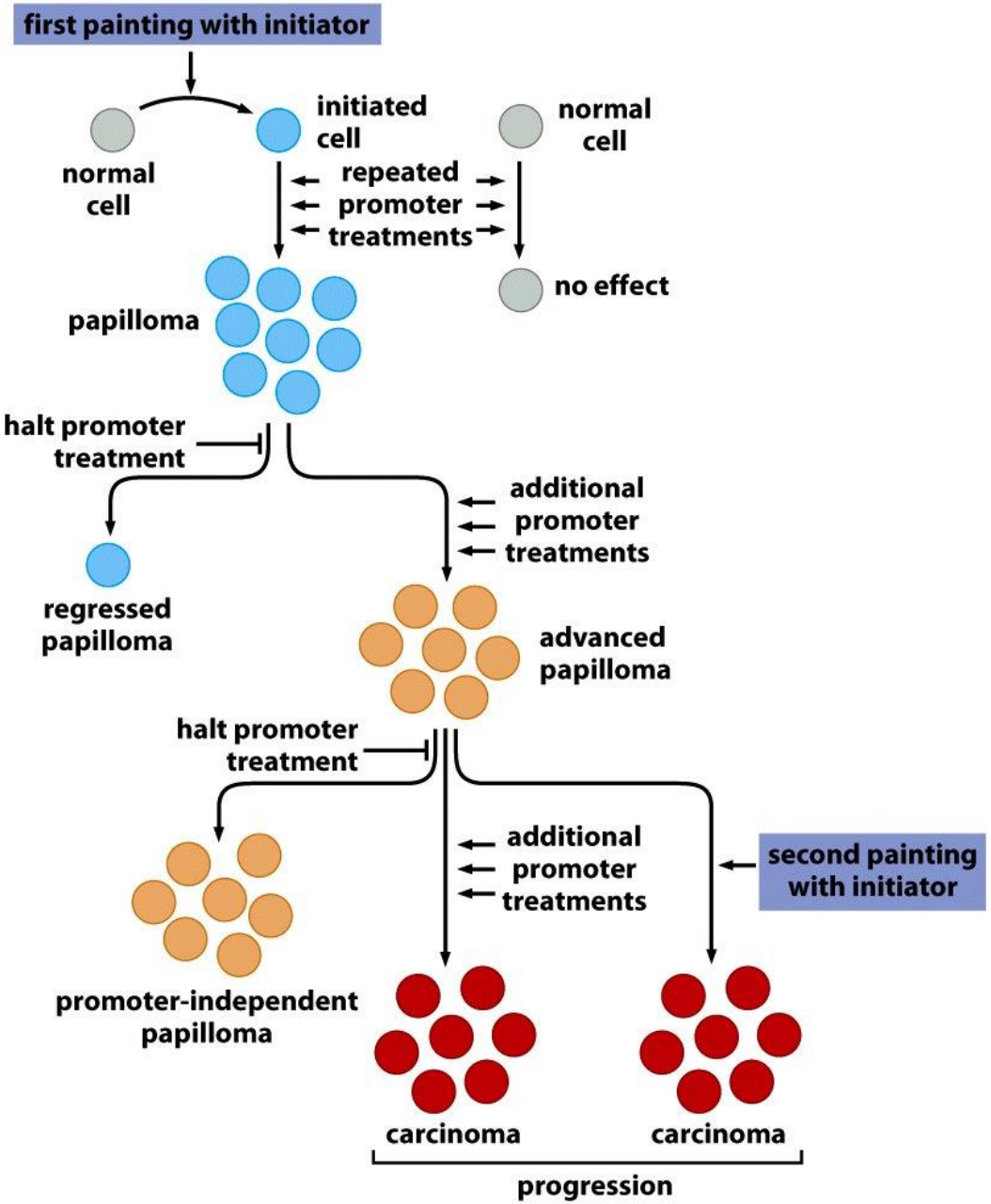


Figure 11-29 The Biology of Cancer (© Garland Science 2007)

- Iniciadores – agentes carcinogênicos
- Promotores – agentes tóxicos ou mitógenos

alcool

Table 11.3 Known or suspected human tumor promoters and their sites of action

Agent or process	Cancer site
Hormones	
Estrogen	endometrium
Estrogen and progesterone	breast
Ovulation	ovary
Testosterone	prostate
Drugs	
Oral contraceptives, anabolic steroids	liver
Analgesics	renal pelvis
Diuretics	kidney
Infectious agents	
Hepatitis B/C viruses	liver
Schistosoma haematobium—blood fluke	bladder
Schistosoma japonicum—blood fluke	colon
Clonorchis sinensis—liver fluke	biliary tract
Helicobacter pylori—bacterium	stomach
Malarial parasites	B cell
Tuberculosis bacillus	lung
Chemical agents	
Betel nut, lime	oral cavity
Chewing tobacco	oral cavity
Bile	small intestine
Salt	stomach
Acid reflux	esophagus
Physical or mechanical trauma	
Asbestos	mesothelium, lung
Gallstones	gallbladder
Coarsely ground corn	stomach
Head injury	meninges
Chronic irritation/inflammation	
Tropical ulcers	skin
Chronic ulcerative colitis	colon
Chronic cystitis	bladder
Chronic pancreatitis	pancreas

Adapted in part from S. Preston-Martin, M.C. Pike, R.K. Ross et al., *Cancer Res.* 50:7415–7421, 1990.

Relembrando...
oncogenes e genes supressores de tumor

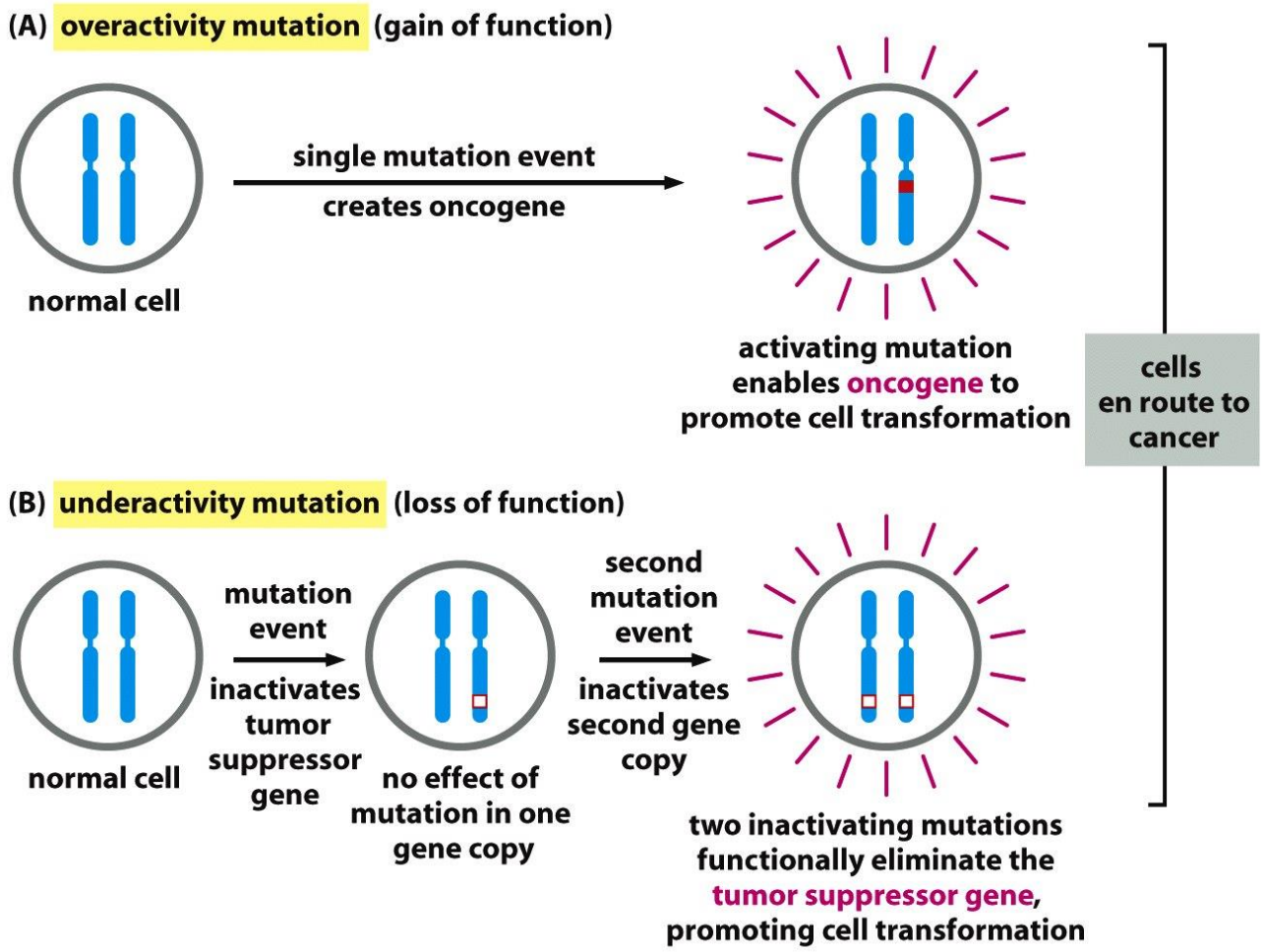


Figure 20-27 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Relembrando:

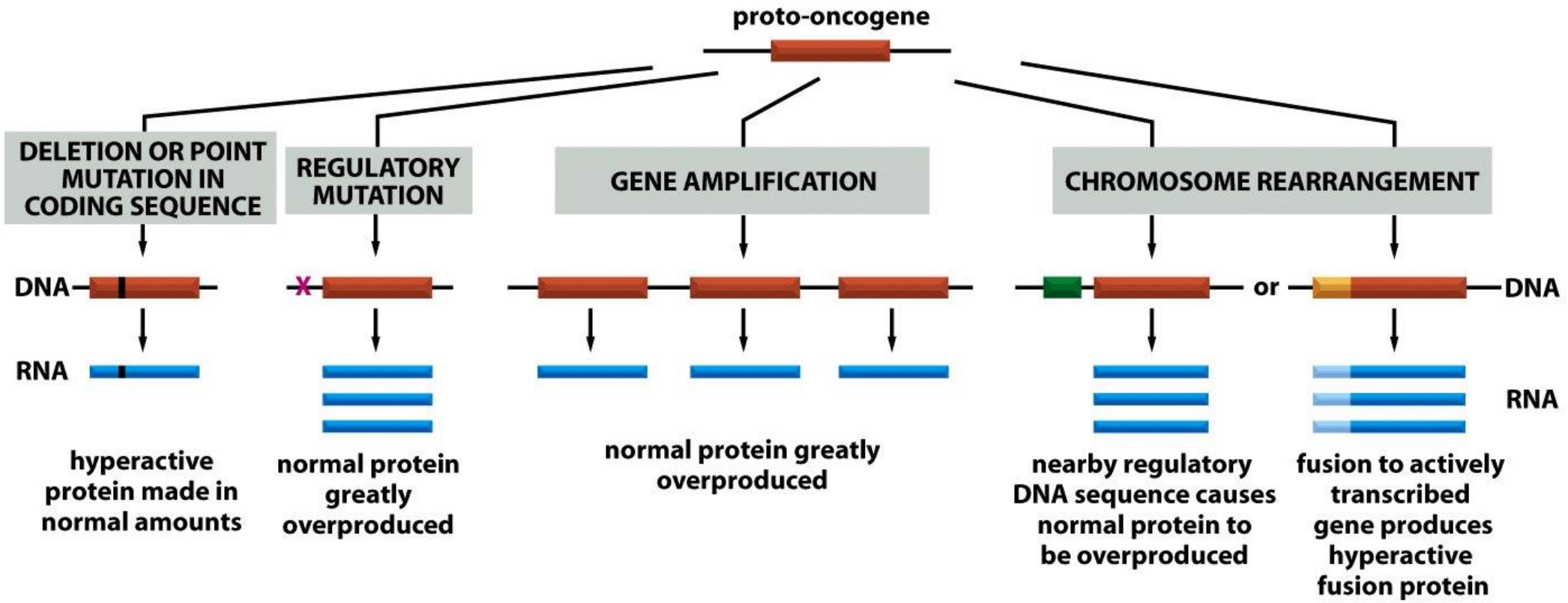


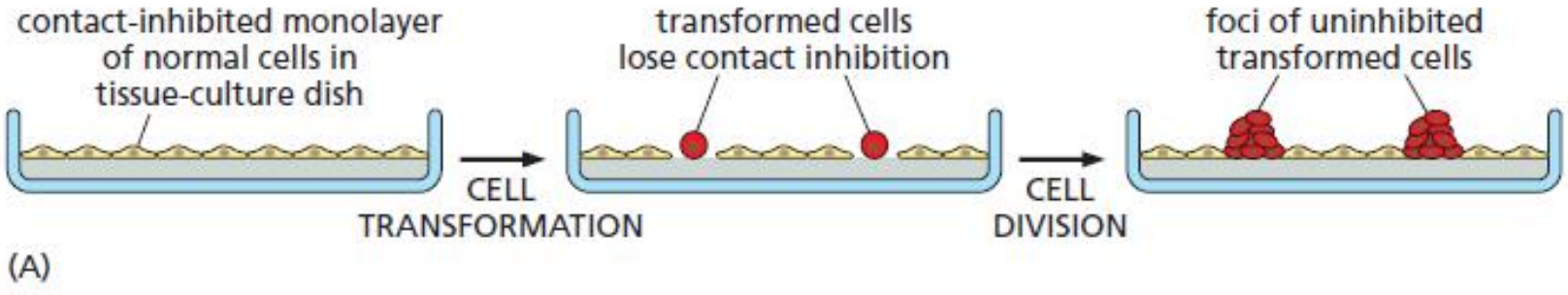
Figure 20-33 Molecular Biology of the Cell 5/e (© Garland Science 2008)

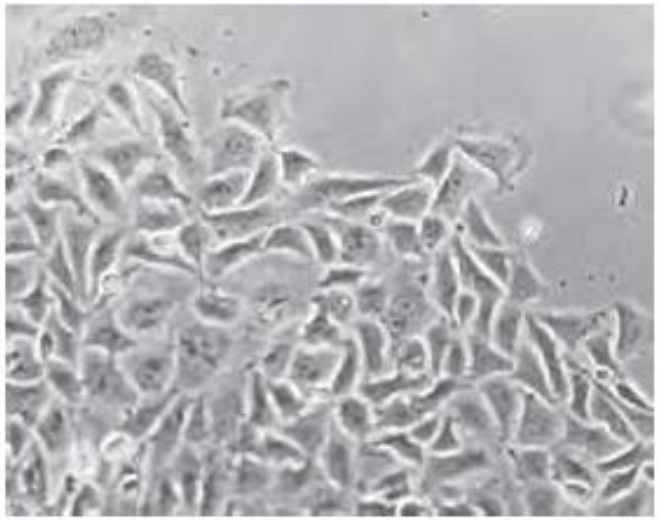
Imortalidade replicativa
vida eterna!

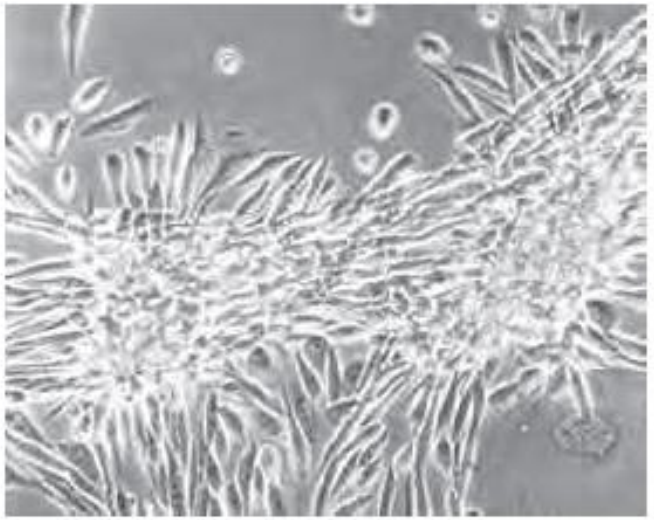
- Proliferar continuamente = não morrer, não diferenciar e não tornar-se quiescente - COMO ?
  - Evadir os sinais de parada do ciclo celular pelos genes supressores de tumor
  - Evadir os sinais indutores de morte celular
  - Ser independente de fatores de proliferação = ativação de oncogenes
  - Ajuste metabólico para sustentar a demanda energética imposta pela replicação

Células tumorais são também chamadas células <u>transformadas</u>

Células tumorais proliferam de forma independente e sem controle

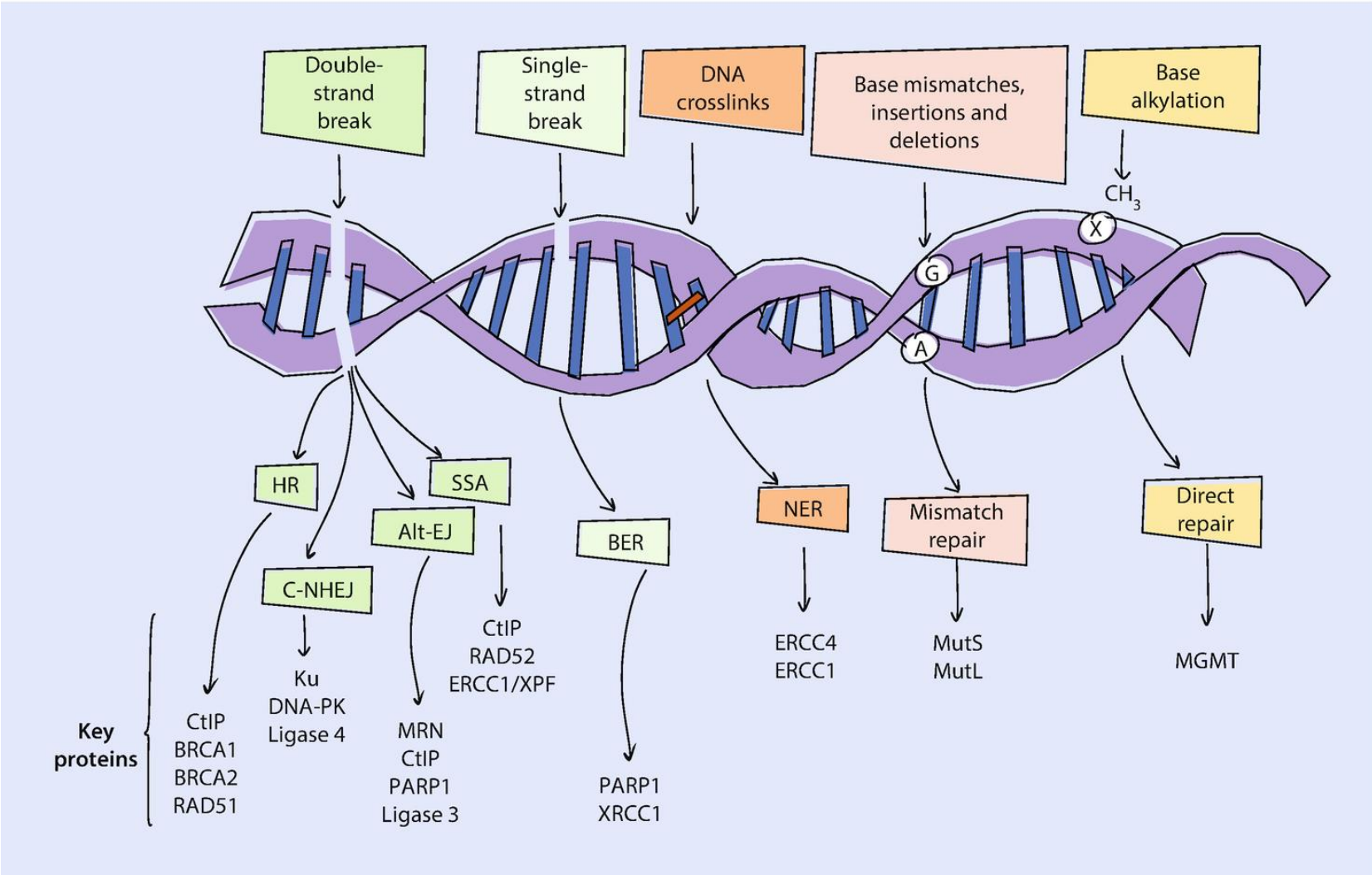



(B)


(C)

Células normais “respeitam” seus limites, células tumorais NÃO

Quanto mais uma célula vive e PROLIFERA, mais exposta ela está:



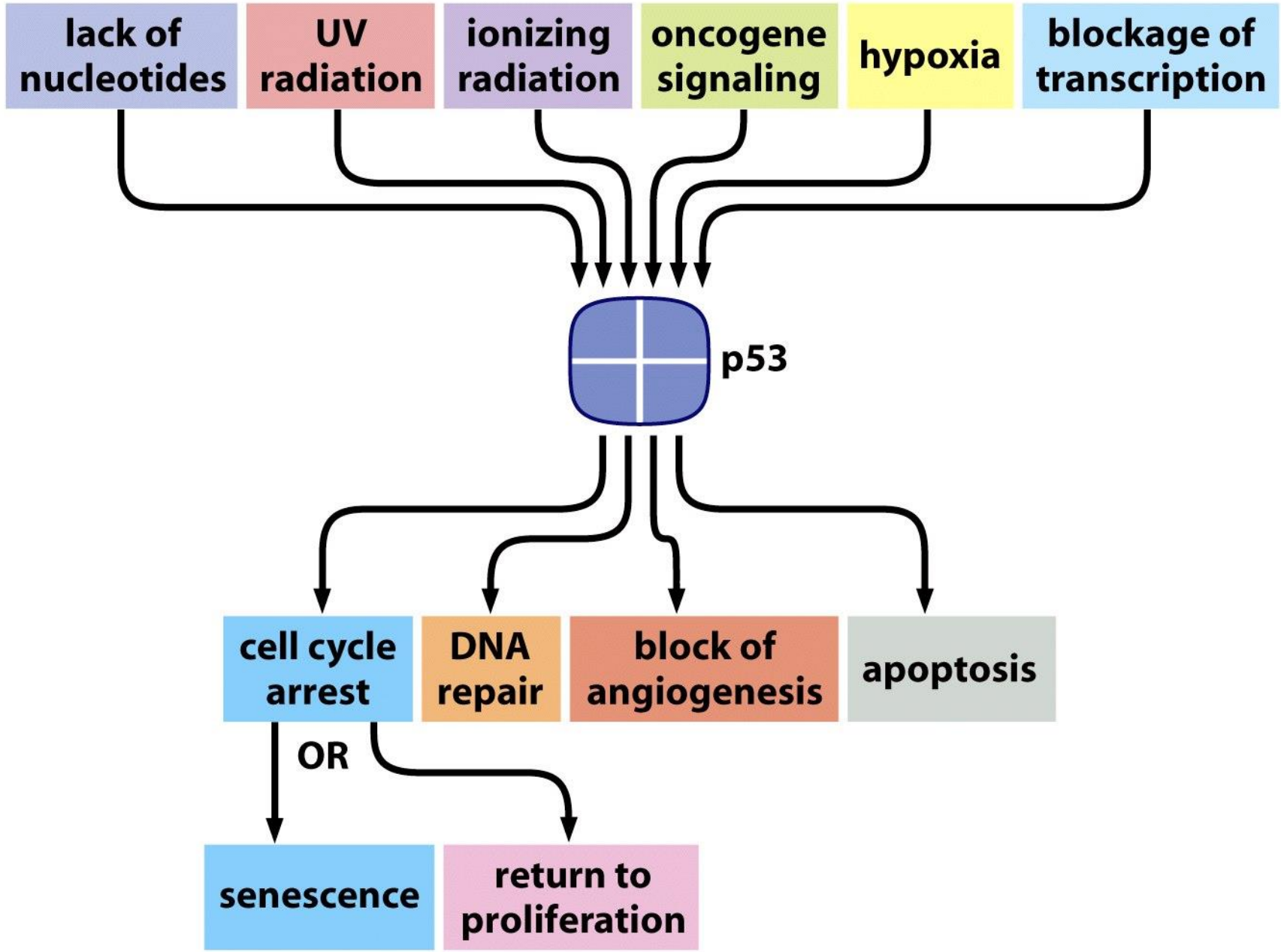
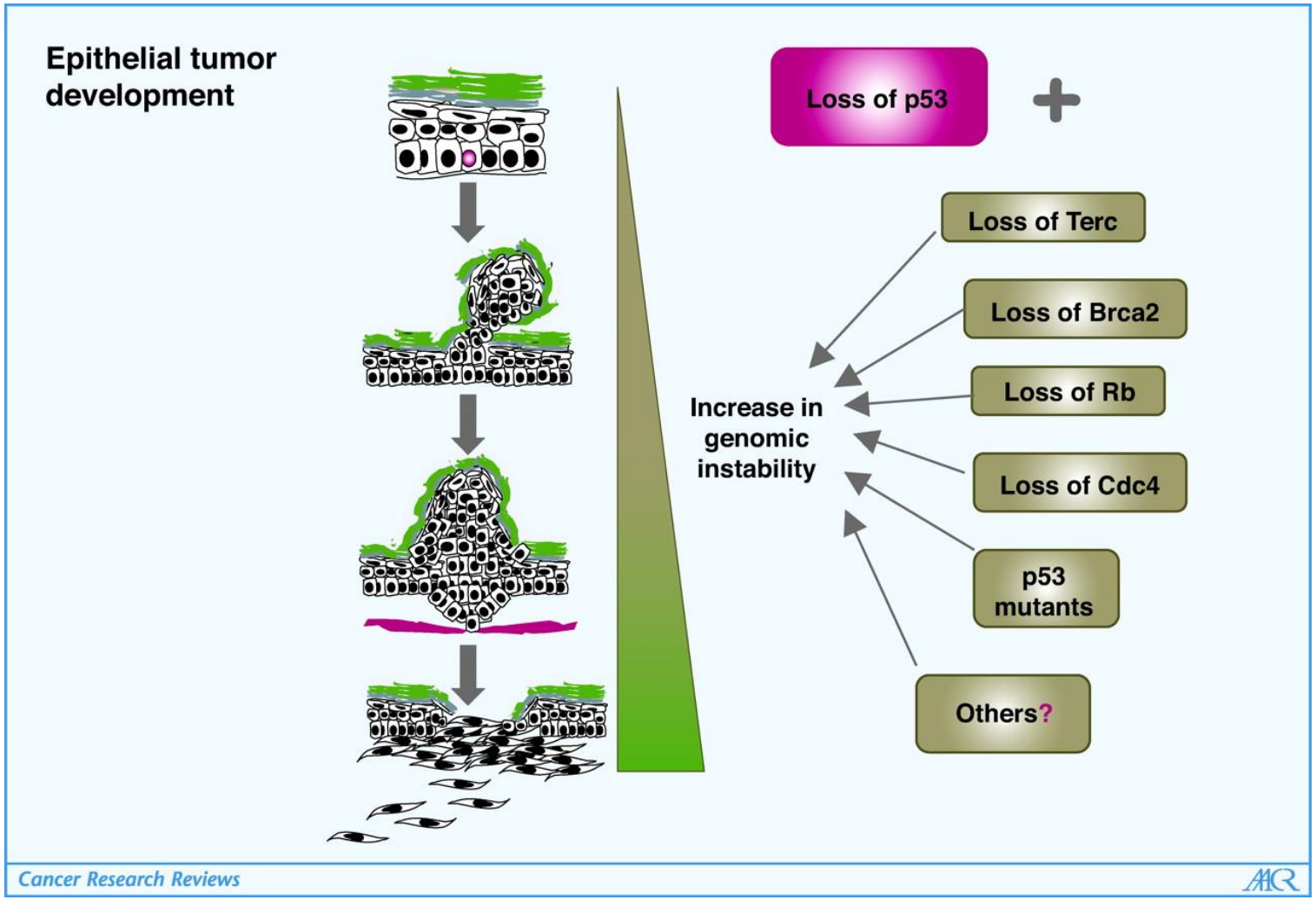


Figure 9-8 The Biology of Cancer (© Garland Science 2007)



Jesus Perez-Losada et al. Cancer Res 2005;65:6488-6492

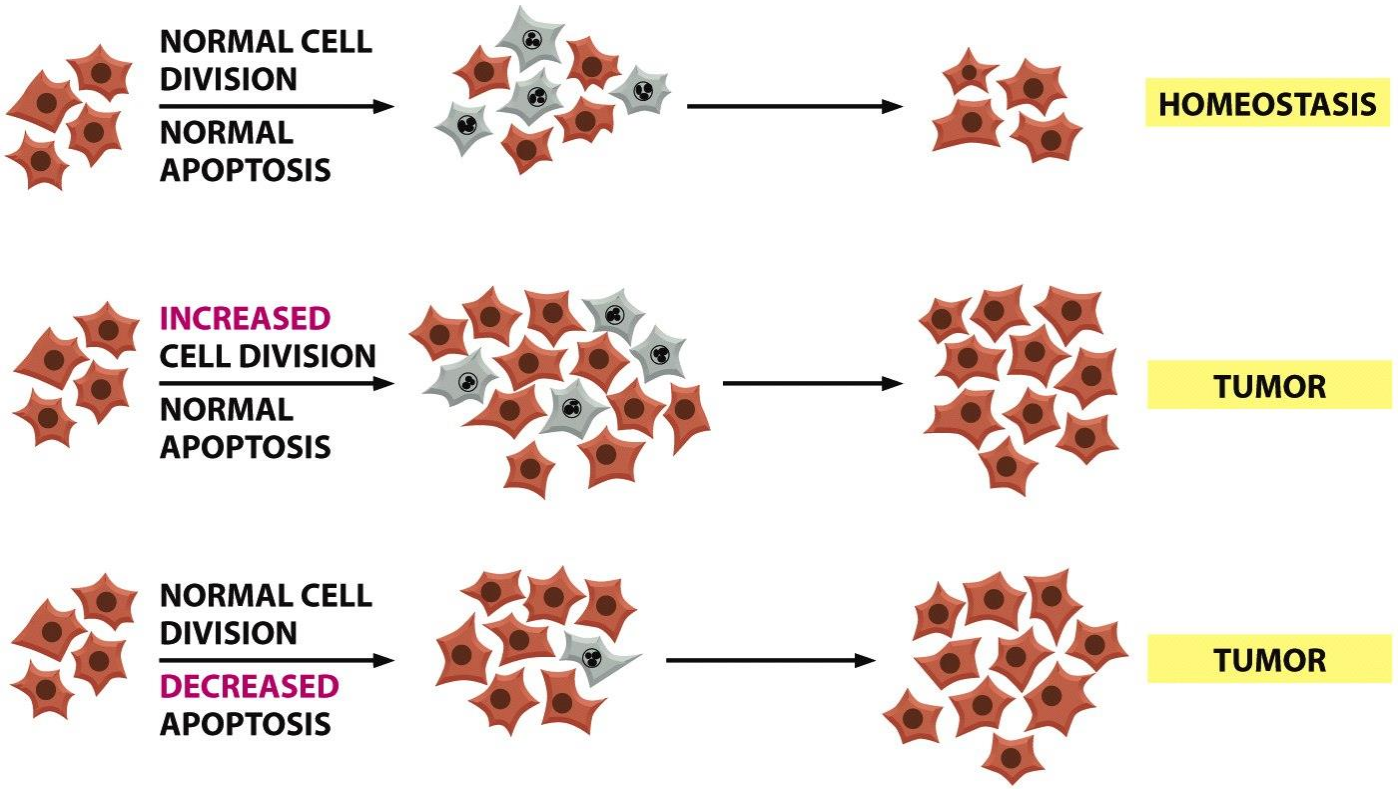


Figure 20-14 Molecular Biology of the Cell 5/e (© Garland Science 2008)

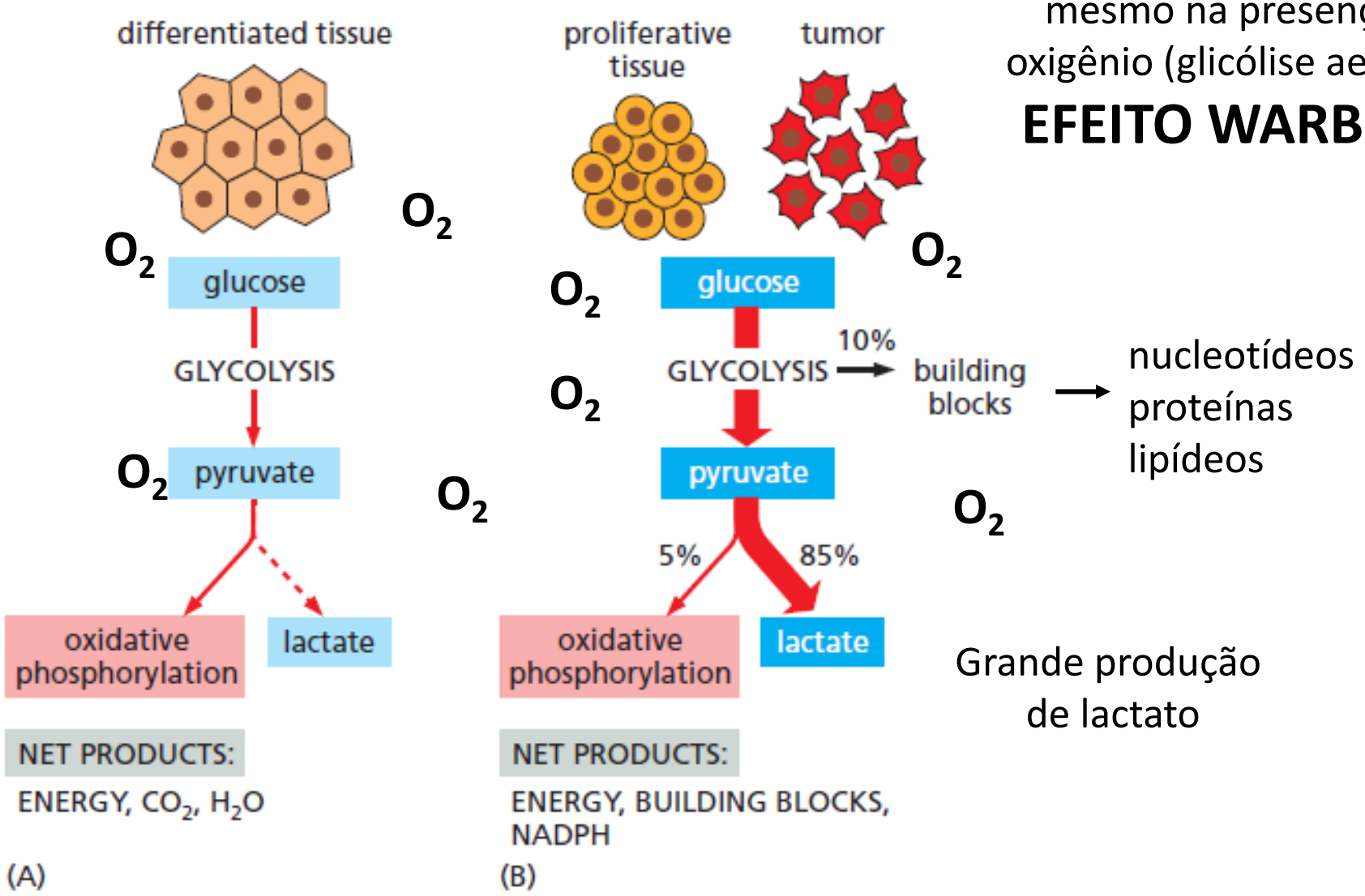
Imortalidade replicativa
vida eterna!

- Proliferar continuamente = não morrer, não diferenciar e não tornar-se quiescente - COMO ?
  - Evadir os sinais de parada do ciclo celular pelos genes supressores de tumor
  - Evadir os sinais indutores de morte celular
  - Ser independente de fatores de proliferação = ativação de oncogenes
  - Ajuste metabólico para sustentar a demanda energética imposta pela replicação

Células tumorais importam glicose do sangue a uma taxa 100X maior do que células normais

Células tumorais degradam a glicose na via glicolítica mesmo na presença de oxigênio (glicólise aeróbica)

EFEITO WARBURG



nucleotídeos
proteínas
lipídeos

Grande produção de lactato

O início – mutações somáticas

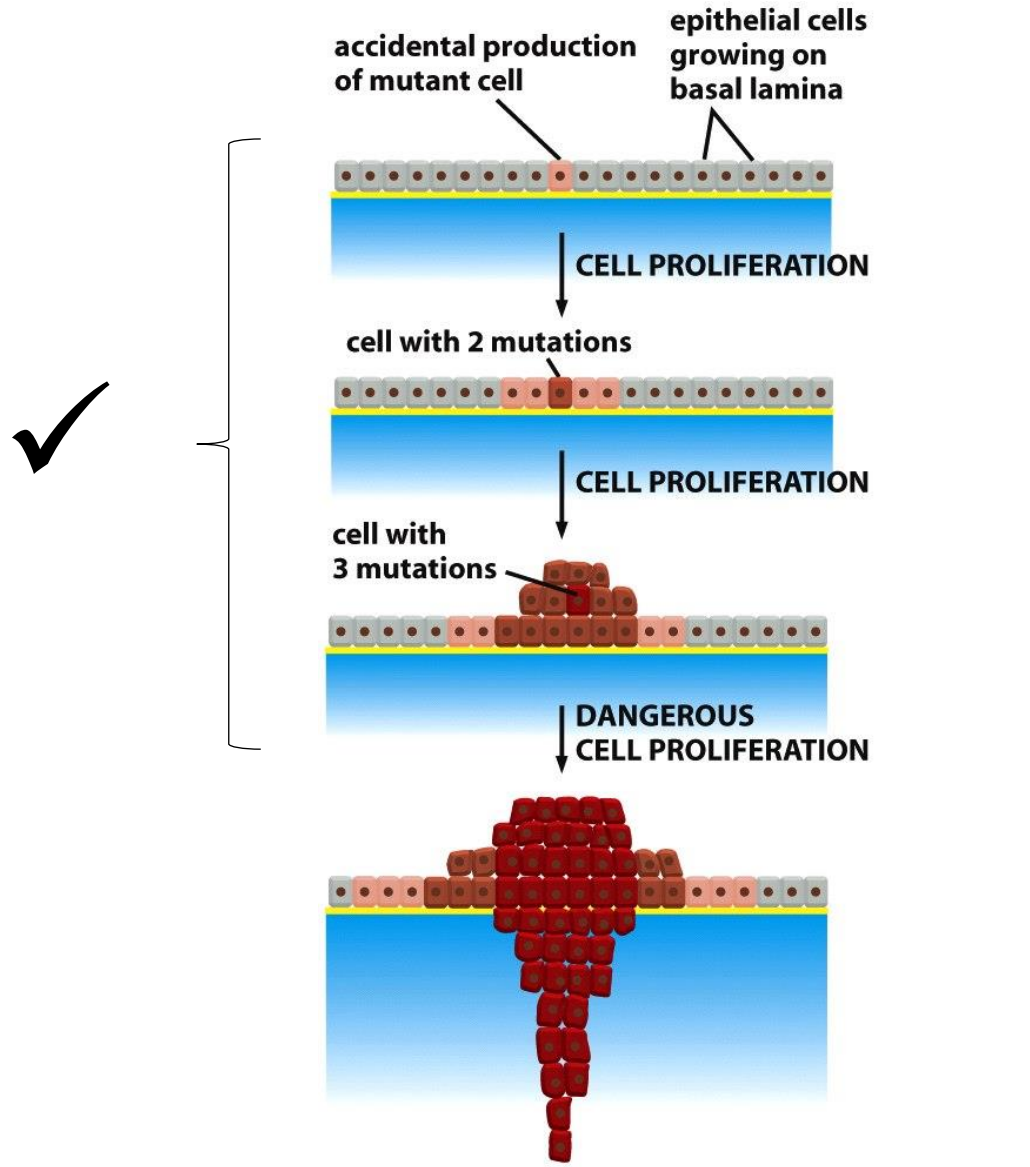


Figure 20-11 Molecular Biology of the Cell 5/e (© Garland Science 2008)

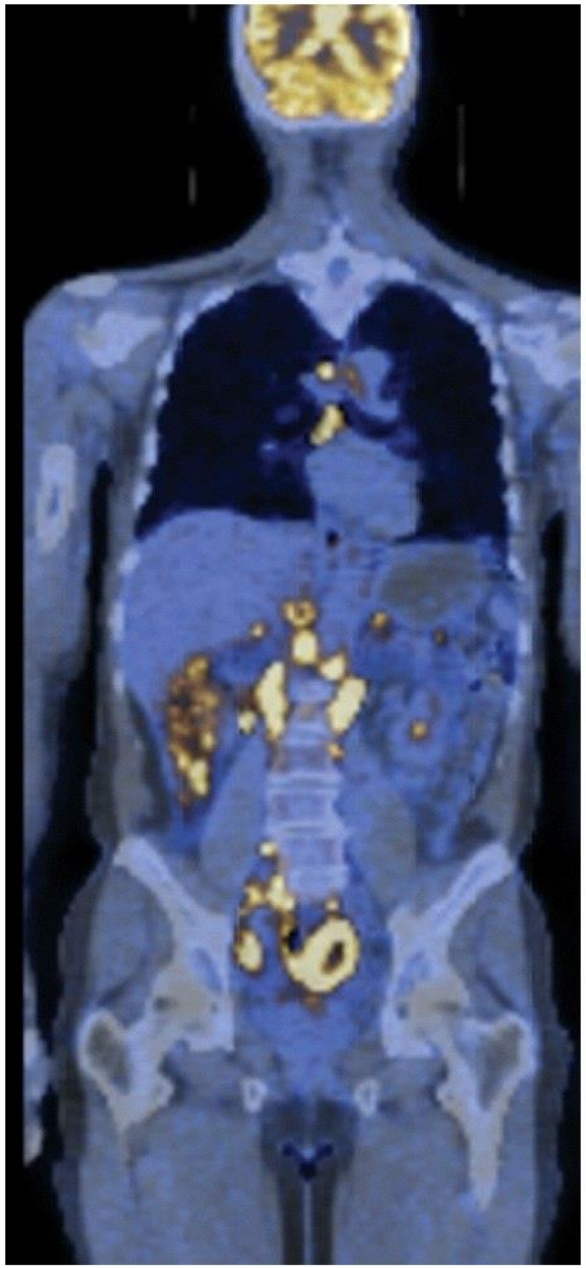


Figure 14-1 The Biology of Cancer (© Garland Science 2007)

metástase

pósitron-emission tomography (fluoredeoxiglicose)

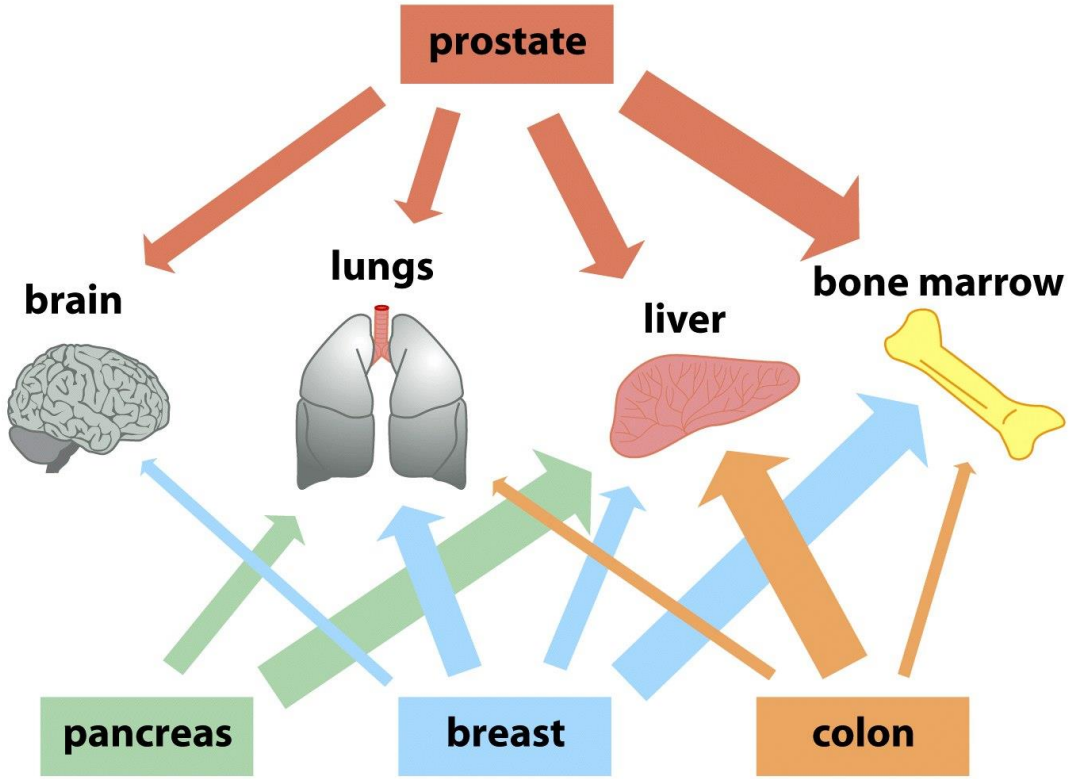


Figure 14-42 The Biology of Cancer (© Garland Science 2007)

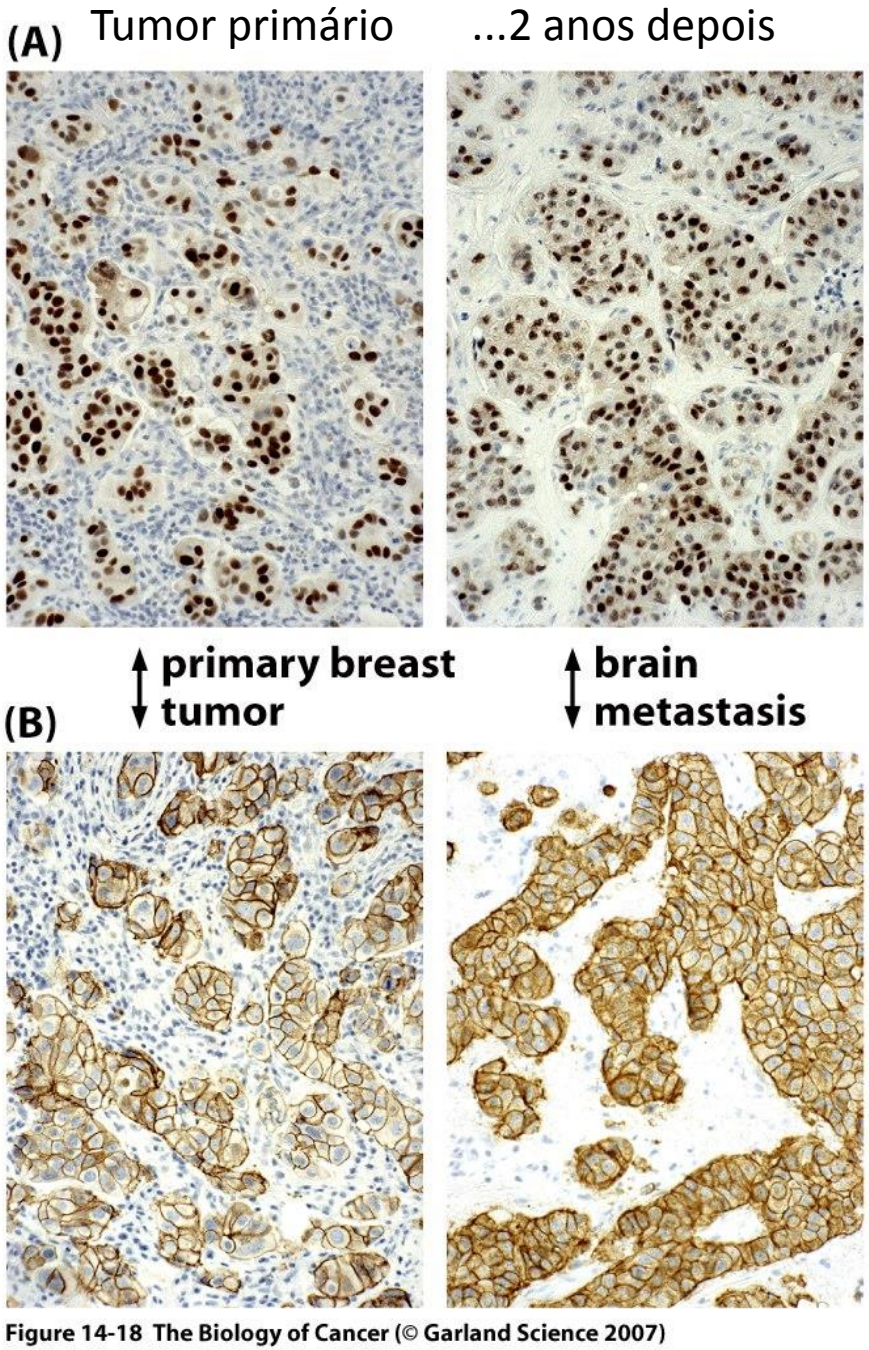


Figure 14-18 The Biology of Cancer (© Garland Science 2007)

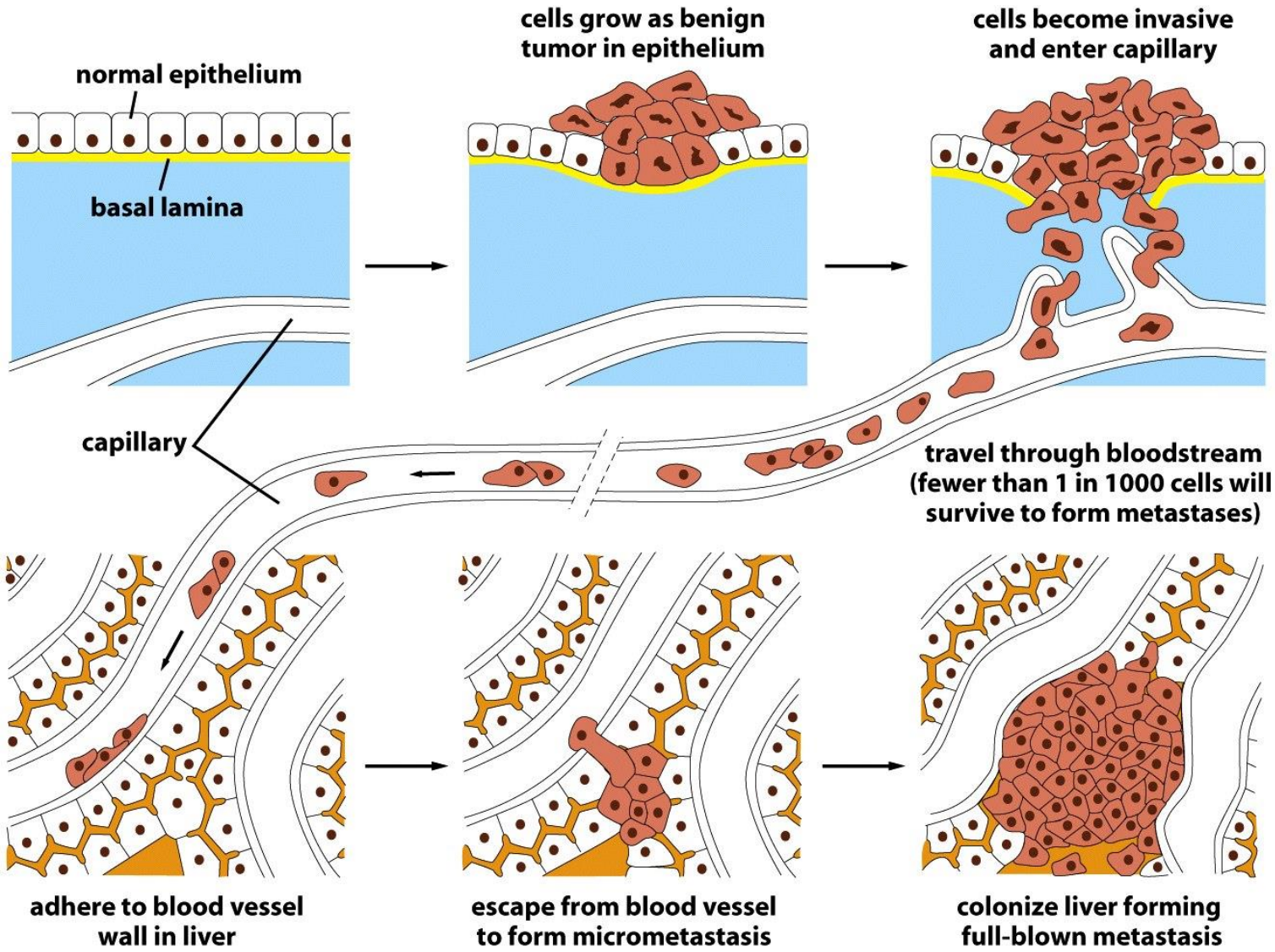


Figure 20-17 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Transição epitélio-mesenquimal – EMT
Transição mesenquimo-epitelial – MET

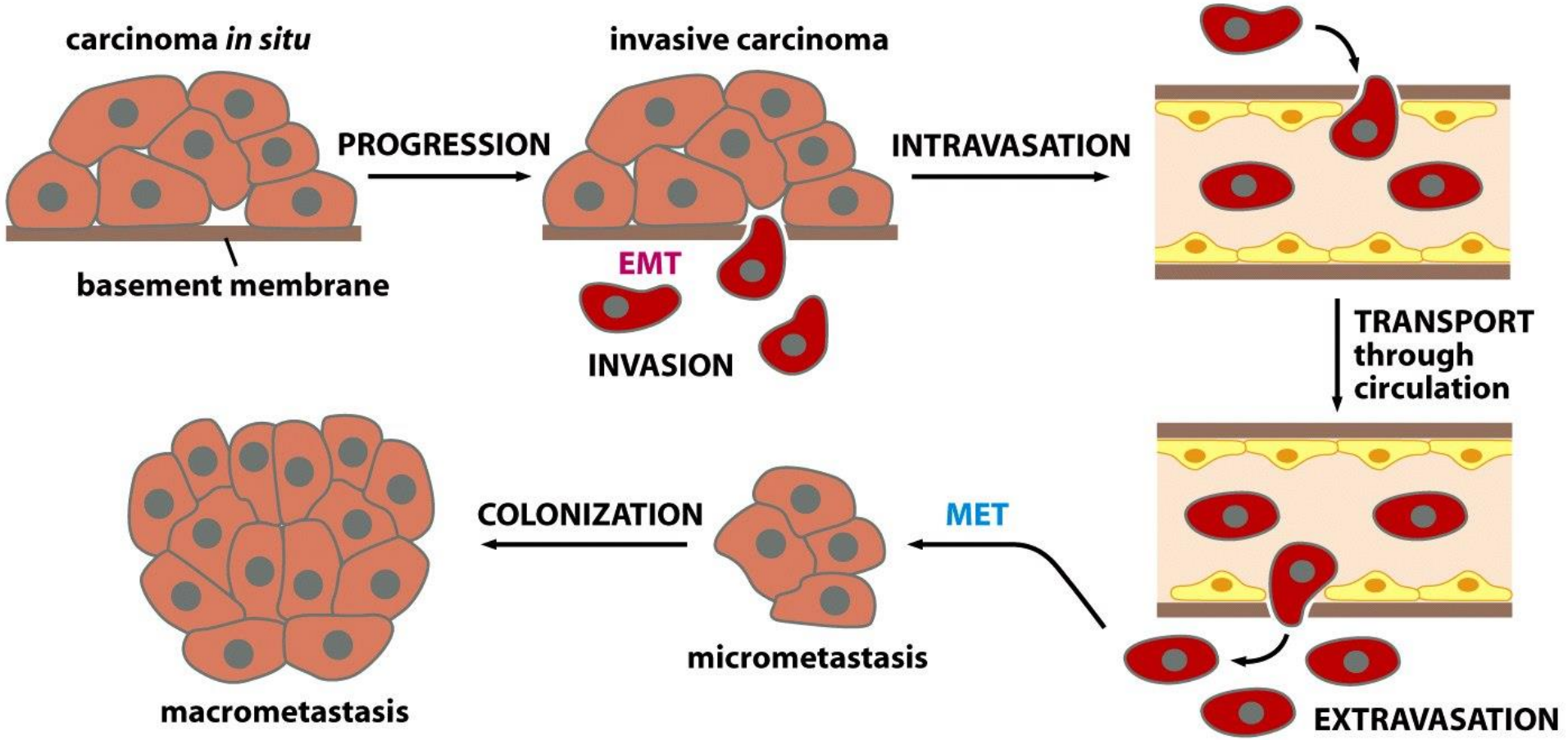
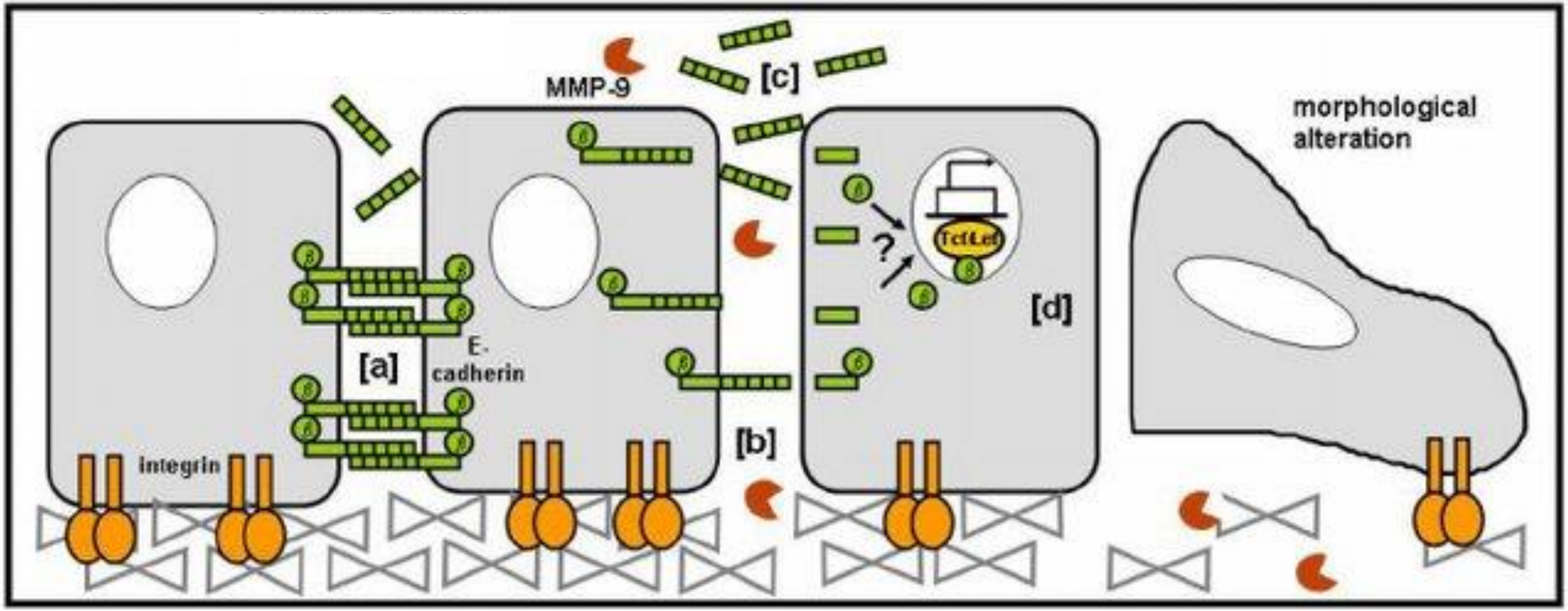


Figure 14-17b The Biology of Cancer (© Garland Science 2007)

Na EMT ocorre perda da adesão célula-célula mediada por E-caderina e degradação da matriz extracelular



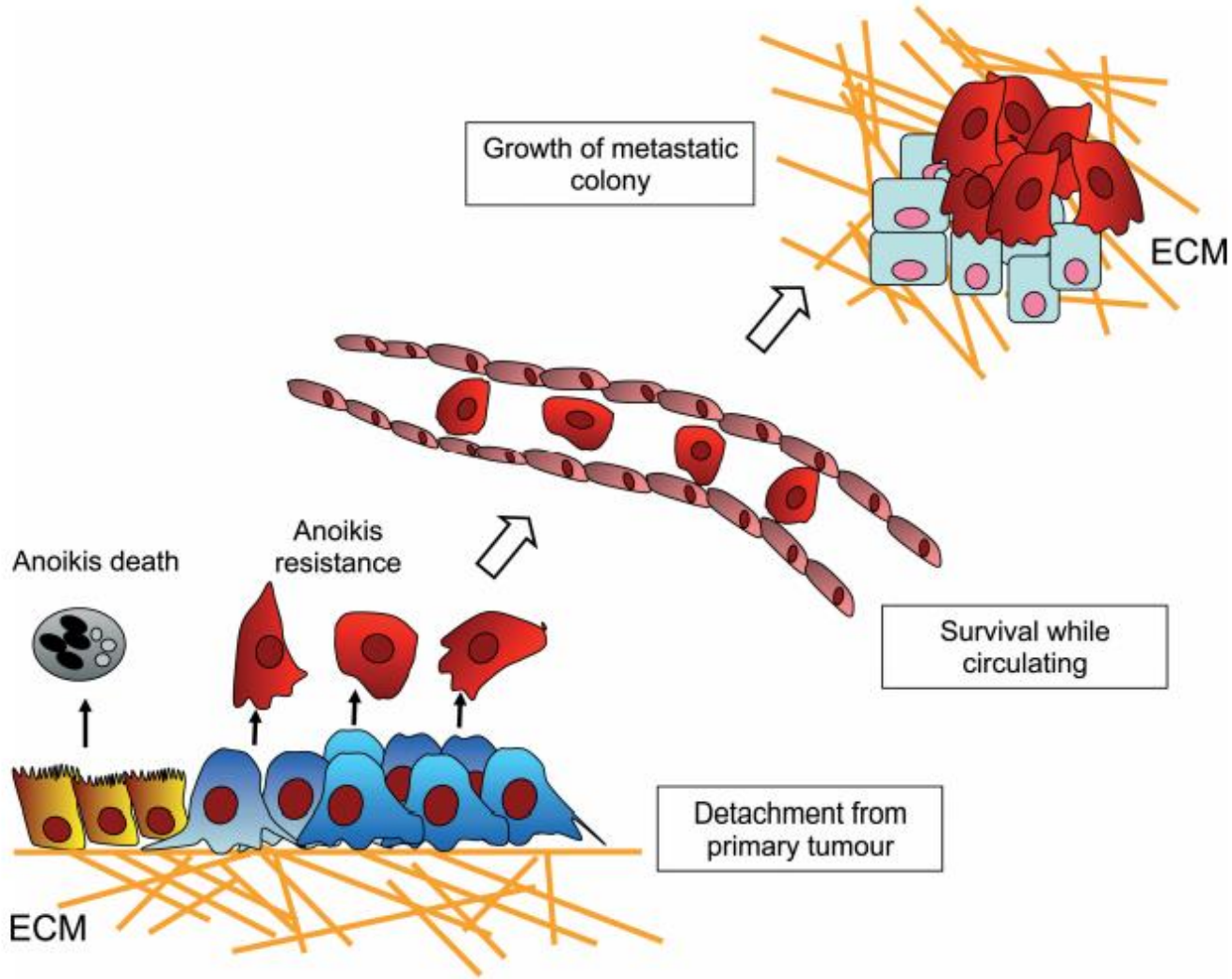
Matriz extracelular metaloproteases **E-caderinas**

Table 14.2 Cellular changes associated with the epithelial–mesenchymal transition

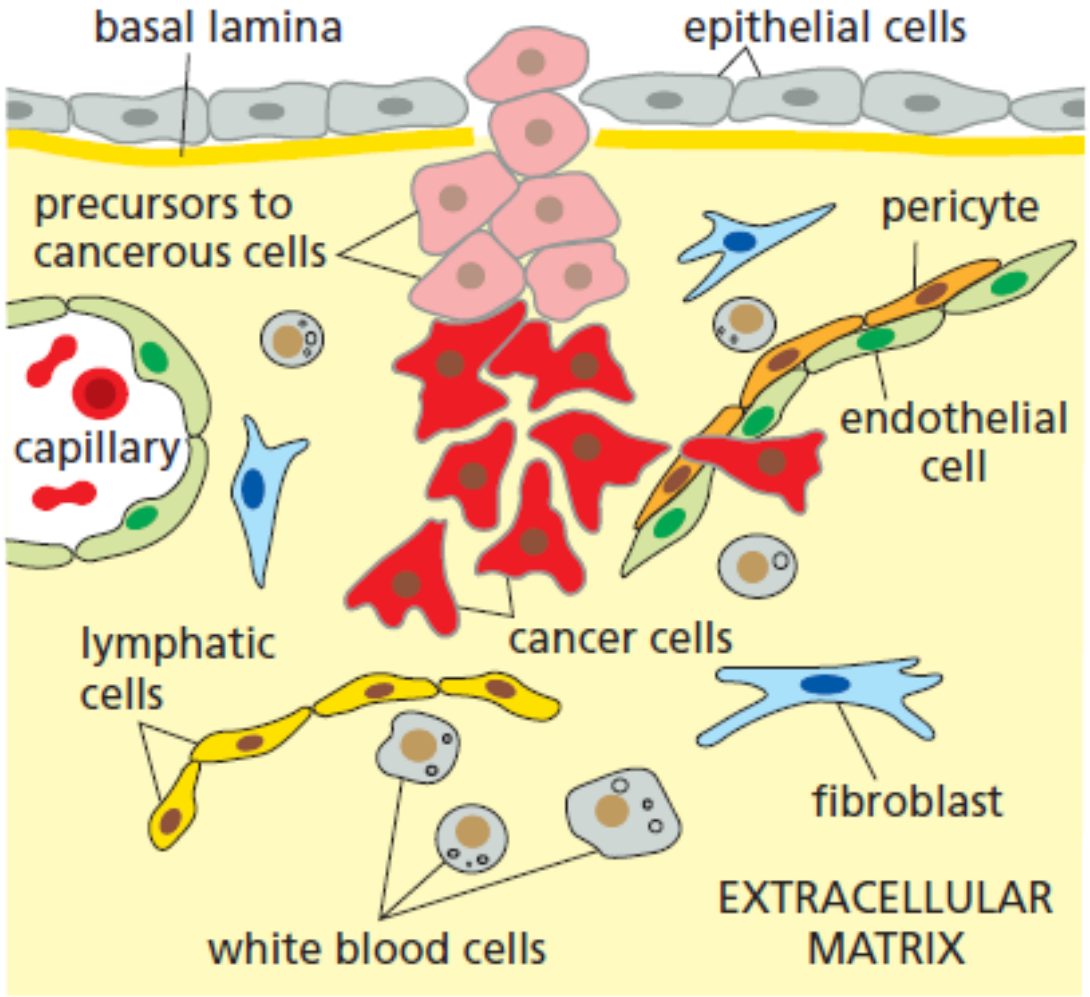
Loss of
Cytokeratin (intermediate filament) expression
Epithelial adherens junction protein (E-cadherin)
Epithelial cell polarity
Acquisition of
Fibroblast-like shape
Motility
Invasiveness
Mesenchymal gene expression program
Mesenchymal adherens junction protein (N-cadherin)
Protease secretion (MMP-2, MMP-9)
Vimentin (intermediate filament) expression
Fibronectin secretion
PDGF receptor expression
αvβ6 integrin expression

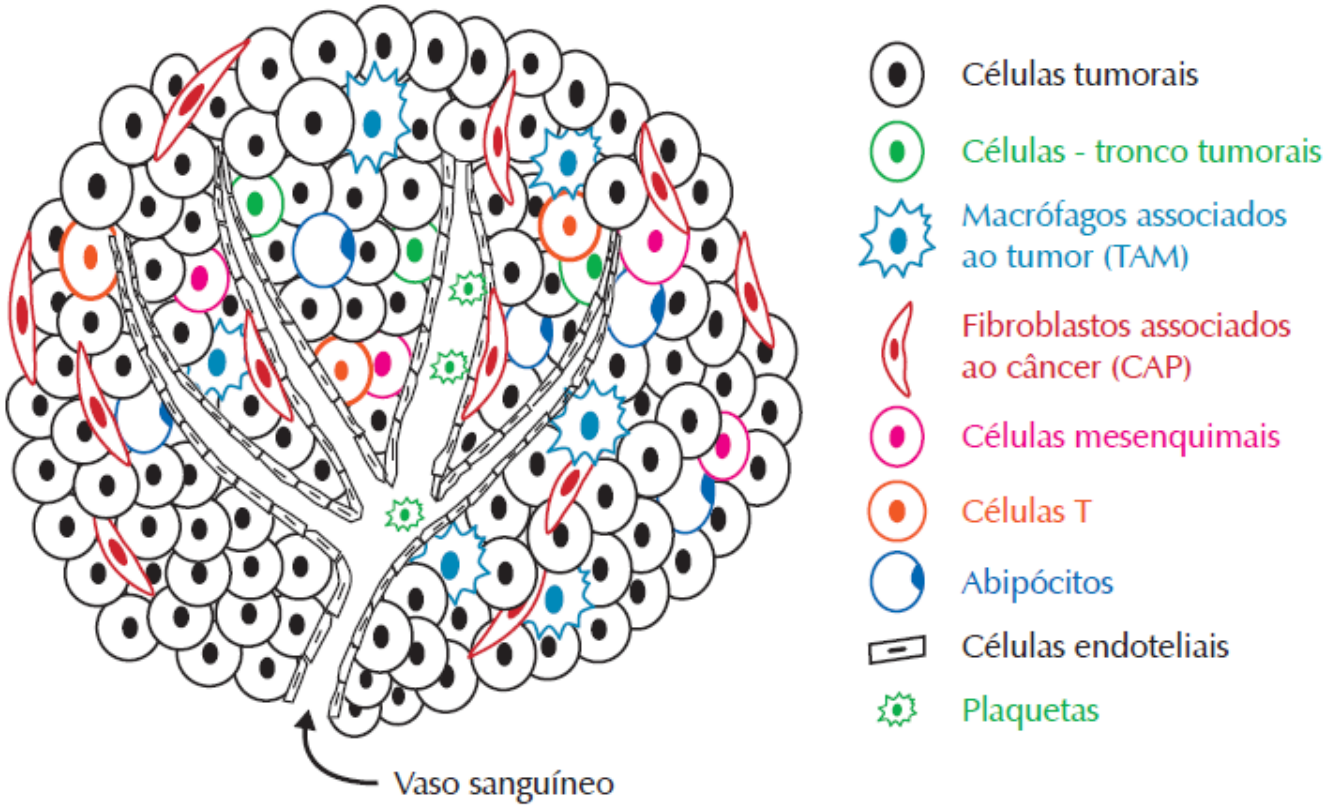
Table 14-2 The Biology of Cancer (© Garland Science 2007)

Células tumorais são resistentes à *anoikis* (= morte celular induzida por perda de adesão à matriz):



A metástase depende da interação do tumor com o seu microambiente

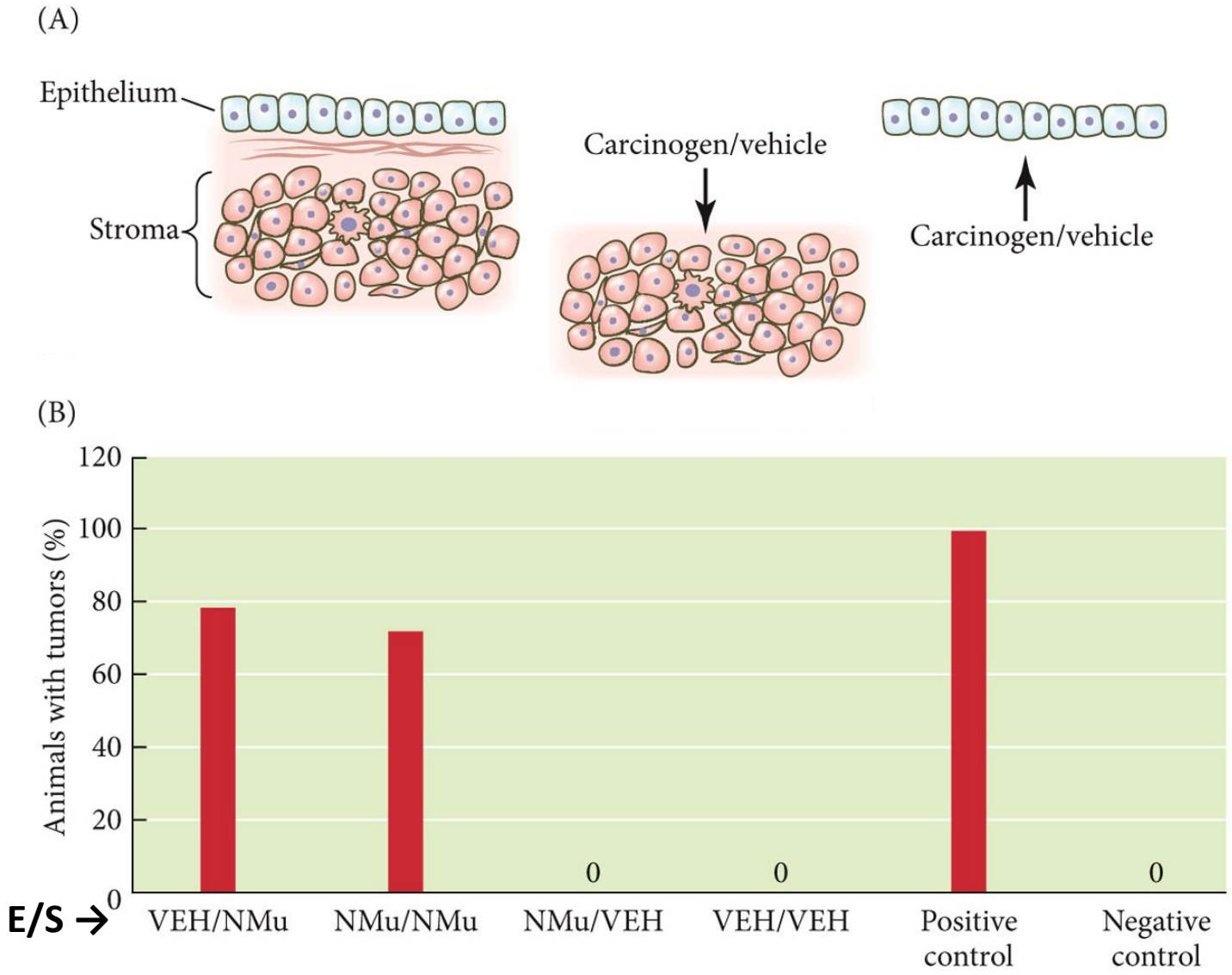




Fundamentos de Oncologia Molecular, Saito RF, Lana MVG, Medrano, RFV, Chammas R Editora Atheneu 2016

Exemplos da importância do microambiente tumoral

NMu – carcinógeno
VEH - veículo



DEVELOPMENTAL BIOLOGY 11e, Figure 24.18

Somente quando o estroma (= microambiente) é exposto ao carcinógeno ocorre formação de tumor

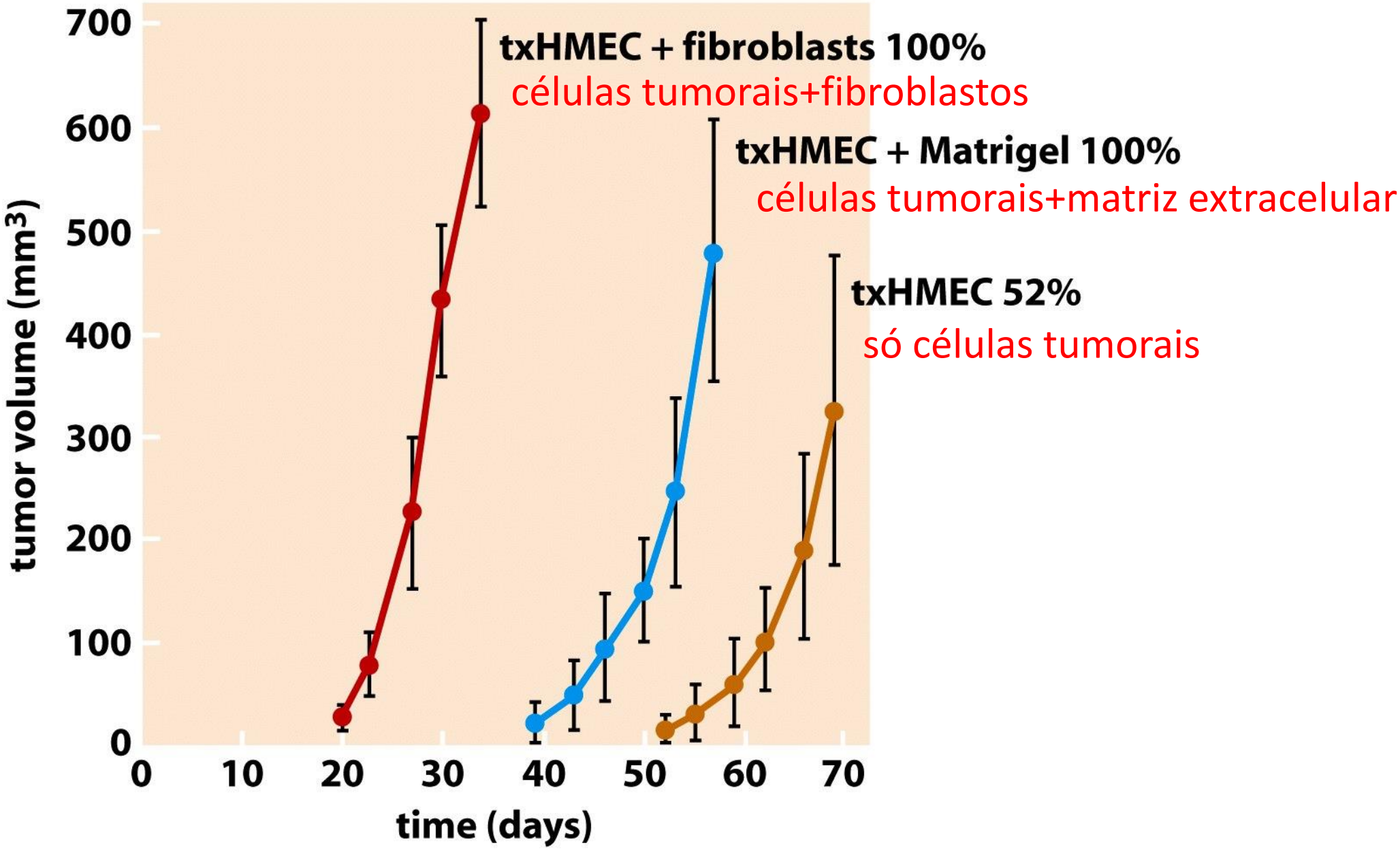
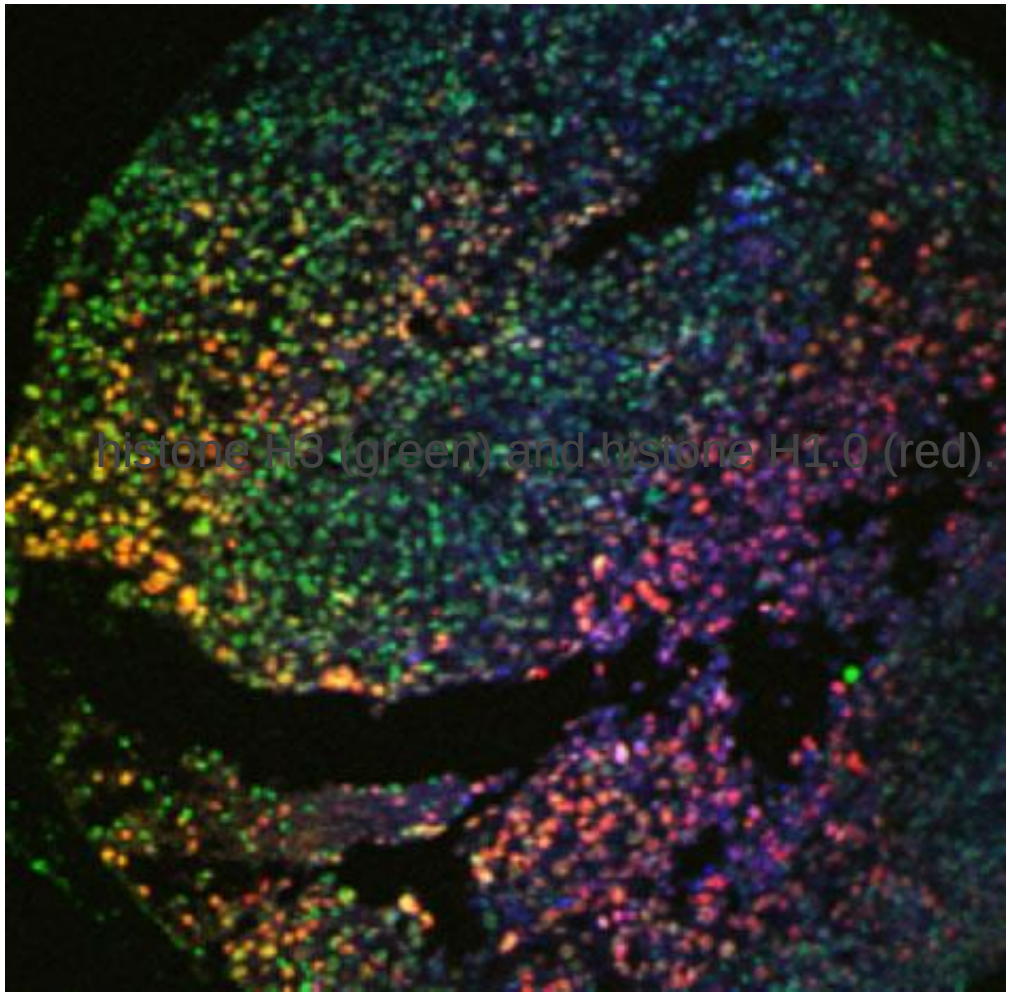


Figure 13-20 The Biology of Cancer (© Garland Science 2007)

Tumores são heterogêneos

methylated histone H3
methylated histone H1



Heterogeneidade **intra**tumoral
Heterogeneidade **inter**tumoral

https://www.crick.ac.uk/research/a-z-researchers/researchers-p-s/paola-scaffidi/

Tumores têm origem em uma única célula...

De onde vem a heterogeneidade?

Modelo de evolução clonal

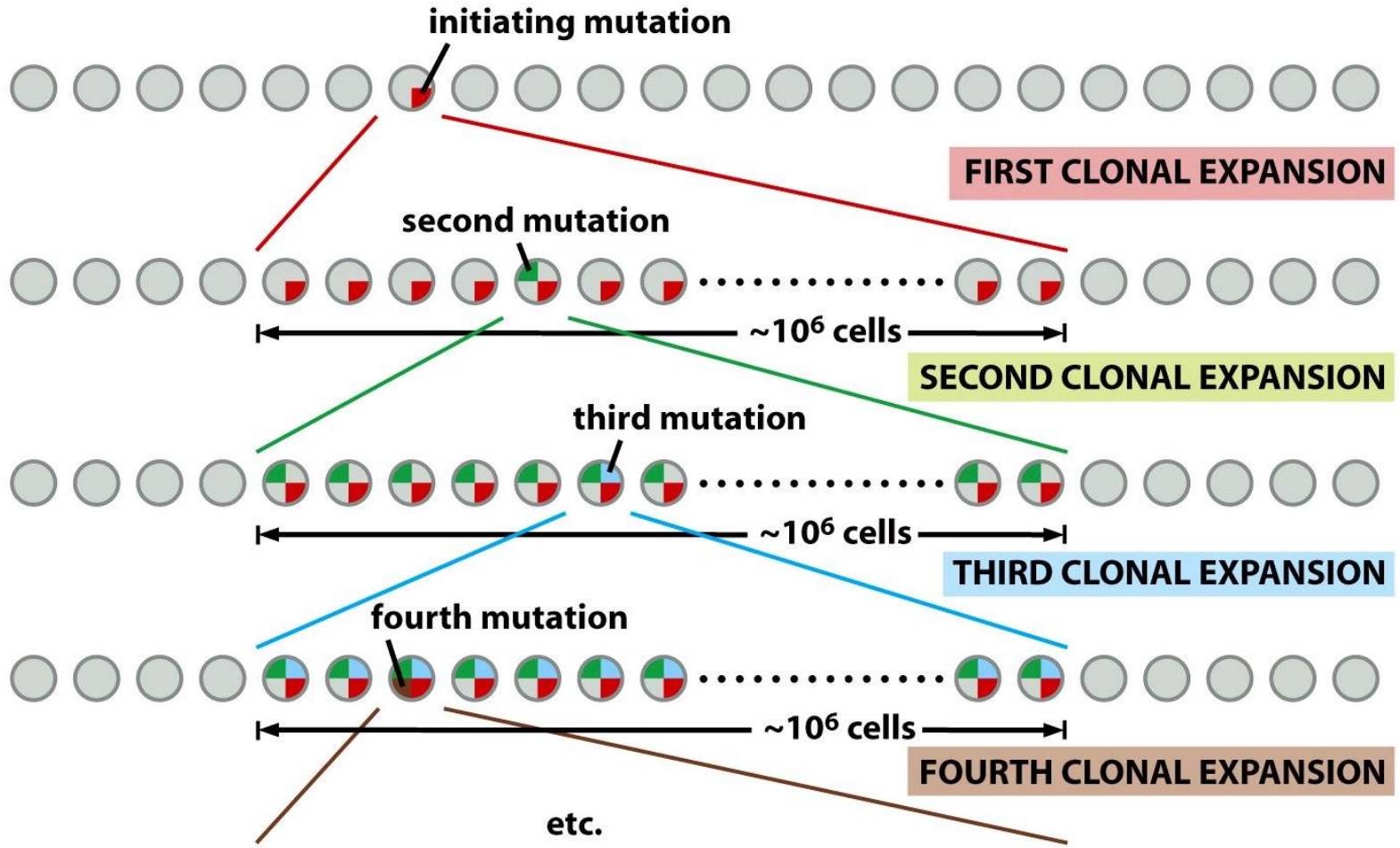


Figure 11-12 The Biology of Cancer (© Garland Science 2007)

Modelo de célula-tronco tumoral

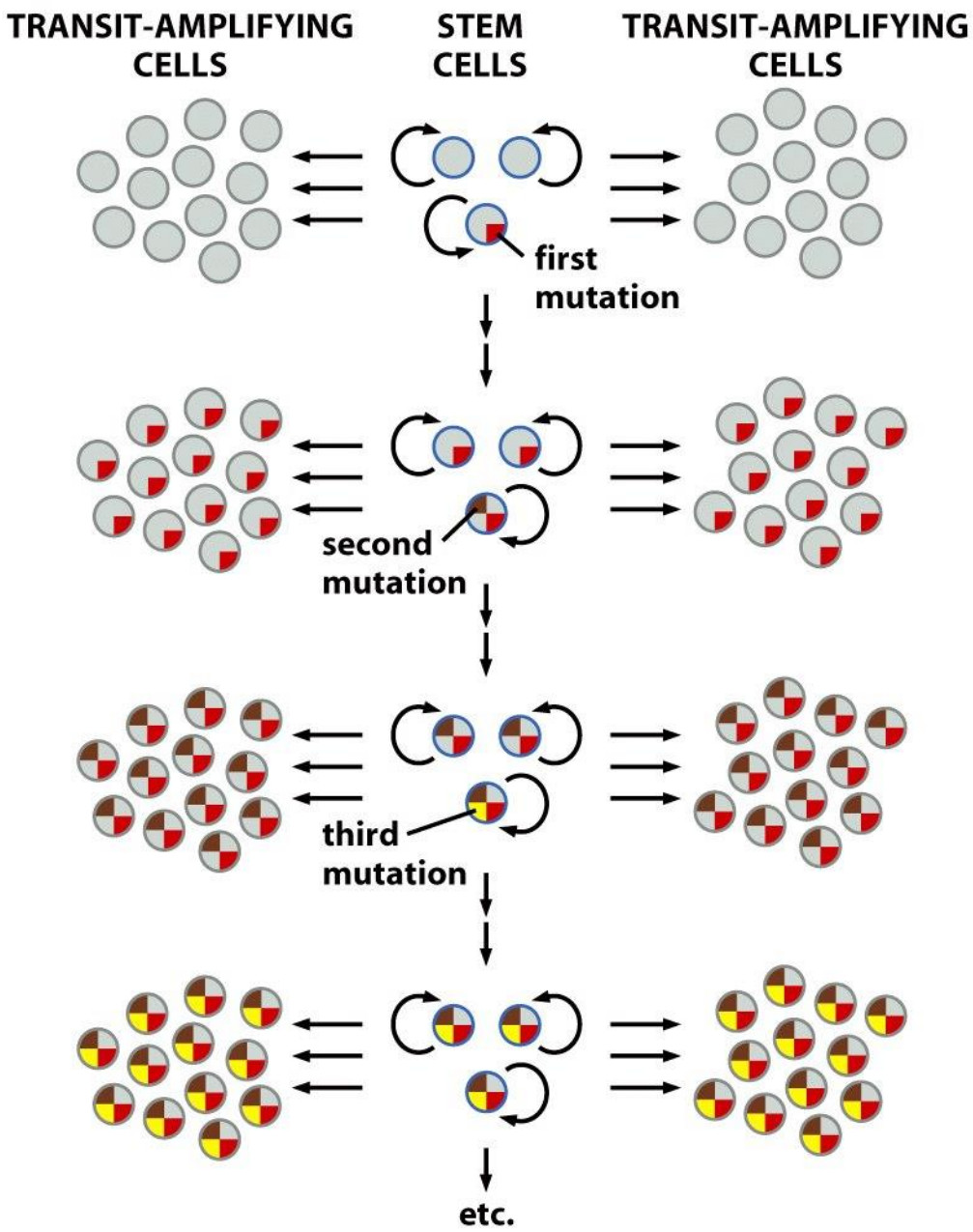


Figure 11-17 The Biology of Cancer (© Garland Science 2007)

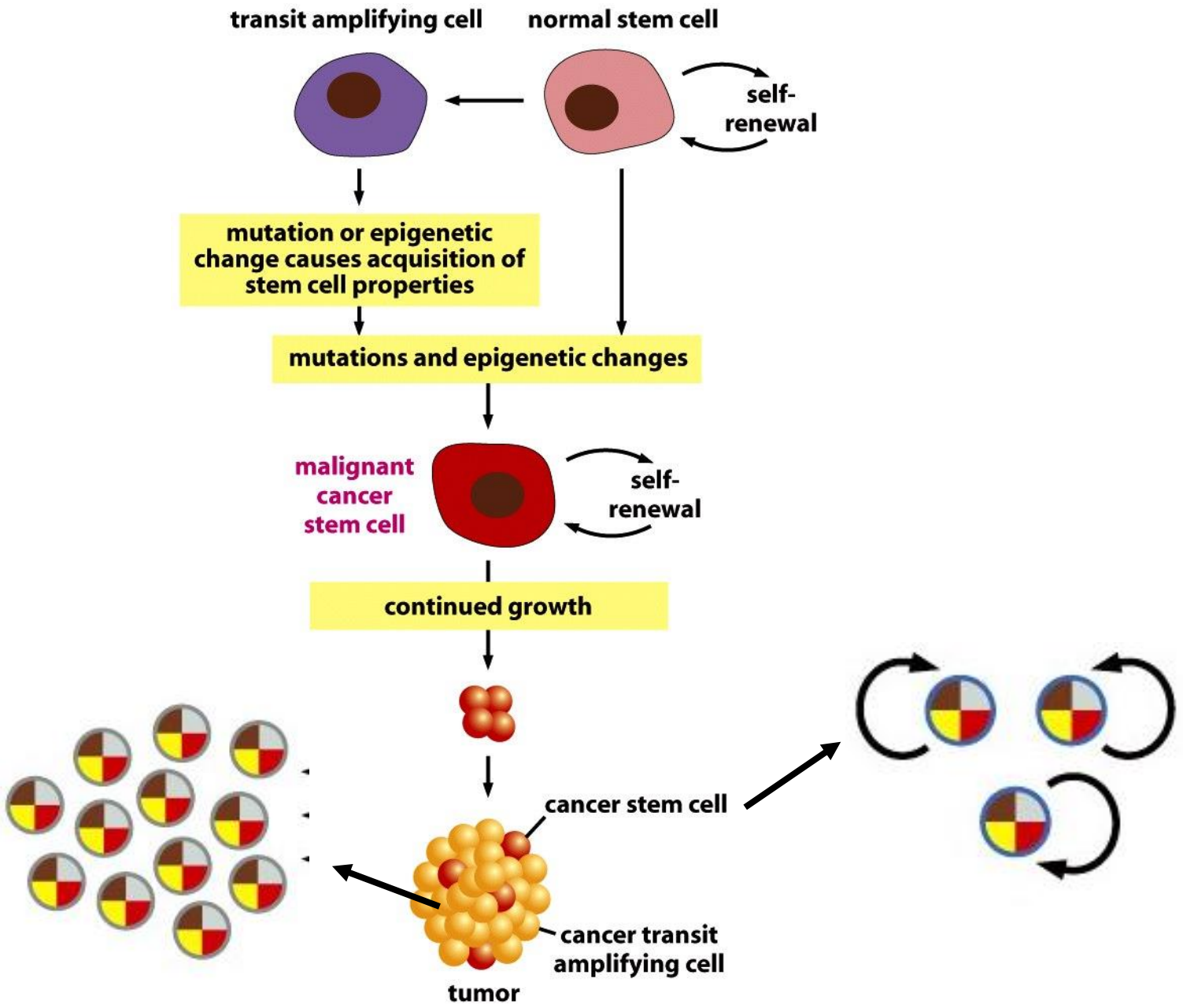


Figure 20-16 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Como se identifica células-tronco tumorais?

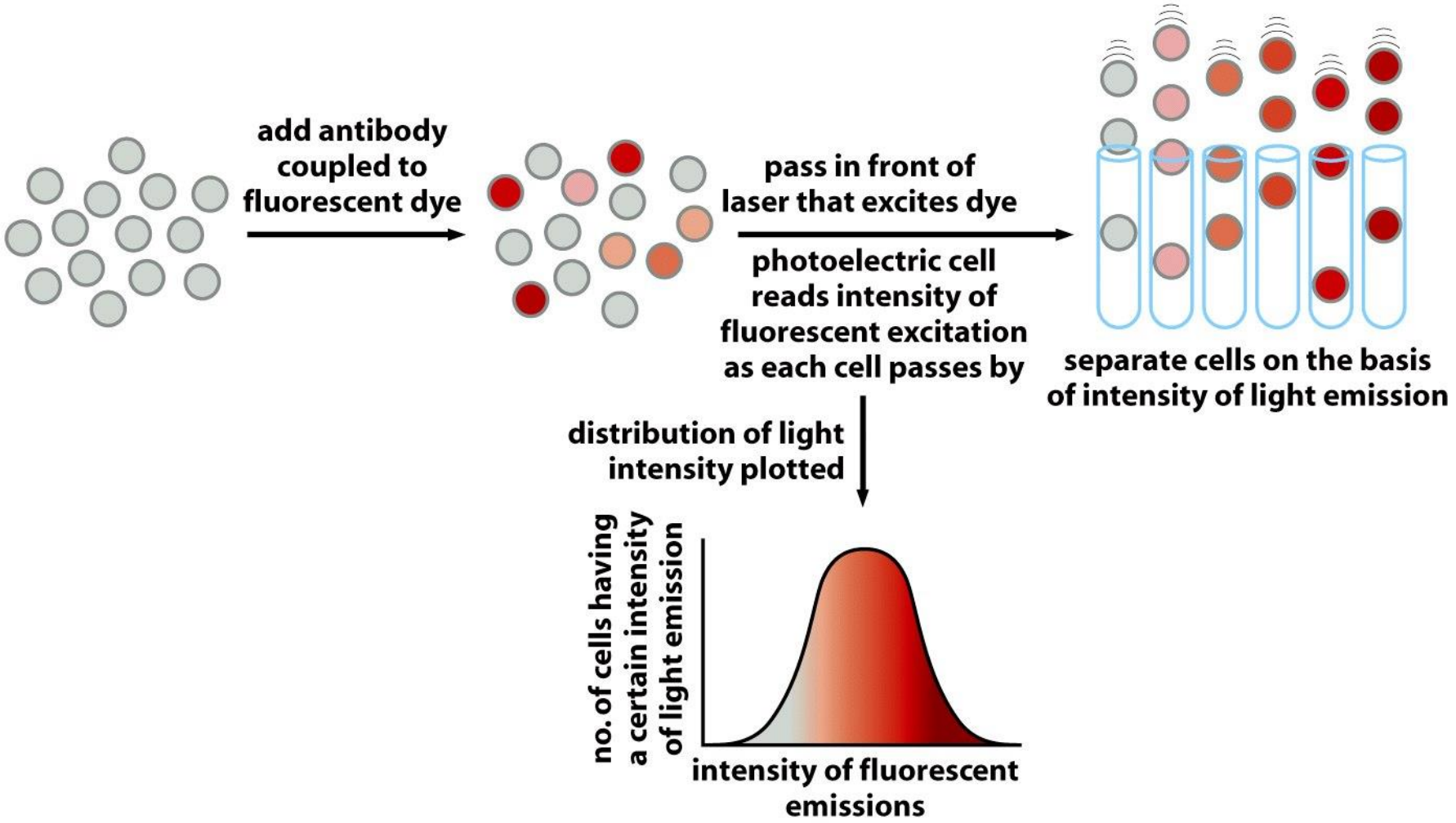


Figure 11-13 The Biology of Cancer (© Garland Science 2007)

CD133 – marcador de célula-tronco neuronal

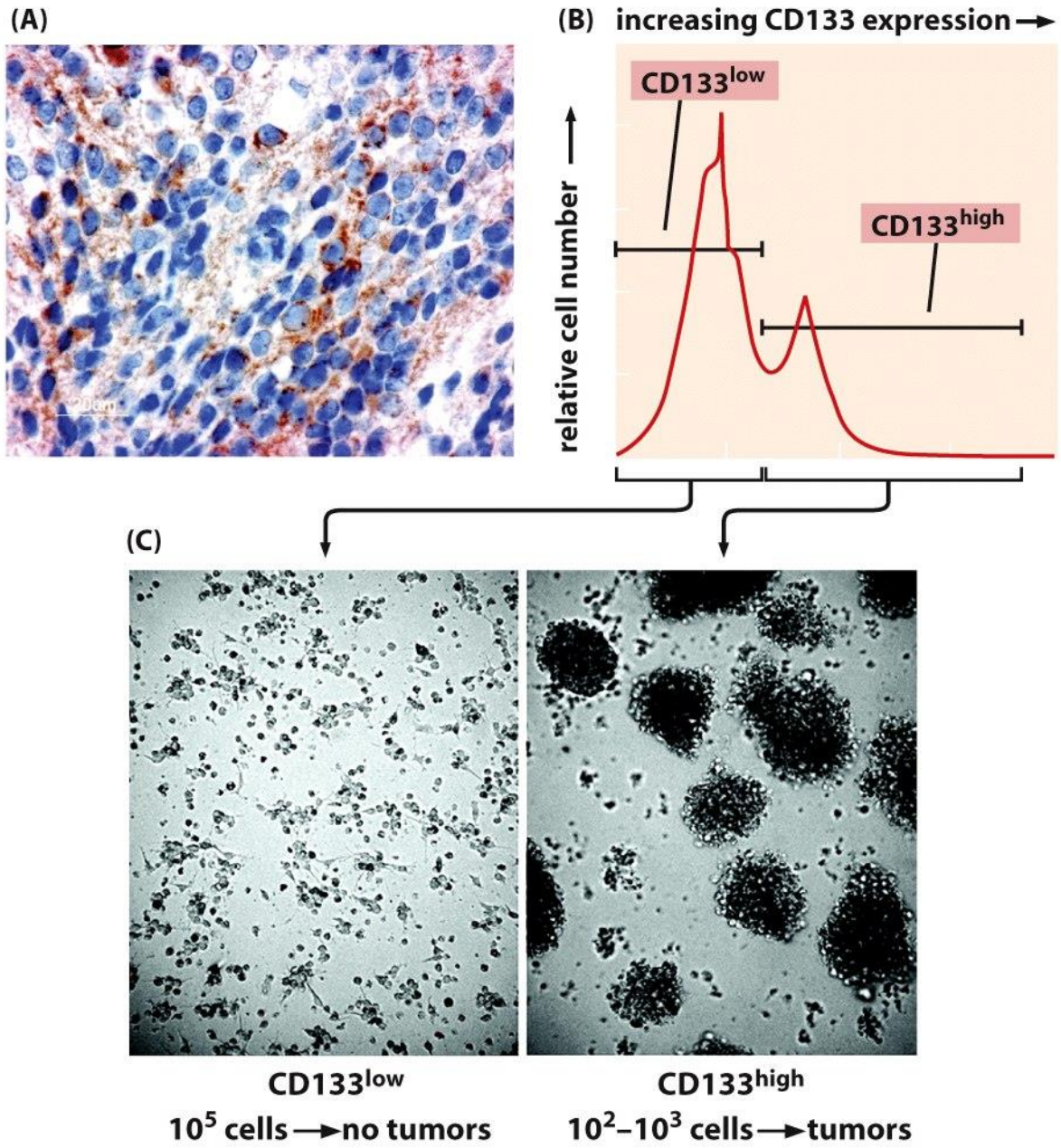
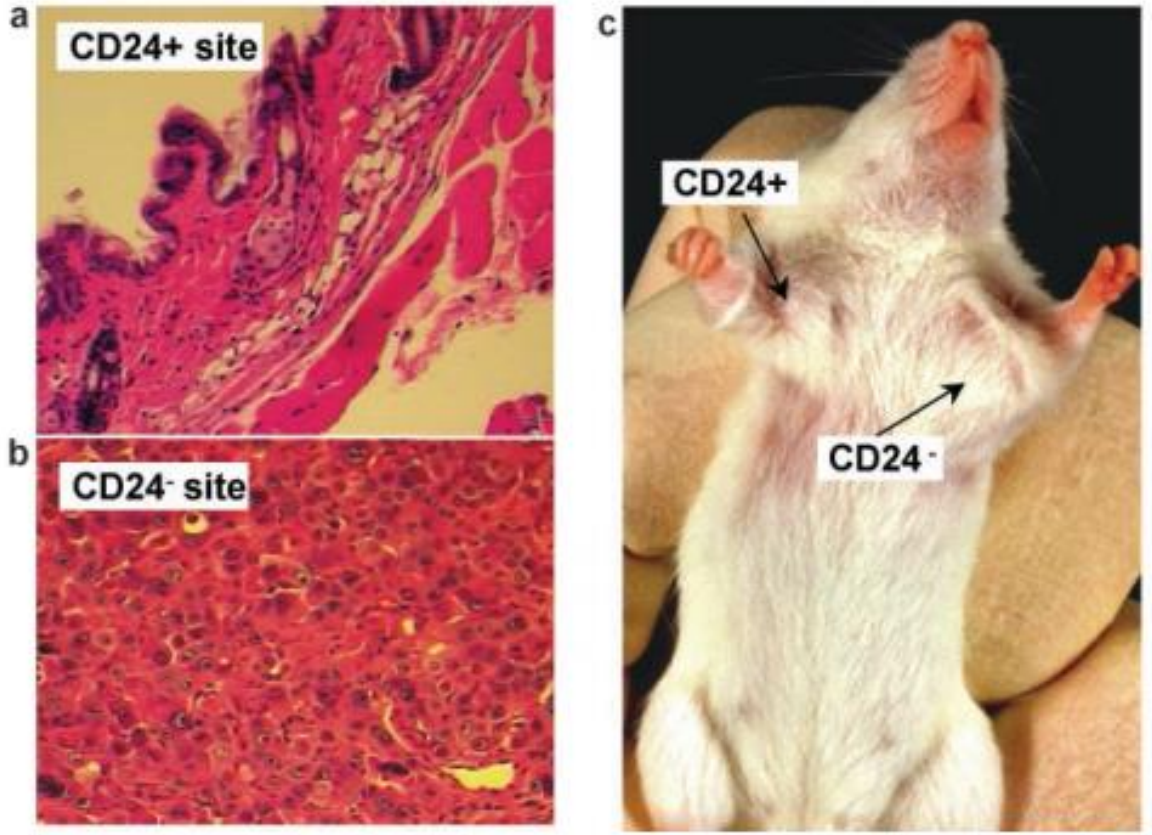


Figure 11-15 The Biology of Cancer (© Garland Science 2007)

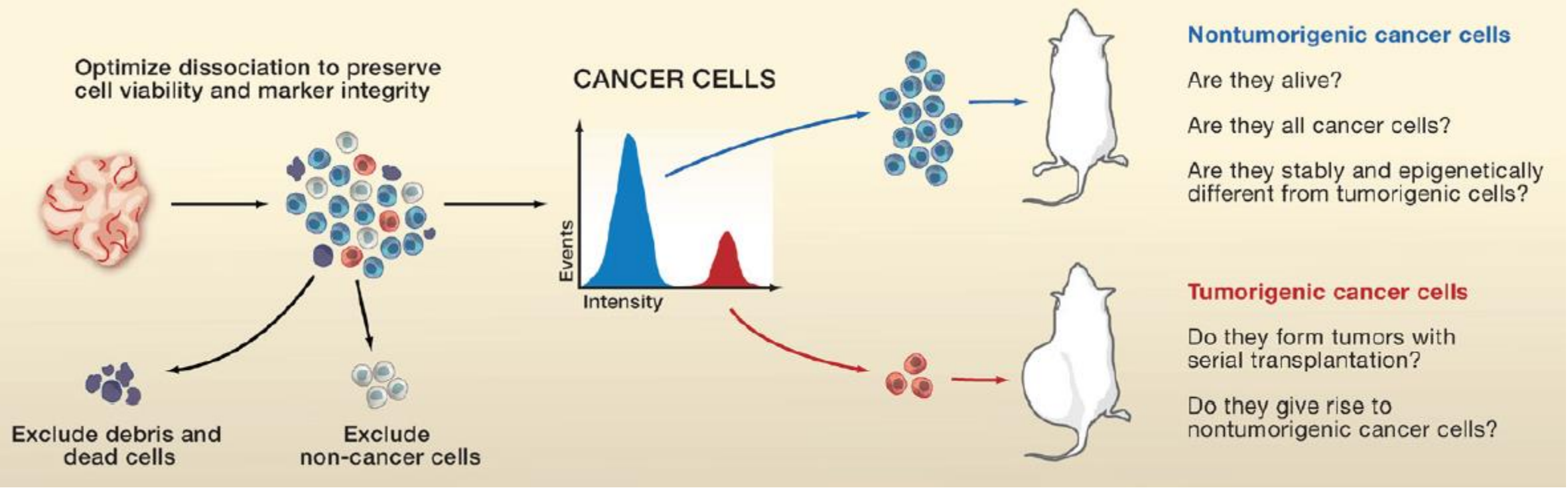
Table 2. Tumor formation ability of sorted cells

	Tumors/injections		
	8×10^5	5×10^5	2×10^5
Passaged T1			
$CD44^-$	0/2	0/2	—
$CD44^+$	2/2	2/2	—
$B38.1^-$	0/2	0/2	—
$B38.1^+$	2/2	2/2	—
$CD24^+$	—	—	1/6
$CD24^-$	—	—	6/6
Passaged T2			
$CD44^-$	0/2	0/2	—
$CD44^+$	2/2	2/2	—
$B38.1^-$	0/2	0/2	—
$B38.1^+$	2/2	2/2	—
$CD24^+$	—	—	1/6
$CD24^-$	—	—	6/6



Al-Hajj M, WichaMS, Benito-Hernandez A,Morrison SJ, Clarke MF. 2003. Prospective identification of tumorigenic breast cancer cells. *PNAS* 100:3983–88

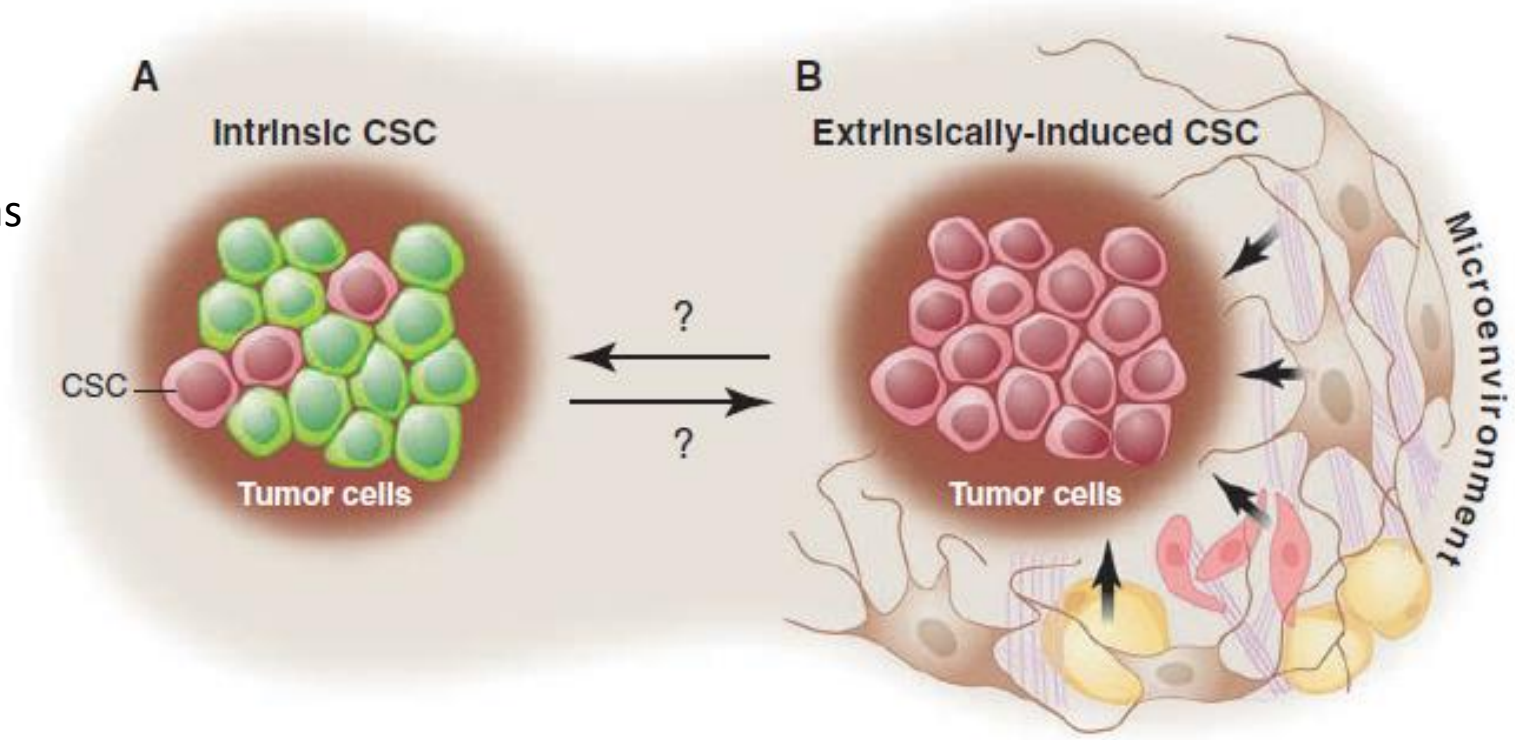
Em resumo:



Mark Shackleton et al, 2009. Heterogeneity in Cancer: Cancer Stem Cells versus Clonal Evolution, Cell, 138, 822

Regulação das células-tronco tumorais

EMT
Alterações epigenéticas



Microambiente:

Células endoteliais
Matriz extracelular
Hipóxia
Inflamação
Fibroblastos

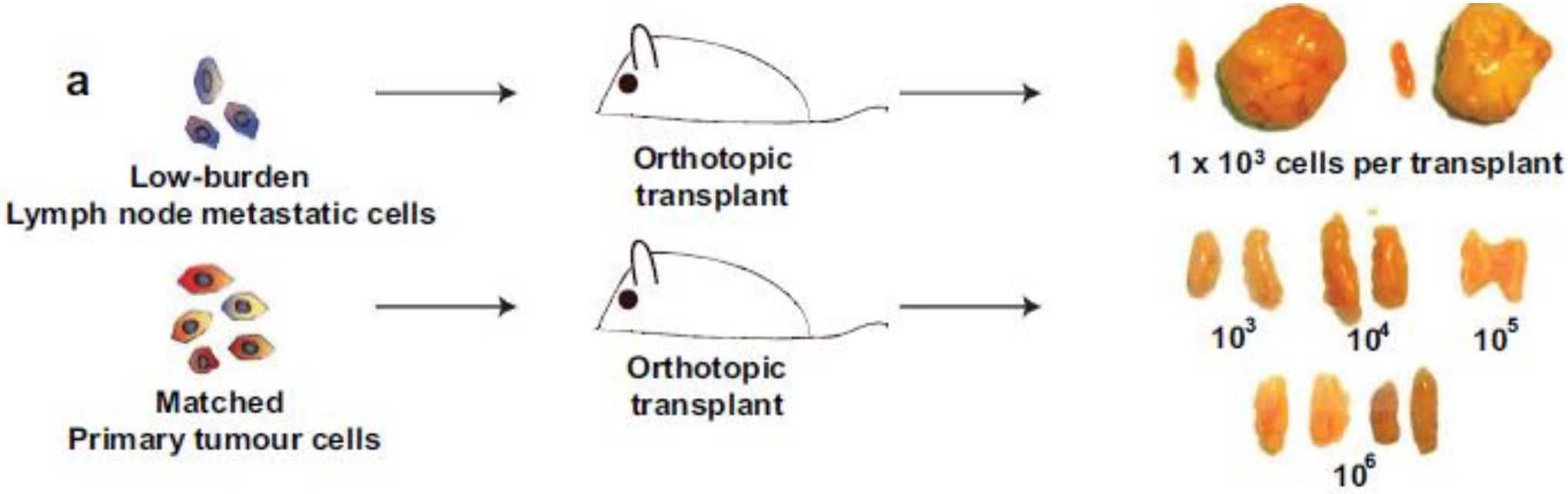
Jeffrey M. Rosen & Craig T. Jordan, 2009. The Increasing Complexity of the Cancer Stem Cell Paradigm, Science 324, 1670

As células-tronco tumorais têm algum papel na metástase?

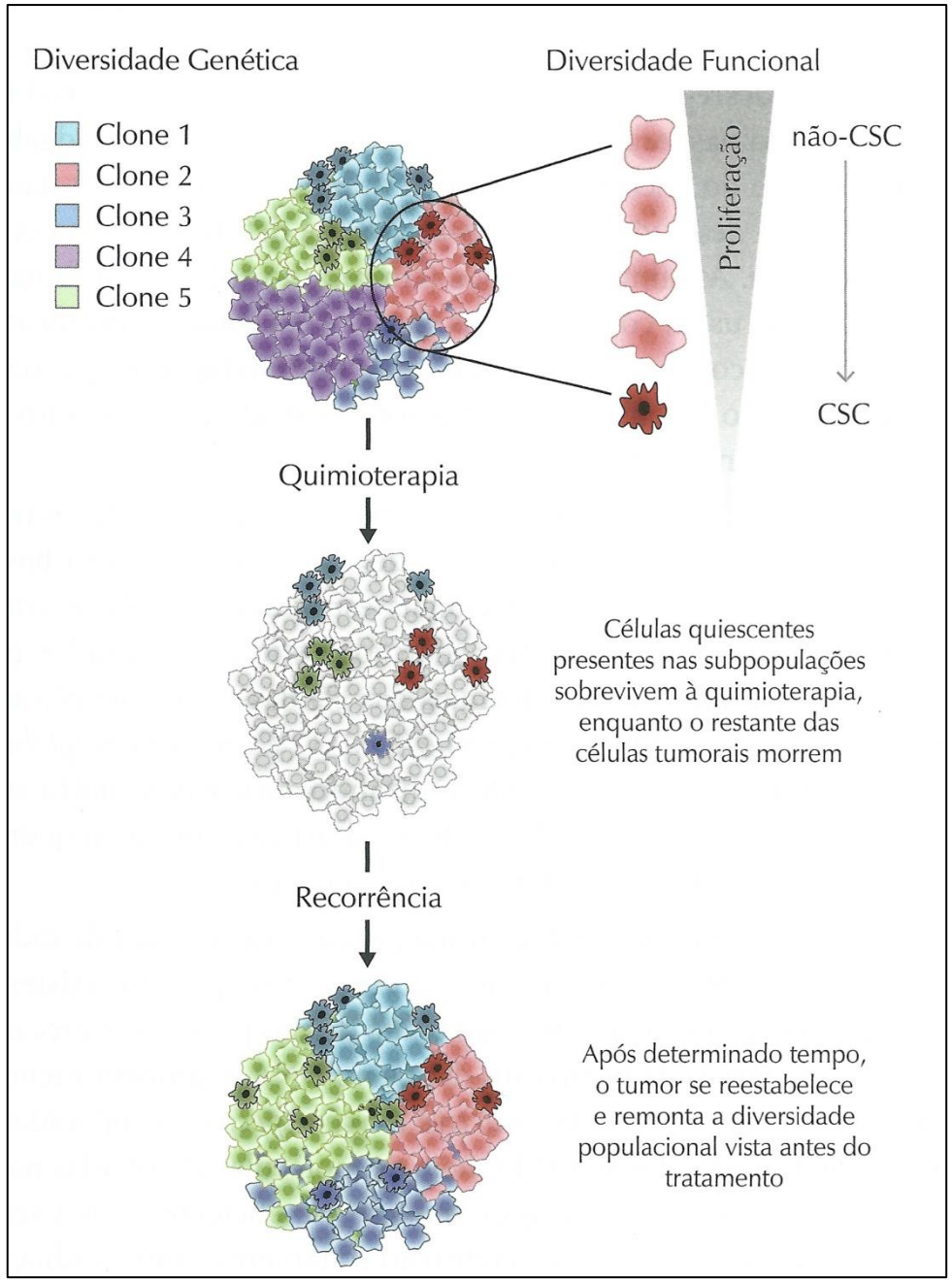
Lawson et al, 2015. Nature, 526, 131

Single-cell analysis reveals a stem-cell program in human metastatic breast cancer cells

Devon A. Lawson[1]†, Nirav R. Bhakta[2], Kai Kessenbrock[1,3]†, Karin D. Prummel[1]†, Ying Yu[1], Ken Takai[1]†, Alicia Zhou[3], Henok Eyob[3], Sanjeev Balakrishnan[3], Chih-Yang Wang[1,4], Paul Yaswen[5], Andrei Goga[2,3] & Zena Werb[1]

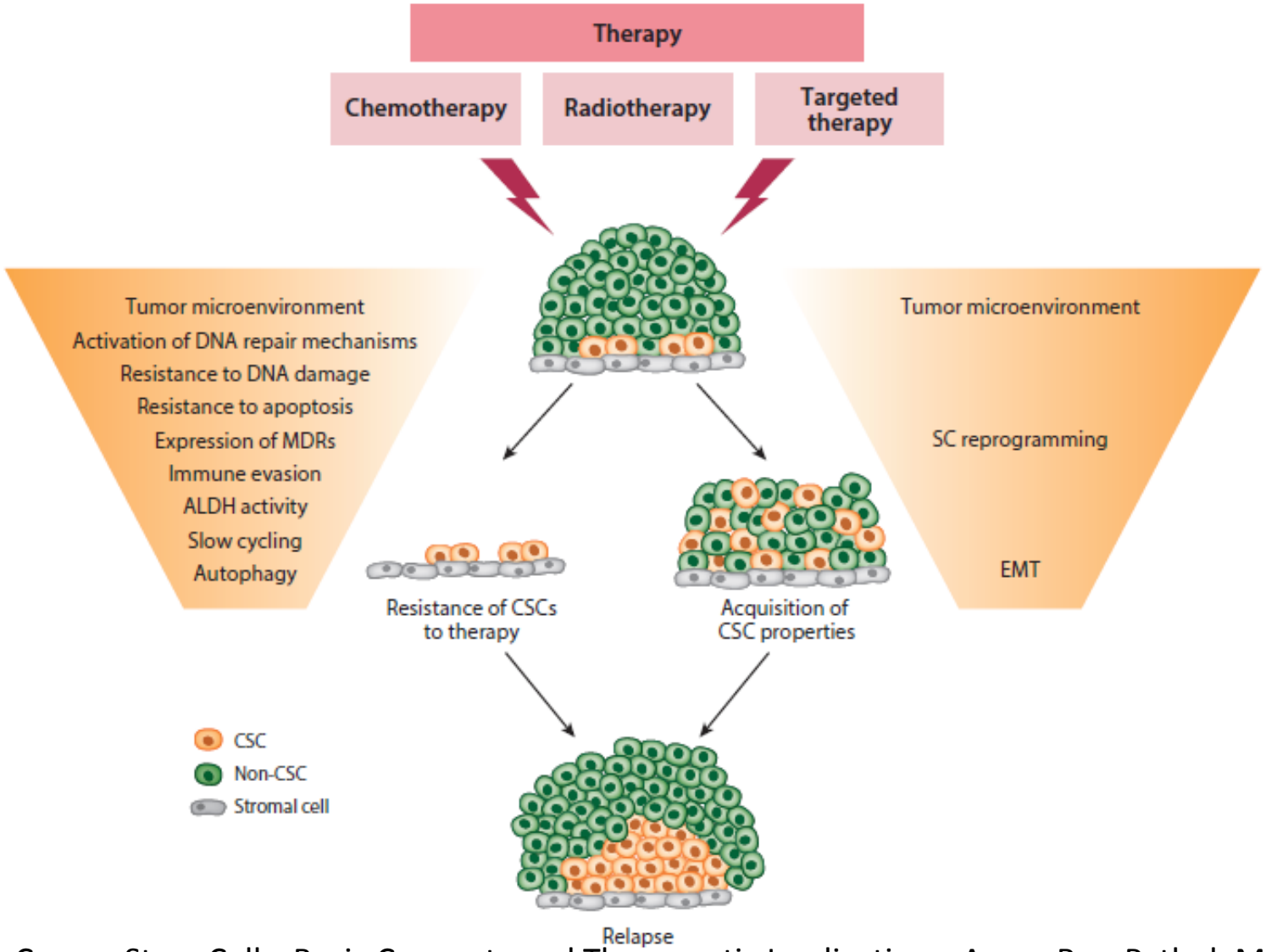


Diversidade tumoral e resposta ao tratamento



Fundamentos da Oncologia Molecular, 2015

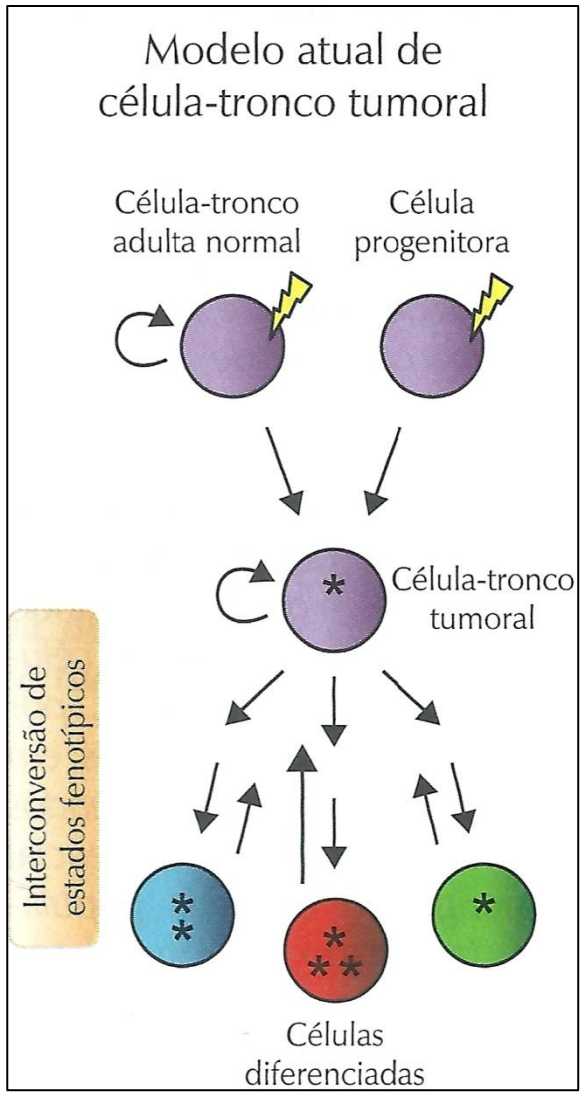
Resistência das células-tronco tumorais à terapia



Nassar & Blanpain, 2016. Cancer Stem Cells: Basic Concepts and Therapeutic Implications. Annu. Rev. Pathol. Mech. Dis. 2016. 11:47–76

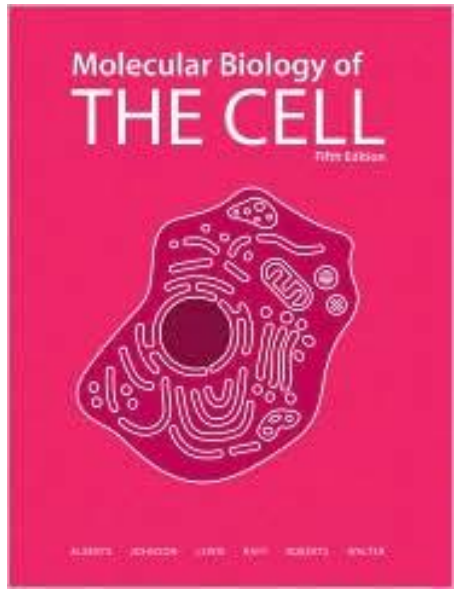
Modelo atual de células-tronco tumorais

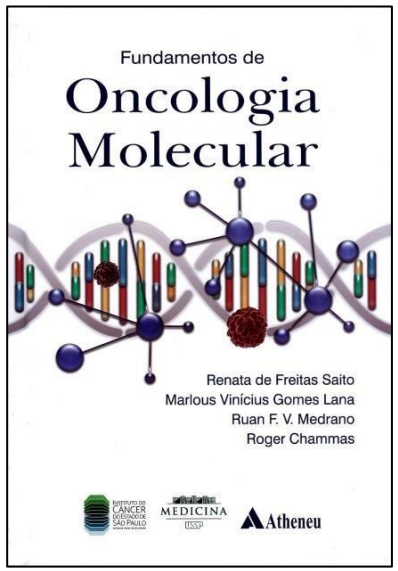
GRANDE PLASTICIDADE

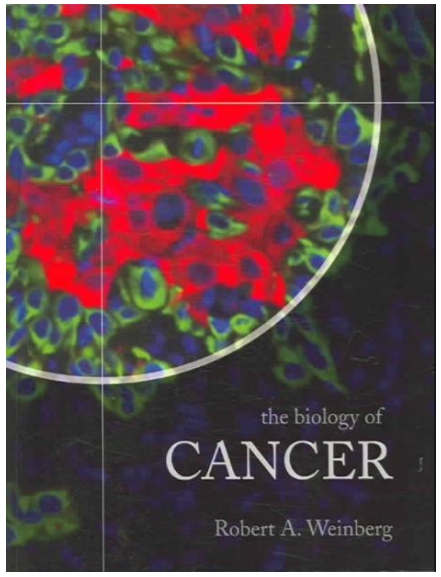


Fundamentos da Oncologia Molecular, 2015

Capítulos 20







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