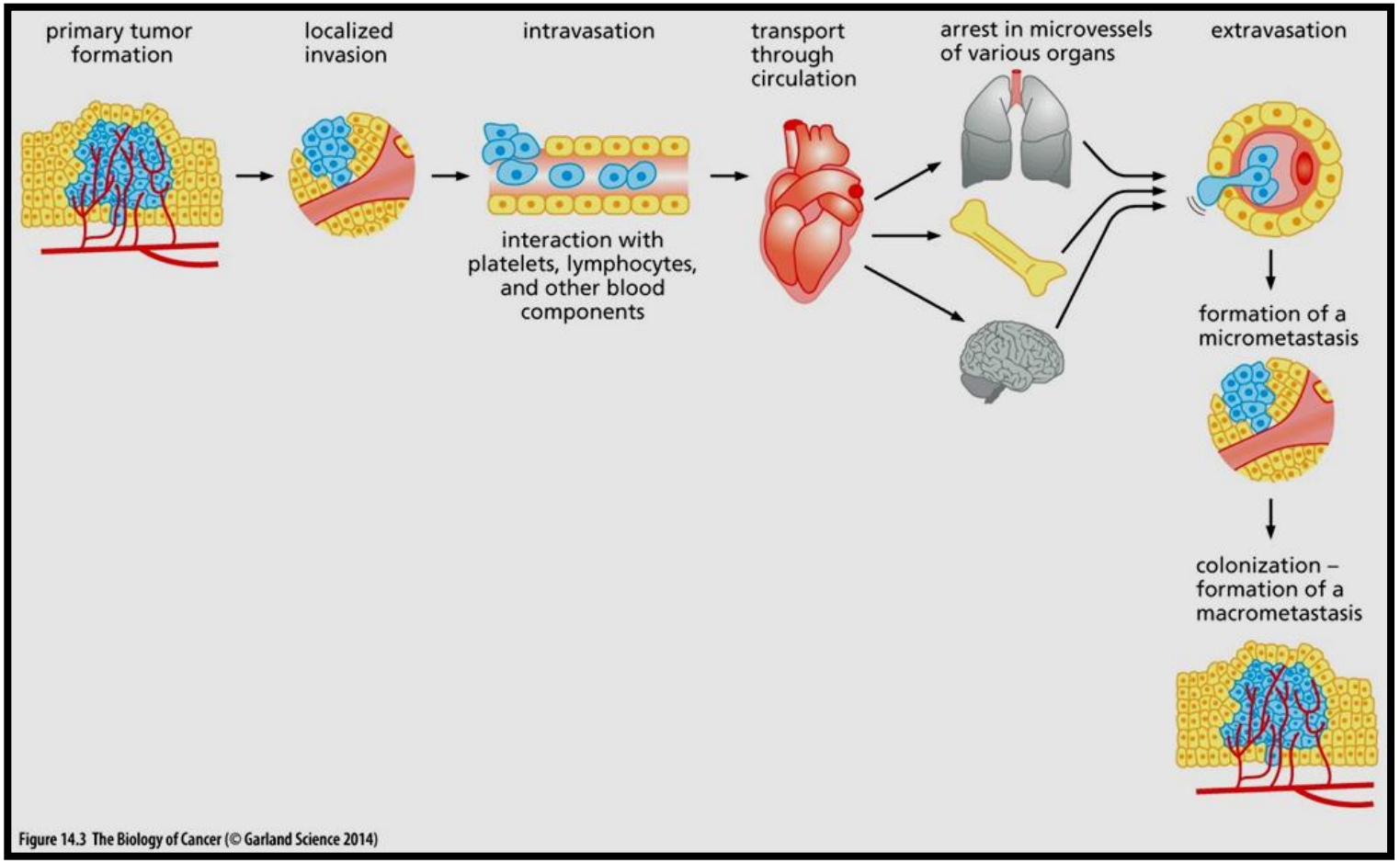
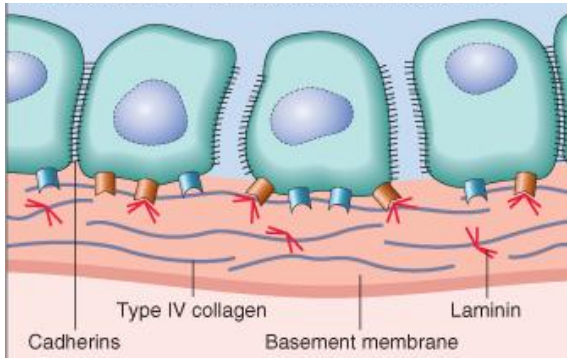
From invasion to metastasis



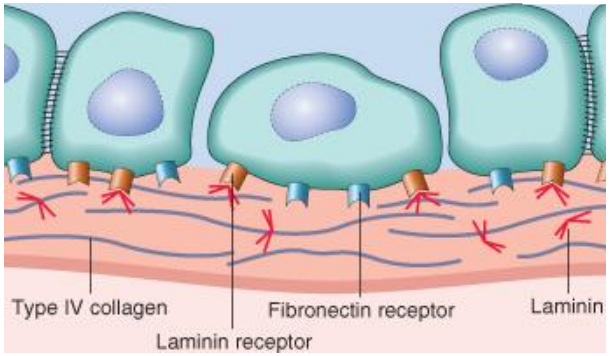
https://www.youtube.com/watch?v=q_JDp-VePAs

INFILTRATION/INVASION

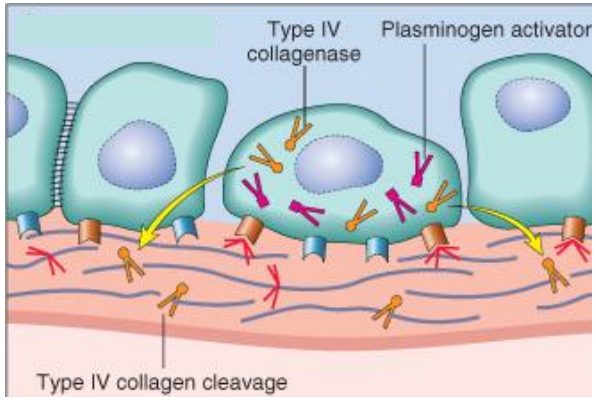
Cell junction relaxing



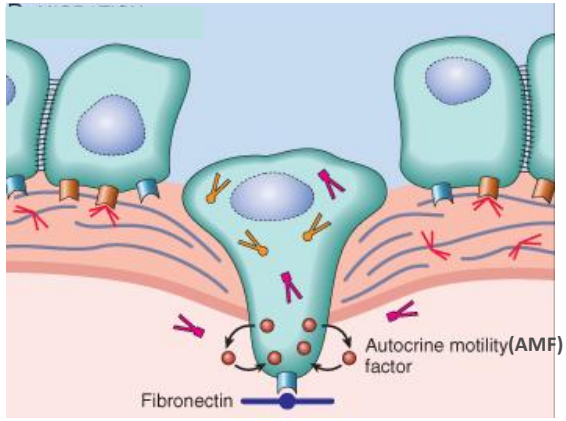
Adesion to ECM proteins



Matrix proteolysis



Neoplastic cell detachment and migration



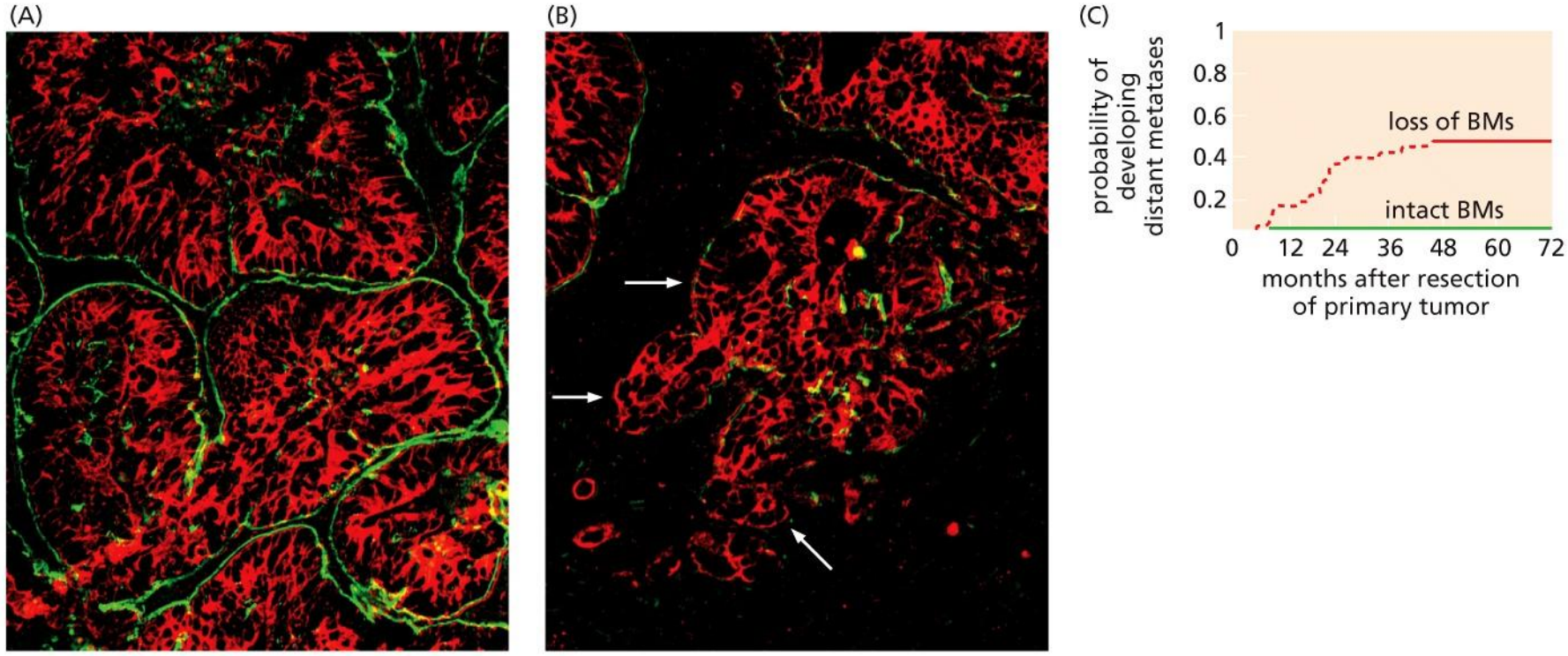
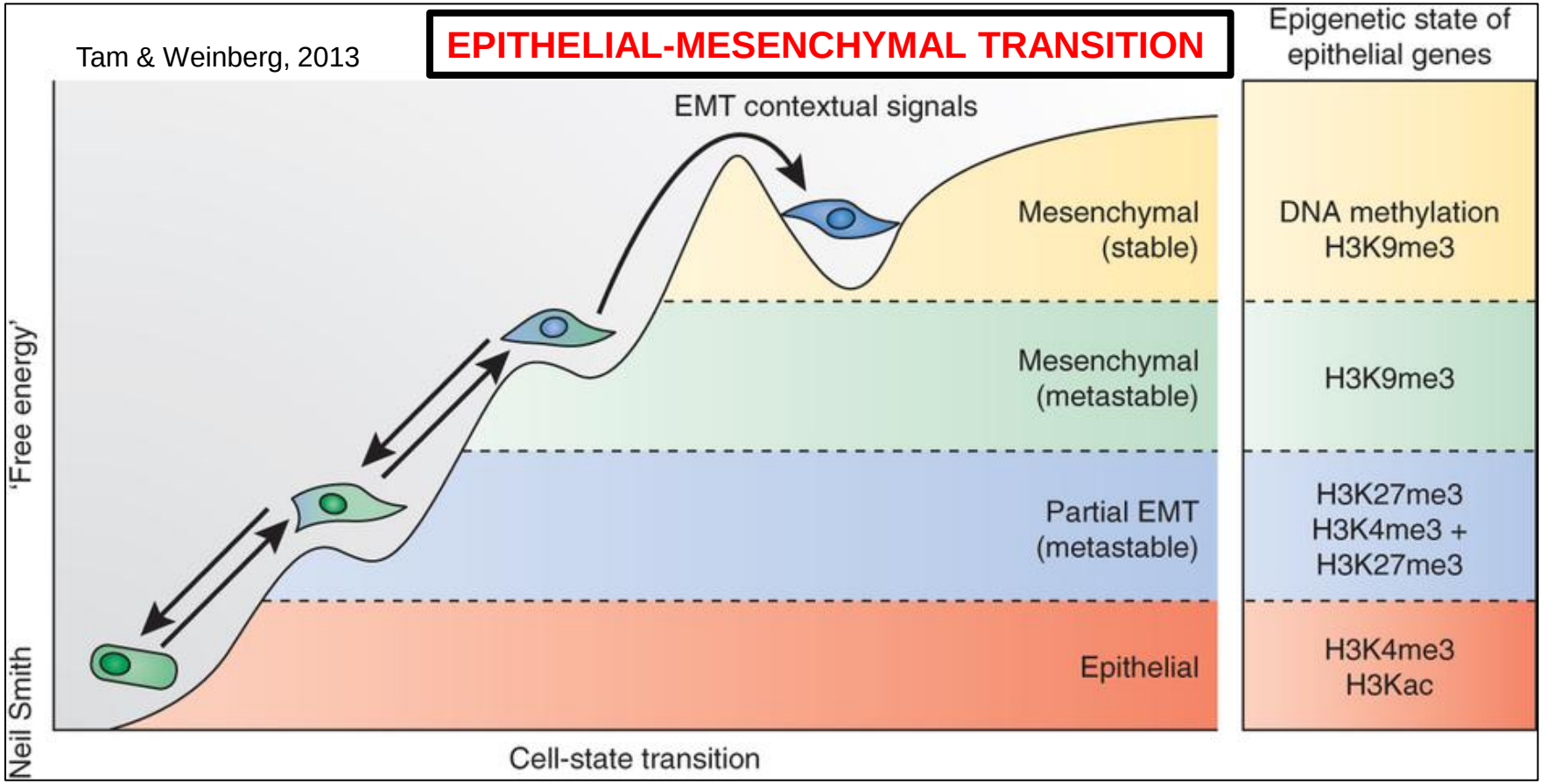
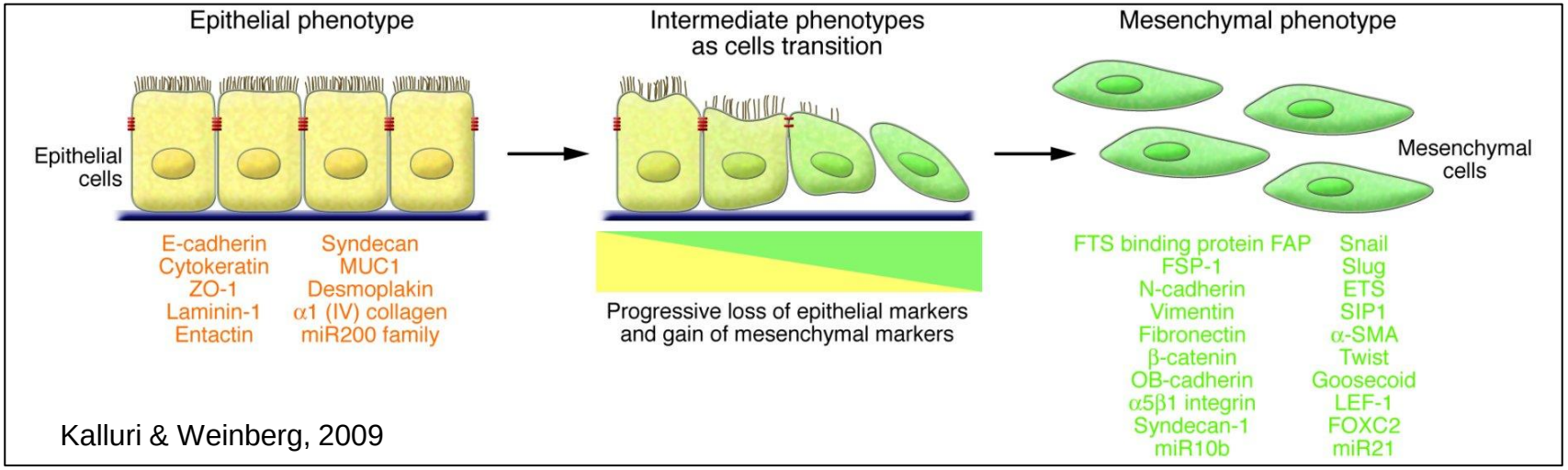


Figure 14.4 The Biology of Cancer (© Garland Science 2014)

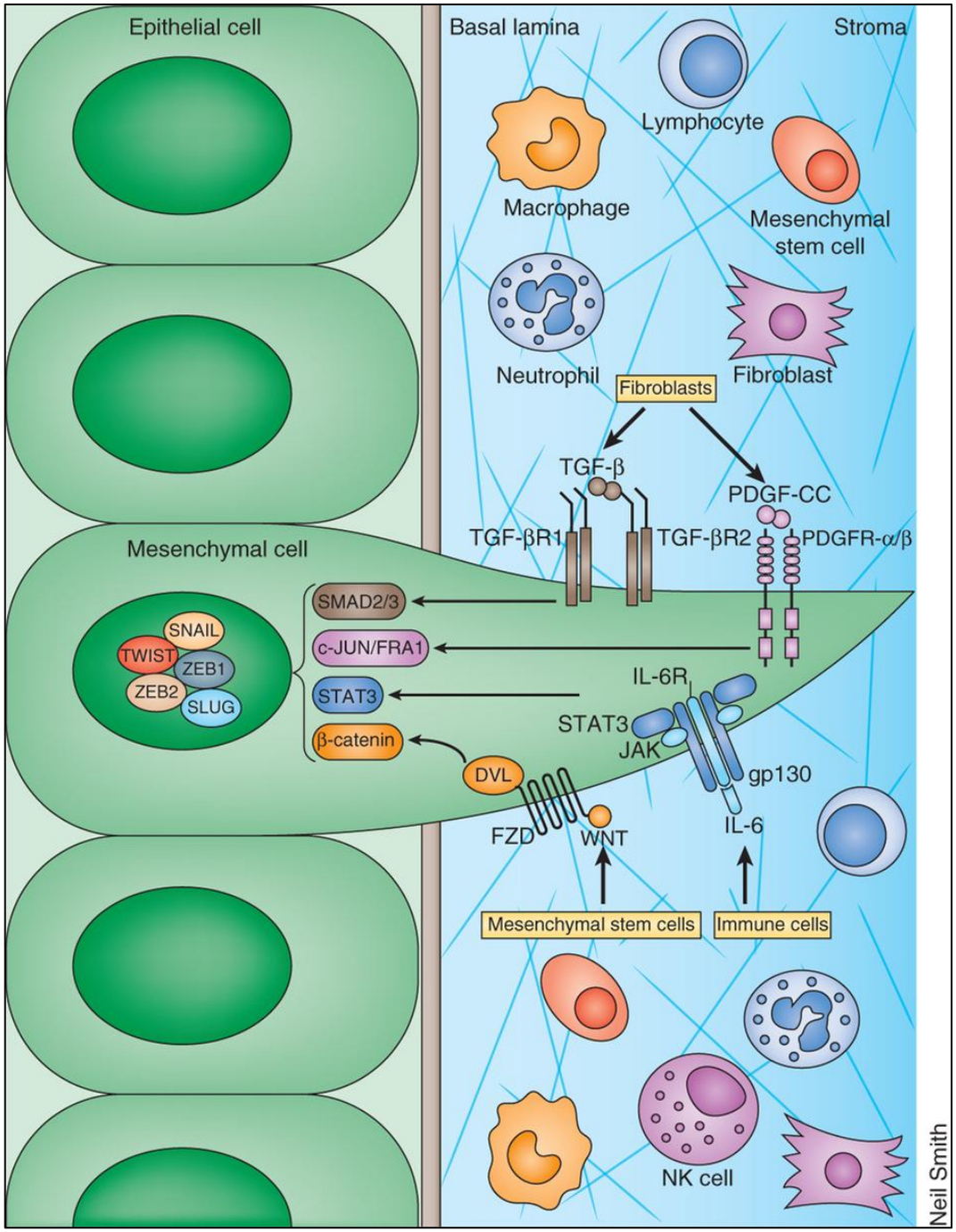
Tam & Weinberg, 2013

EPITHELIAL-MESENCHYMAL TRANSITION

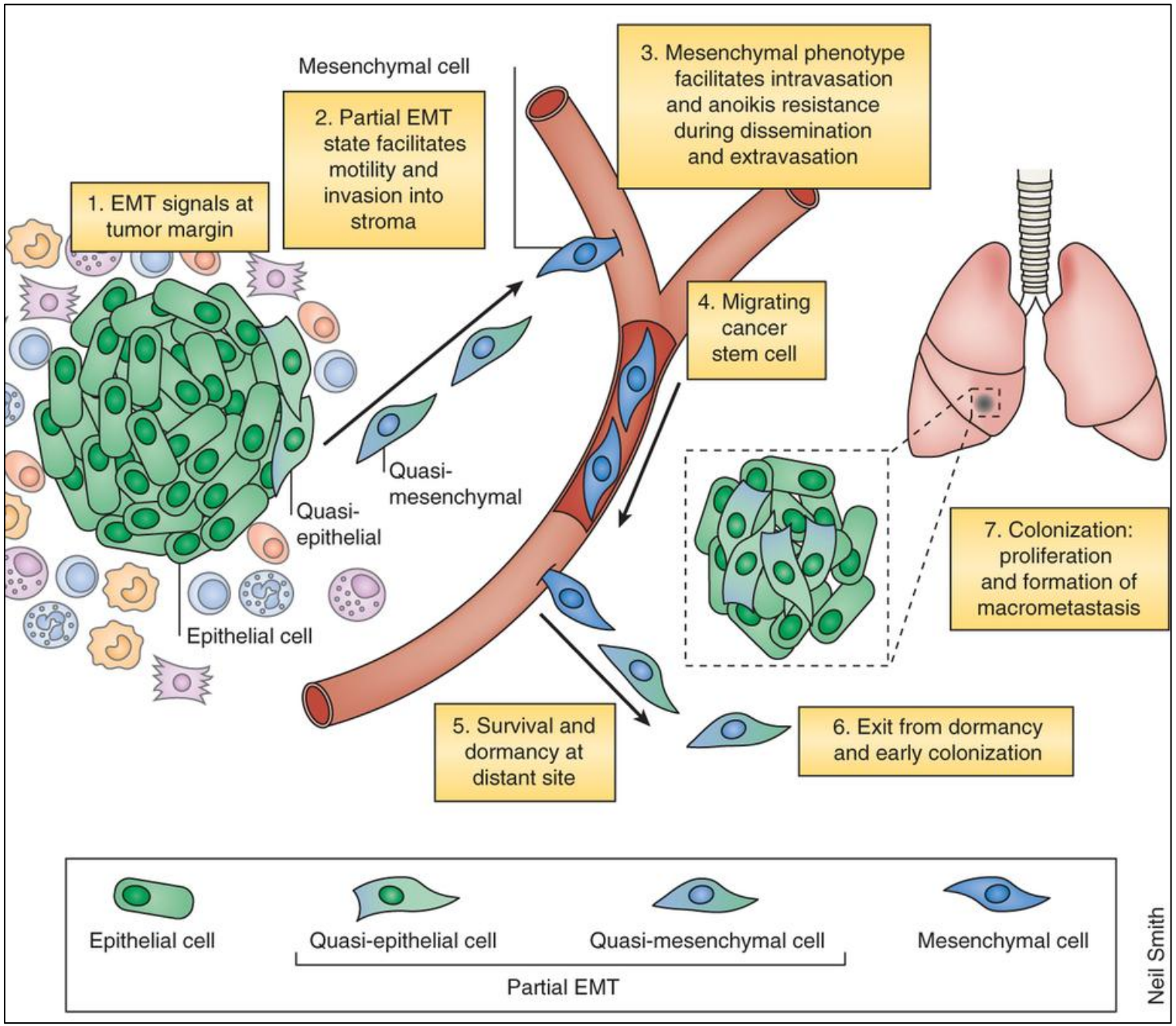




Kalluri & Weinberg, 2009



Tam & Weinberg, 2013



Tam & Weinberg, 2013

EMT at tumor invasive side

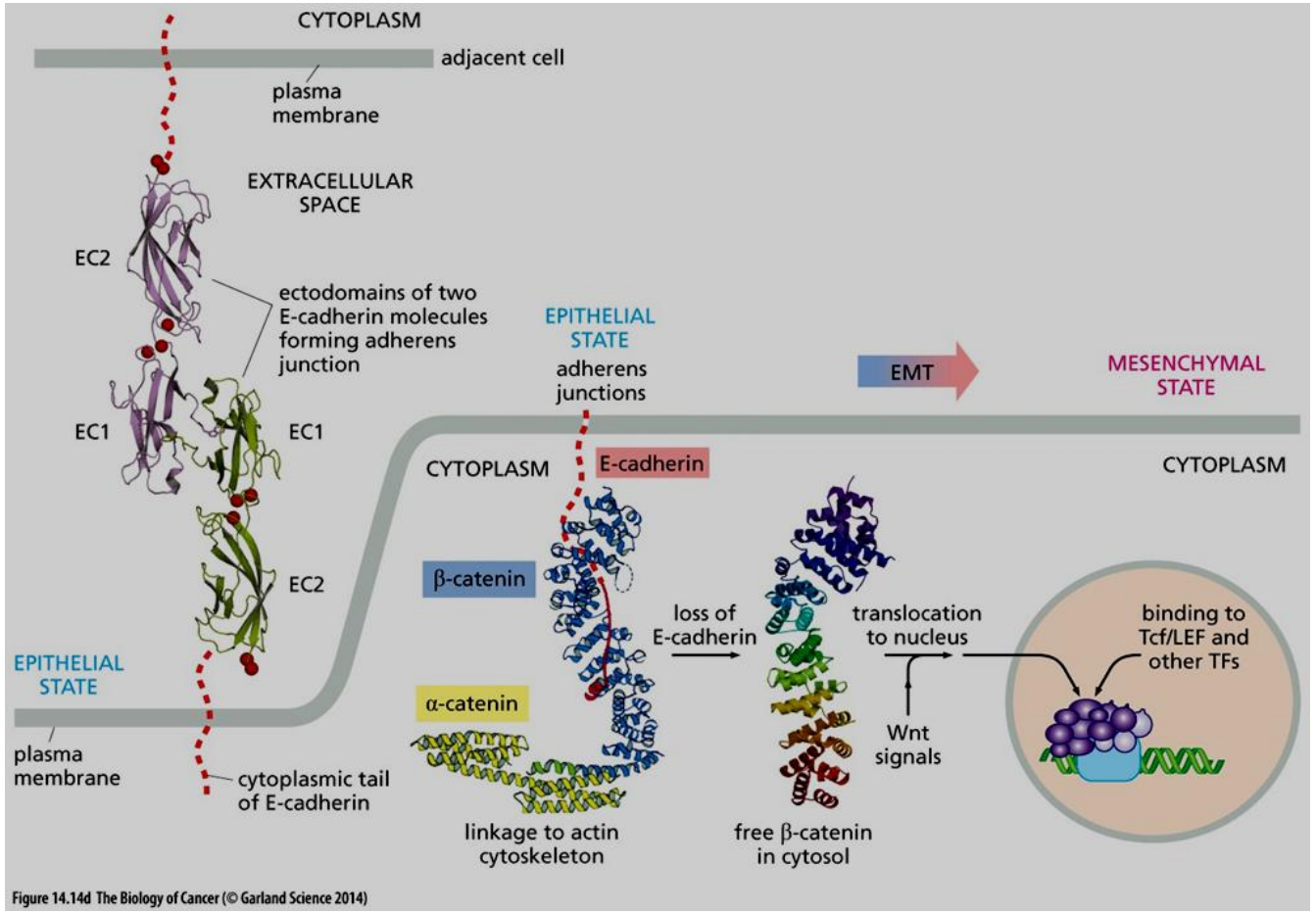


Figure 14.14d The Biology of Cancer (© Garland Science 2014)

Cadherin switch and invasivity

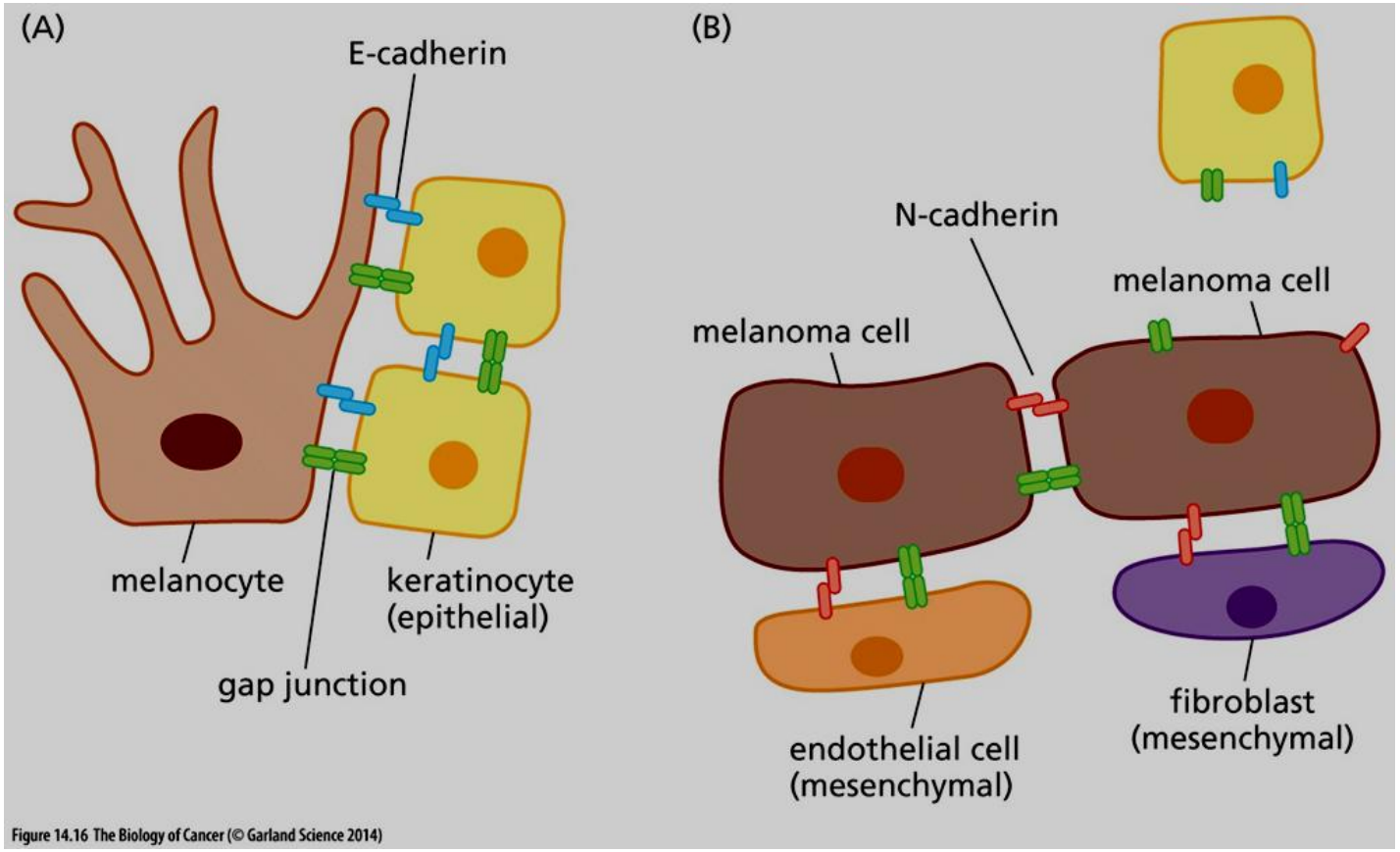


Figure 14.16 The Biology of Cancer (© Garland Science 2014)

Table 14.2 Cellular changes associated with an epithelial–mesenchymal transition

Loss of
Cytokeratin (intermediate filament) expression
Tight junctions and epithelial adherens junctions involving E-cadherin
Epithelial cell polarity
Epithelial gene expression program
Acquisition of
Fibroblast-like shape
Motility
Invasiveness
Increased resistance to apoptosis
Mesenchymal gene expression program including EMT-inducing transcription factors
Mesenchymal adherens junction protein (N-cadherin)
Protease secretion (MMP-2, MMP-9)
Vimentin (intermediate filament) expression
Fibronectin secretion
PDGF receptor expression
$\alpha_v\beta_6$ integrin expression
Stem cell-like traits

Table 14.2 The Biology of Cancer (© Garland Science 2014)

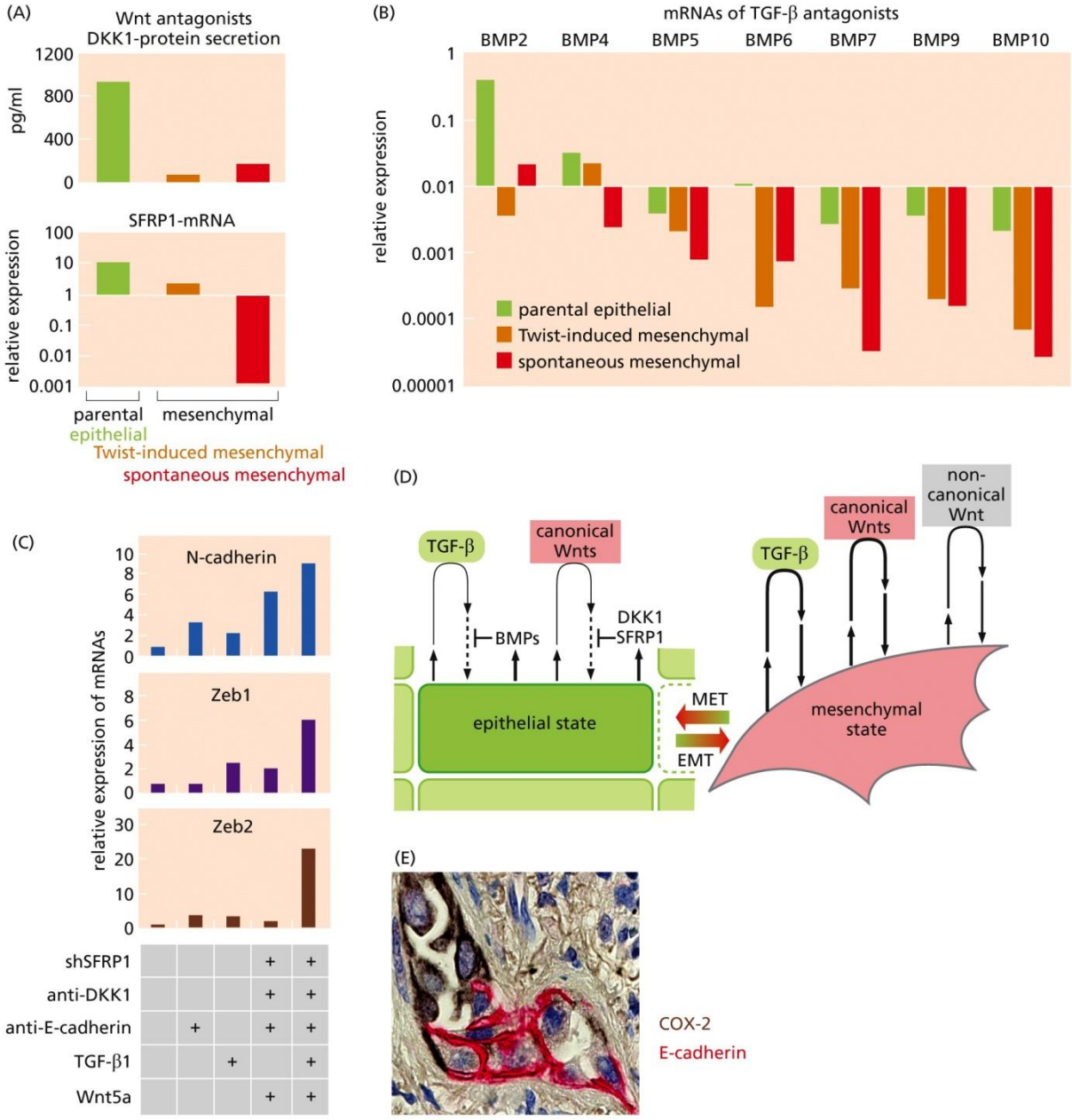


Figure 14.20 The Biology of Cancer (© Garland Science 2014)

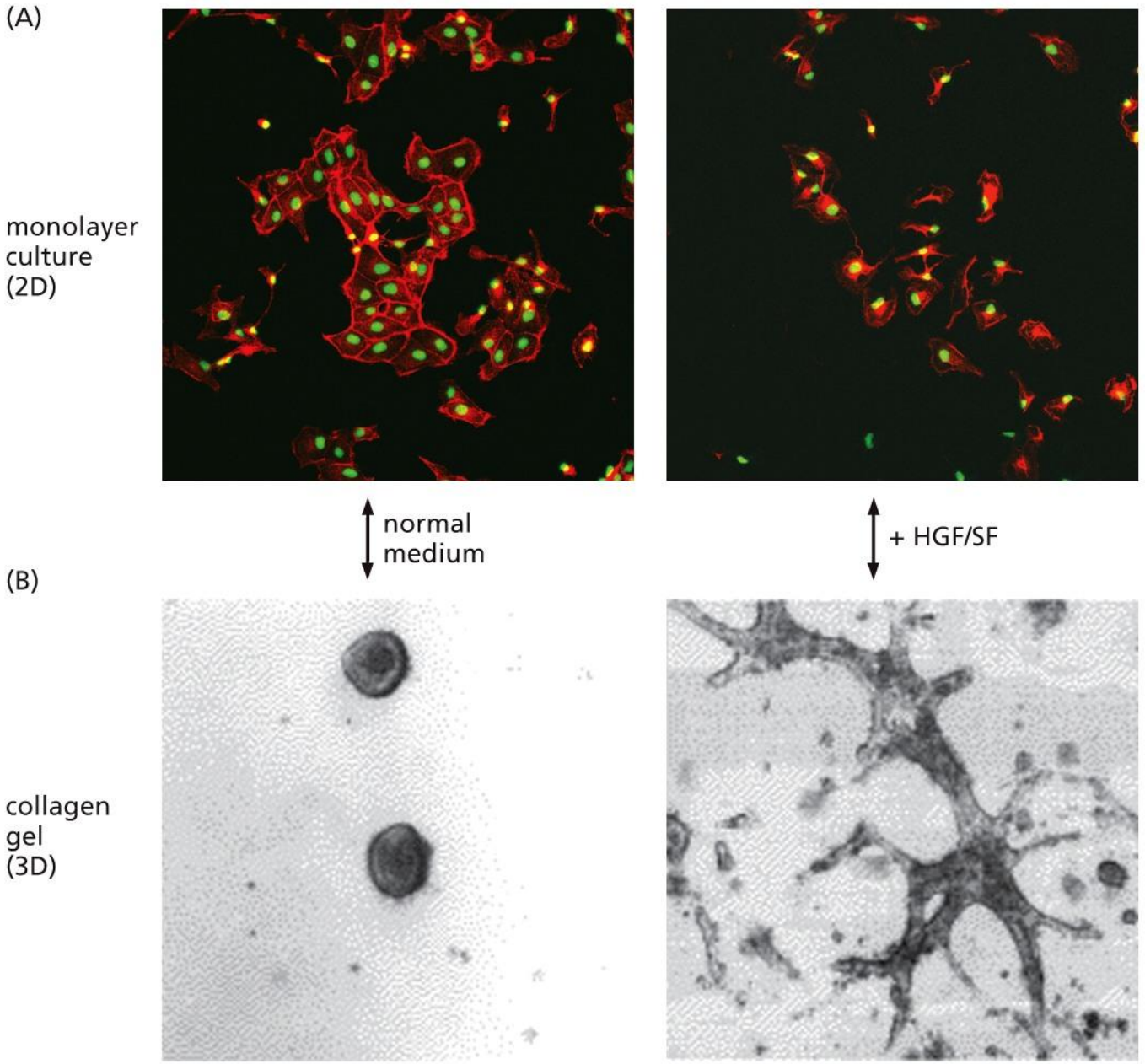


Figure 14.23 The Biology of Cancer (© Garland Science 2014)

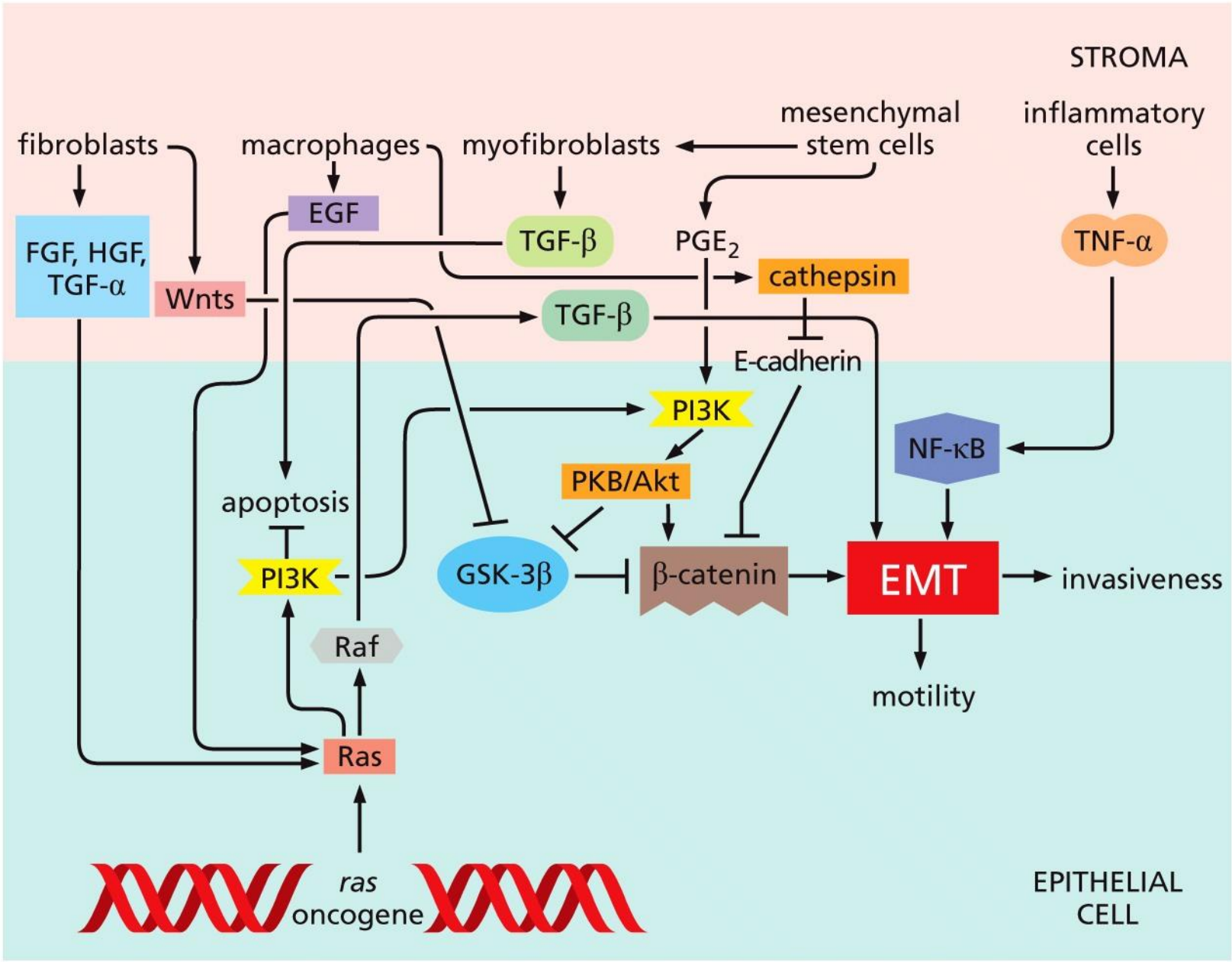


Figure 14.24 The Biology of Cancer (© Garland Science 2014)

Table 14.3 Transcription factors orchestrating an EMT

Name	Where first identified	Type of transcription factor	Cancer association
Snail (SNAI1)	mesoderm induction in *Drosophila*; neural crest migration in vertebrates	C2H2-type zinc finger	invasive ductal carcinoma
Slug (SNAI2)	delamination of the neural crest and early mesoderm in chicken	C2H2-type zinc finger	breast cancer cell lines, melanoma
Twist	mesoderm induction in *Drosophila*; emigration from neural crest	bHLH	various carcinomas, high-grade melanoma, neuroblastoma
Goosecoid	gastrulation in frog	paired homeodomain	various carcinomas
FOXC2	mesenchyme formation	winged helix/forkhead	basal-like breast cancer
ZEB1 (δEF1)	postgastrulation mesodermal tissue formation	2-handed zinc finger/ homeodomain	wide variety of cancers
ZEB2 (SIP1)	neurogenesis	2-handed zinc finger/ homeodomain	ovarian, breast, liver carcinomas
E12/E47 (Tcf3)[a]	associated with E-cadherin promoter	bHLH	gastric cancer

[a]It remains unclear whether E12/E47 can function on its own to induce an EMT, or whether this bHLH functions as a subunit of a heterodimeric TF complex formed with other well-validated EMT-TF proteins such as Twist.

Table 14.3 The Biology of Cancer (© Garland Science 2014)

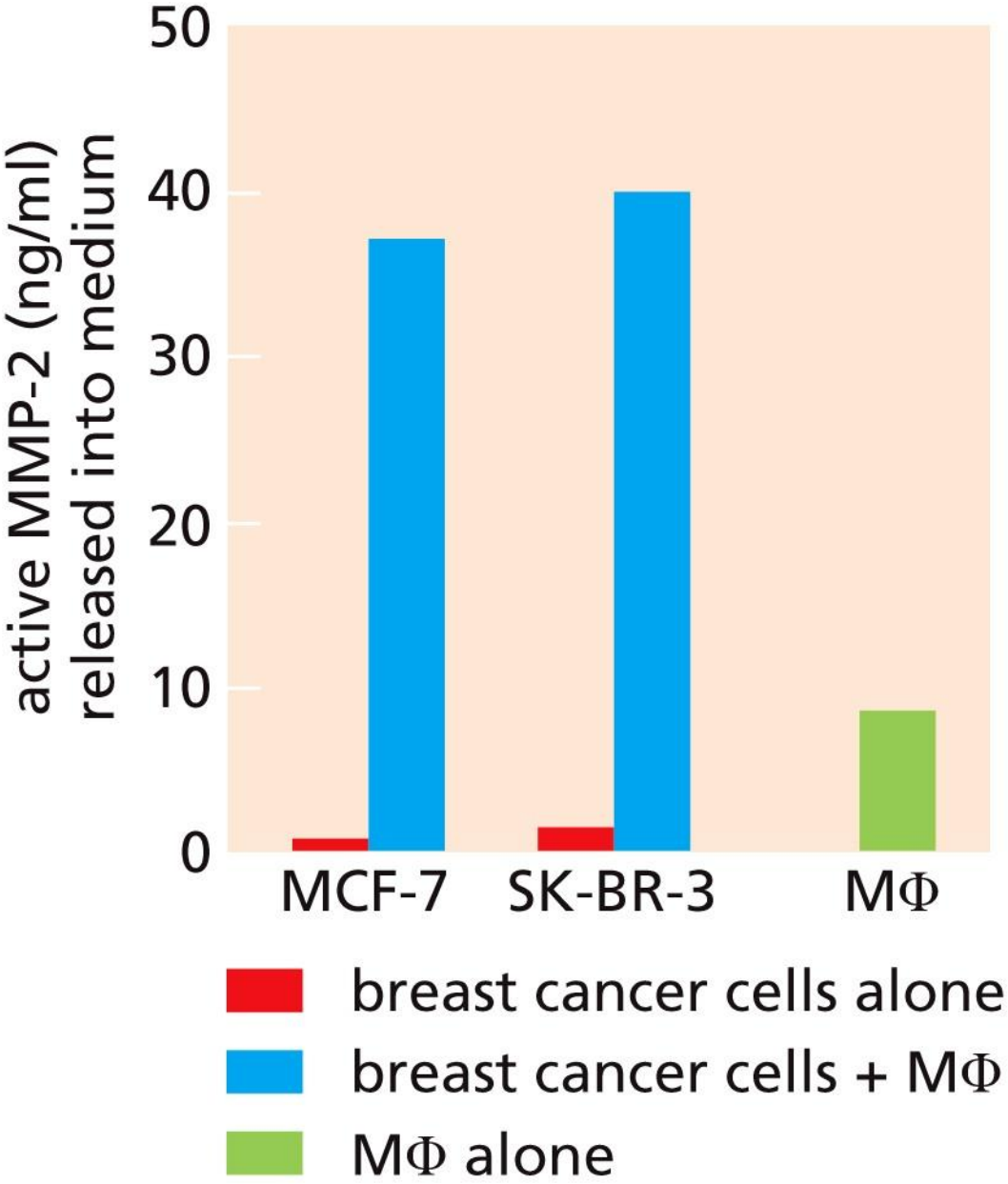


Figure 14.32c The Biology of Cancer (© Garland Science 2014)

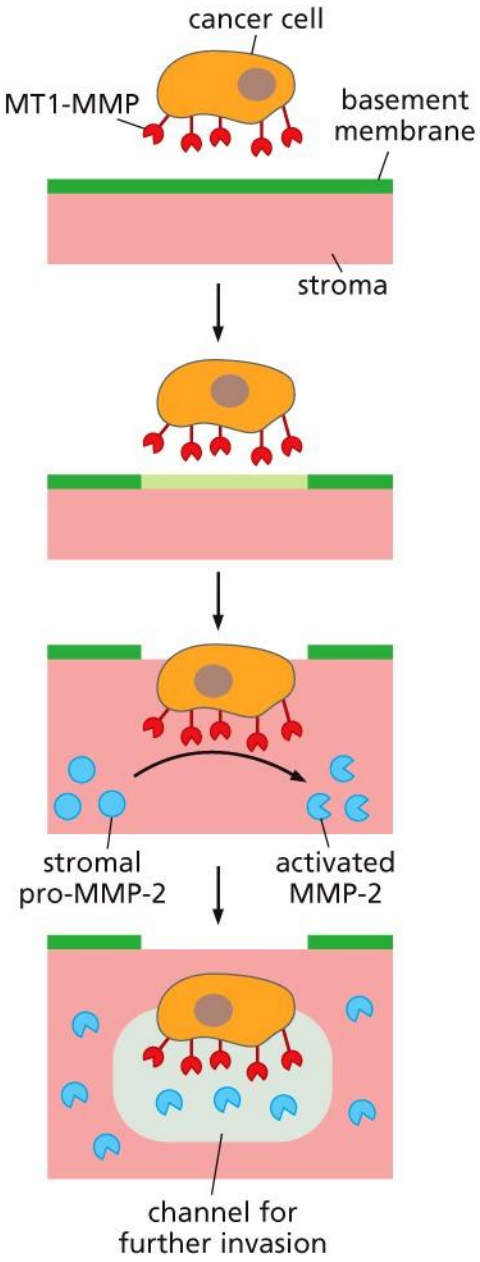
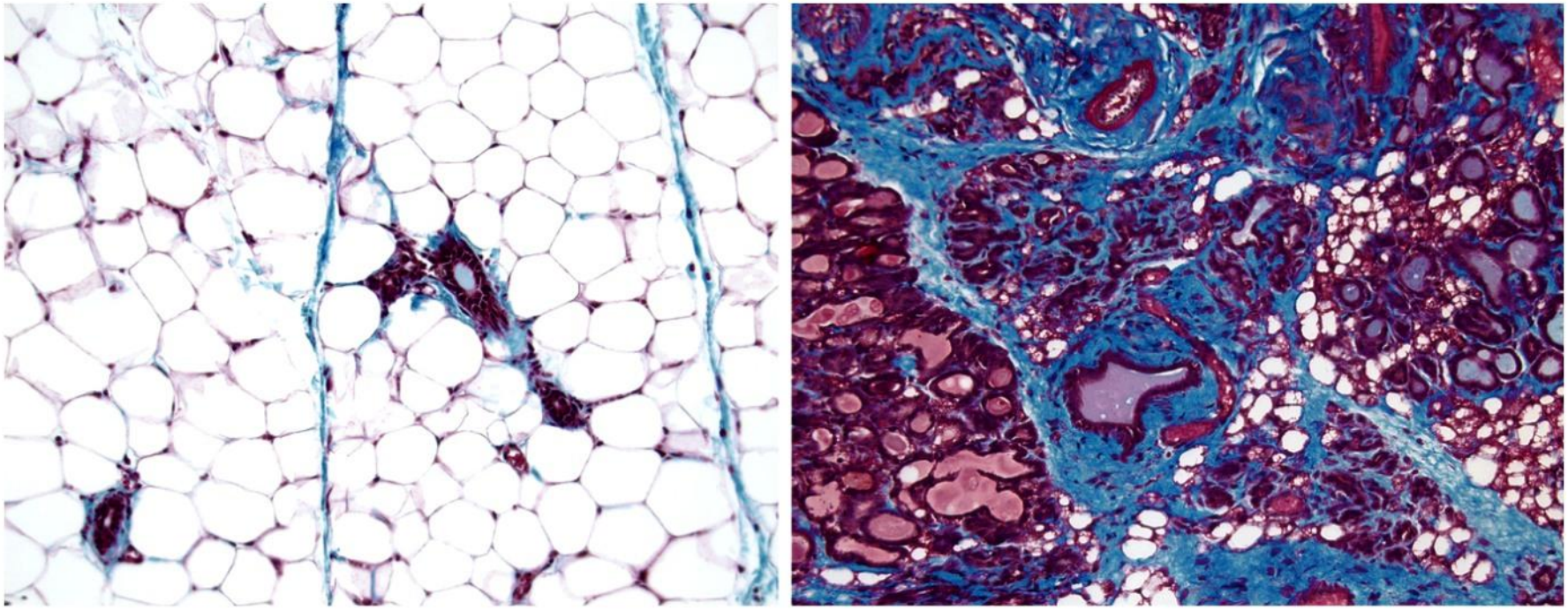


Figure 14.34 The Biology of Cancer (© Garland Science 2014)



normal mammary gland

+ ectopic MMP-3

Figure 14.35 The Biology of Cancer (© Garland Science 2014)

Stephen Paget (1855-1926)

The ‘seed and soil’ hypothesis

disseminated cancers form metastasis in distant tissue that offer an environment permissive for survival and proliferation

however, contralateral metastasis are relatively rare

Figure 14.44 The Biology of Cancer (© Garland Science 2014)

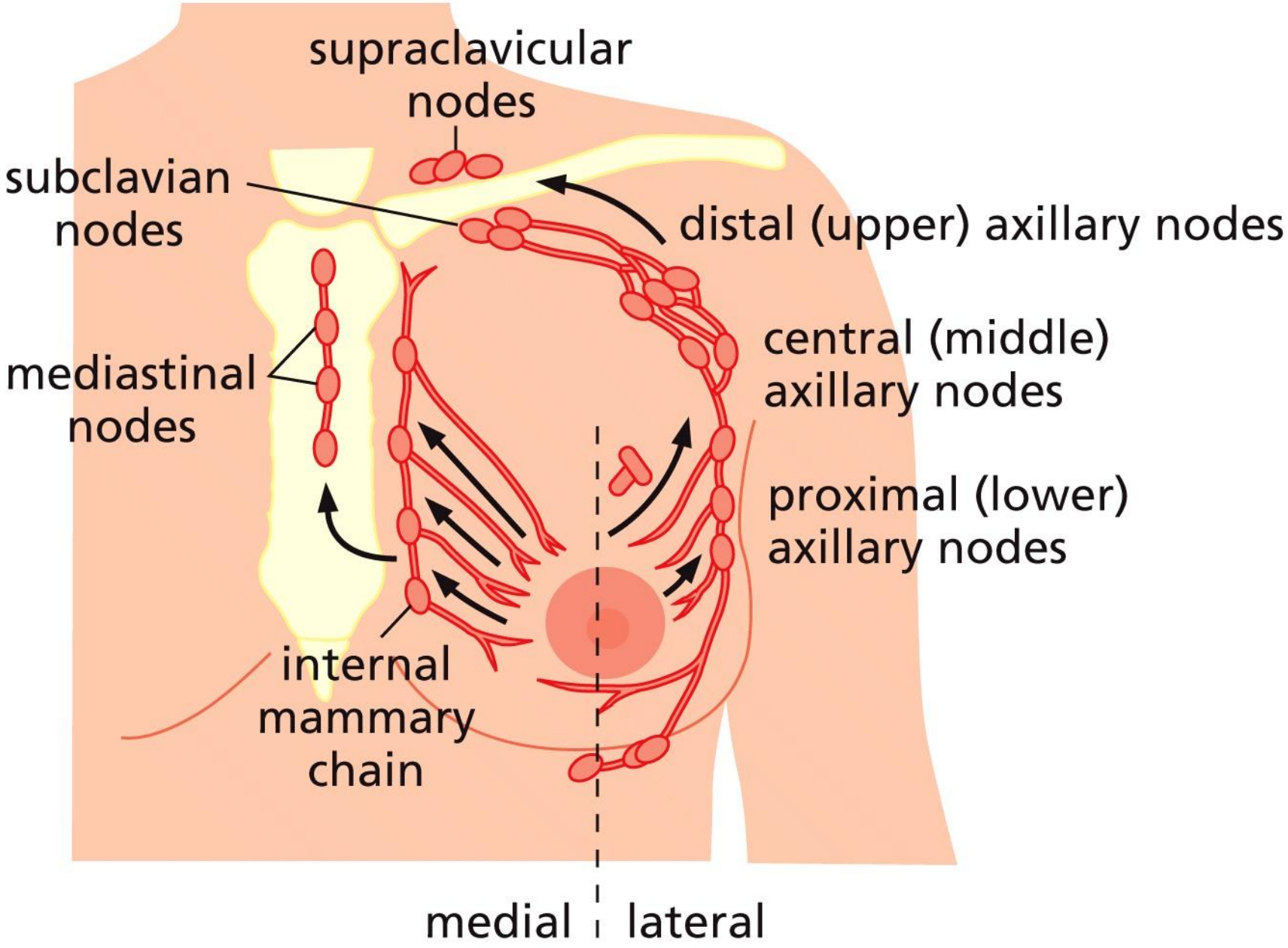


Figure 14.42a The Biology of Cancer (© Garland Science 2014)

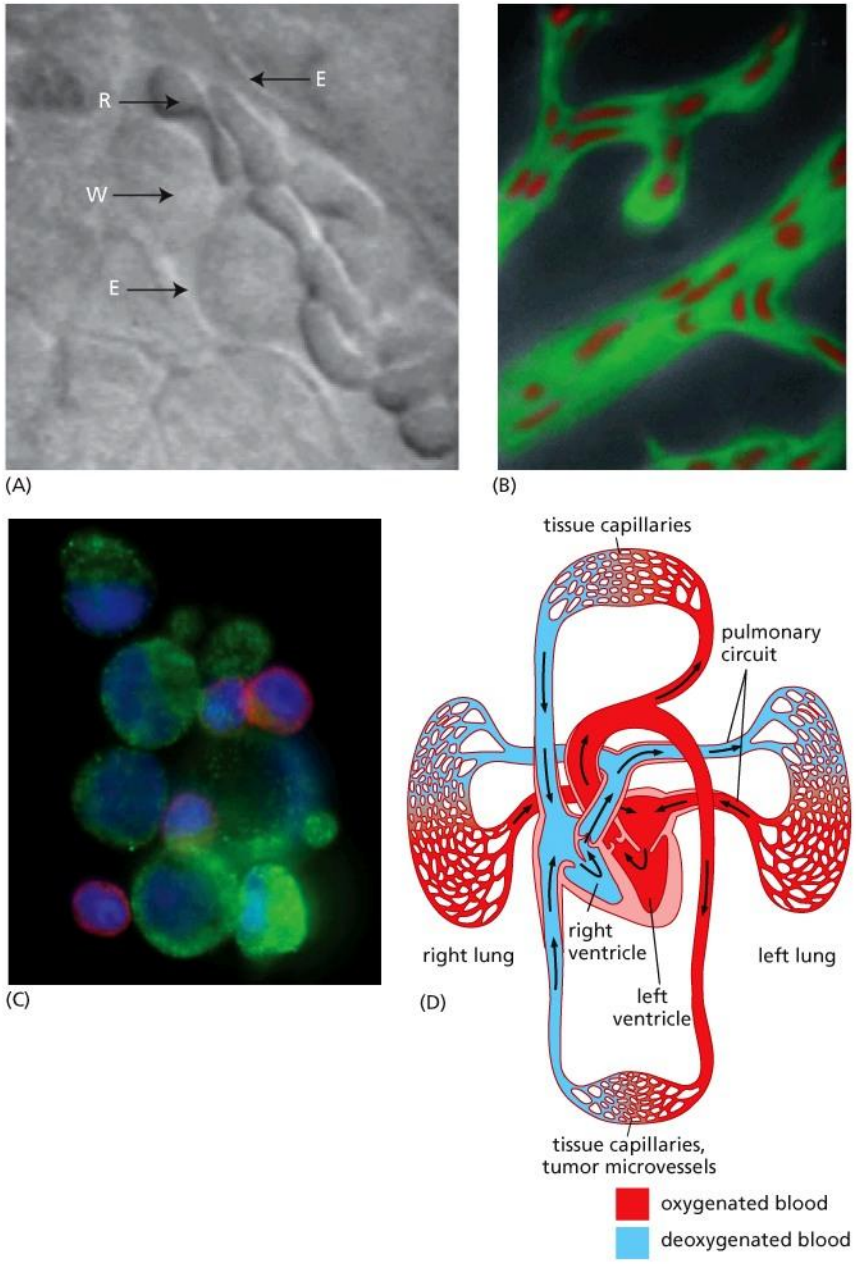


Figure 14.8 The Biology of Cancer (© Garland Science 2014)

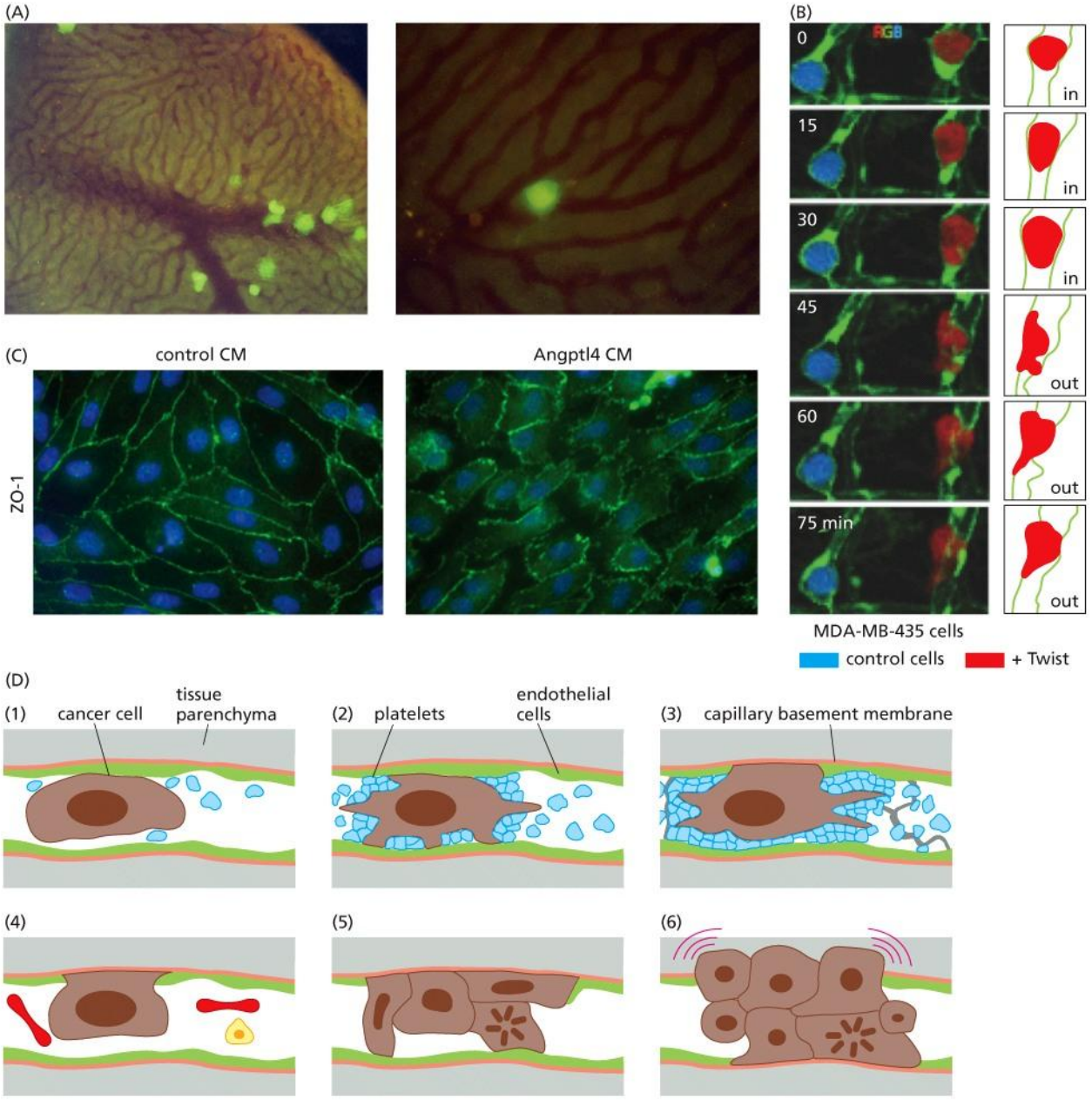


Figure 14.9 The Biology of Cancer (© Garland Science 2014)

EMT reversibility

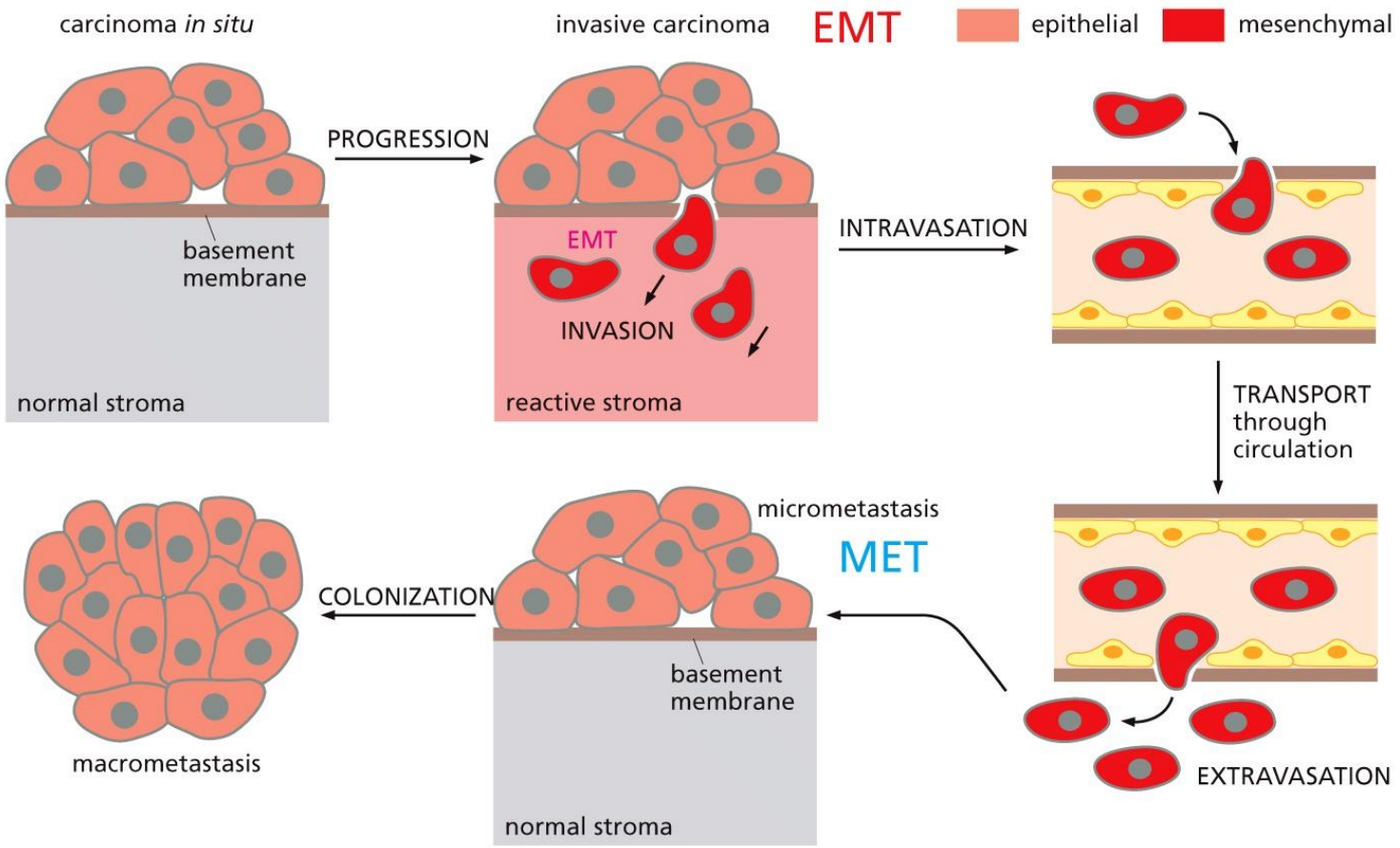


Figure 14.18b The Biology of Cancer (© Garland Science 2014)

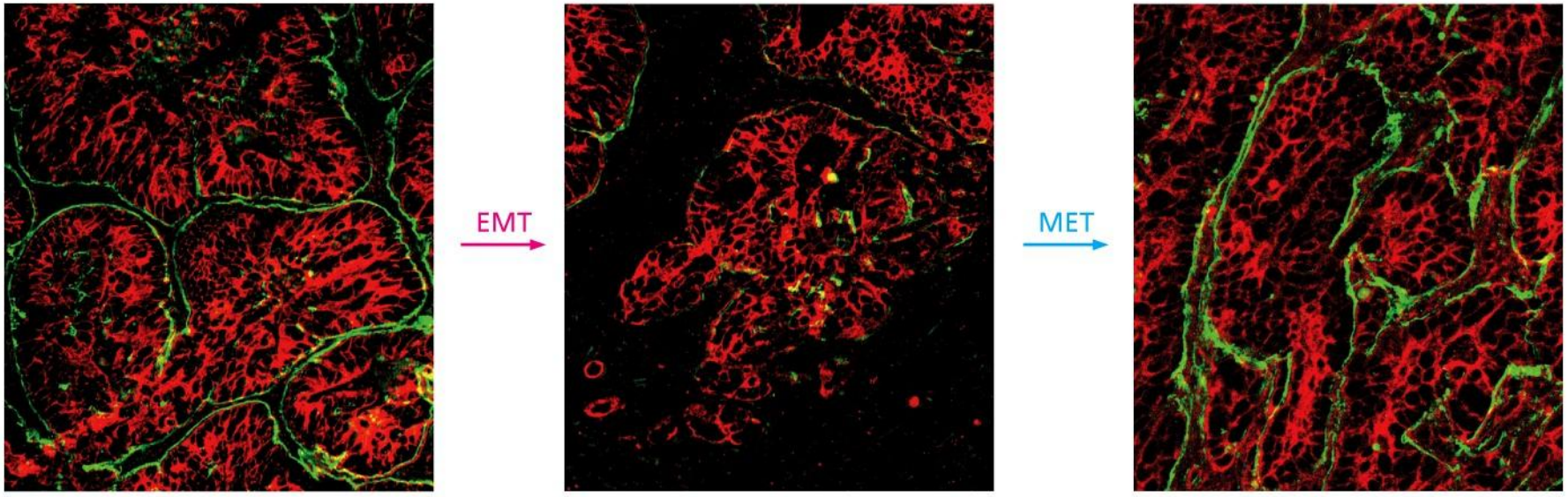


Figure 14.18a The Biology of Cancer (© Garland Science 2014)

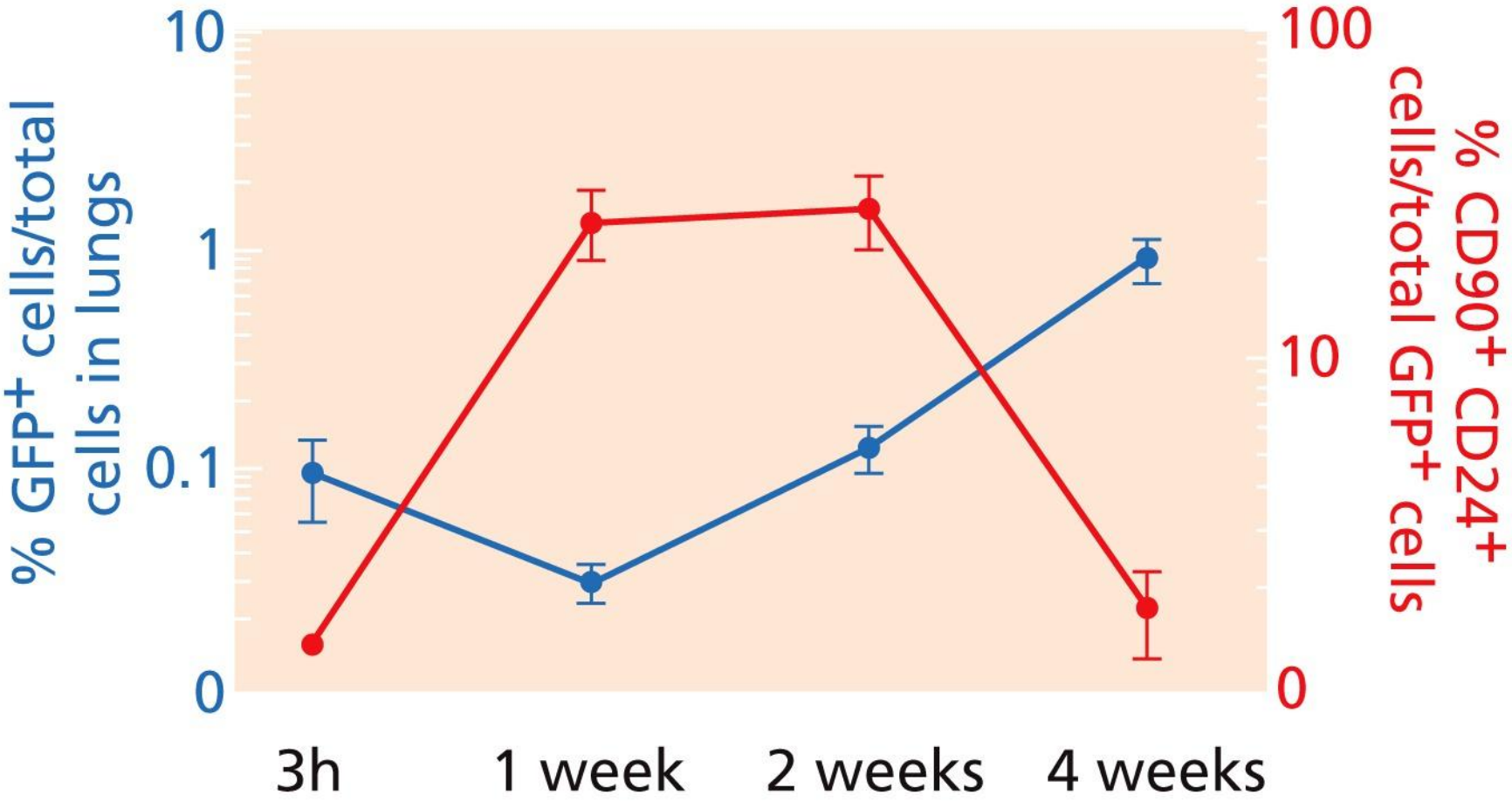
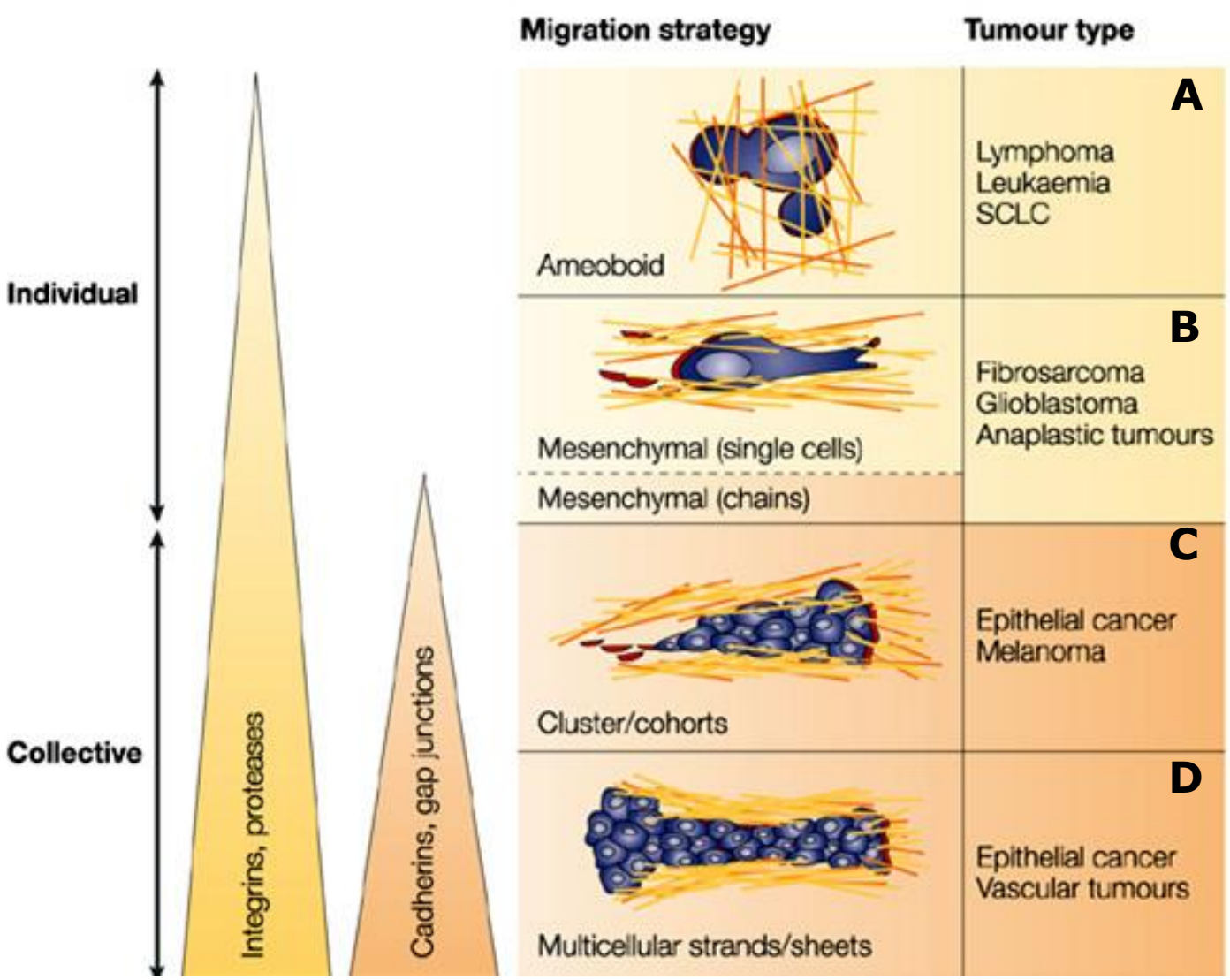
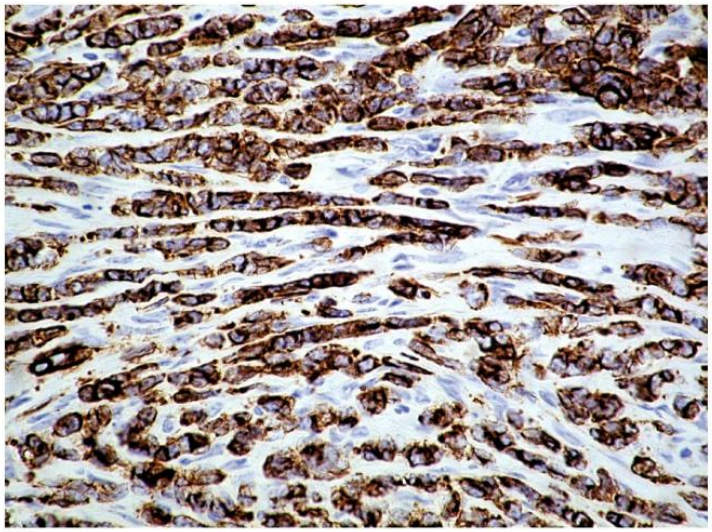


Figure 14.18c The Biology of Cancer (© Garland Science 2014)

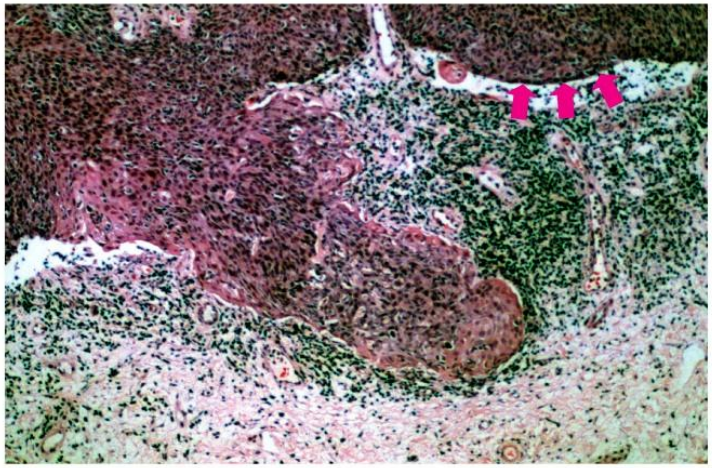
blu line: resident tumor cells; red line: mesenchymal tumor cells


Migration strategy
Tumour type
Individual
Collective
Integrins, proteases
Cadherins, gap junctions
Ameoboid
Lymphoma
Leukaemia
SCLC
A
Mesenchymal (single cells)
Mesenchymal (chains)
Fibrosarcoma
Glioblastoma
Anaplastic tumours
B
Cluster/cohorts
Epithelial cancer
Melanoma
C
Multicellular strands/sheets
Epithelial cancer
Vascular tumours
D

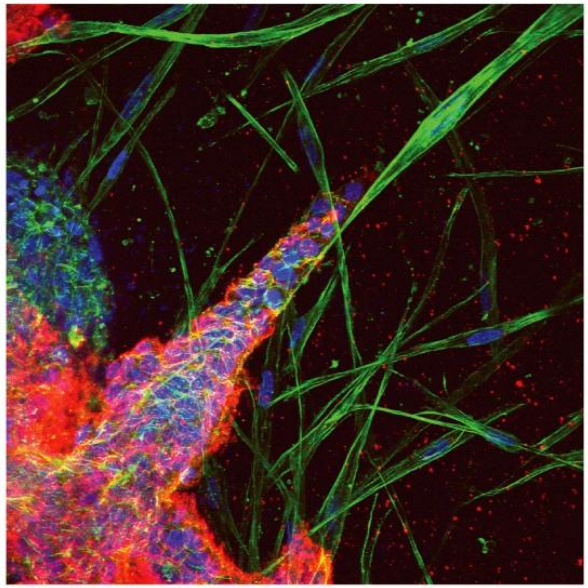
Invasion patterns



(A)



(B)



(C)

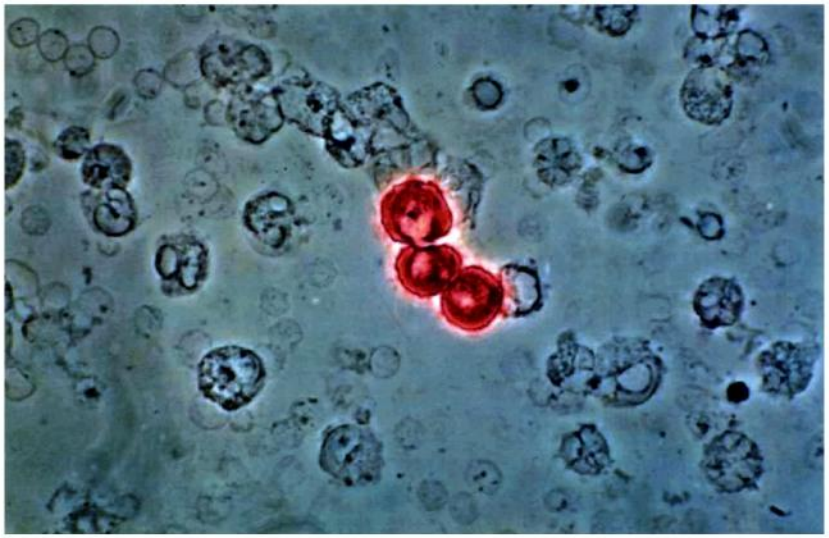
A. Breast cancer

B. Uterine cervical tumor (with inflammatory infiltrate, arrows)

C. MCF7 cells and fibroblasts in tridimensional matrix

Figure 14.5 The Biology of Cancer (© Garland Science 2014)

(A)



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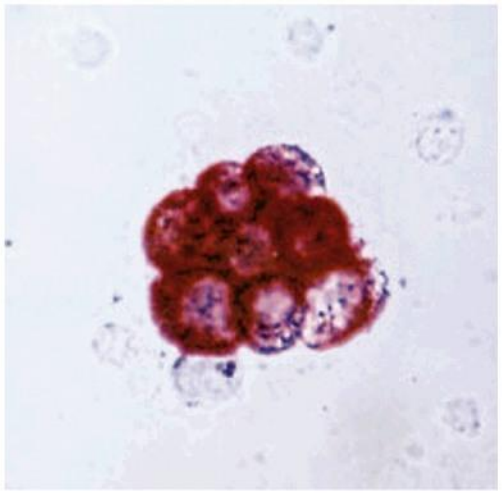

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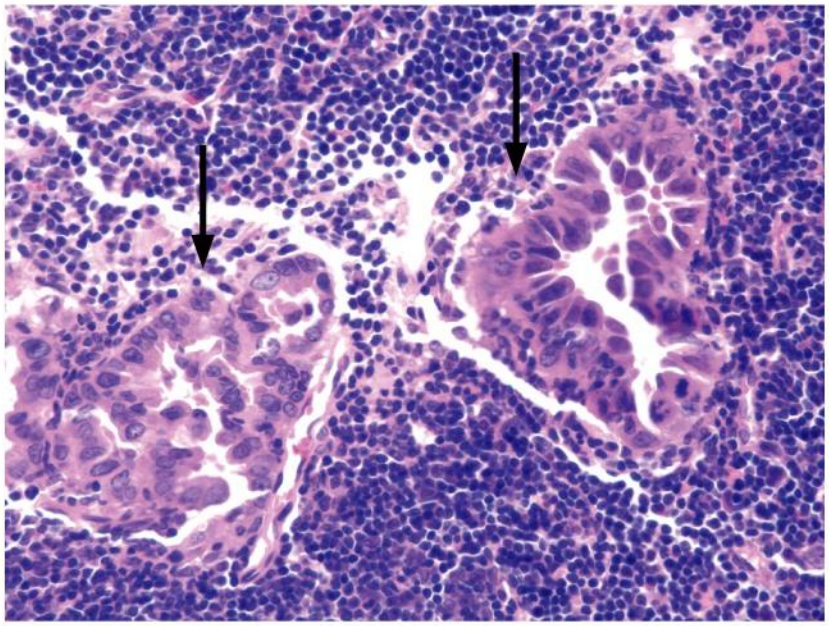

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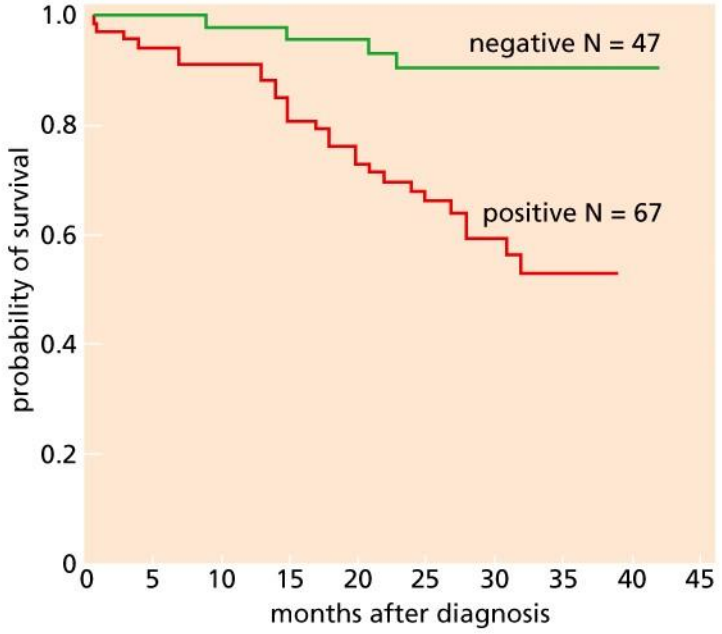


Figure 14.10 The Biology of Cancer (© Garland Science 2014)

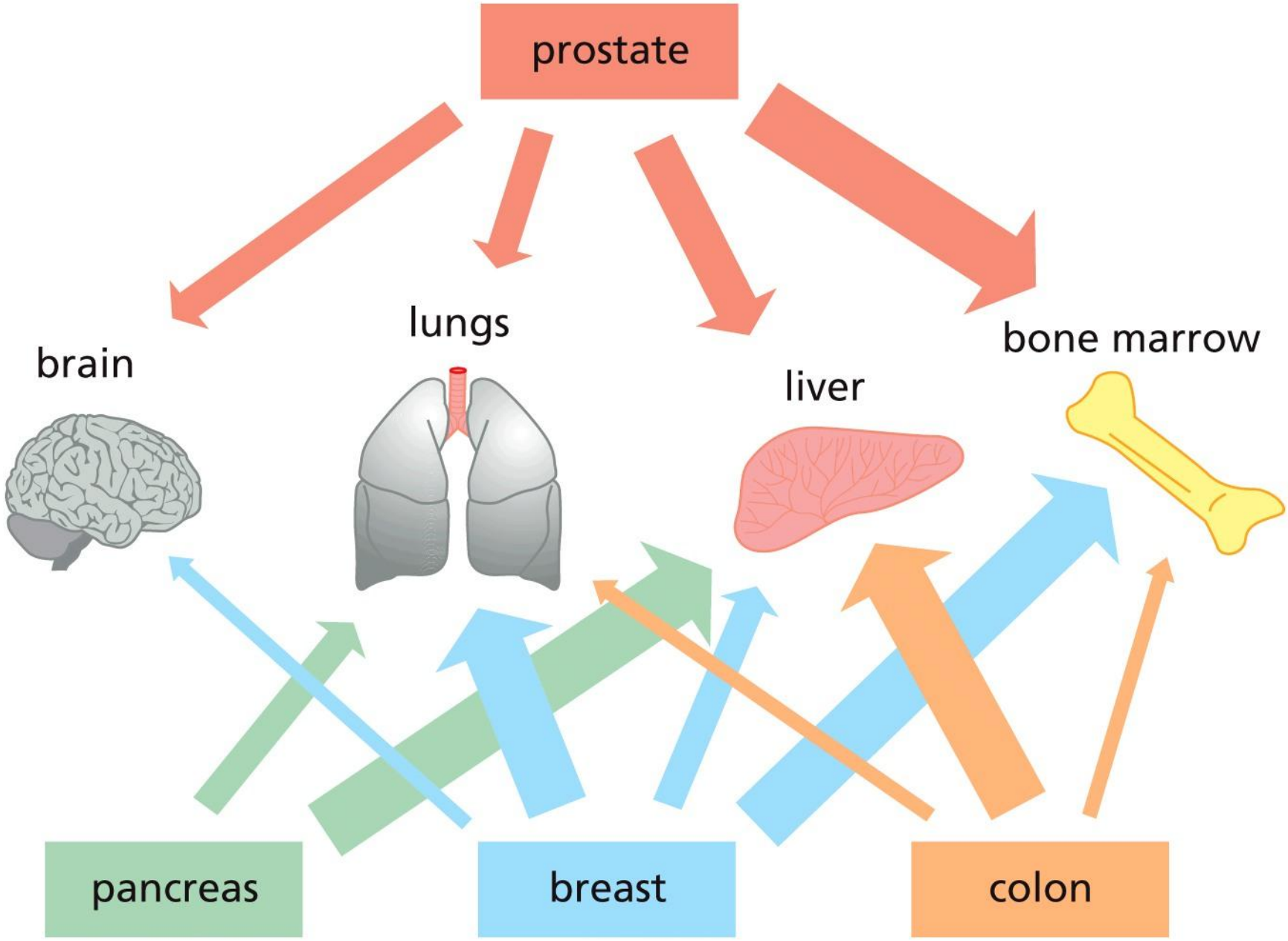
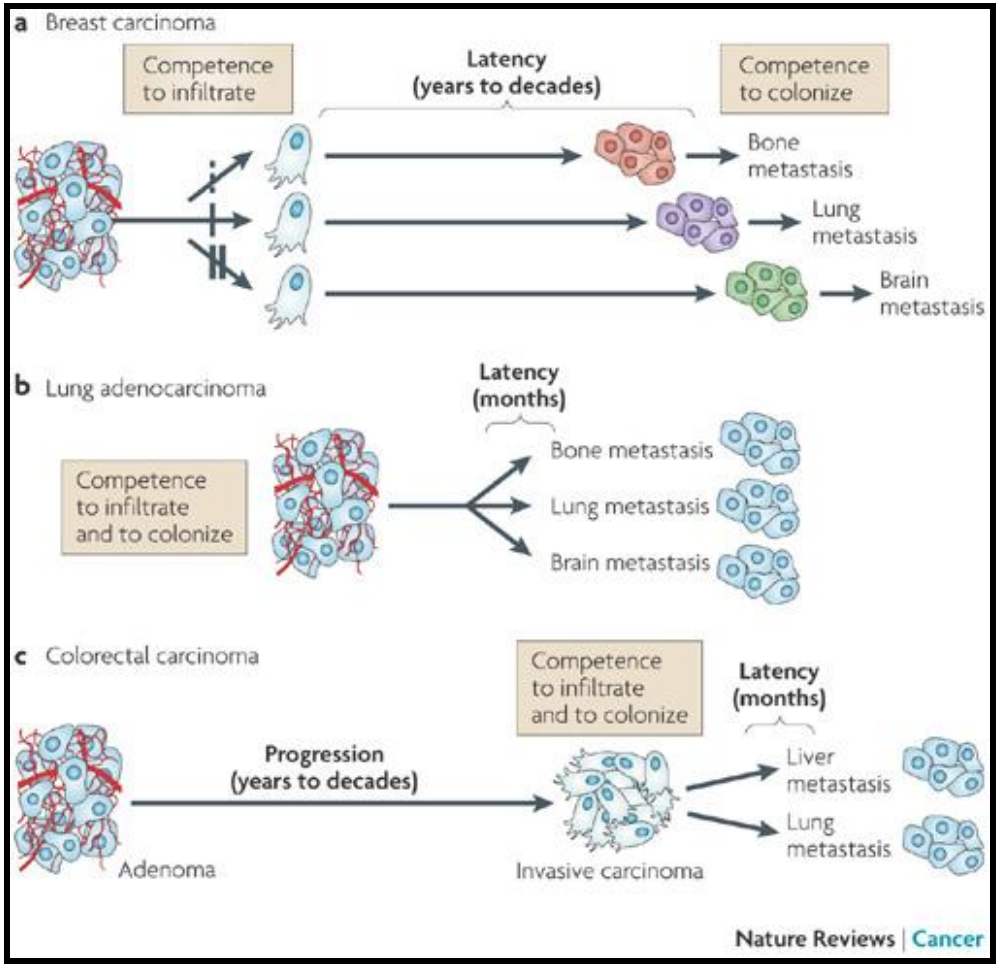
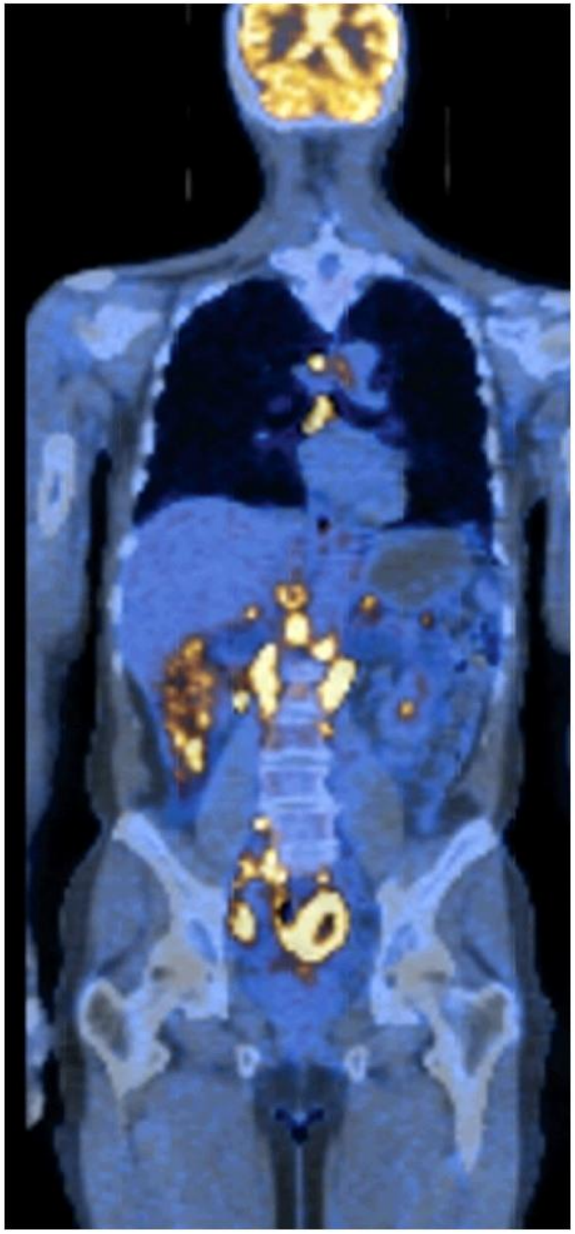


Figure 14.43 The Biology of Cancer (© Garland Science 2014)



Nguyen et al., 2009



CT + PET total body
Metastatic lymphoma

Figure 14.1 The Biology of Cancer (© Garland Science 2014)

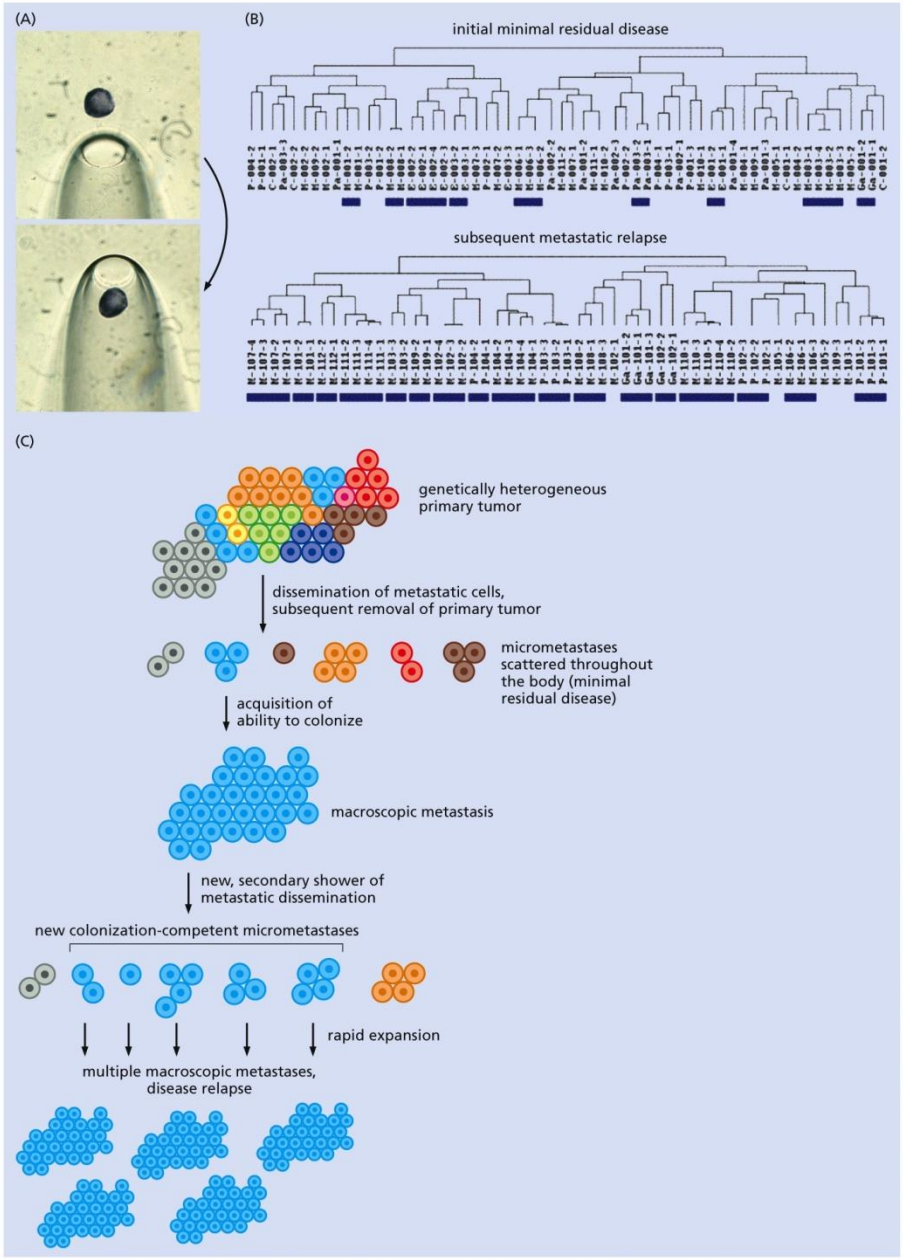


Figure 14.11 The Biology of Cancer (© Garland Science 2014)

Table 14.4 Candidate metastasis suppressor genes

Name	Cellular location	Mechanism of action
BRMS1	nuclear protein	involved in chromatin remodeling
CRSP3	nuclear protein	transcription factor
KAI1/CD82	transmembrane protein	cell–cell associations
KISS1	secreted protein	ligand of G-protein–coupled receptor
NM23	cytoplasmic kinase	regulator of MAPK cascade (?)
p63	nuclear transcription factor	multiple targets
RhoGDI-2	cytoplasmic protein	negative regulator of Rho action
SseCKs	cytoplasm	cytoskeleton-associated protein
VDUP1	cytoplasm	regulator of MAPK cascade (?)
CDH1 (= E-cadherin)	cell surface adhesion	favors formation of epithelial cell sheets
TIMPs	secreted protein	inhibitor of metalloproteinases
MKK4	cytoplasm	protein kinase component of MAPK cascade
DICER	cytoplasm	miRNA processing

Adapted in part from P.S. Steeg, *Nat. Rev. Cancer* 3:55–63, 2003.

Table 14.4 The Biology of Cancer (© Garland Science 2014)

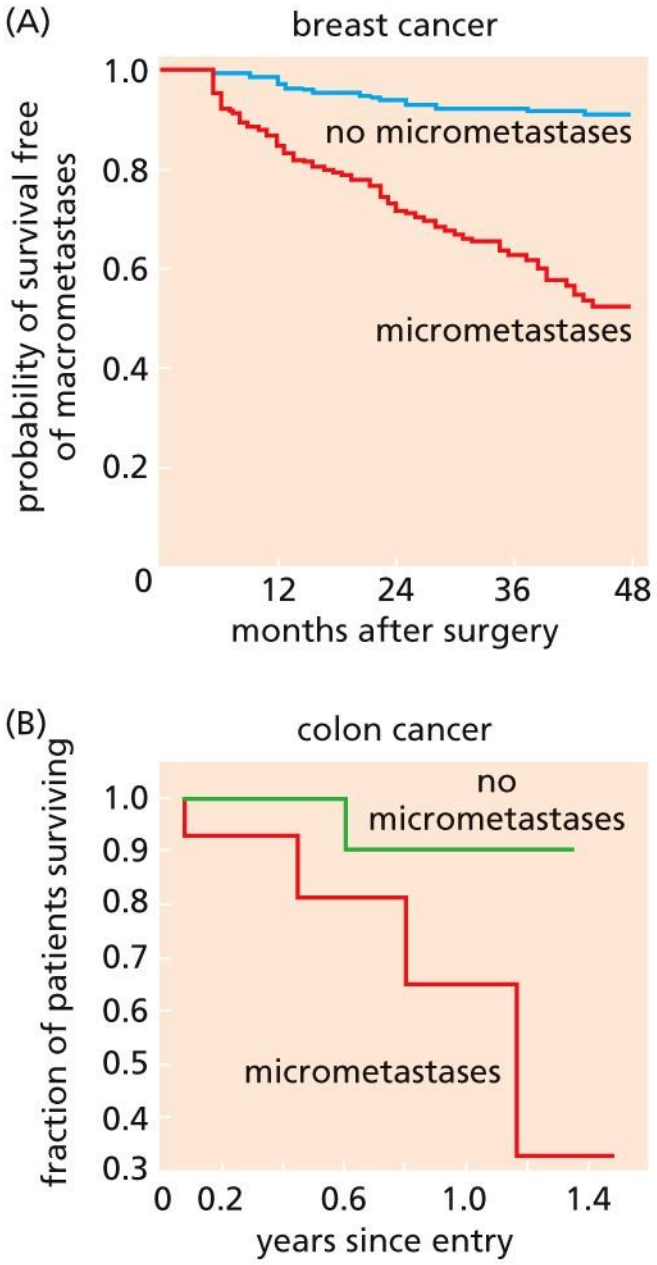


Figure 14.50 The Biology of Cancer (© Garland Science 2014)

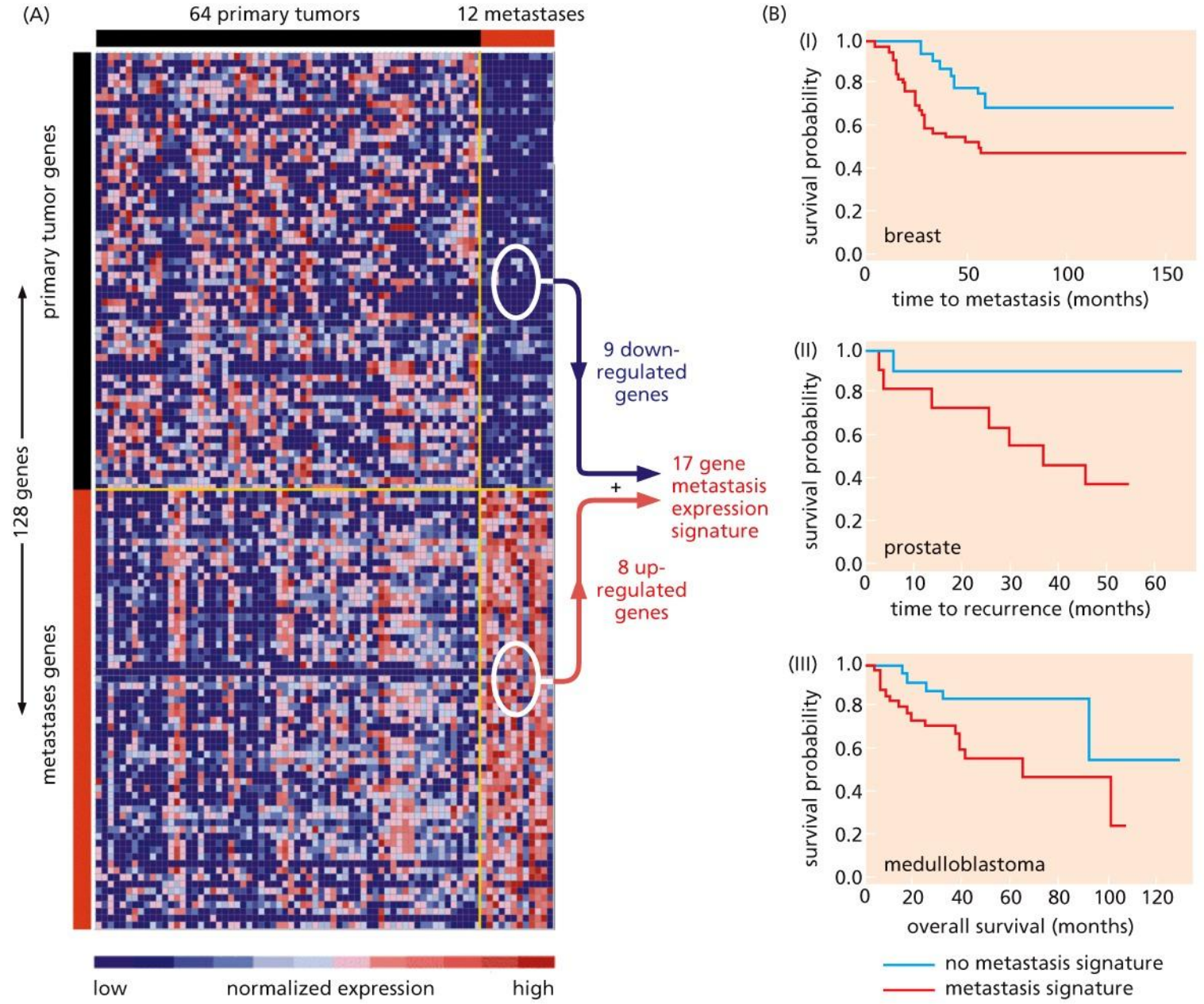


Figure 14.51 The Biology of Cancer (© Garland Science 2014)

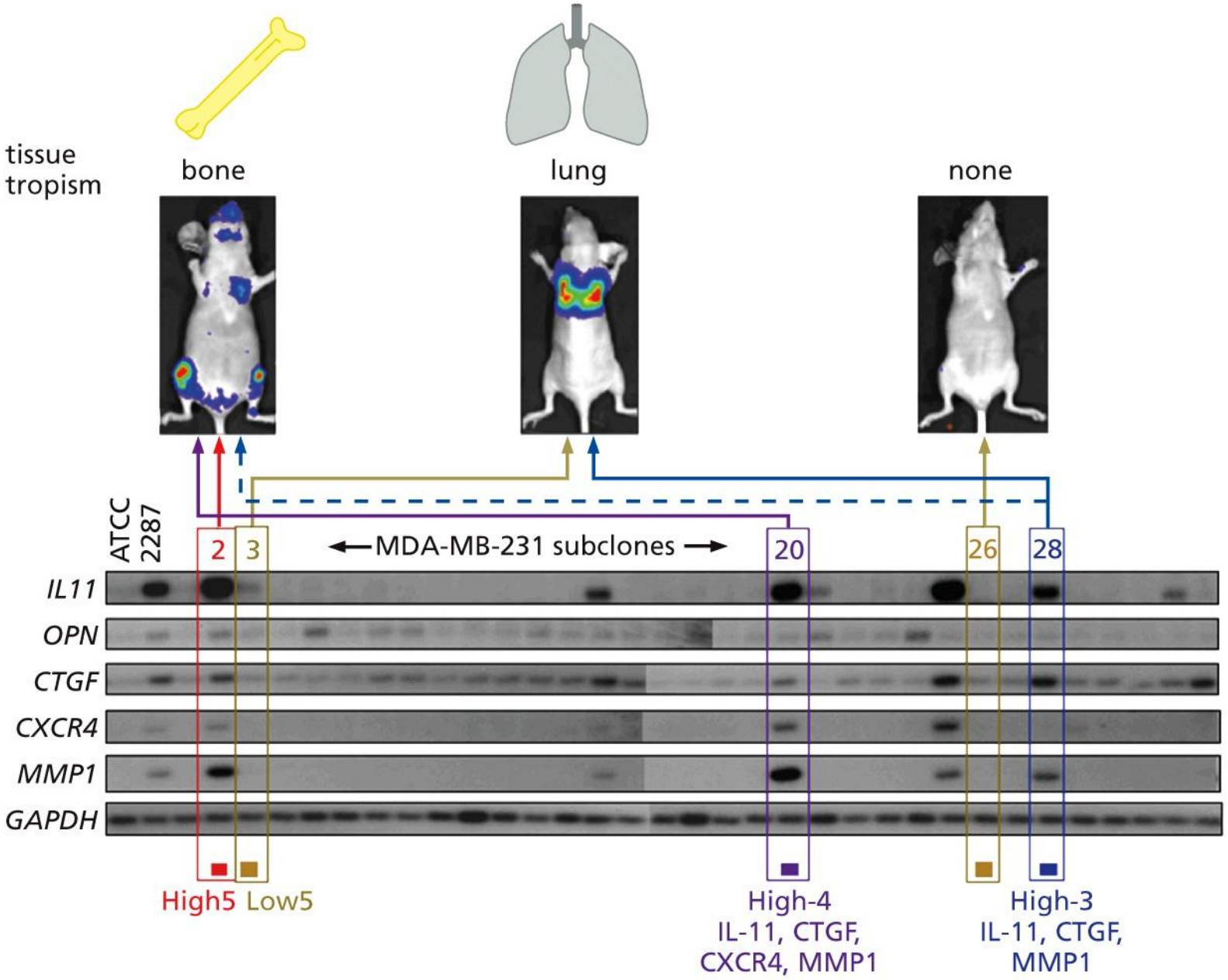
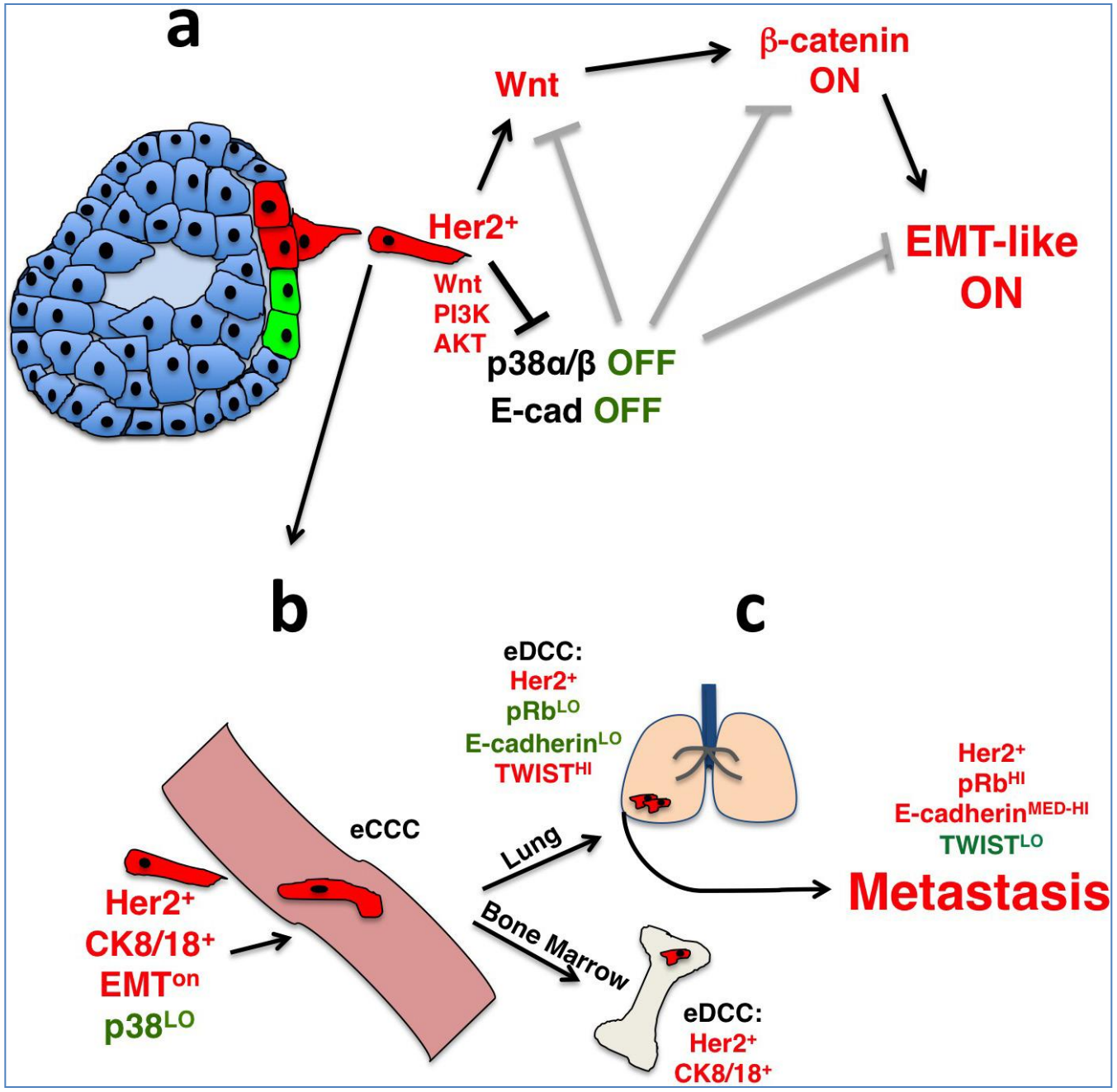


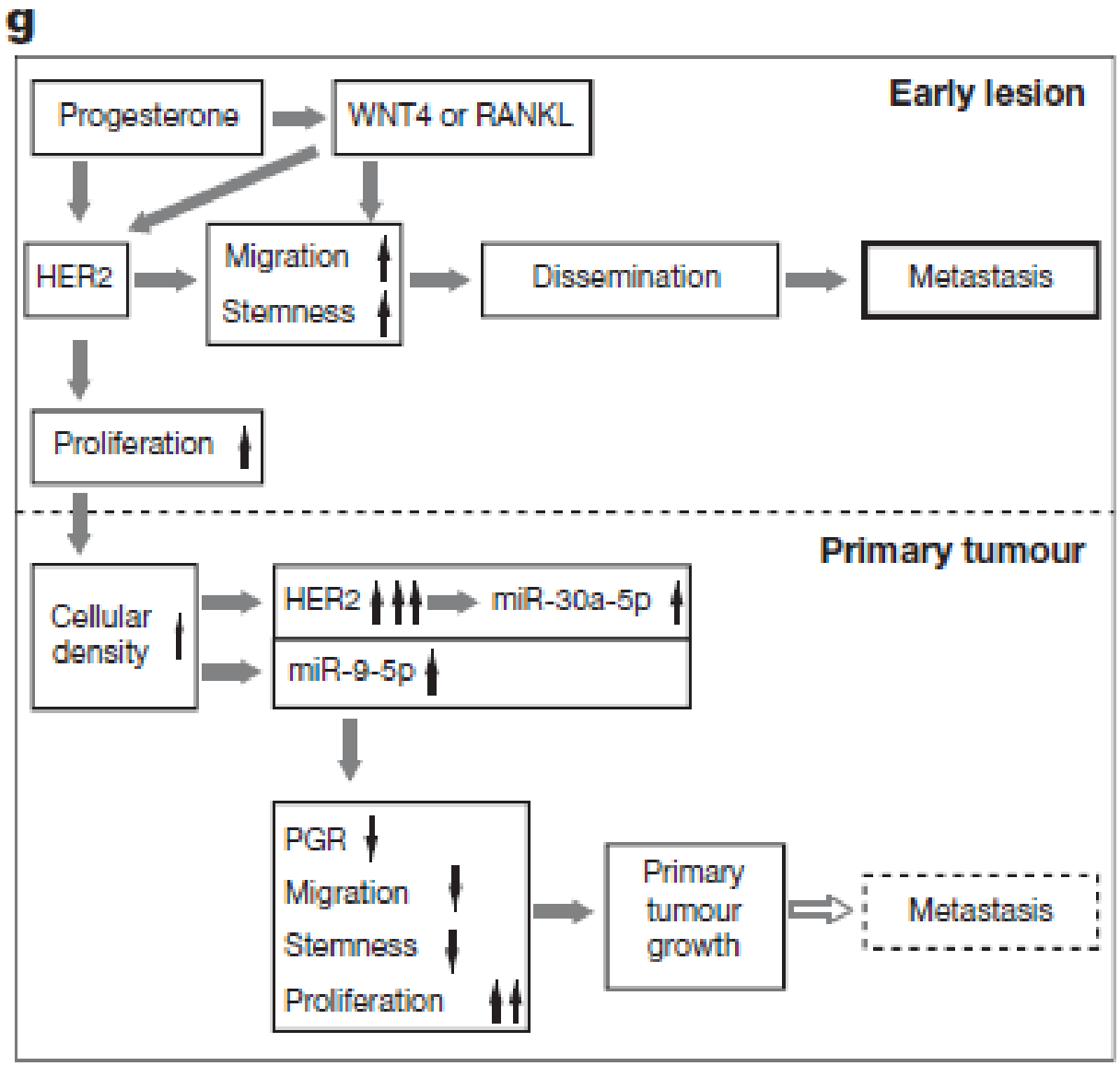
Figure 14.53 The Biology of Cancer (© Garland Science 2014)



Extended Data Figure 9 | Cartoon depicting the mechanism of early dissemination by Her2+ early lesion cells.

a, Early Her2+ early lesion cancer cells (red) turn on Wnt, PI3K and AKT signalling, inhibit p38 activation and E-cadherin-junction formation allowing for a Twist1hi EMT-like invasive program; p38 and E-cadherin inhibit the Wnt- and β -catenin-driven EMT-like program and invasion (grey inhibitory symbols). b, Her2+p-p38loTwist1hiE-cadlo early lesion cancer cells, which retain CK8/18 expression can intravasate and disseminate. c, In lungs more than 85% of eDCCs (red) were Her2+E-cadlo(p-Rb or p-H3)lo, suggesting a large population of dormant cells. Most eDCCs are also Twist1hiE-cadlo. Nevertheless, eDCCs can initiate metastasis, which correlated with the acquisition of a Twist1loE-cadmed–hi phenotype. In the bone marrow, eDCCs were Her2+CK8/18+ and remain dormant for the duration of the experiments, as bone lesions were never observed.

Harper et al., 2016



Hosseini et al., 2016