

INVAZIVITA A METASTÁZOVÁNÍ - dokončení

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Epithelial-Mesenchymal Transition (EMT)

- Změna buněčného fenotypu spojená se ztrátou adheze a zvýšením motility

Table 14.1 Examples of EMTs during mouse embryonic development

Process	Transition	
	From	To
Gastrulation	epiblast	mesoderm
Prevalvular mesenchyme in the heart	endothelium	atrial and ventricular septum
Neural crest cells	neural plate	neural crest cells, which can yield bone, muscle, peripheral nervous system
Somitogenesis	somite walls	sclerotome
Palate formation	oral epithelium	mesenchymal cells
Müllerian duct regression	Müllerian tract	mesenchymal cells

Adapted from P. Savagner, *BioEssays* 23:912–923, 2001.

EMT & nádory

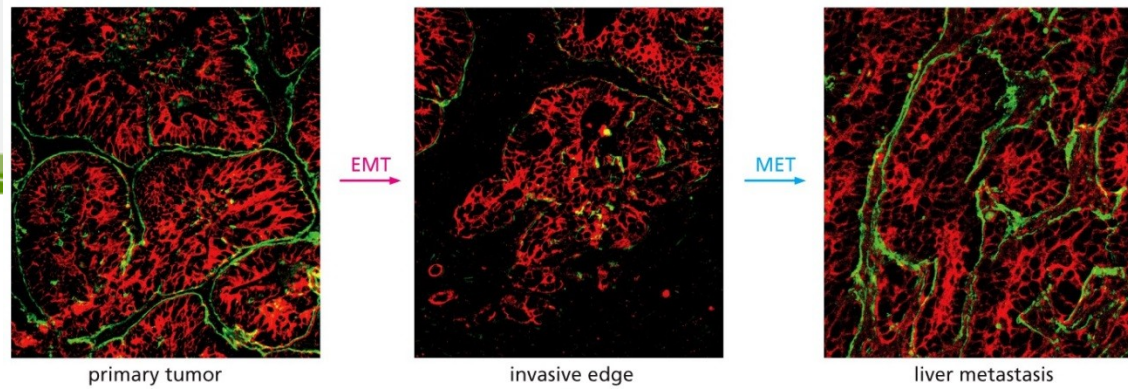


Figure 14.18a The Biology of Cancer (© Garland Science 2014)

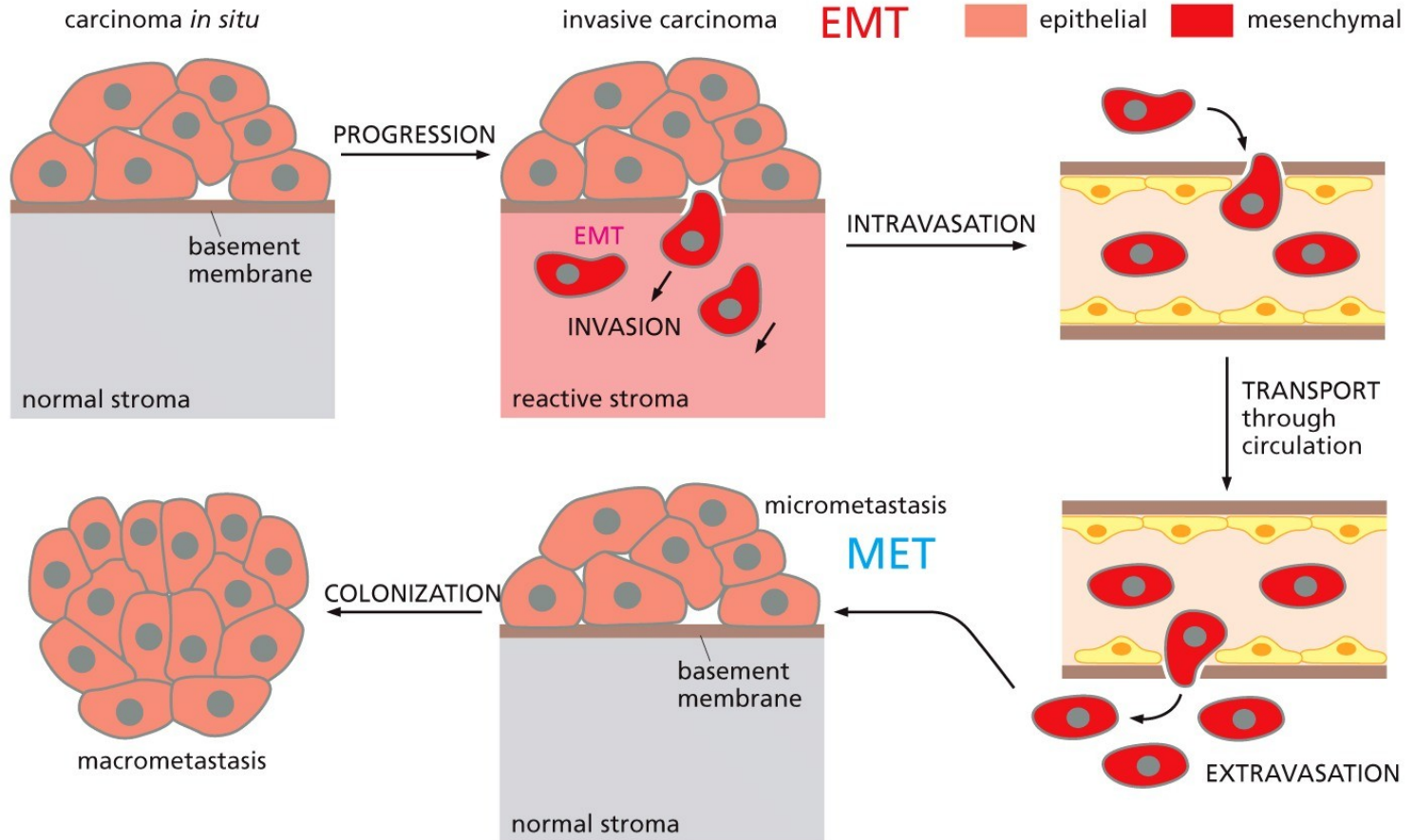
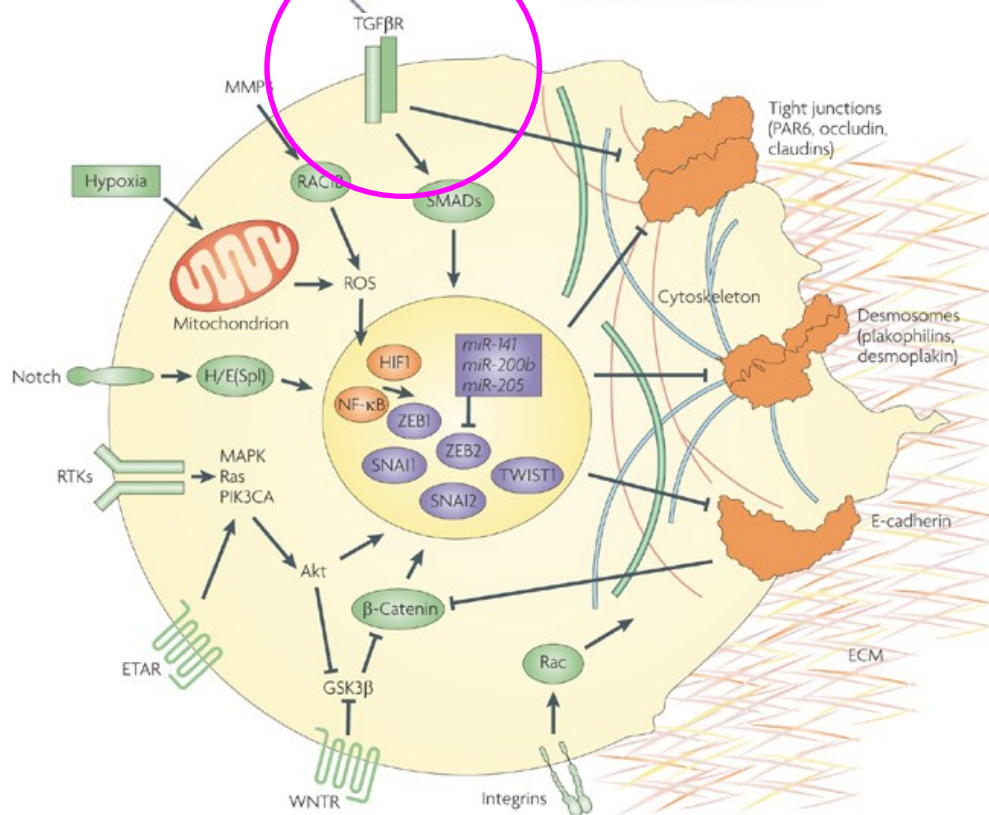
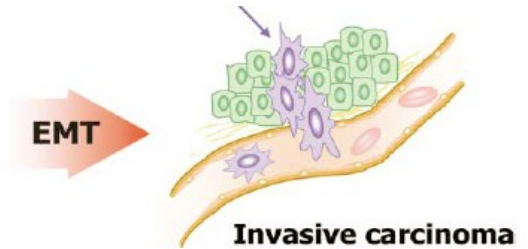
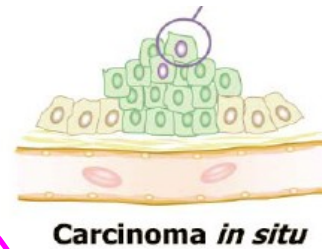


Figure 14.18b The Biology of Cancer (© Garland Science 2014)

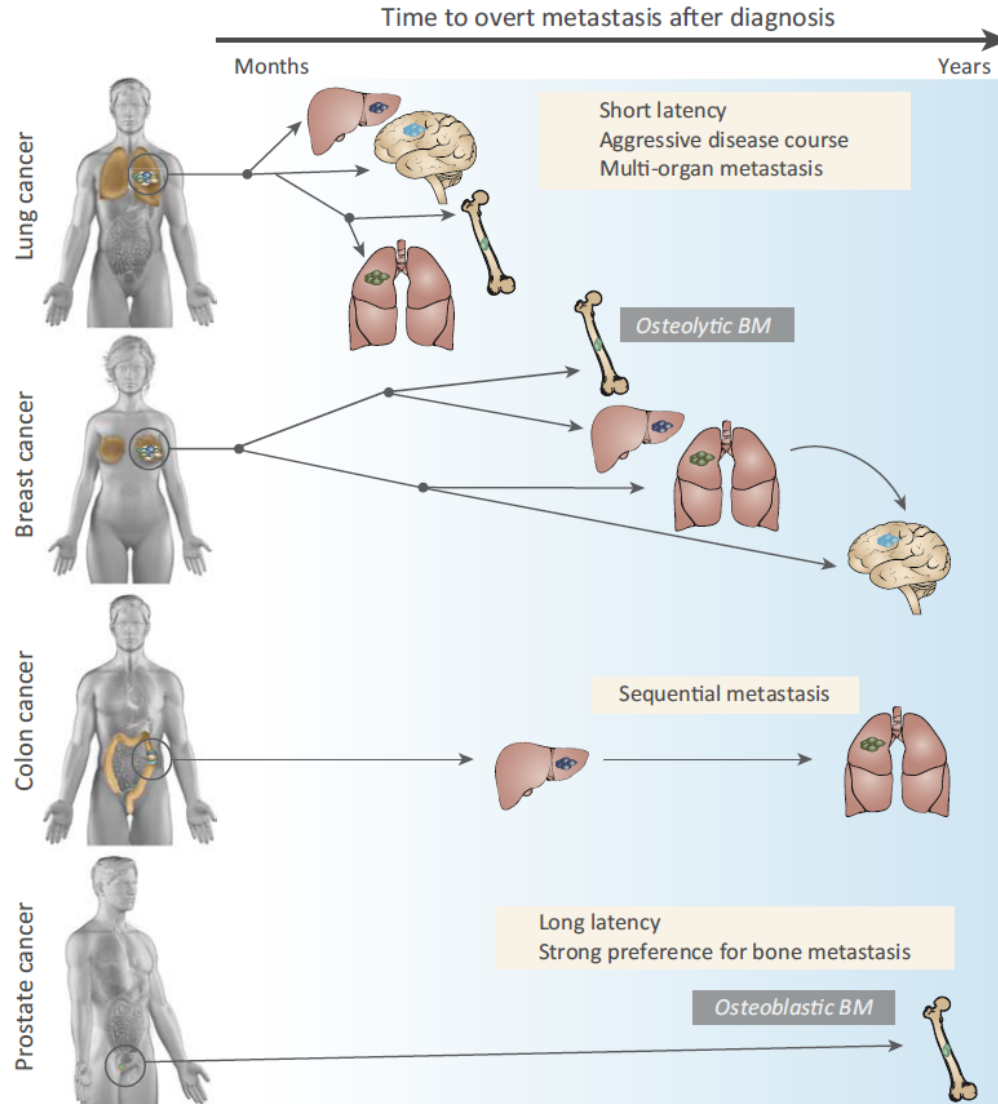
Znaky a regulatory EMT

EMT Program	<i>E-cadherin</i>	Epithelial markers repressed
	<i>α-catenin</i> <i>γ-catenin</i>	
	<i>Vimentin</i> <i>Fibronectin</i> <i>N-cadherin</i>	Mesenchymal markers induced



Kornelia Polyak & Robert A. Weinberg
Nature Reviews Cancer **9**, 265-273 (April 2009)

Diseminace solidních nádorů



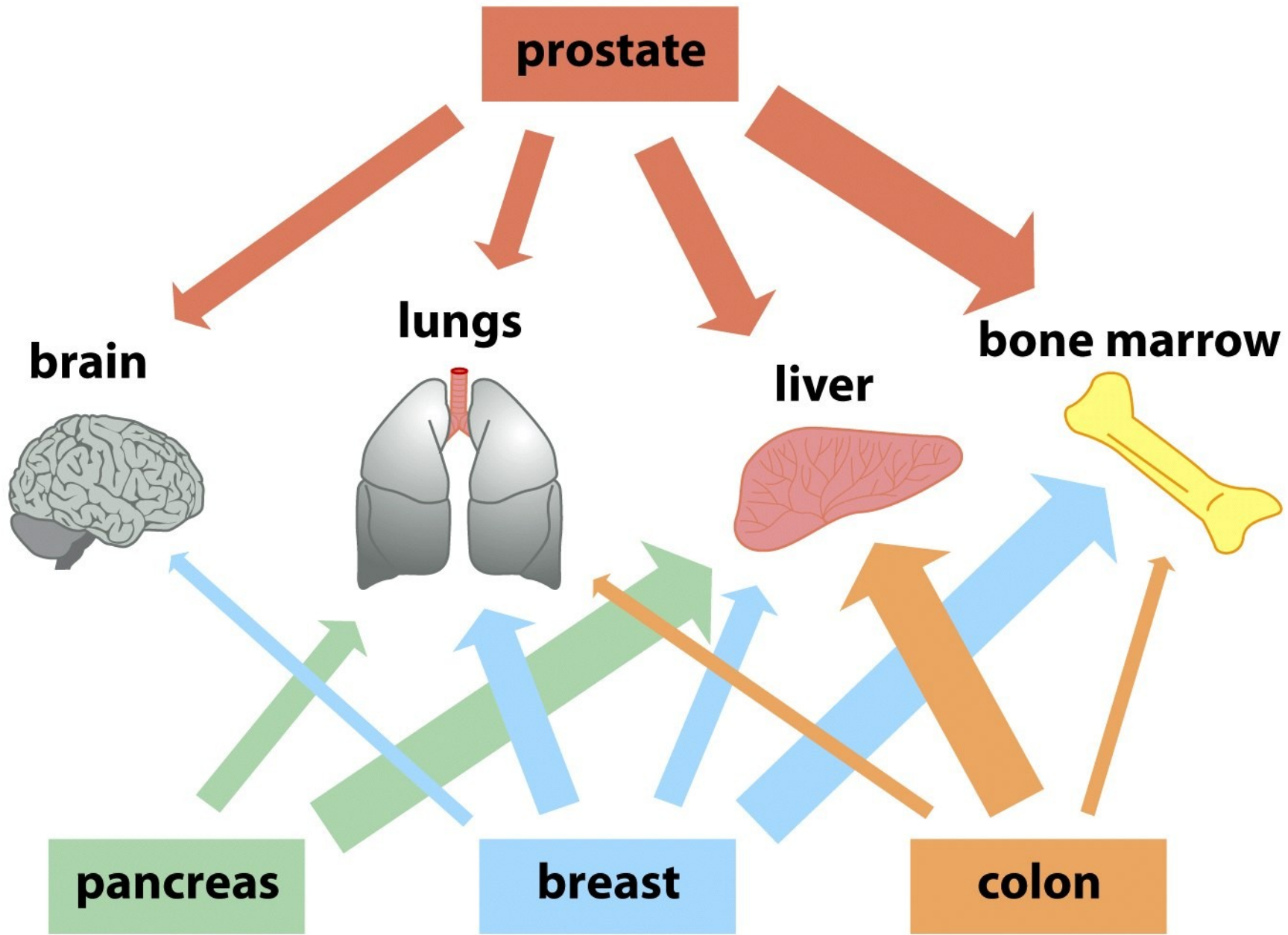


Figure 14.42 *The Biology of Cancer* (© Garland Science 2007)

Metastatický tropismus

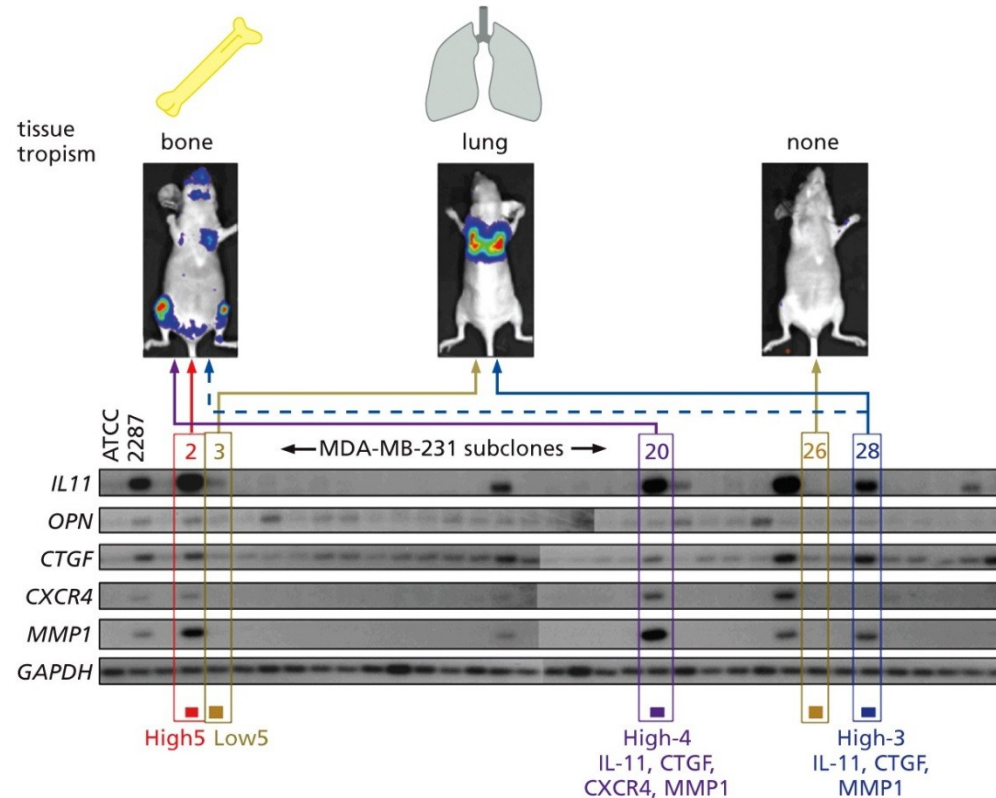
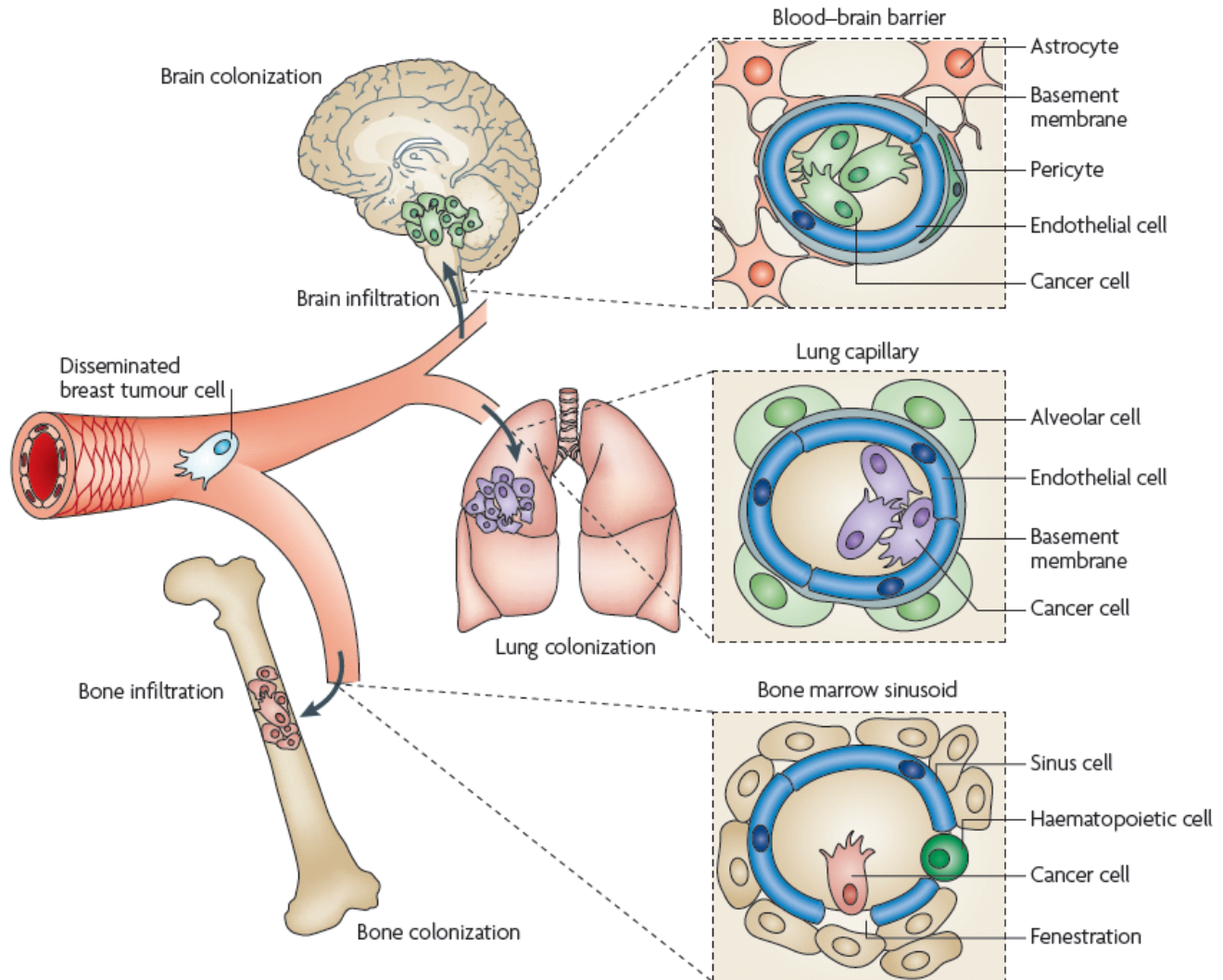


Figure 14.53 The Biology of Cancer (© Garland Science 2014)

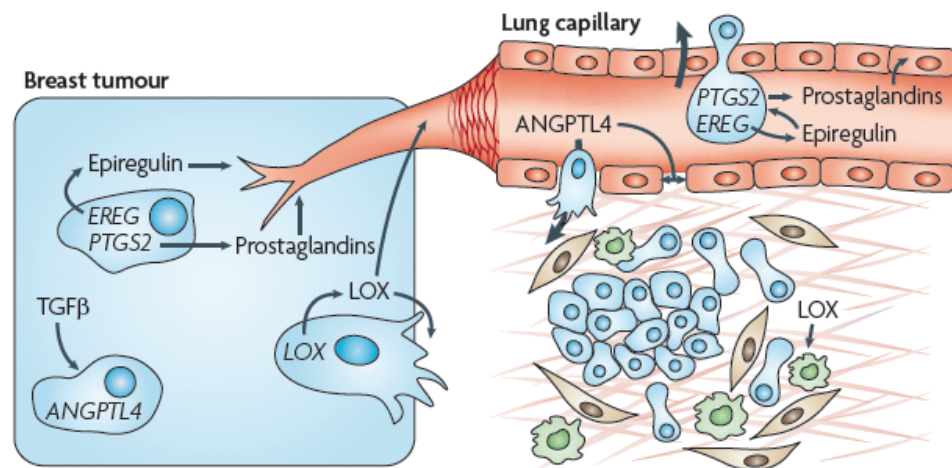
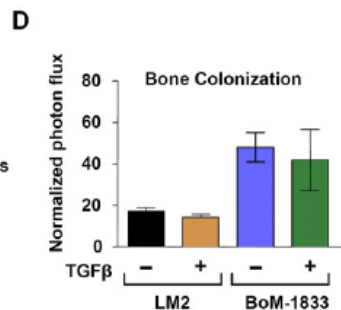
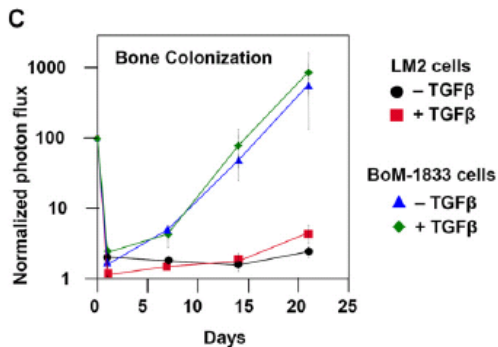
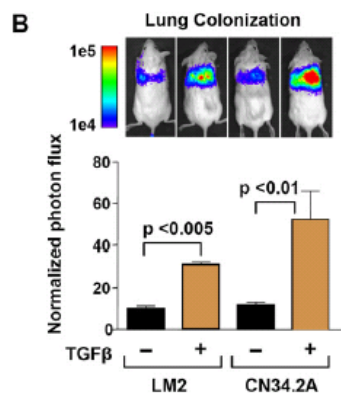
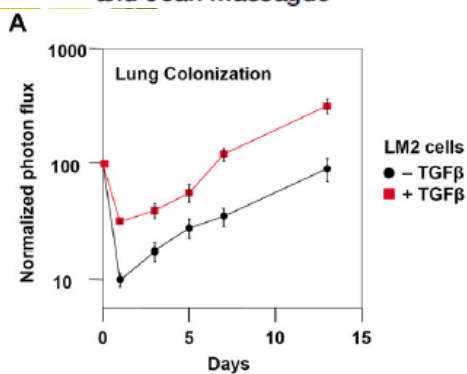
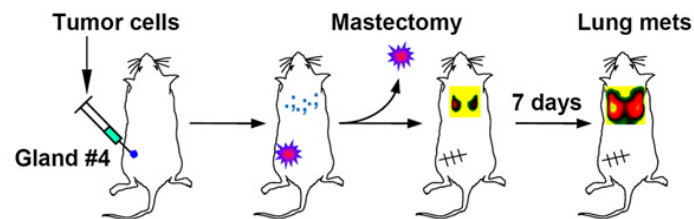
- Thirty-three cells from a large population of human MDA-MB-231 cells were each expanded into a clonal population in culture. The mRNA expression pattern of each subclone was analyzed (columns, arrayed left to right) using probes for the mRNAs of five genes—*IL11* (interleukin-11), *OPN* (osteopontin), *CTGF* (connective tissue growth factor), *CXCR4* (chemokine receptor 4), and *MMP1* (matrix metalloproteinase-1)—and, as loading control, a probe for *GAPDH* (glyceraldehyde-3-phosphate dehydrogenase) mRNA. In addition, the expression patterns of the original tumor cell population (ATCC, left column) and a subcloned cancer cell population termed 2287 (which was selected for its ability to generate osteolytic metastases; 2nd column) were analyzed. The five experimental genes were chosen because of their overexpression in osteotropic metastatic cells and their known biological properties in promoting osteolytic metastases. Clone 2 cells (red box), when injected into the arterial circulation of mice, showed a tendency to produce osteotropic metastases, as indicated by *in vivo* imaging; these cells expressed high levels of all five experimental mRNAs. Clone 3 cells (yellow box), in contrast, expressed low levels of all five mRNAs and preferentially formed lung metastases. And clone 26 genes (yellow box), which expressed essentially none of these mRNAs, formed no metastases at all. Moreover, when otherwise poorly metastatic cells were forced to express combinations of three of these genes, they acquired the ability to form bone metastases efficiently (*not shown*), pointing to the causal role of these genes in forming these metastases. Metastases were visualized through the presence of a luciferase gene in the tumor cells, which causes cells to release a bioluminescent signal. (From Y. Kang et al., *Cancer Cell* 3:537–549, 2003.)

Orgánově specifické bariéry



TGF β Primes Breast Tumors for Lung Metastasis Seeding through Angiopoietin-like 4

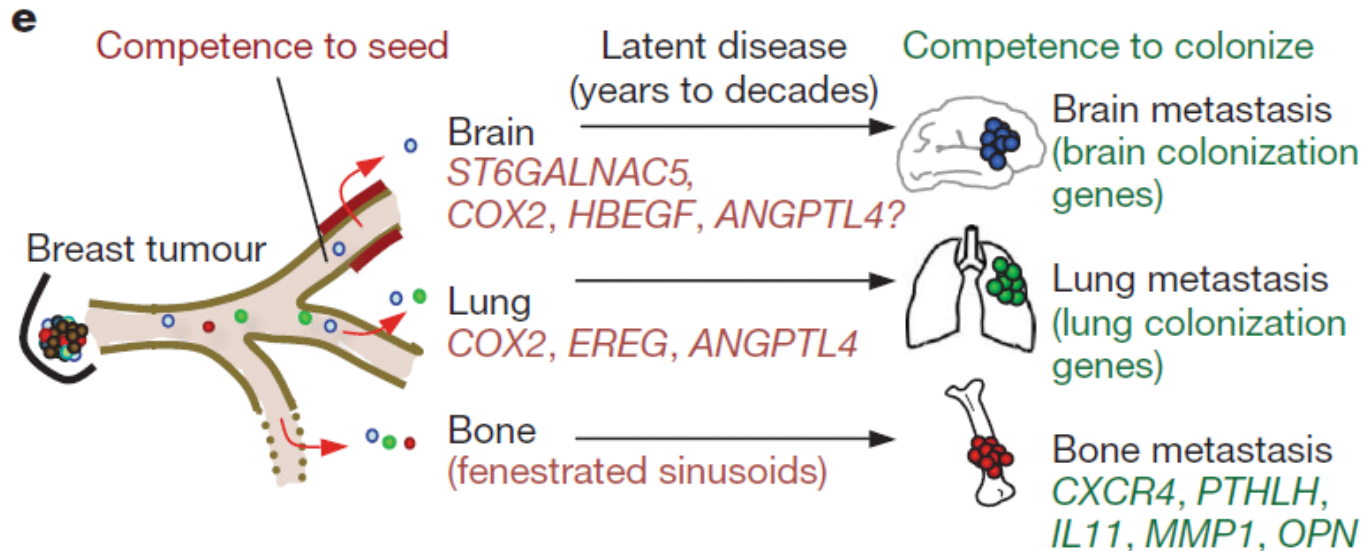
David Padua,¹ Xiang H.-F. Zhang,¹ Qionqing Wang,¹ Cristina Nadal,⁵ William L. Gerald,² Roger R. Gomis,⁴ and Joan Massagué^{1,3,*}



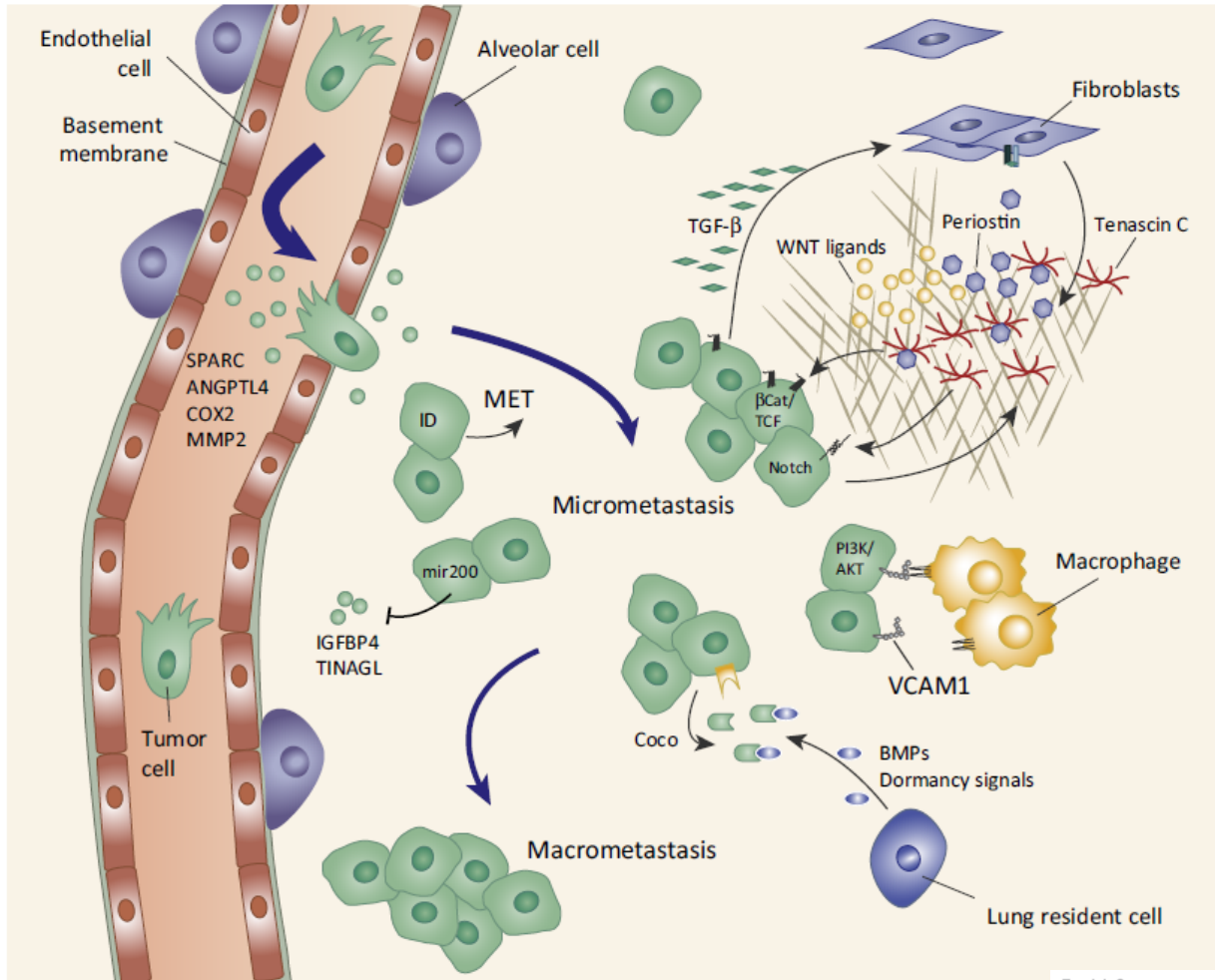
LETTERS

Genes that mediate breast cancer metastasis to the brain

Paula D. Bos¹, Xiang H.-F. Zhang¹, Cristina Nadal^{1†}, Weiping Shu¹, Roger R. Gomis^{1†}, Don X. Nguyen¹, Andy J. Minn², Marc J. van de Vijver³, William L. Gerald⁴, John A. Foekens⁵ & Joan Massagué^{1,6}



Metastatická kolonizace plic

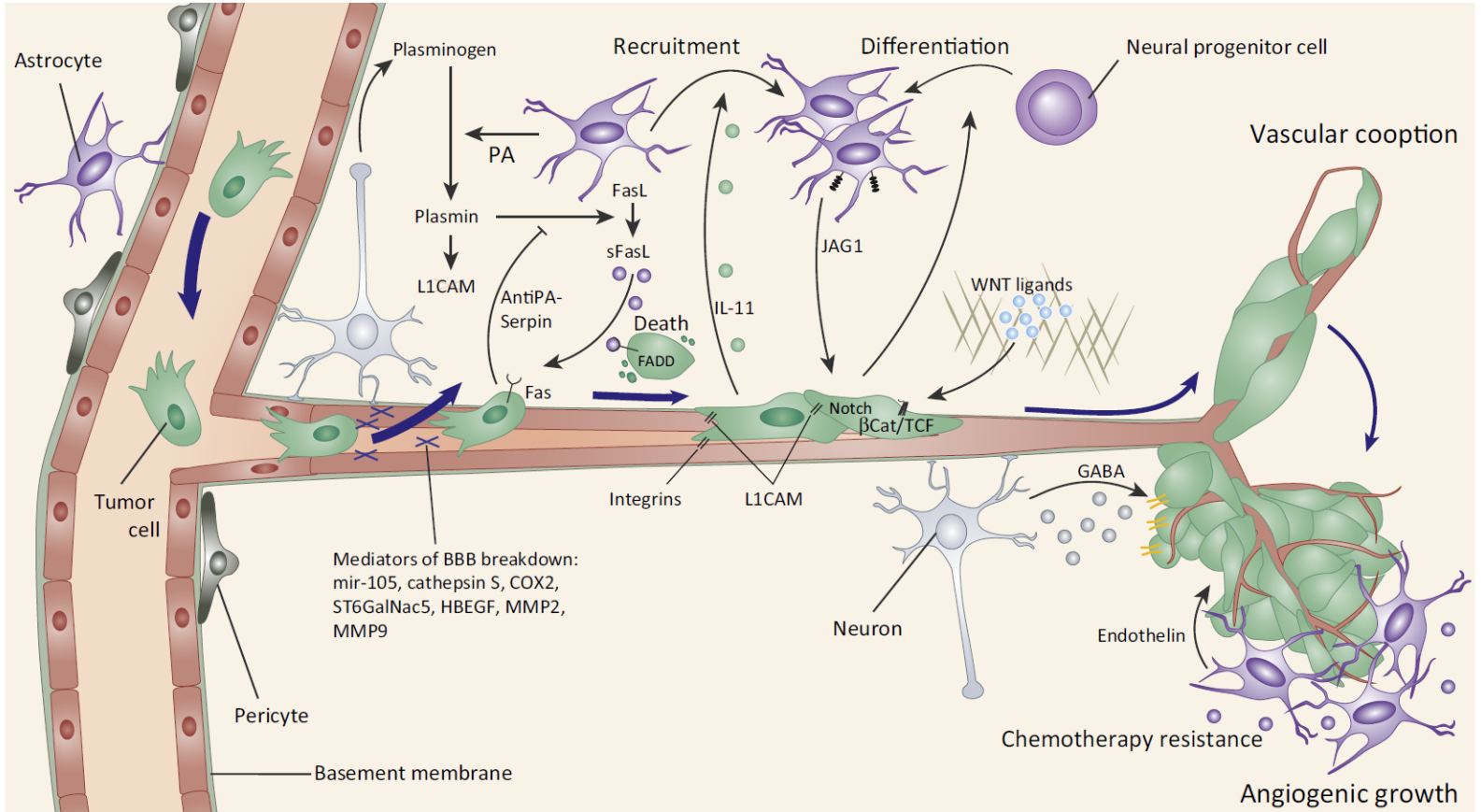


Trends in Cancer

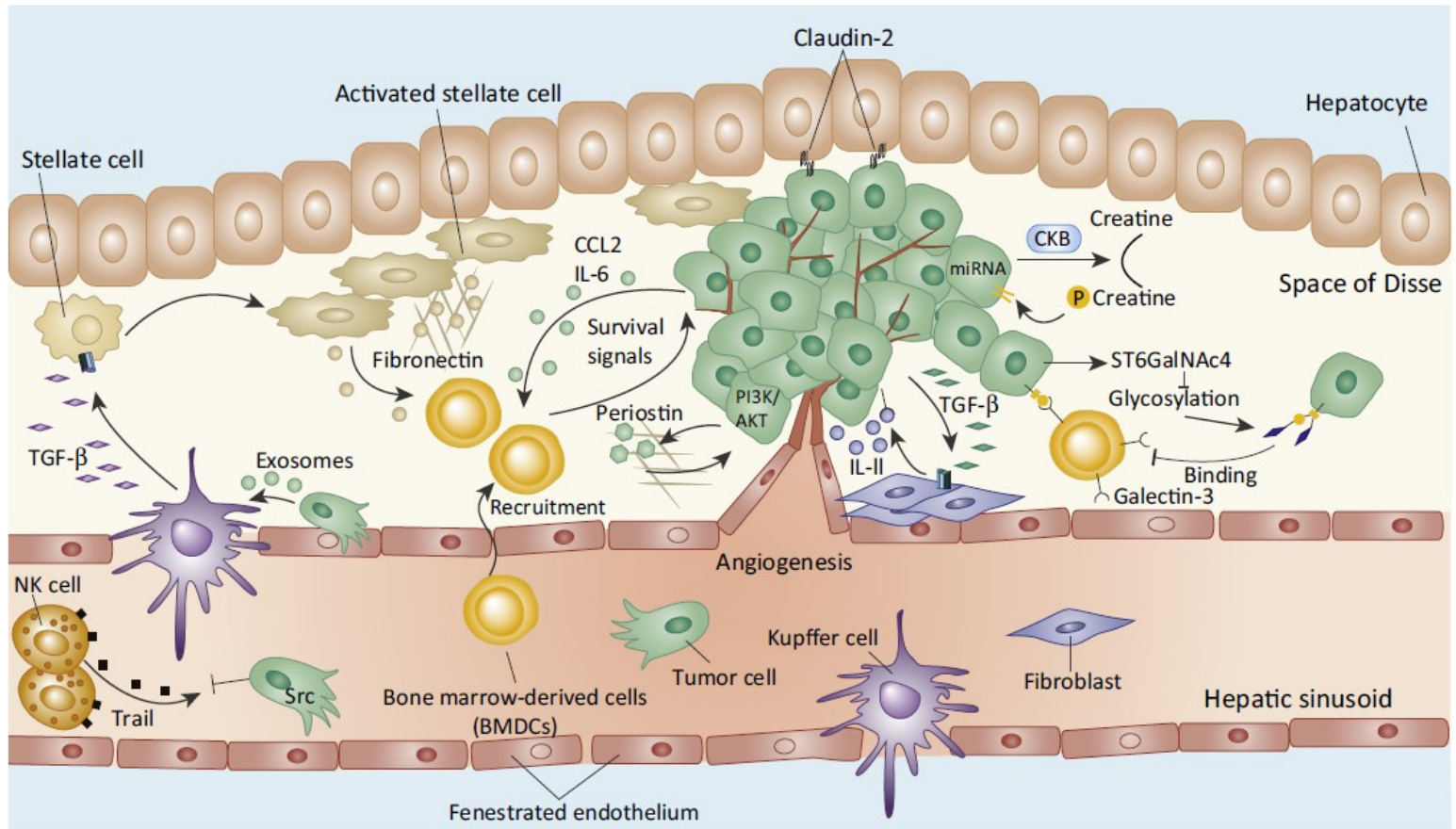
CellPress

Review
Surviving at a Distance:
Organ-Specific Metastasis
Anna C. Obenauf¹ and Joan Massagué^{1,*}

Metastatická kolonizace mozku



Metastatická kolonizace jater



Osteotropní metastáze

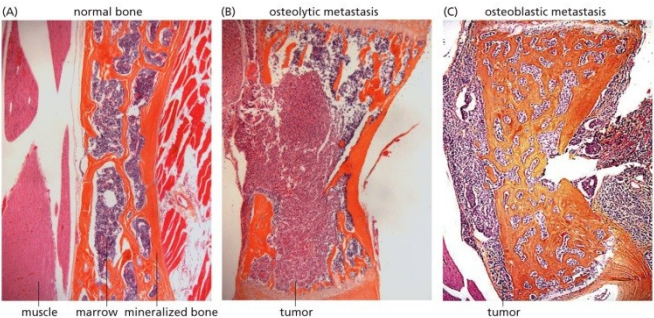
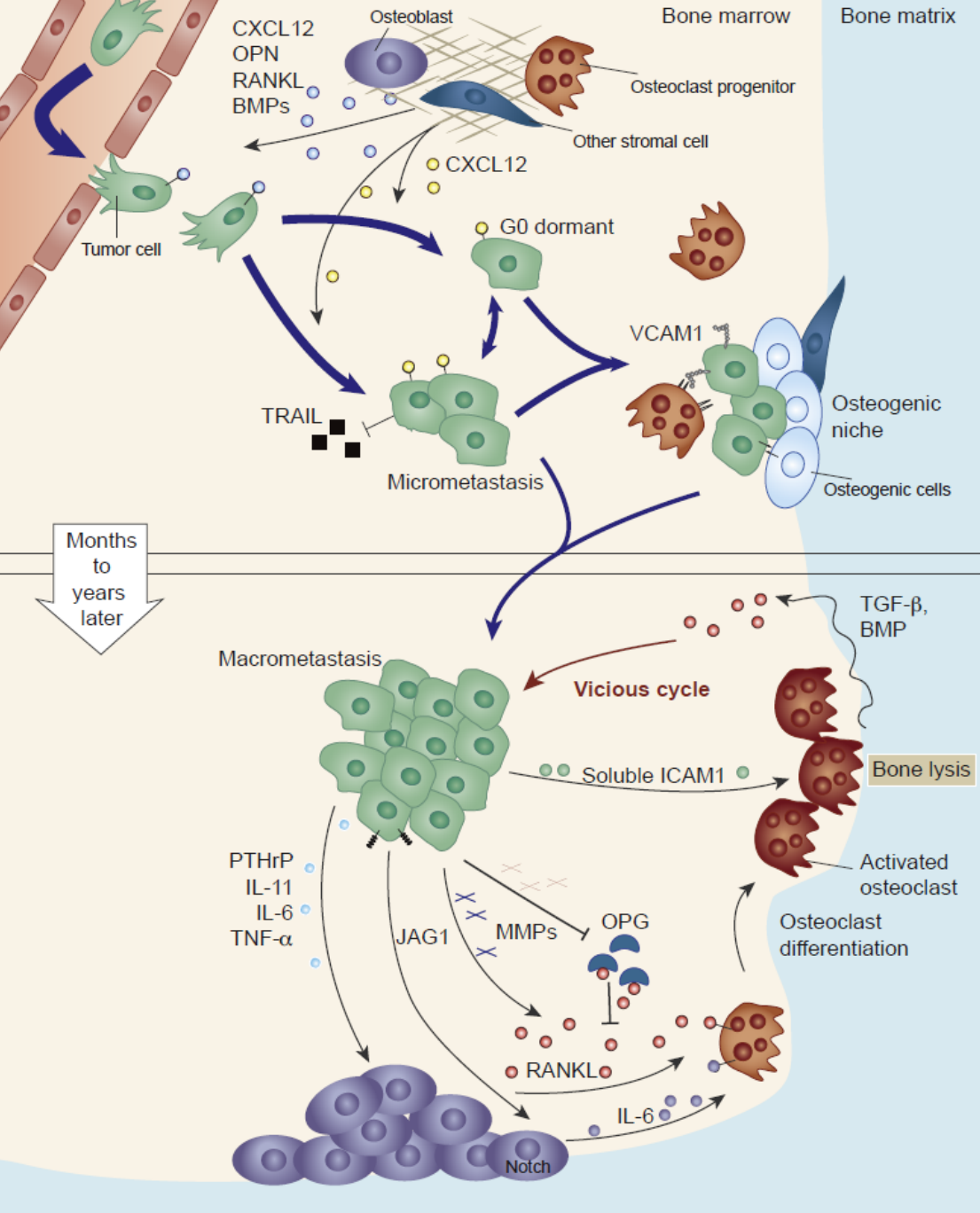


Figure 14.47abc The Biology of Cancer (© Garland Science 2014)

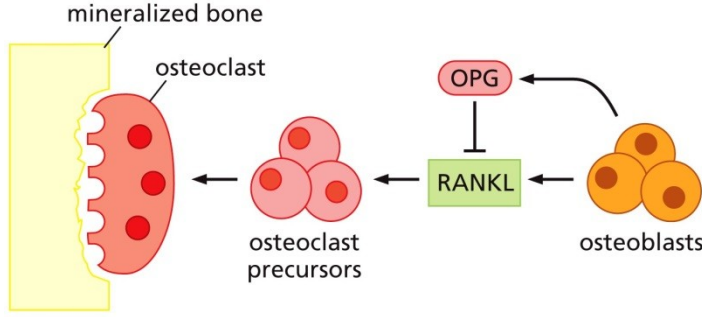


Figure 14.48a The Biology of Cancer (© Garland Science 2014)

Osteotropní metastáze

- ▶ Parathyroid hormone-related peptide (PTHrP)
- ▶ Behém laktace produkován normálními MECs - mammary epithelial cells -> mobilizace vápníku
- ▶ Nádorové buňky - adaptují tento mechanismus - osteolýza kostí vede k uvolnění řady růsových faktorů stimulujících nádorové buňky

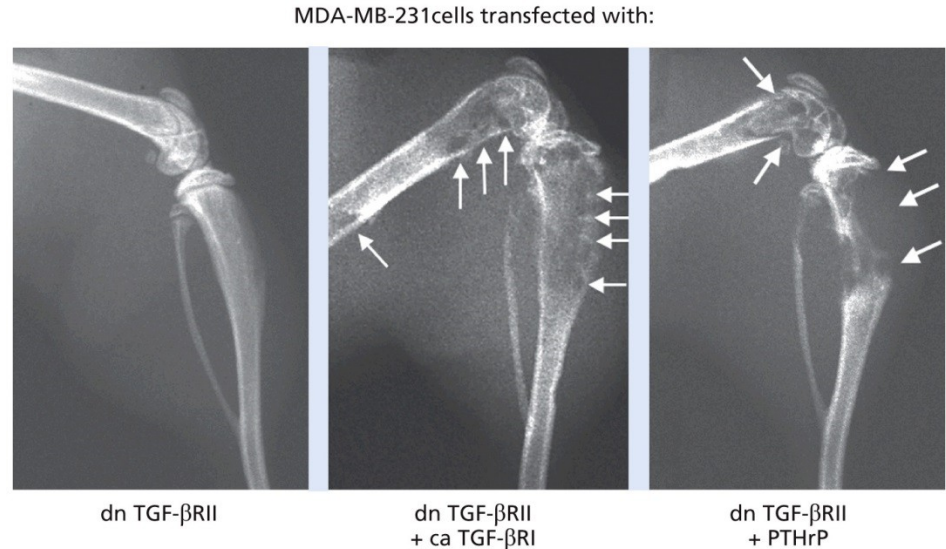


Figure 14.49 The Biology of Cancer (© Garland Science 2014)

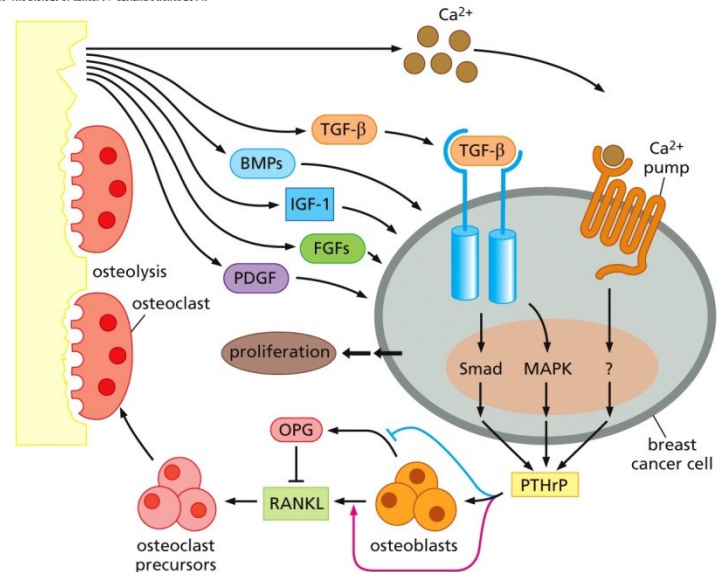
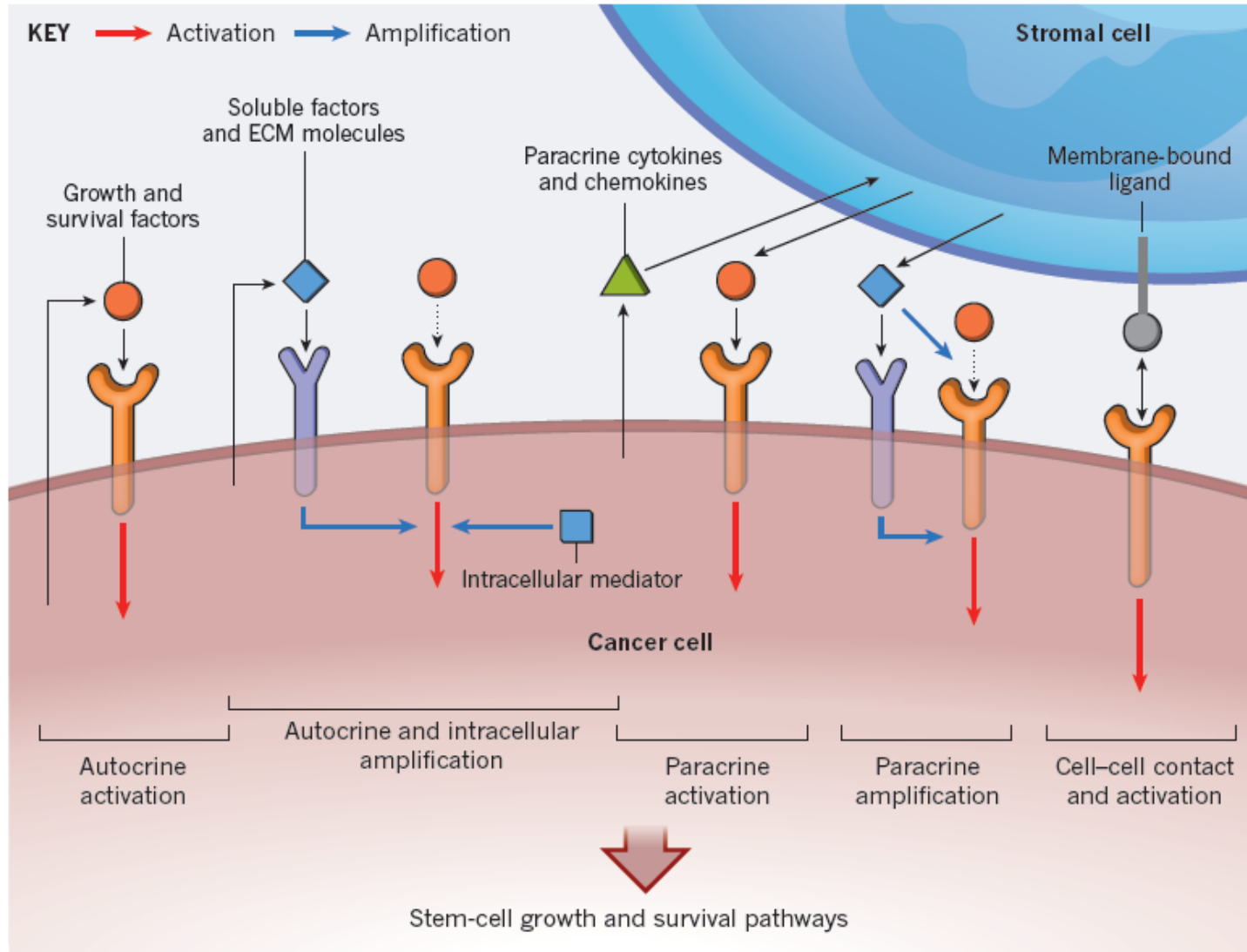
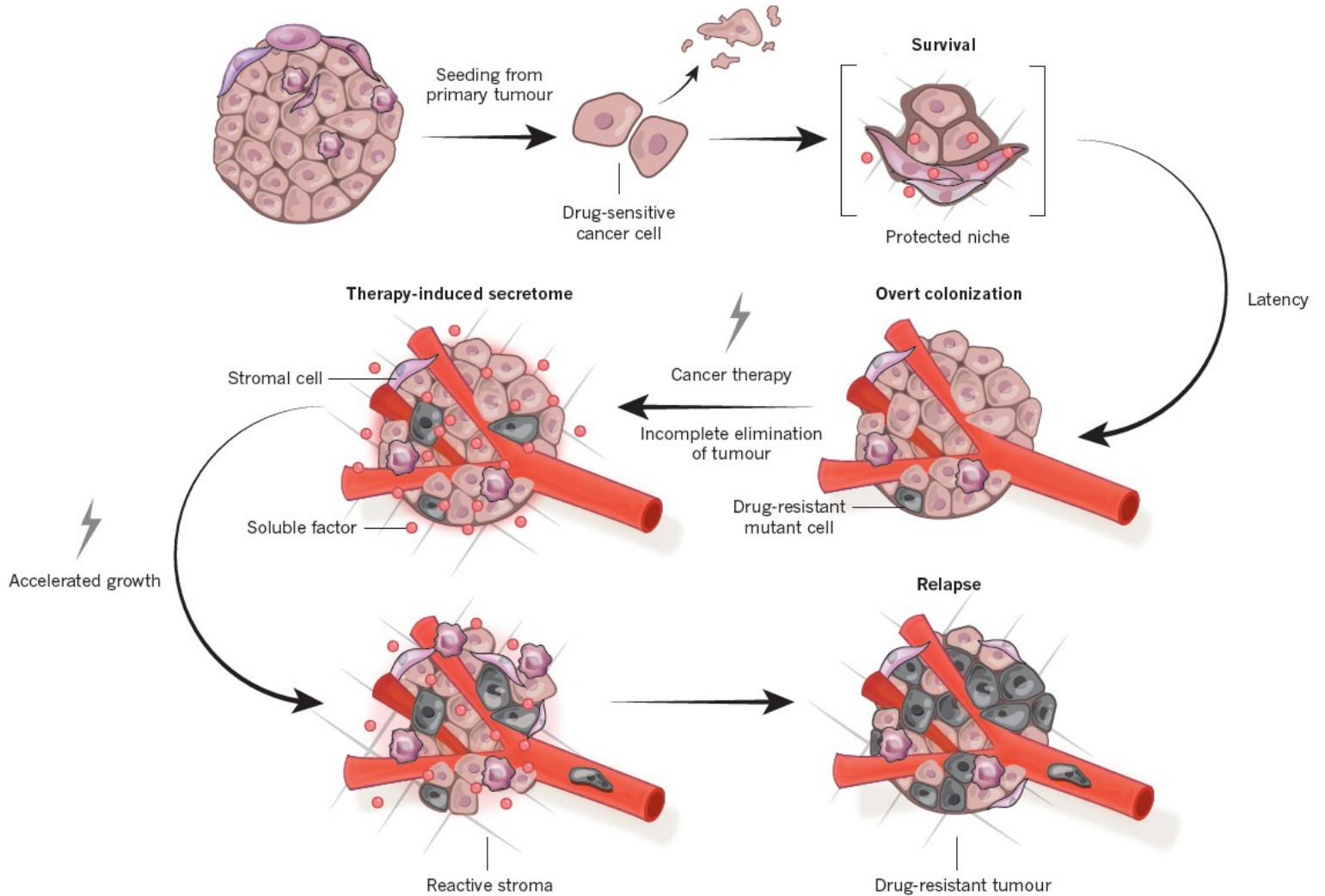


Figure 14.48b The Biology of Cancer (© Garland Science 2014)

Aktivace růstových signálů

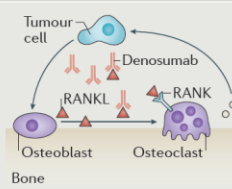
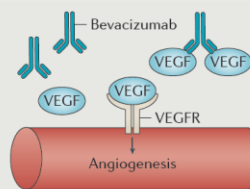
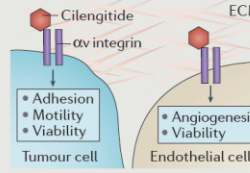
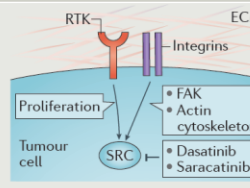


Metastáze před a po terapii



Terapie cílena na metastázování

Table 1 | Preclinical and clinical history of four metastasis-directed drug development efforts

Description	Pathway	Preclinical validation	Pivotal trials and end points	Outcomes
<p>Denosumab</p> <p>Monoclonal antibody to RANKL</p> 	<p>RANKL activates osteoclasts and promotes bone destruction; denosumab reduced bone resorption in mice expressing human RANKL²⁹</p>	<p>SREs* in metastatic setting; adjuvant trials used time to first bone metastasis or fracture³⁰⁻³³</p>	<p>FDA approved for prevention of SREs in solid tumours; approved as adjuvant therapy in prostate cancer</p>	
<p>Bevacizumab</p> <p>Monoclonal antibody to VEGF</p> 	<ul style="list-style-type: none"> • Bevacizumab inhibited corneal angiogenesis and lymphangiogenesis²⁴⁴ • In multiple cancer xenograft models, bevacizumab reduced primary tumour growth rates and, in some studies, enhanced survival. Reduced angiogenesis and vessel normalization was observed²⁴⁵ • Prevention or, less frequently, abrogation of metastasis^{246,247} 	<ul style="list-style-type: none"> • Recurrent ovarian cancer, PFS^{35,36} • Metastatic colorectal cancer, OS^{260,261} • Metastatic or resistant HER2⁺ breast cancer, PFS³⁸ • Metastatic renal cancer, PFS²⁶² • Glioblastoma, OS, PFS²⁶³ • Advanced lung cancer, OS³⁷ • Adjuvant therapy in triple-negative breast cancer, DFS⁴¹ 	<ul style="list-style-type: none"> • FDA approved for resistant ovarian, cervical and colorectal cancers, glioblastoma, also advanced or metastatic lung, colorectal and renal cancers • Revoked for metastatic breast cancer • Negative trials for first-line treatment of glioblastoma 	
<p>Cilengitide</p> <p>$\alpha v \beta 3$ and $\alpha v \beta 5$ integrin peptide inhibitor</p> 	<ul style="list-style-type: none"> • Stabilization of glioma growth and angiogenesis. Synergistic inhibition of glioma with TMZ⁶¹⁻⁶⁴ • Synergy with therapeutics in melanoma primary tumour growth⁶³, synergy with radio-immunotherapy in breast cancer tumour growth²⁴⁸ • Inhibition of metastasis⁶² • Synergy with verapamil increased angiogenesis and reduced metastasis²⁴⁹ 	<ul style="list-style-type: none"> • Phase III CENTRIC EORTC, with radiation therapy and TMZ, for glioma, OS. Newly diagnosed glioma, same combination, recurrence⁶⁵ • Phase II trials in melanoma and lung and prostate cancers, PFS⁶⁶⁻⁶⁸ 	<p>All advanced trials were negative</p>	
<p>Dasatinib and saracatinib</p> <p>SRC kinase and BCR-ABL kinase inhibitor</p> 	<ul style="list-style-type: none"> • Inhibition of CML models²⁵⁰ • Inhibition of primary tumour growth in multiple model systems, as monotherapy or in combination²⁵¹⁻²⁵³ • Prevention of metastasis in multiple cancer model systems²⁵⁴⁻²⁵⁸, but not osteosarcoma²⁵⁹ • Inhibition of prostate cancer growing in bone and bone remodelling^{62,63} 	<ul style="list-style-type: none"> • Cytogenetic response end points for CML • Response for advanced solid tumours⁷¹⁻⁸⁰ • OS in Phase III prostate cancer⁸⁷ 	<ul style="list-style-type: none"> • FDA approved for CML and resistant ALL • Discontinued in advanced lung, ovarian, colorectal and breast cancers • Negative in prostate cancer Phase III trial with docetaxel • Multiple adjuvant trials terminated 	

ALL, acute lymphoblastic leukaemia; CML, chronic myelogenous leukaemia; DFS, disease-free survival; ECM, extracellular matrix; FAK, focal adhesion kinase; FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival; RANK, receptor activator of NF- κ B; RANKL, RANK ligand; RTK, receptor tyrosine kinase; TMZ, temozolomide; VEGF, vascular endothelial growth factor. *Skeletal-related event (SRE) captures the deleterious effects of new lesions and progression of existing lesions to cause patient morbidity.

Shrnutí

- 90% úmrtí na nádorová onemocnění souvisí s metastázováním
- Invazivní kaskáda zahrnuje: lokální invazi, intravazaci, transport, extravazaci, formování mikrometastáz a kolonizaci
- Nízká efektivita celé kaskády, nejméně efektivní je kolonizace
- EMT, řízena pleiotropními TF v různých fázích embryogeneze, adaptována během tumorigeneze
- Motilita je řízena malými GTPasami, Rho rodina
- Proteázy (MMP) umožňují invazi nádorových buněk, degradace ECM
- Tkáňový tropismus nádorových buněk lze v některých případech vysvětlit organizací oběhového systému, často prozatím neobjasněn

Stále nezodpovězené otázky ...

- Kde vznikají znaky orgánově specifické kolonizace – primární nádor vs. distantní orgán?
- Jaký je původ těchto metastatických znaků – genetický, epigenetický?
- Využívají metastatické buňky různé niky pro iniciační přežití, stav dormance a agresivní růst?
- Co umožňuje metastatickým buňkám vstup do dormance a zároveň reaktivaci jejich proliferace?
- Jaké signály jsou zodpovědné za exit z dormance a aktivaci proliferace?
- Jak získají nádorové buňky vlastnosti orgánově specifické kolonizace během dormance?
- Jsou orgány kde dochází k akumulaci dormantních buněk zároveň orgány kde se rozvíjí metastazující onemocnění?
- Jsou mechanismy podporující přežívání buněk během extravazace společné s mechanismy podporující přežívání buněk během protinádorové léčby?
- Jaké jsou základy známé rezistence metastatických buněk v mikroprostředí vzdálených orgánů?
- Je možné prokázat efektivní strategii prevence vzniku metastáz tak, že specificky zacílíme mechanismy podporující přežití dormantních buněk?

ZÁNĚT, NÁDOROVÉ MIKROPROSTŘEDÍ A NEOANGIOGENEZE

Karel Souček

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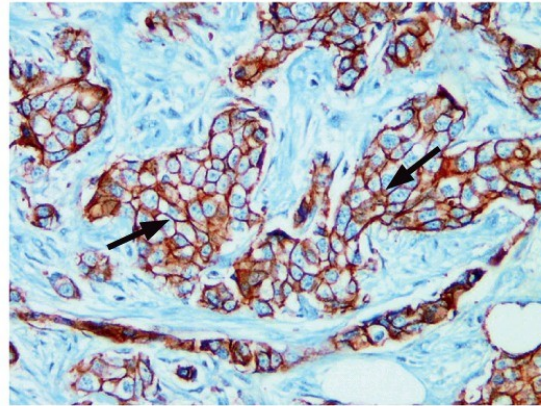
Typické znaky nádorové buňky

- podpůrné proliferační signály
- deregulace supresorů růstu/prolifera
- odolnost k buněčné smrti
- neomezená replikace
- **neoangiogeneze**
- invaze a metastázování
- mutace a genomická nestabilita
- **záněť**
- přestavba energetického metabolismu
- únik před zničením imunitním systé

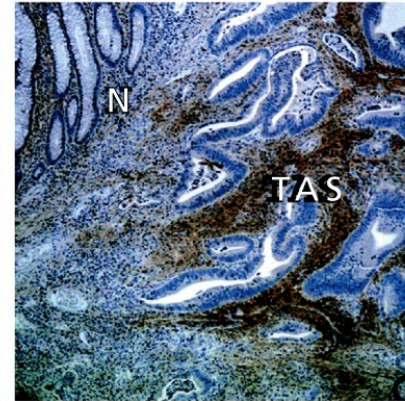


Stromální komponenta karcinomu

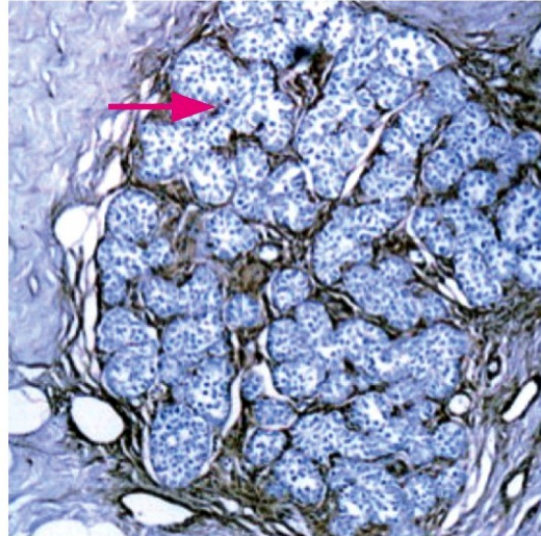
(A) duktální karcinom prsu



(B) karcinom střeva



(C)



(D)

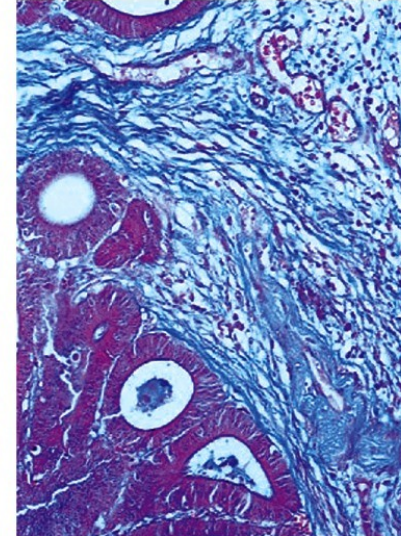


Figure 13.1 The Biology of Cancer (© Garland Science 2014)

lobulární karcinom prsu adenokarcinom žaludku

Variabilita poměru neoplastických buněk a stromatu

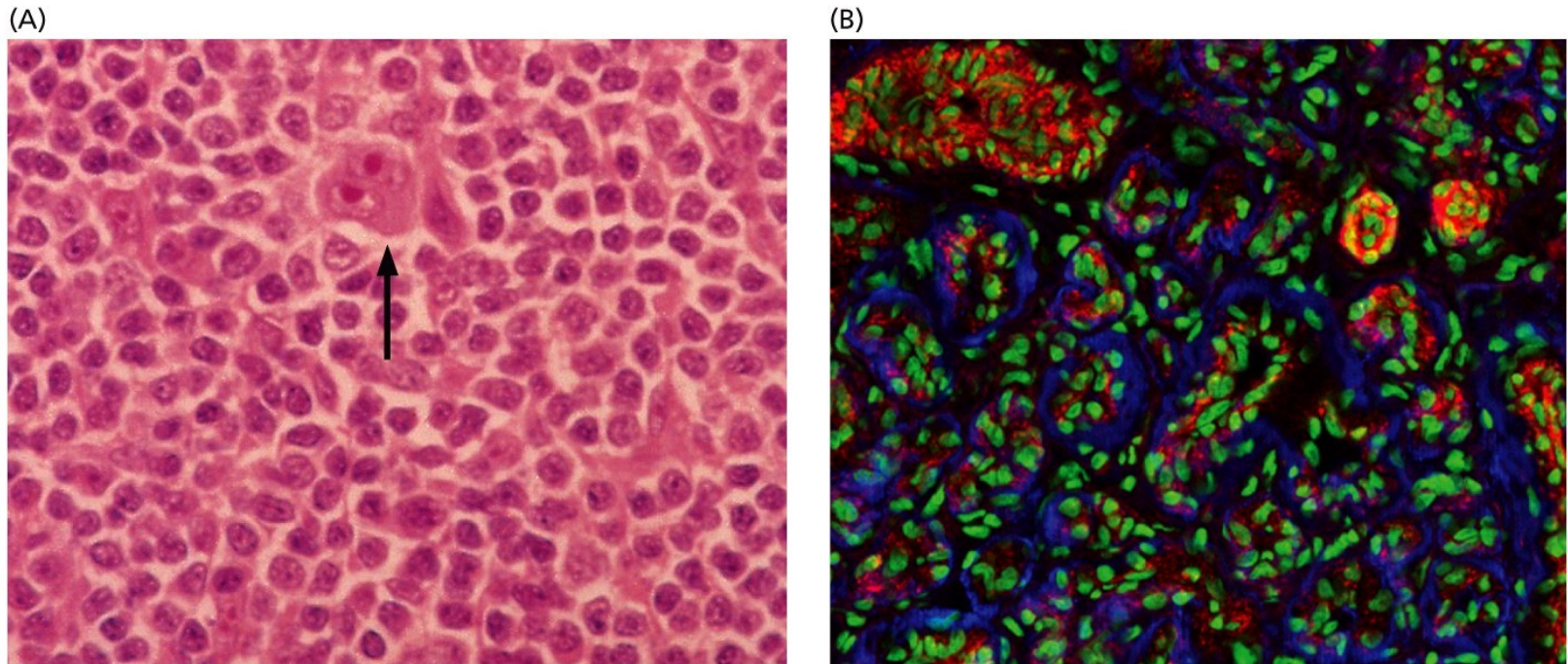


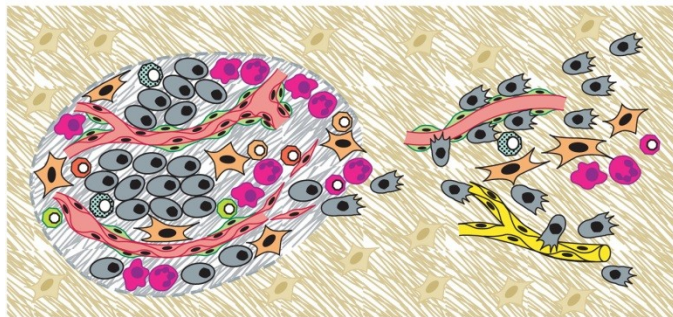
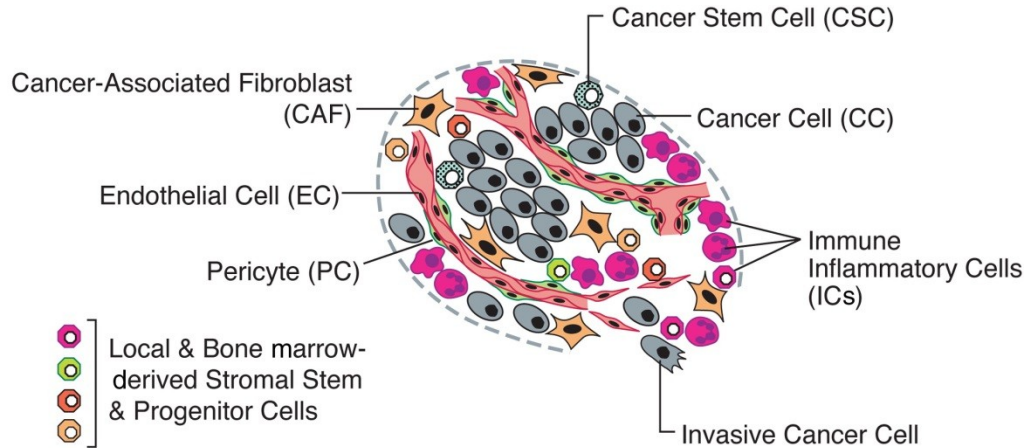
Figure 13.2 The Biology of Cancer (© Garland Science 2014)

Příklad:

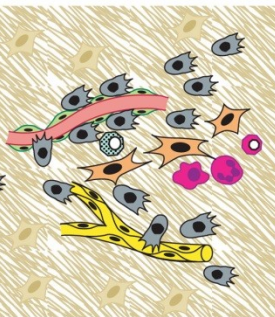
- Hodgkinův lymfom – 99% buněk normální lymfocyty obklopující Reed-Sternebergovu buňku
- Hemangiom – neoplastické endoteliální buňky tvoří většinu masy nádoru

Základní principy a znaky karcinogeneze

➤ Rakovina není onemocnění jedné buňky



Core of Primary Tumor microenvironment



Invasive Tumor microenvironment



Metastatic Tumor microenvironment

Heterotypická signalizace

- Výměna mitogenních signálů mezi různými typy buněk v normální tkáni
- Řada těchto interakcí přetrvává i v neoplastických tkáních
 - Důkaz – autologní transplantace nádorů kůže (1961)
 - Uplná nezávislost - ascit

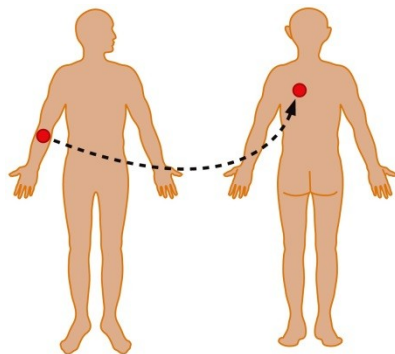


Figure 13.5a The Biology of Cancer (© Garland Science 2014)

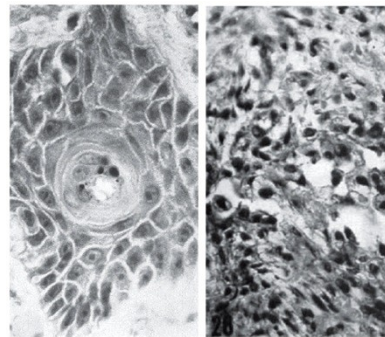


Figure 13.5b The Biology of Cancer (© Garland Science 2014)

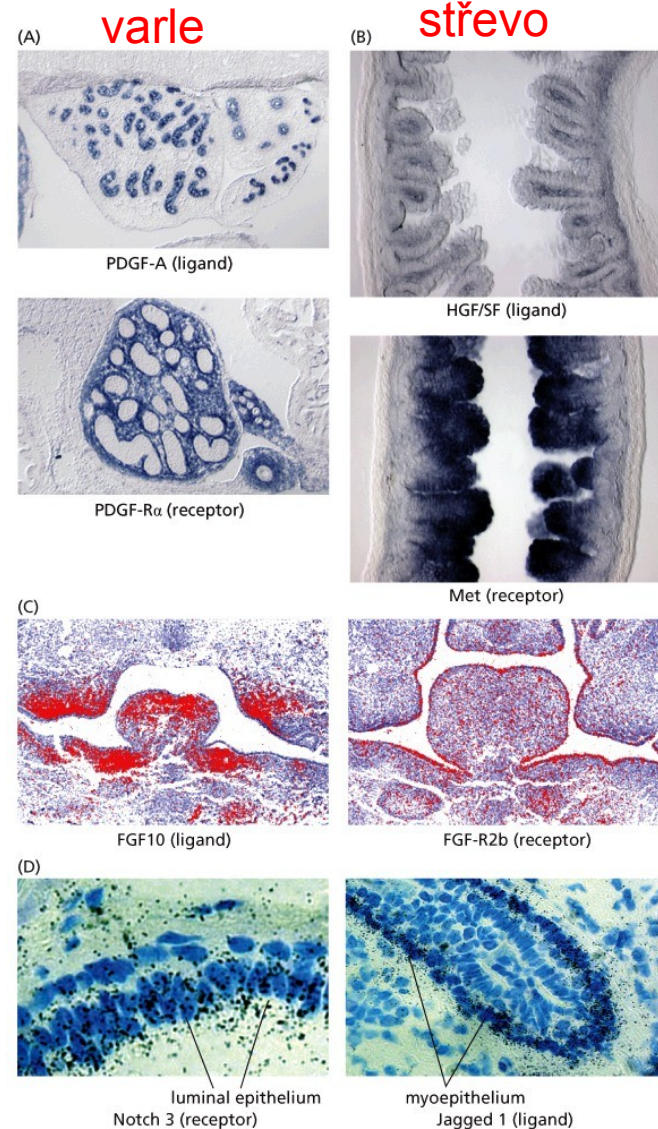


Figure 13.4 The Biology of Cancer (© Garland Science 2014)

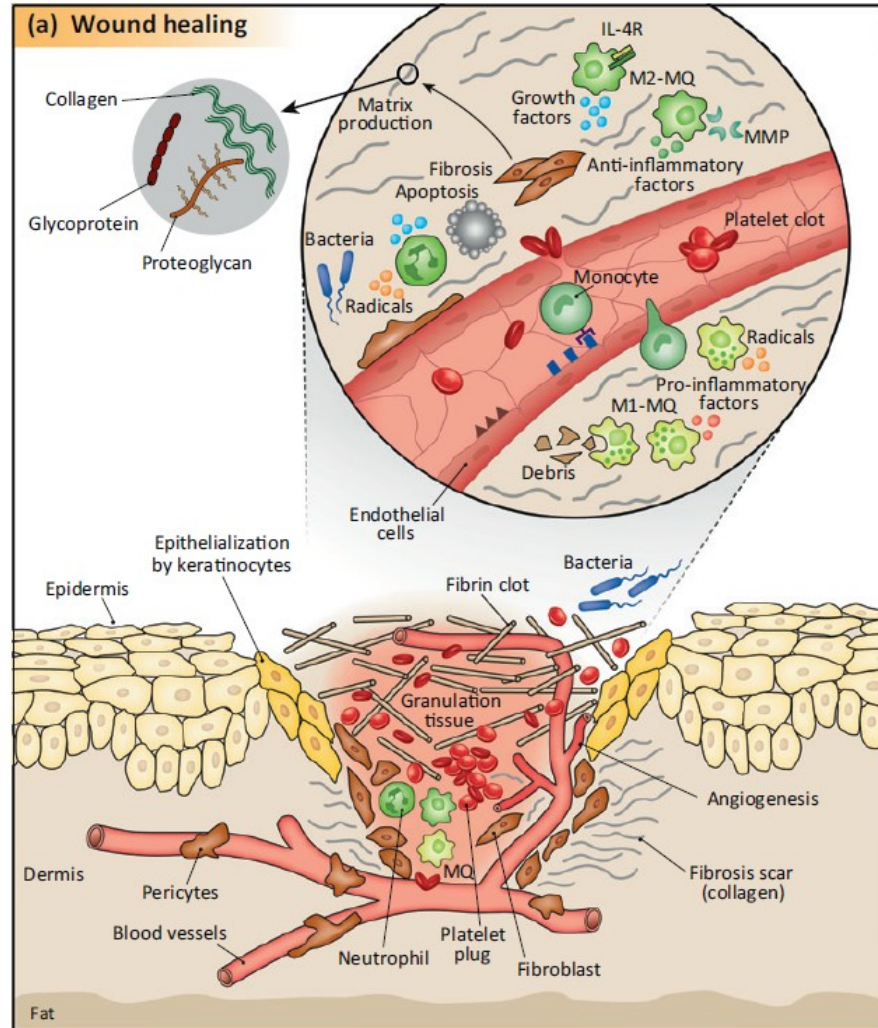
Ústní dutina

Prsní žláza

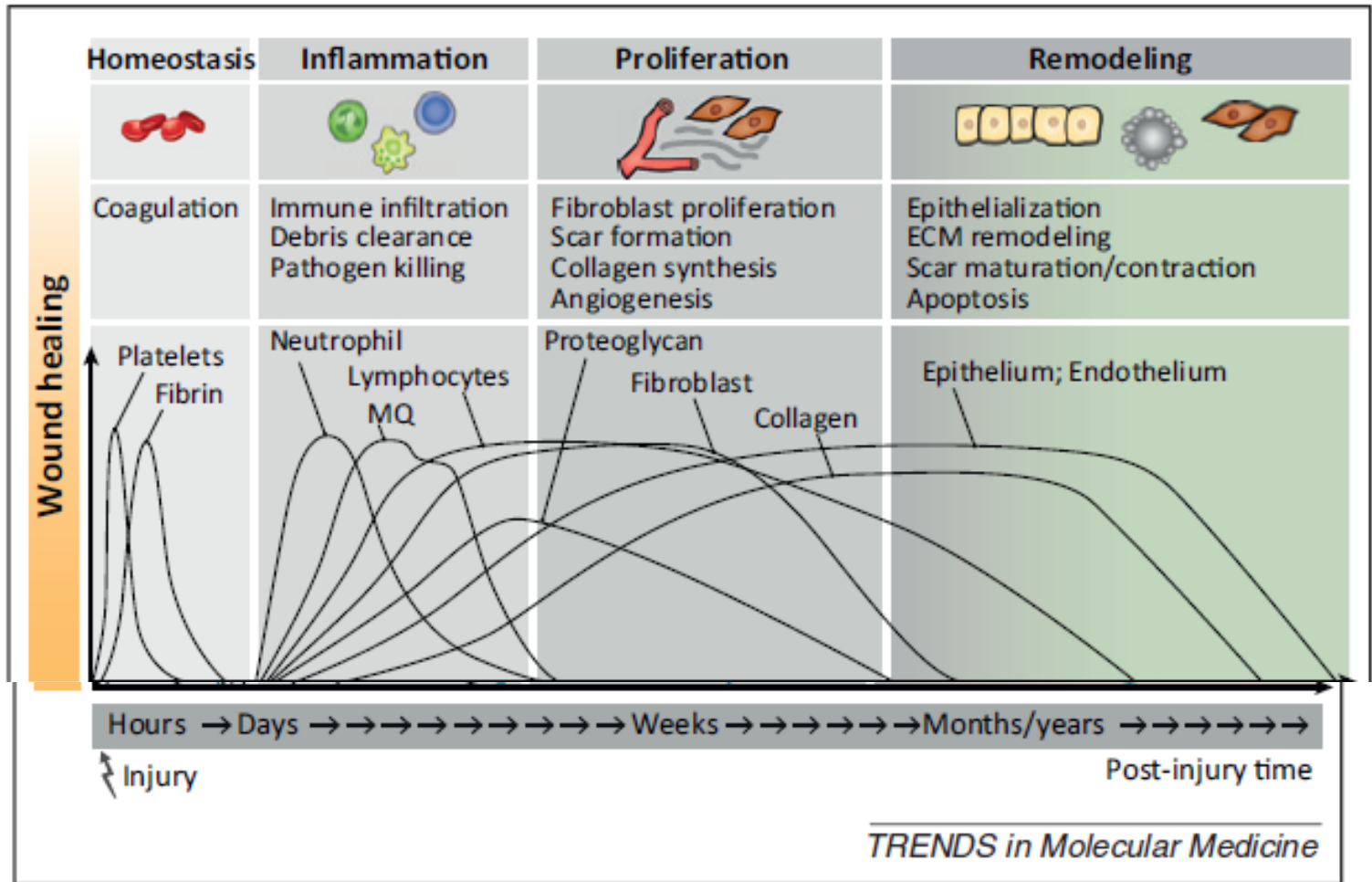
Hojení rány

- ▶ Zajištění homeostázy (sekundy – minuty)
 - ▶ Koagulace
 - ▶ Provizorní ECM
- ▶ Zánět (hodiny – dny)
 - ▶ Infiltrace leukocytů
 - ▶ Trofické faktory stimulují migraci a proliferaci dalších buněk
- ▶ Proliferace (dny – týdny)
 - ▶ Vstup fibroblastů a endoteliálních buněk do rány
 - ▶ Reorganizace ECM
- ▶ Remodelace a maturace (týdny – měsíce – roky)
 - ▶ Reorganizace kolegenové ECM
 - ▶ Zakrytí rány epitelem
 - ▶ Migrace keratinocytů, ustanovení nové bazální membrány

Hojení rány



Hojení rány



Nádor – nehojící se rána

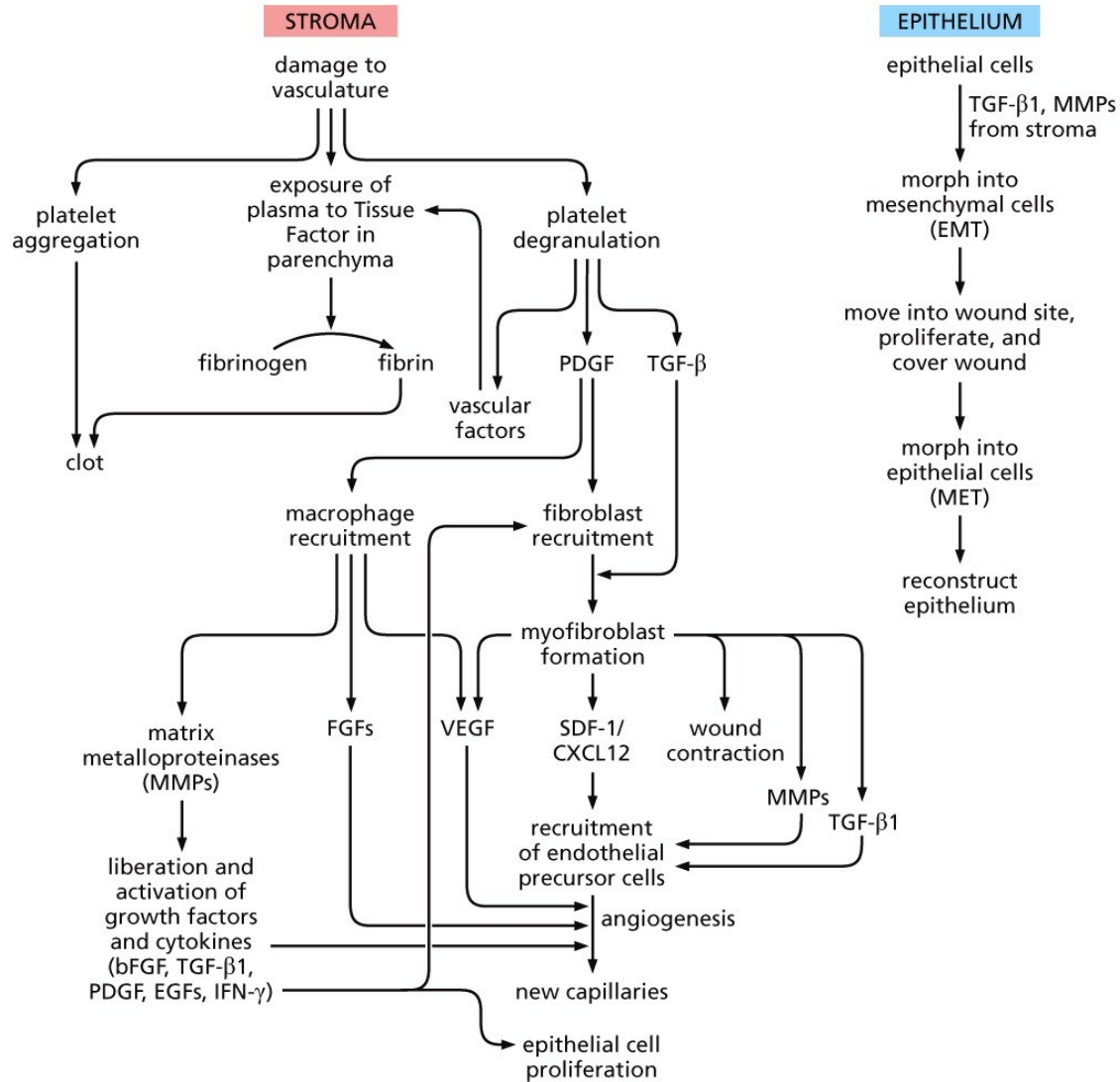


Figure 13.11 The Biology of Cancer (© Garland Science 2014)

Remodelace epiteliální tkáně během hojení, EMT, MET

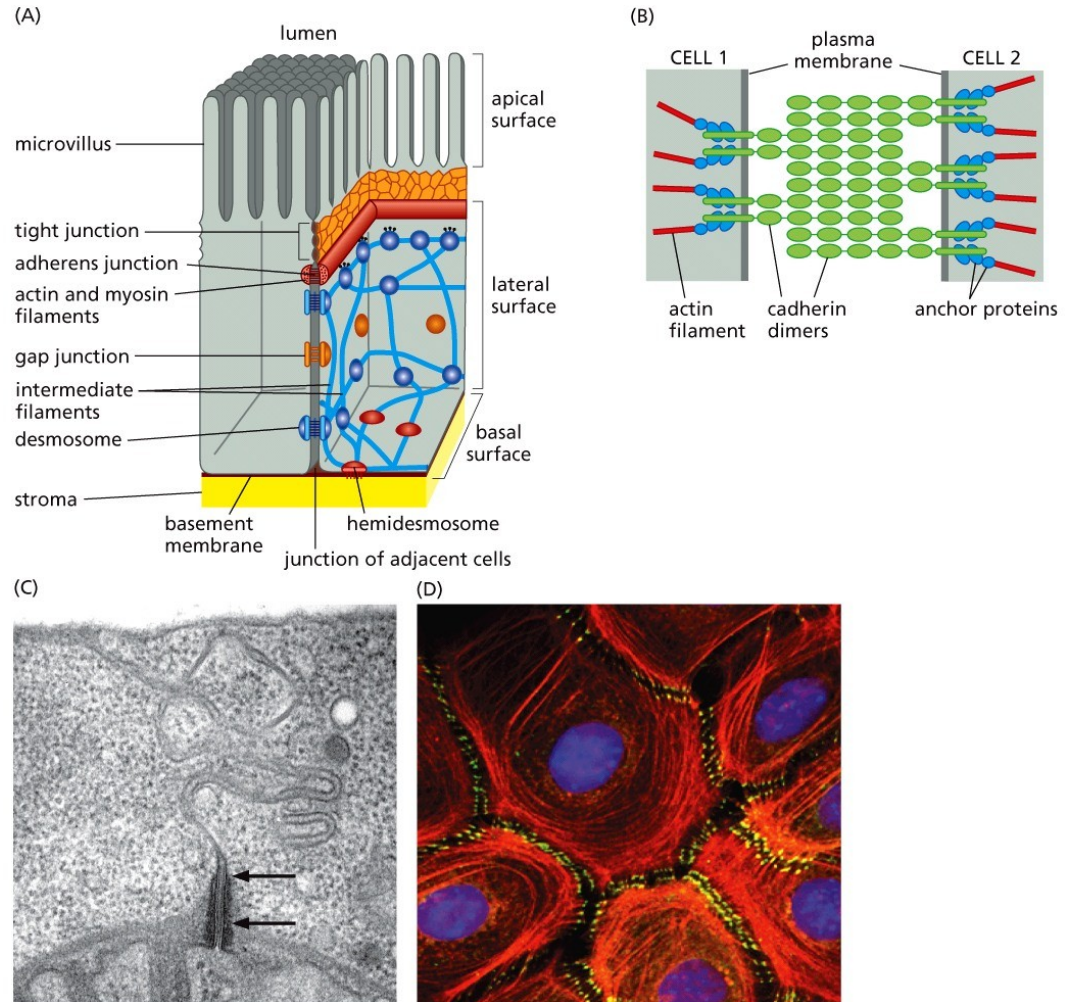


Figure 13.12 The Biology of Cancer (© Garland Science 2014)

Remodelace epiteliální tkáně během hojení, EMT, MET

- Exprese **vimentinu** (mes.) během hojení u normálních epiteliálních buněk
- Příklad plasticity buněk – spontánní indukce **α -SMA** (mes.) z ztráta exprese **cytokeratinu** (ep.)
- Induce EMT působením MMP-3

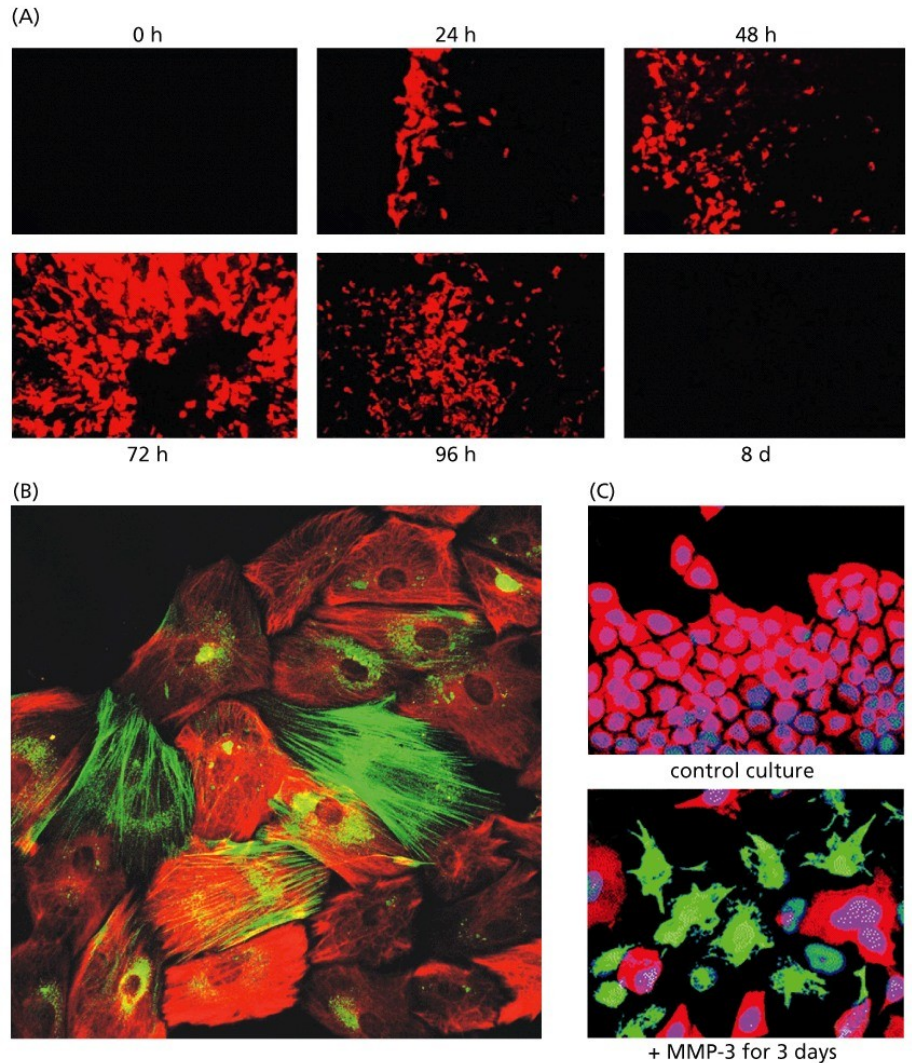
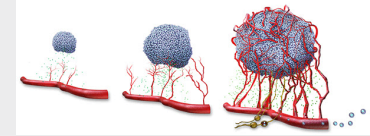


Figure 13.13 The Biology of Cancer (© Garland Science 2014)

Neoangiogeneze



- ▶ nádor, stejně jako zdravá tkáň, vyžaduje přísun živin a kyslíku a odvod metabolitů a CO₂
- ▶ Nové endoteliální buňky vznikají v průběhu embryogeneze – dochází k vaskulogenezi – formování cév
- ▶ v dospělosti je tento proces utlumen, aktivován jen přechodně - hojení ran, ovulační cyklus
- ▶ Během nádorové progrese je trvale aktivní
 - ▶ VEGF-A (induktor) vs. TSP-1 (inhibitor)
- ▶ Exprese VEGF-A je indukována hypoxií a řadou onkogenů
- ▶ Pericyty a buňky derivované z kostní dřeně přispívají k nádorové neoangiogenezi
- ▶ Chronická aktivace neoangiogeneze v nádoru vede k tvorbě nenormálních cév
 - ▶ Neorganizovaně, složitě větvených
 - ▶ Zdeformované, zvětšené
 - ▶ Nestálý průtok krve
 - ▶ Krvácivost, netěsnost
 - ▶ Abnormální proliferace a apoptóza endoteliálních buněk

Makrofágy hrají důležitou úlohu v angiogenezi

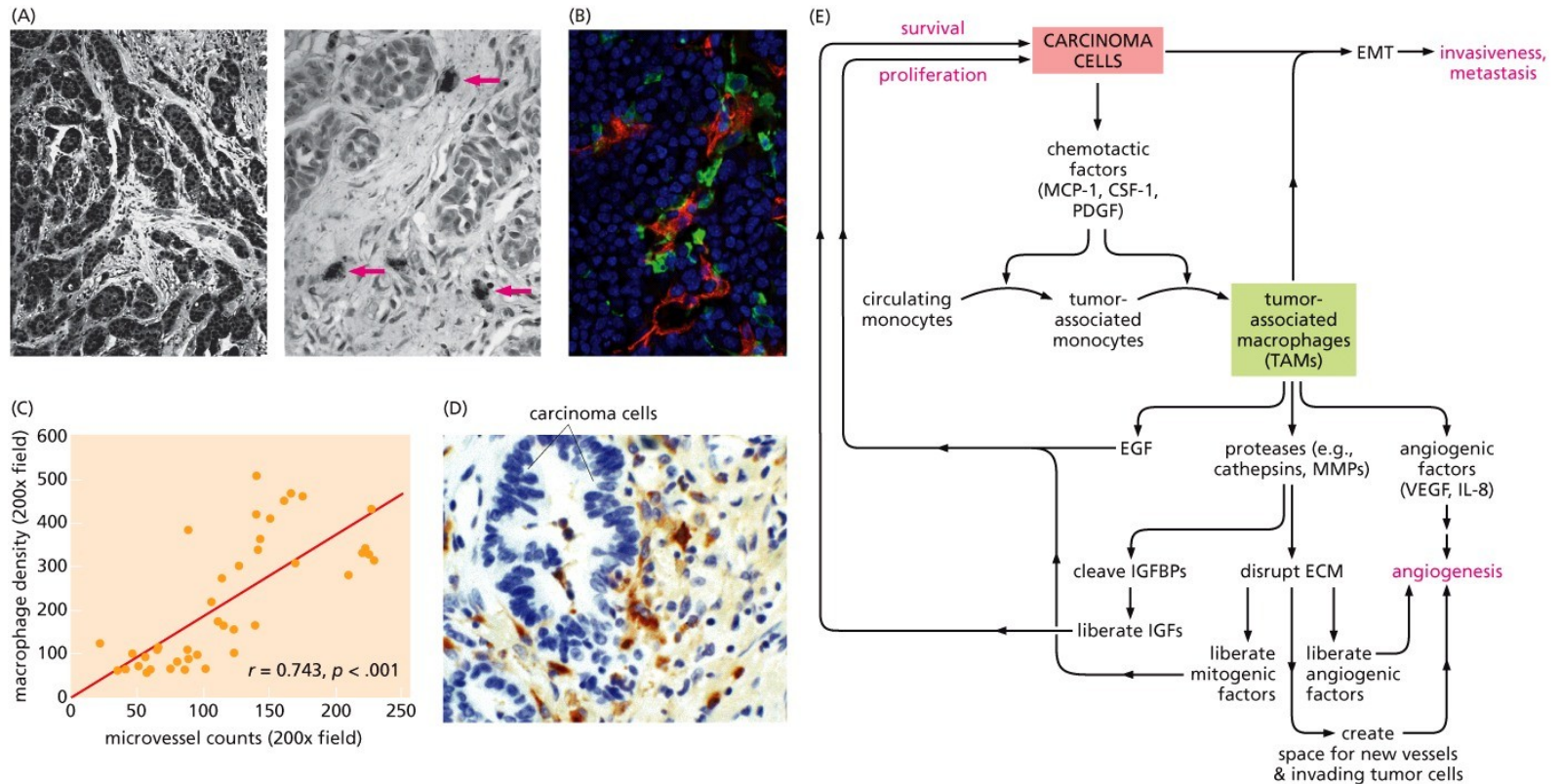


Figure 13.25 The Biology of Cancer (© Garland Science 2014)

- Makrofágy mohou produkovat VEGF, asociují s neovaskulogenezí, produkují MMP-9, produkují mitogenní faktory a reorganizují stroma

Hypoxie, neoangiogeneze

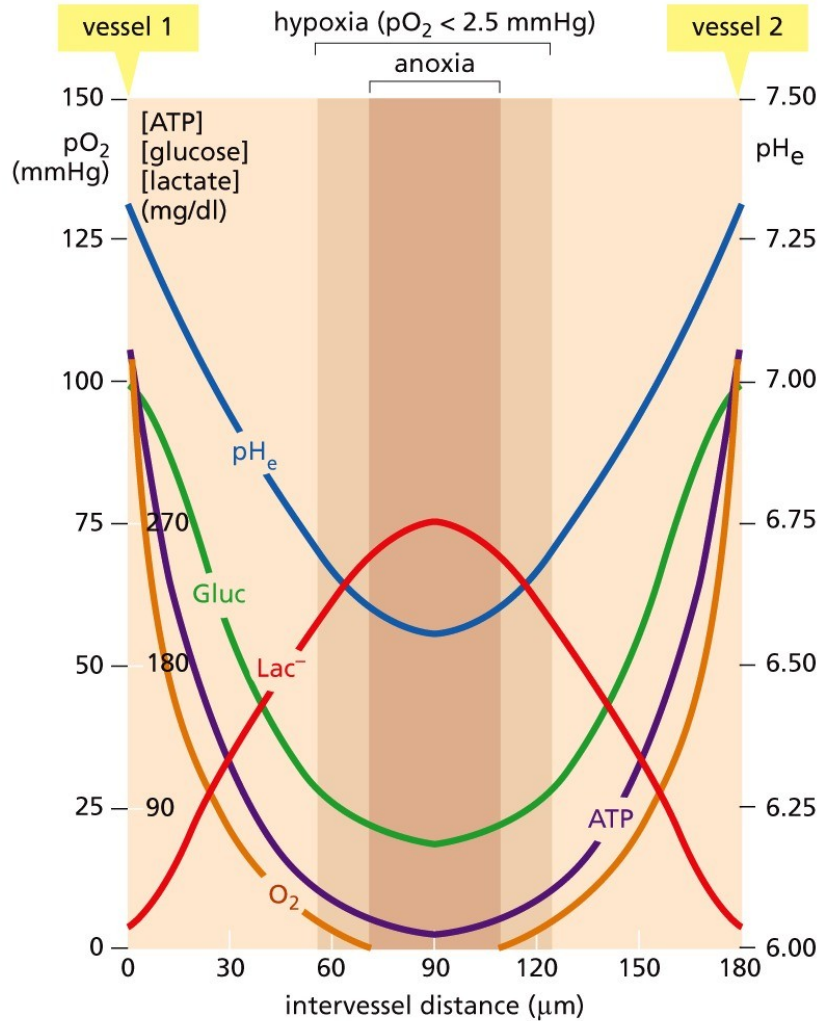
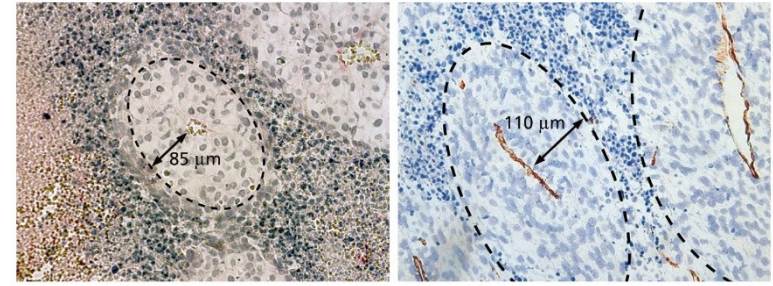


Figure 13.27d The Biology of Cancer (© Garland Science 2014)



human melanoma

rat prostate cancer

Figure 13.27b The Biology of Cancer (© Garland Science 2014)

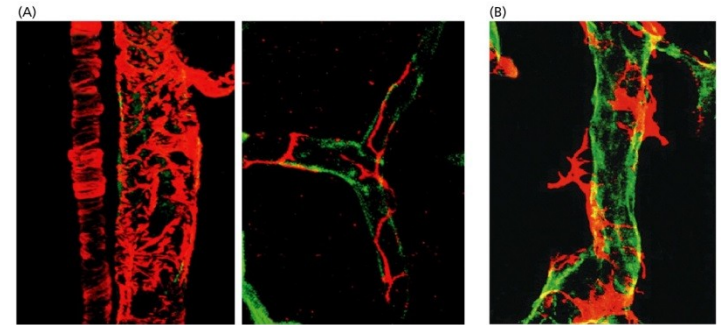
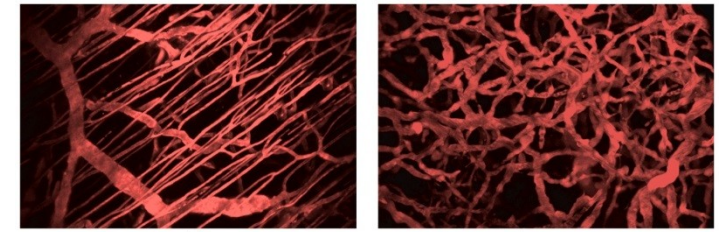


Figure 13.32 The Biology of Cancer (© Garland Science 2014)



normal tissue

tumor

Figure 13.33b The Biology of Cancer (© Garland Science 2014)

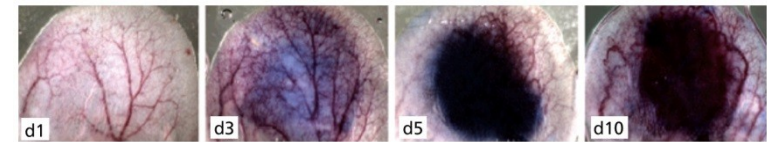


Figure 13.34c The Biology of Cancer (© Garland Science 2014)

Angiogeneze a klinická prognóza

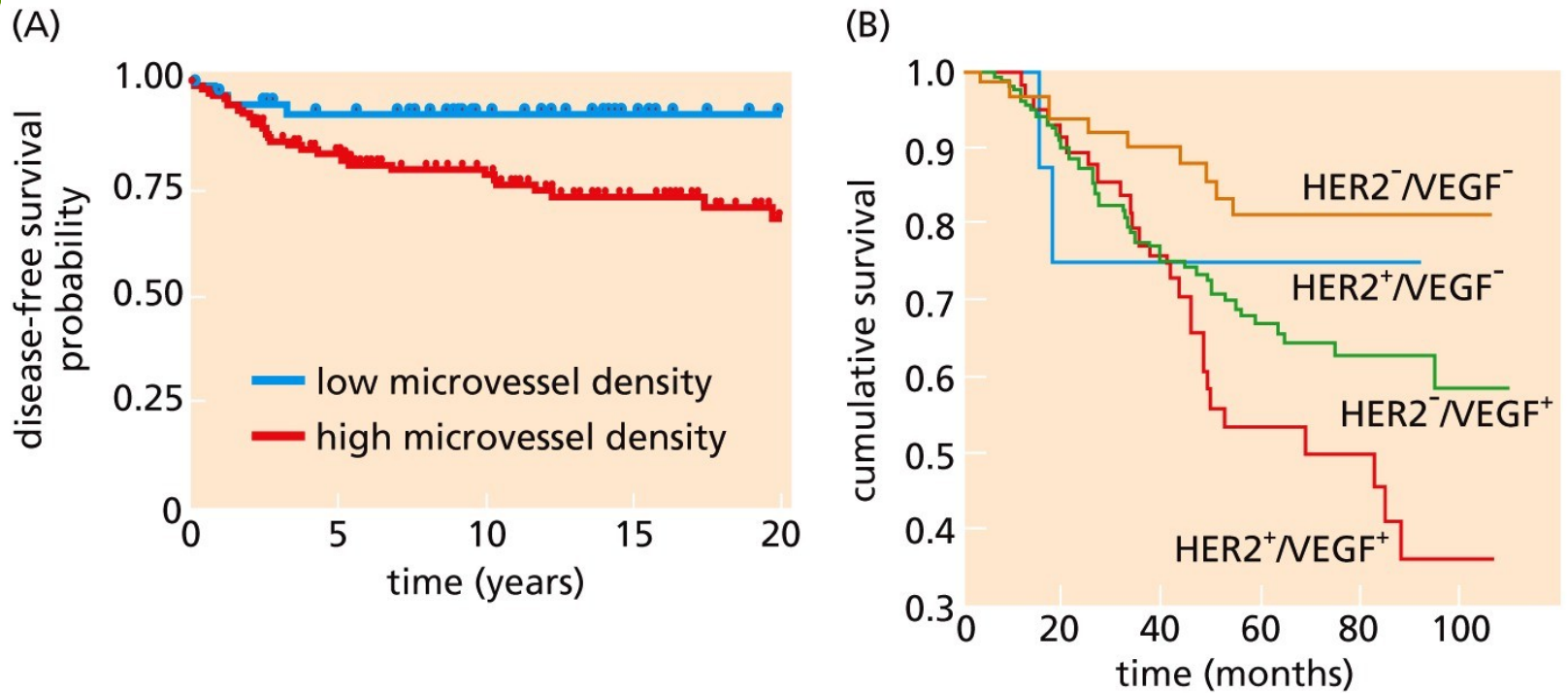
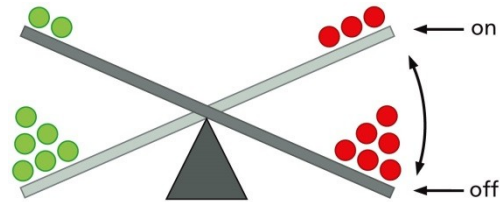


Figure 13.41 The Biology of Cancer (© Garland Science 2014)



- **activators**
 VEGF-A
 VEGF-B, -C
 FGF1 (aFGF)
 FGF2 (bFGF)
 other FGFs
 etc.
- **inhibitors**
 thrombospondin-1, -2
 interferon α/β
 angiostatin
 endostatin
 collagen IV fragments
 etc.

Angiogeneze jako cíl protinádorové léčby

Table 13.6 Summary of clinically approved anti-angiogenic drugs^a

Agent	Nature of agent	Approved indication	% of patients responding ^b	Improvement ^b in PFS (months)	Improvement ^b in OS (months)	
Bevacizumab (Avastin) ^c	anti-VEGF-A MoAb	metastatic CRC ^{d,e}	10	4.4	4.7	
			0	1.4	1.4	
			7.8	2.8	2.5	
			14.1	2.6	2.1	
		metastatic non-squamous NSCLC ^d (with chemotherapy)	20	1.7	2.0	
			10.3–14.0	0.4–0.6	NR	
			metastatic breast cancer (with chemotherapy)	15.7	5.9	NS
				9–18	0.8–1.9	NS
				11.8–13.4	1.2–2.9	NS ^d
			9.9	2.1	NS	
recurrent GBM ^f	28		2–3			
metastatic RCC ^d (with IFN- α)	18	4.8	NS			
	12.4	3.3	NS			
Sunitinib (Sutent) ^c	inhibitor of RTKs ^g	metastatic RCC ^c	35	6.0	4.6	
		GIST ^e		4.5		
		pancreatic neuroendocrine tumors ^c		4.8		

Table 13.6 (part 1 of 2) The Biology of Cancer (© Garland Science 2014)

Angiogeneze jako cíl protinádorové léčby

Table 13.6 Summary of clinically approved anti-angiogenic drugs^a

Agent	Nature of agent	Approved indication	% of patients responding ^b	Improvement ^b in PFS (months)	Improvement ^b in OS (months)
Sorafenib (Nexavar)	inhibitor of VEGF-R, cRaf, PDGF-R, and Kit TKs ^h	metastatic RCC ^d	8	2.7	NS
		unresectable HCC ^d	1	NS	2.8
			2	1.4	2.3
Pazopanib (Votrient)	inhibitor of RTKs ⁱ	metastatic RCC ^d	27	5.0	NR
		soft tissue sarcoma ^e		3.0	
Vandetanib (Caprelsa)	inhibitor of VEGF-R, EGF-R, and Ret TKs	metastatic medullary thyroid carcinoma ^d		6.2	
Axitinib ^e (Inlyta)	inhibitor of VEGF-Rs, PDGF-R and Kit TKs	advanced RCC ^e		2.0	

^a“Clinically approved” indicates approval for use by the U.S. Food and Drug Administration (FDA). “Inhibitor” indicates in all cases a low molecular weight pharmacologic agent. In addition, as of March 2011, derivatives of thalidomide have been found to have substantial therapeutic utility in treating multiple myeloma; they are not included here, however, because the drugs have adverse physiologic effects, notably neurotoxicity. The mTOR inhibitor Everolimus has been approved for treatment of a series of different tumor types and has anti-angiogenic effects; it has not been listed here because it also has effects on apoptosis, nutrient uptake, and proliferation that may explain part or most of its effects.

^bImprovement relative to standard treatment.

^cFDA approval for use against breast cancer was revoked in 2011.

^dFirst-line therapy.

^eSecond-line therapy. Axitinib was approved because PFS was 2.0 months longer than existing Sorafenib treatment.

^fMonotherapy.

^gInhibitor of VEGF-R, PDGF-R, FLT-3, Ret, and Kit TKs; Raf/B-Raf.

^hLow-molecular-weight inhibitor of VEGF-Rs and PDGF-Rs.

ⁱInhibitor of VEGF-Rs, PDGF-Rs, and c-Kit TKs.

Abbreviations: CRC, colorectal cancer; GBM, glioblastoma multiforme; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; IFN, interferon; MoAb, monoclonal antibody; NR, not reported; NS, not significant; NSCLC, non-small-cell lung carcinoma; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RTK, receptor tyrosine kinase.

Table adapted from P. Carmeliet and R. Jain, *Nature* 473:298–307, 2011.

Inhibice angiogeneze - paradox

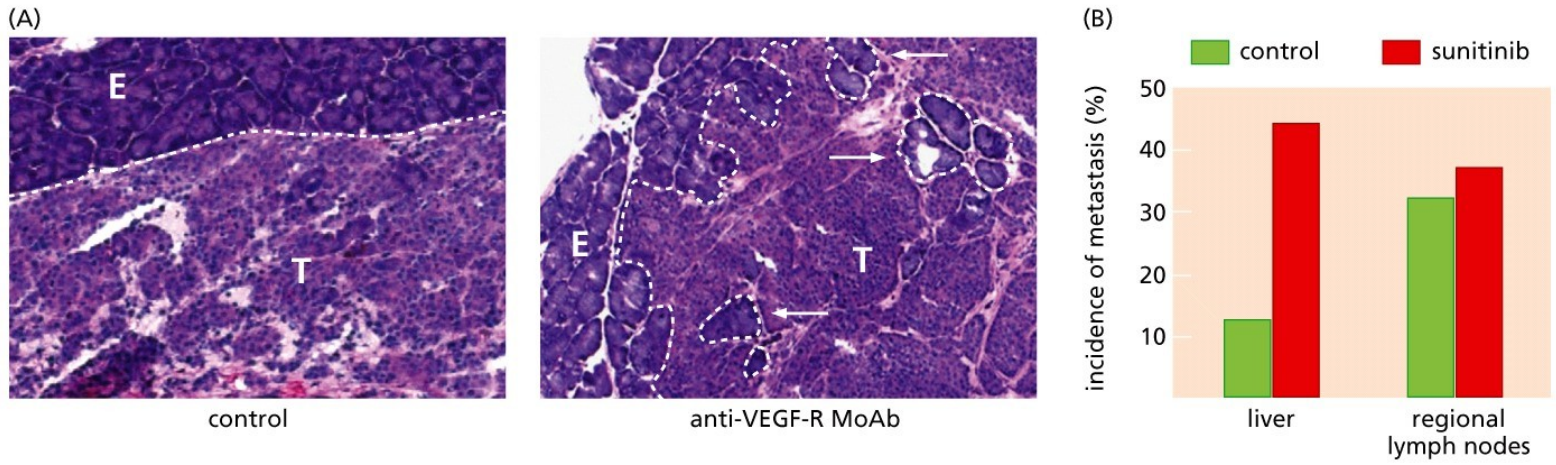


Figure 13.48 The Biology of Cancer (© Garland Science 2014)

Heterotypické interakce jako cíl protinádorové léčby

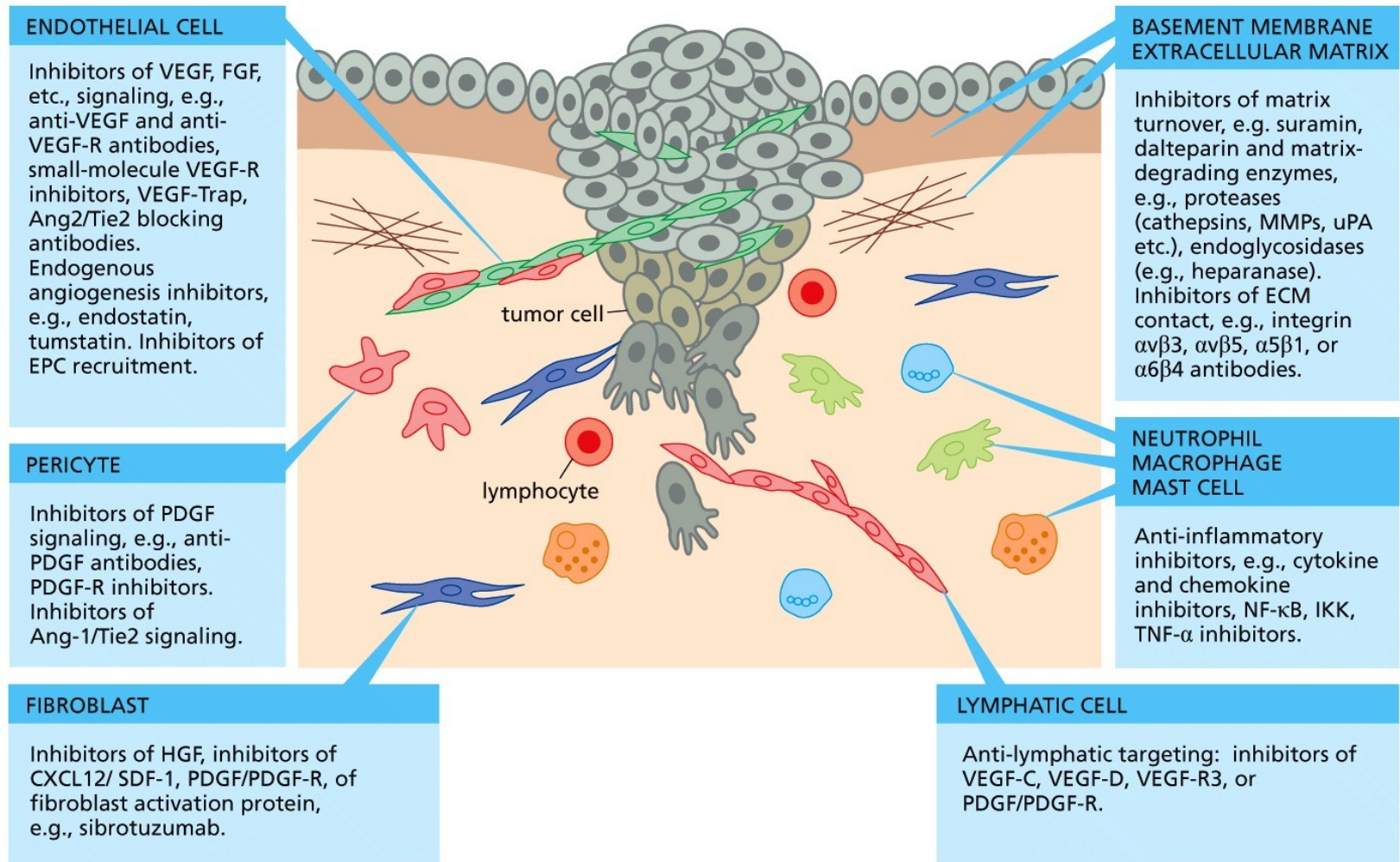
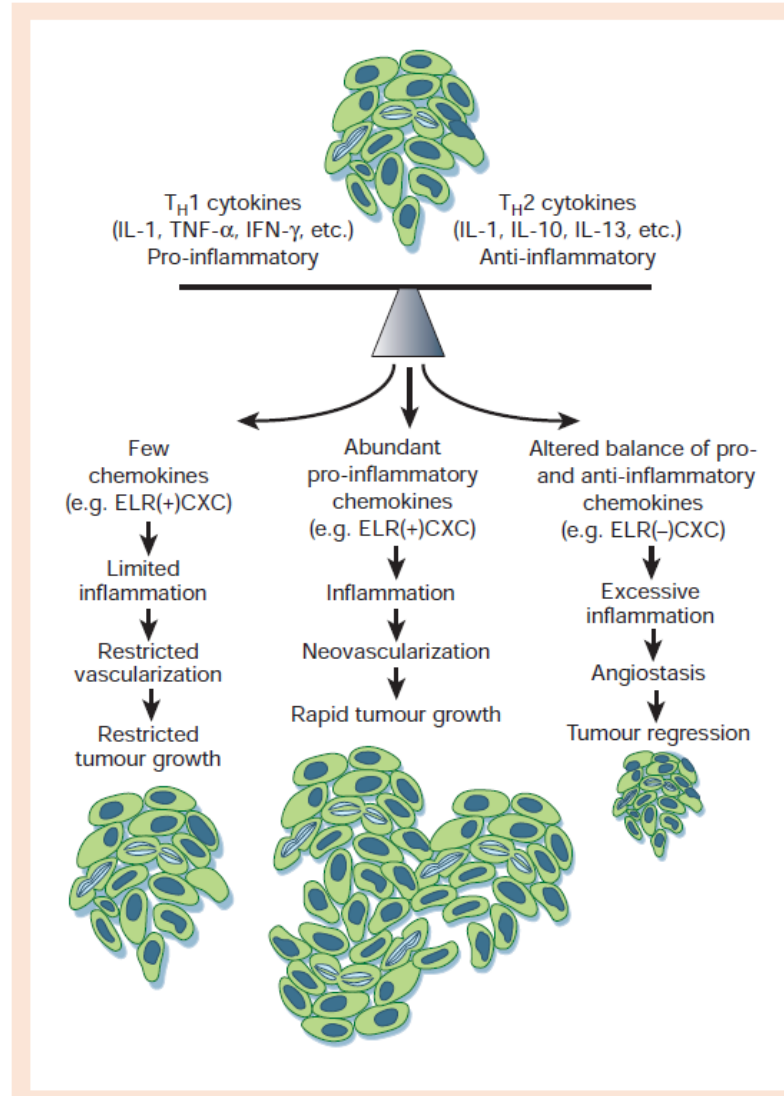


Figure 13.49 The Biology of Cancer (© Garland Science 2014)

Cytokiny a nádorová progrese



Zánět a nádorová progrese

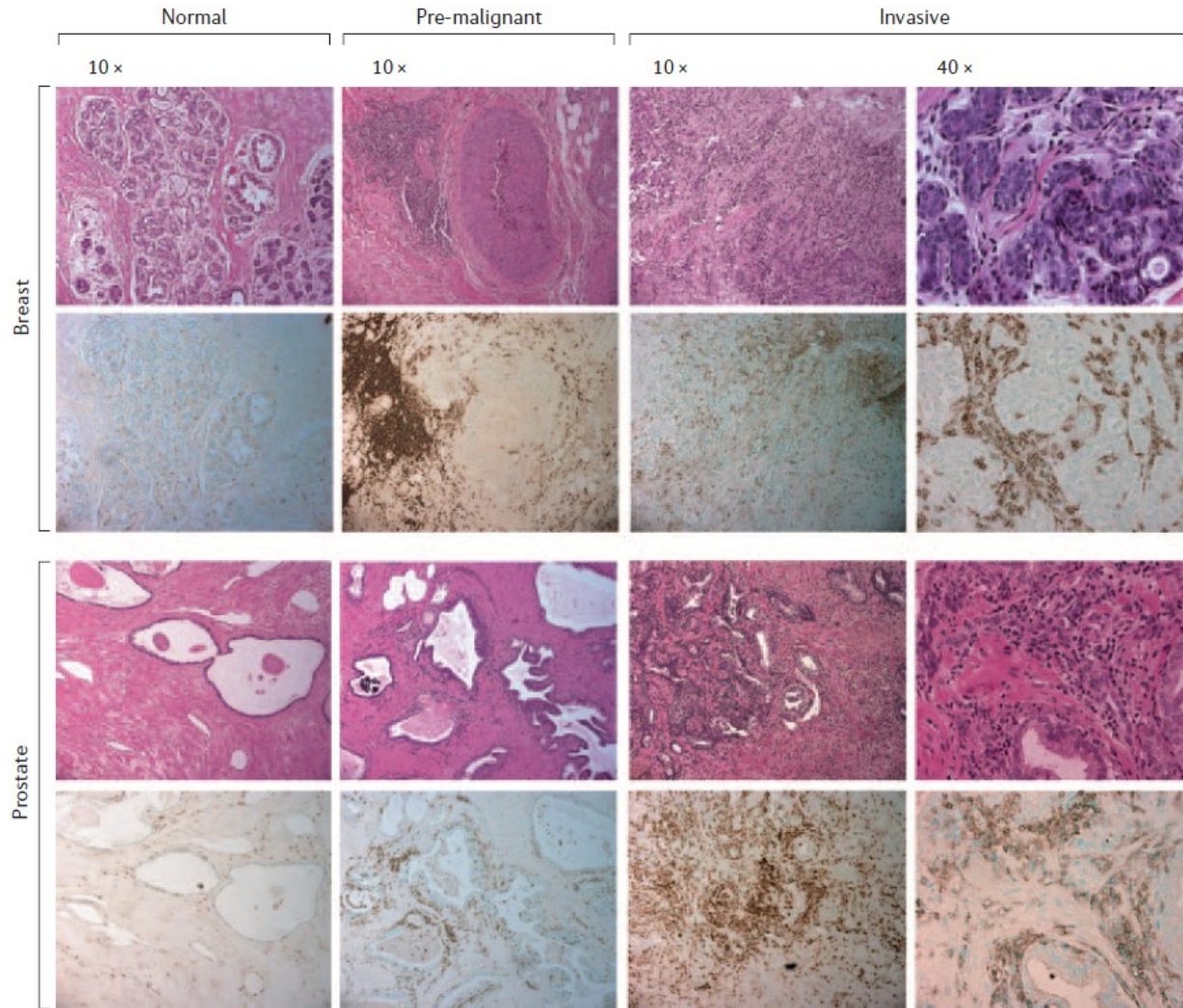
Table 1 Chronic inflammatory conditions associated with neoplasms

Pathologic condition	Associated neoplasm(s)	Aetiologic agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibres, silica particles
Bronchitis	Lung carcinoma	Silica, asbestos, smoking (nitrosamines, peroxides)
Cystitis, bladder inflammation	Bladder carcinoma	Chronic indwelling, urinary catheters
Gingivitis, lichen planus	Oral squamous cell carcinoma	
Inflammatory bowel disease, Crohn's disease, chronic ulcerative colitis	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma	Alcoholism, mutation in trypsinogen gene on Ch. 7
Reflux oesophagitis, Barrett's oesophagus	Oesophageal carcinoma	Gastric acids
Sialadenitis	Salivary gland carcinoma	
Sjögren syndrome, Hashimoto's thyroiditis	MALT lymphoma	
Skin inflammation	Melanoma	Ultraviolet light

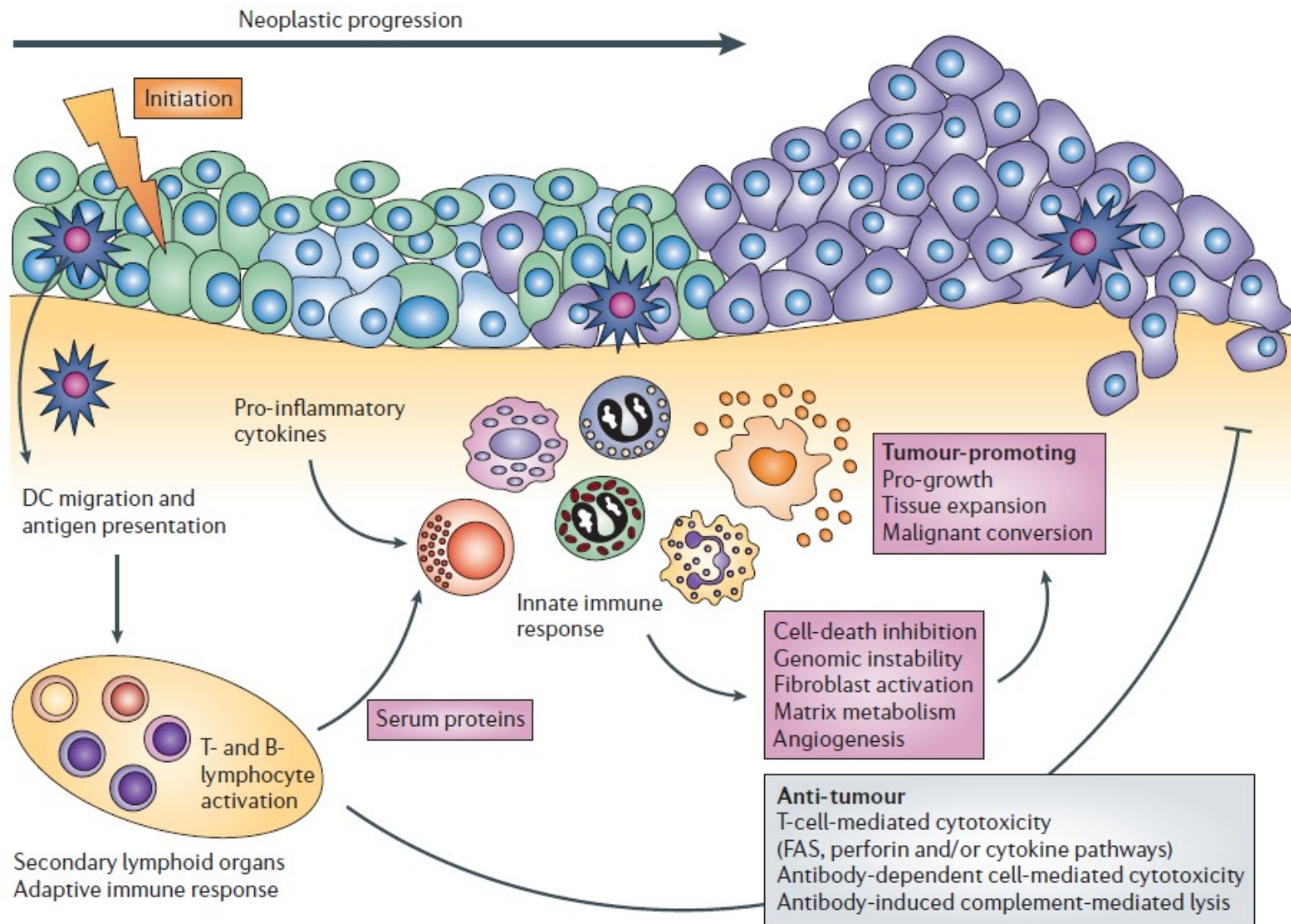
Zánět a nádorová progrese

Cancers associated with infectious agents		
Pathologic condition	Associated neoplasm(s)	Aetiologic agent
<i>Opisthorchis, Cholangitis</i>	Cholangiosarcoma, colon carcinoma	Liver flukes (<i>Opisthorchis viverrini</i>), bile acids
Chronic cholecystitis	Gall bladder cancer	Bacteria, gall bladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	<i>Helicobacter pylori</i>
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Mononucleosis	B-cell non-Hodgkin's lymphoma, Burkitts lymphoma,	Epstein-Barr Virus
AIDS	Non-Hodgkin's lymphoma, squamous cell carcinomas, Kaposi's sarcoma	Human immunodeficiency virus, human herpesvirus type 8
Osteomyelitis	Skin carcinoma in draining sinuses	Bacterial infection
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonorrhoea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen	Schistosomiasis

Infiltrace CD45+ buněk do solidních nádorů



Imunitní systém, zánět a tumorigeneze



Rakovina slinivky



Family History

Risk increases if multiple first-degree relatives had the disease, or any were diagnosed under 50.



Diet

A diet high in red and processed meats may increase risk. A diet high in fruits and vegetable may decrease risk.



Obesity

Obese people have a 20% increased risk of developing the disease compared to people of a normal weight.



Race

African-Americans and Ashkenazi Jews have a higher incidence of pancreatic cancer.



Smoking

Smoking may cause about 20-30% of all exocrine pancreatic cancer cases.



Gender

Slightly more men are diagnosed with pancreatic cancer than women.



Age

The chance of developing pancreatic cancer increases with age.



Diabetes

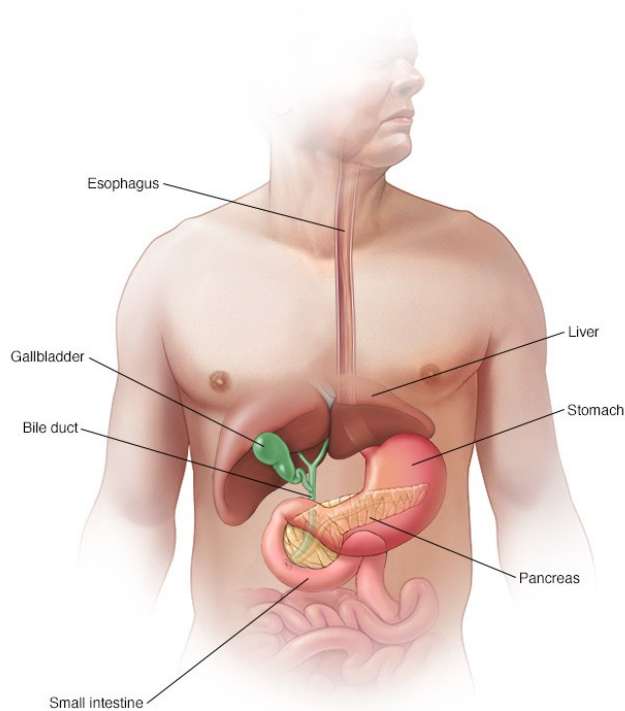
Long standing (over 5 years) diabetes increases risk.



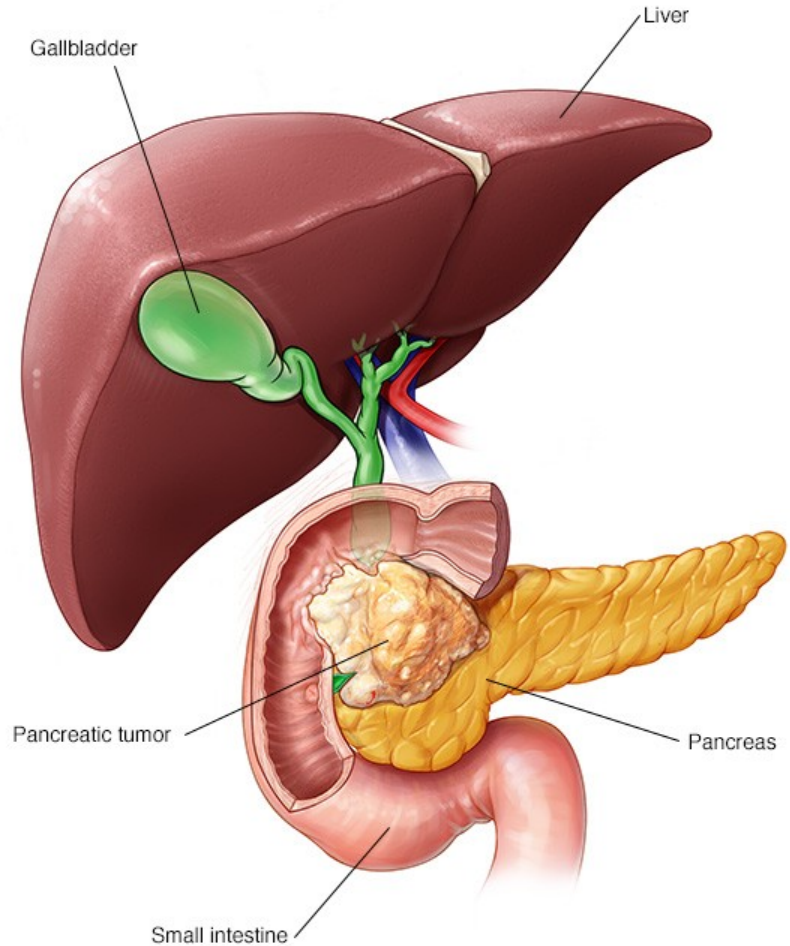
Pancreatitis

Chronic pancreatitis increases risk. Risk is even higher for people with hereditary pancreatitis.

Slinivka břišní, pankreas



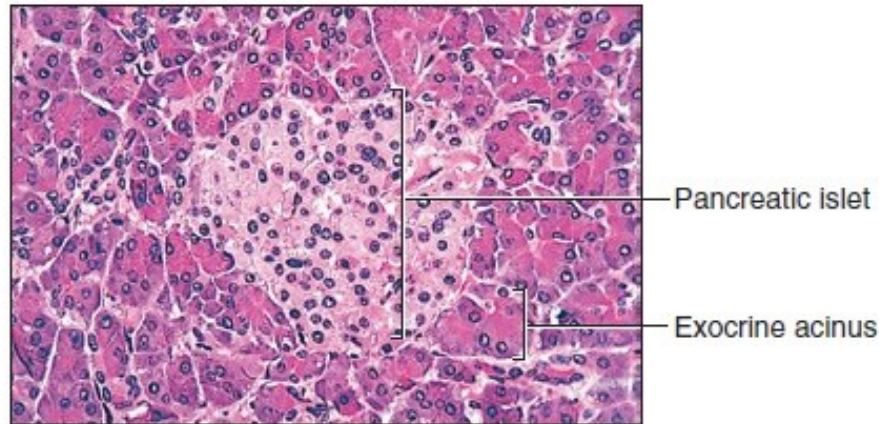
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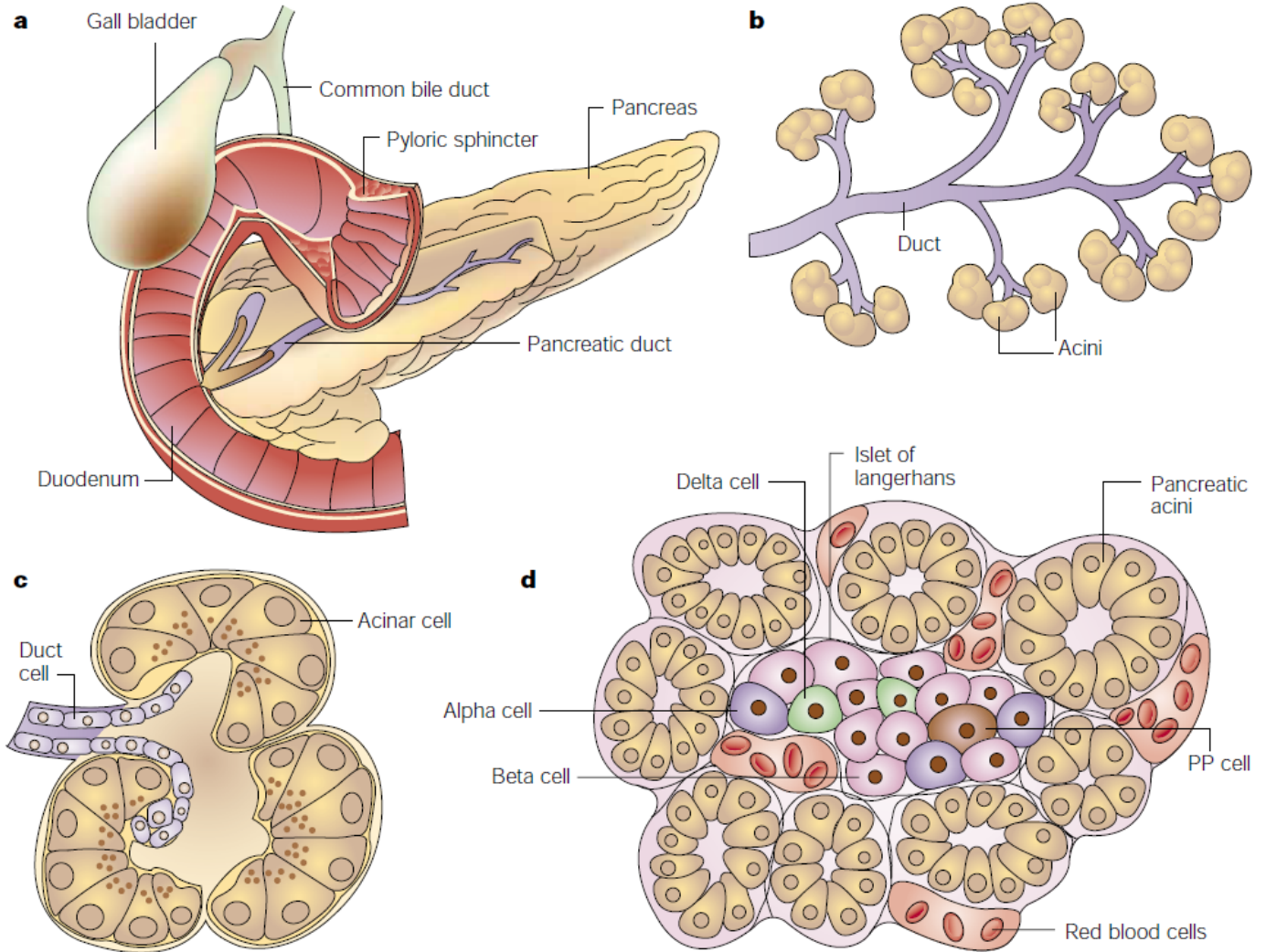
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Slinivka břišní, pankreas

- ▶ smíšená exo/endokrinní žláza, produkující trávicí enzymy a hormony (váha ~ 80g, velikost ~ 15 cm)
- ▶ **stroma:** na povrchu pouzdro (husté vazivo) – z něj vybíhají septa → laloky → lalůčky (cévní + nervové zásobení + větvení vývodů); podkladovou tkání je řídké vazivo
- ▶ **parenchym:** pankreatické aciny + trámčité uspořádání buněk (Langerhansovy ostrůvky)



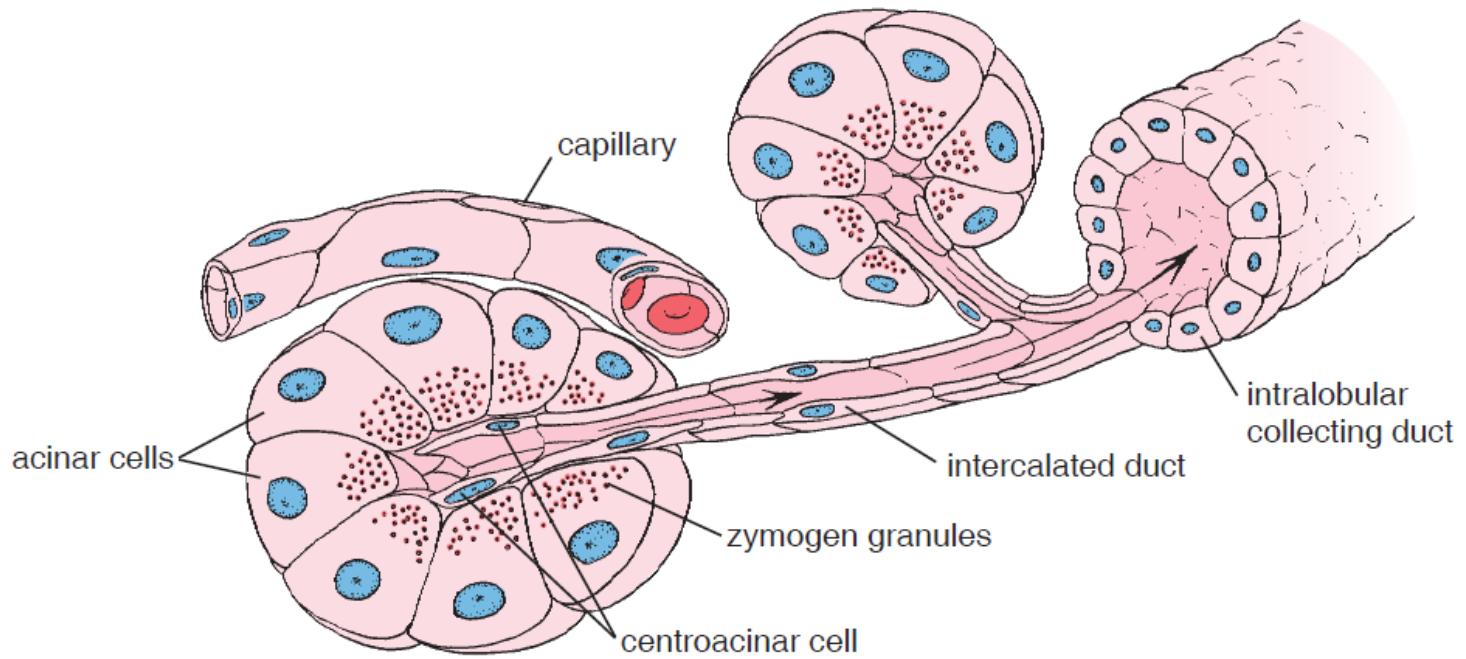
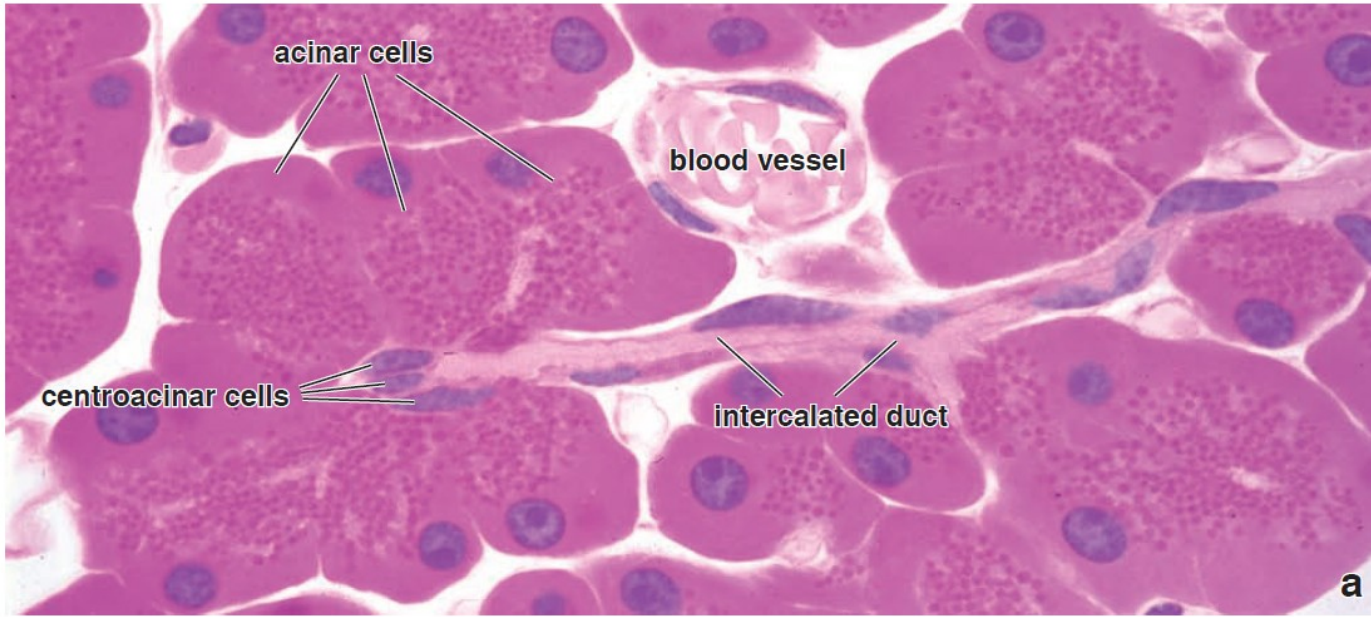
Pankreas



EXOKRINNÍ ČÁST PANKREATU

- složená alveolární žláza
- syntetizuje a produkuje trávicí šťávu (cca 2 L/den): proteolytické endopeptidázy (trypsinogen, chymotrypsinogen), amylázy, lipázy a deoxyribonukleázy → mají za úkol štěpit tráveninu (chymus), přicházející z žaludku
- také zde probíhá produkce látek, podílejících se na alkalizaci sekretu (snížení pH = ↑ funkčnost trávicích enzymů)
- **pankreatické aciny** – bazofilní cytoplazma, množství sekrečních granulí, produkce trávicích enzymů
- **centroacinózní buňky** – světlá cytoplazma, přímo navazují na vsunuté vývody, alkalizace sekretu
- **absence myoepitelových buněk**

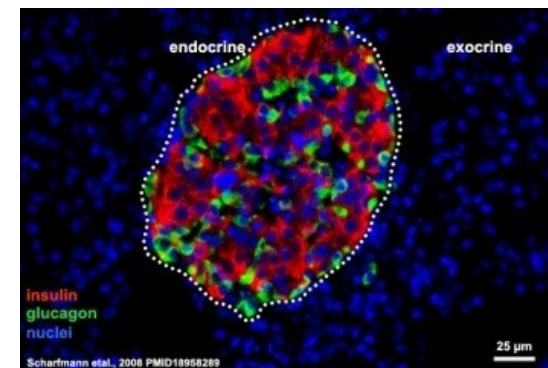
Mechanismy karcinogeneze



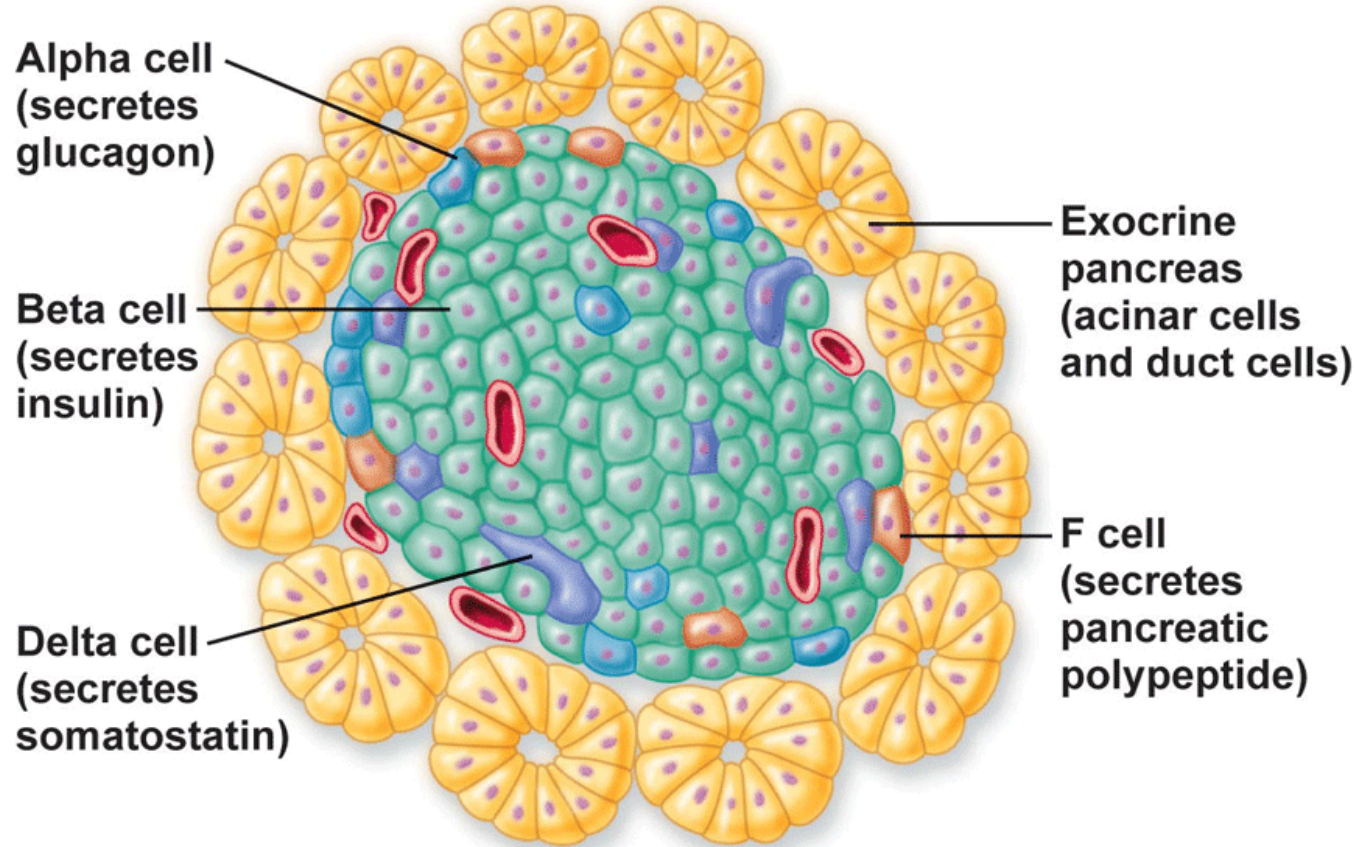
ENDOKRINNÍ ČÁST PANKREATU

Langerhansovy ostrůvky

- velikost 100-200 um, počet ~ 1 mil., 1-2% objemu slinivky
- **trámčitý** stavební typ s bohatým kapilárním zásobením (fenestrované kapiláry)
- ostrůvky jsou obklopeny tenkou vrstvou řídkého vaziva
- součástí „Diffuse Neuroendocrine Systém“ (DNES) systému
- světlá cytoplazma s přítomností sekrečních granulí → 4 typy buněk:
 - **A buňky – glukagon (cca 20%)**
 - **B buňky – inzulín (cca 70%)**
 - **D buňky – somatostatin (cca 5%)**
 - **PP buňky – pankreatický polypeptid (< 5%)**



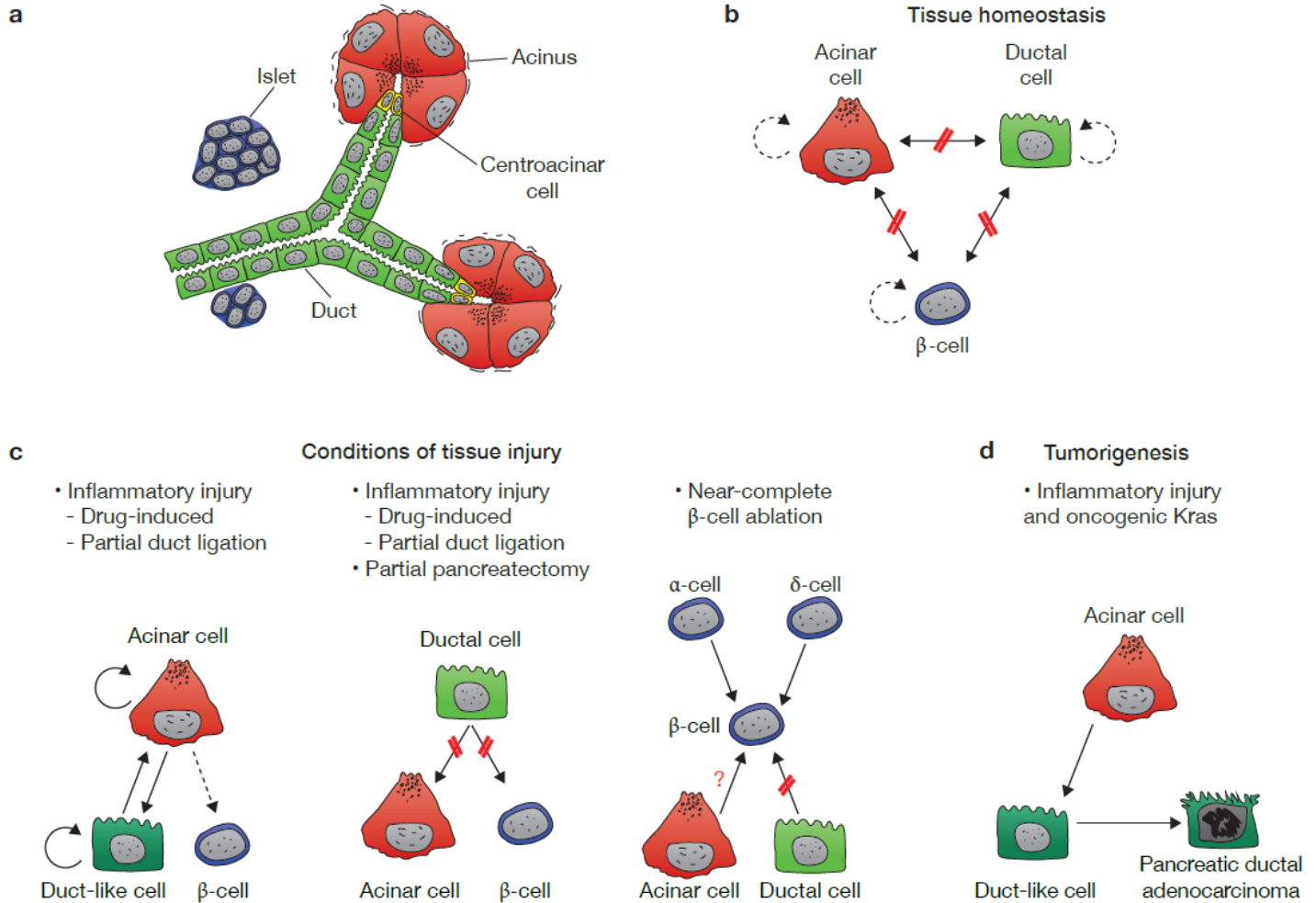
Langerhansův ostrůvek



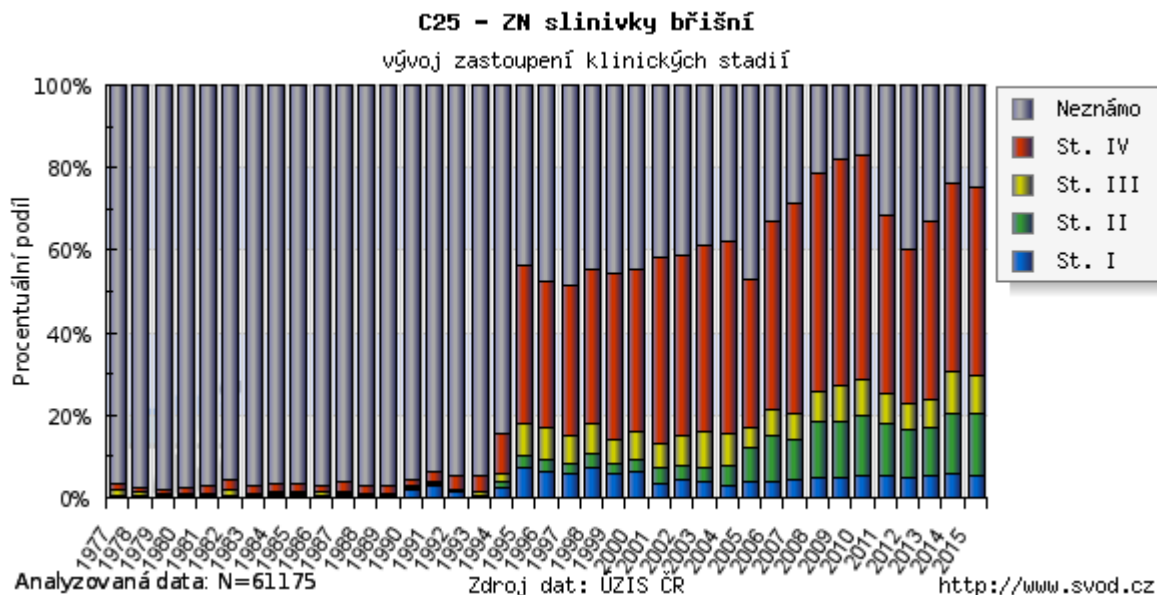
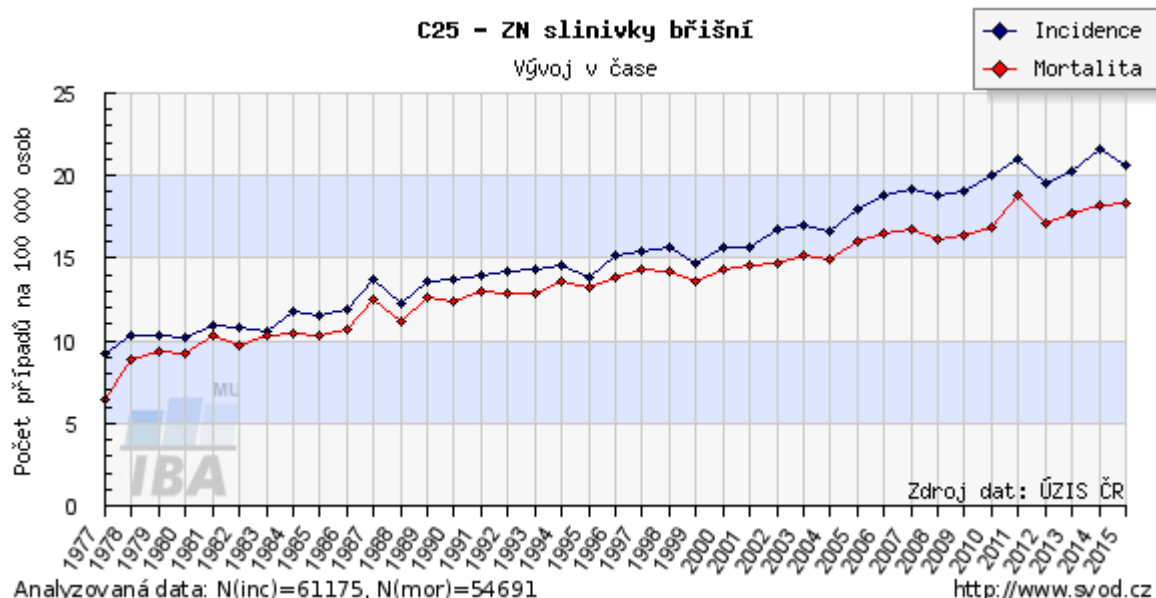
Regenerace pankreatu

- Nízká intenzita proliferace
- Nízká klonogenní kapacita
- Délka života u myších buněk ~ 1 rok (podobně jako u jater)
- Regenerační kapacita odlišná od jaterní
 - Buňky zvýší svoji proliferační kapacitu, ale k úplné obnově poškozené tkáně nedojde
 - Lgr5+ buňky nejsou přítomny, jsou indukovány při poškození v buňkách ductu nebo v podmínkách in vitro – vliv mikroprostředí?
- Buňky pankreatu jsou plastické
 - Během zánětu lze nalézt buňky s ductální i acinární charakteristikou
 - Transdiferenciace
 - Risk pro vznik onemocnění (acinar-to-ductal metaplasia)

Regenerace pankreatu

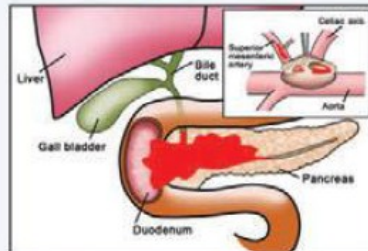
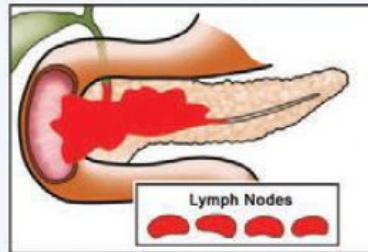
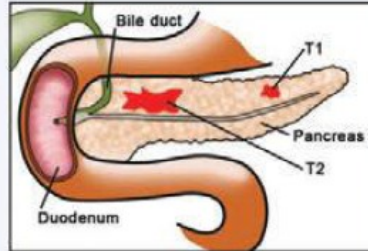


Rakovina slinivky

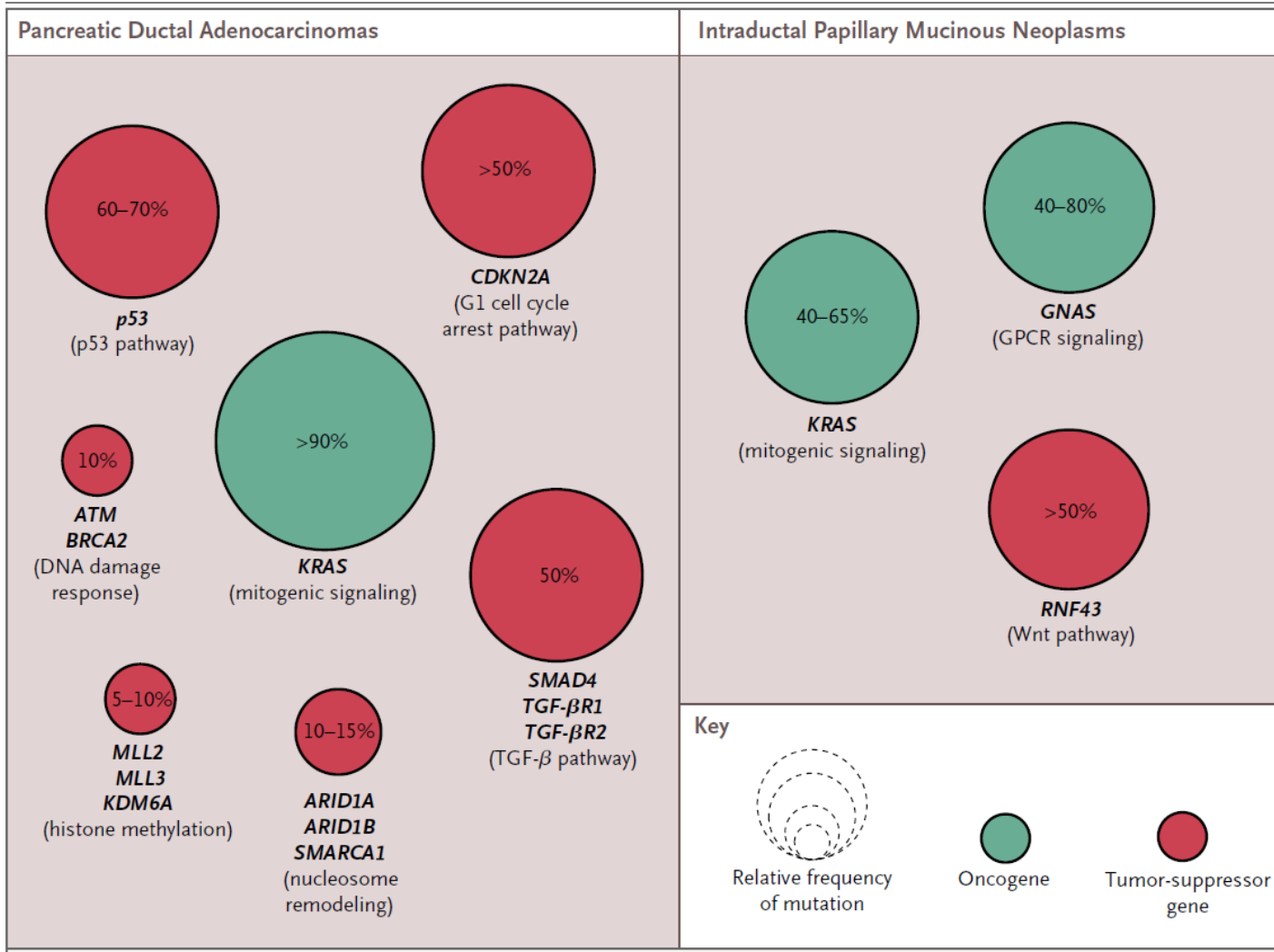


Rakovina slinivky

AJCC Stage	TNM Stage	Extent of Tumor	5 year Survival	Stage at Presentation (14% Unknown)
I	T1/N0	Limited to pancreas ≤ 2cm	20%	7%
	T2/N0	Limited to pancreas > 2cm		
II	T3 or N1	Beyond pancreas or regional lymph node metastases	8%	26%
III	T4 any N	Involves celiac axis or superior mesenteric artery		
IV	M1	Distant metastases	2%	53%

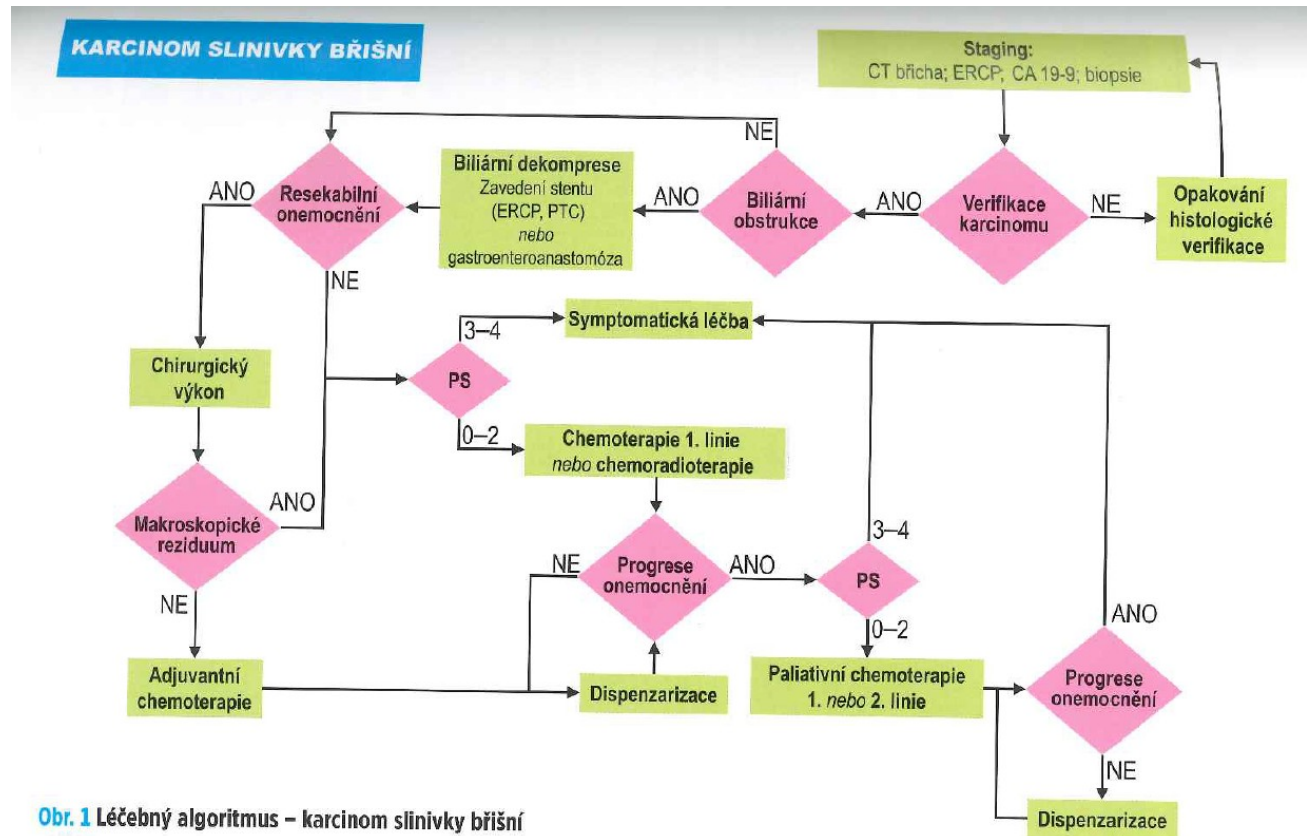
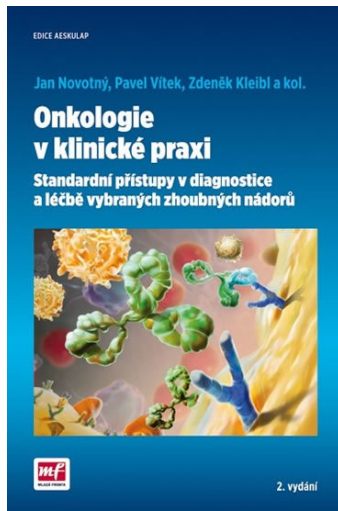


Mutace u nádorů slinivky



Nádor slinivky - léčba

- radikální resekce - stádium I a II
- Adjuvantní terapie
 - Chemorezistentní onemocnění
- radioterapie



Obr. 1 Léčebný algoritmus – karcinom slinivky břišní

Adjuvantní terapie

Table 2. Adjuvant Therapy for Pancreatic Cancer.*

Study	No. of Patients	Treatment	Survival	P Value
GITSG ⁵⁸	43	Observation	10% at 2 yr	0.007
		Fluorouracil plus radiotherapy	20% at 2 yr	
EORTC ⁵⁹	218	Observation	26% at 2 yr	0.10
		Fluorouracil plus radiotherapy	34% at 2 yr	
ESPAC-1 ⁶⁰	289	Observation	16.9 mo (median) [†]	
		Chemoradiotherapy		
		Fluorouracil Chemoradiotherapy plus fluorouracil	21.6 mo 19.9 mo	
CONKO-01 ⁶¹	368	Observation	10.4% at 5 yr	0.01
		Gemcitabine	20.7% at 5 yr	
ESPAC 3 ⁶²	1088	Fluorouracil Gemcitabine	23.0 mo (median) 23.6 mo	0.39
RTOG 9704 ⁶³	451	Fluorouracil plus radiotherapy	22% at 5 yr	0.12
		Gemcitabine plus radiotherapy	18% at 5 yr	
JASPAC-01 ⁶⁴	378	S-1 (oral fluoropyrimidine) Gemcitabine	70% at 2 yr 53% at 2 yr	<0.001

* CONKO-01 denotes Charité Onkologie 01, EORTC European Organization for Research and Treatment of Cancer, ESPAC European Study Group for Pancreatic Cancer, GITSG Gastrointestinal Tumor Study Group, JASPAC-01 Japan Adjuvant Study Group of Pancreatic Cancer, and RTOG 9704 Radiation Therapy Oncology Group 9704.

[†] The estimated 5-year survival rate was 10% among patients who received chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P=0.009).

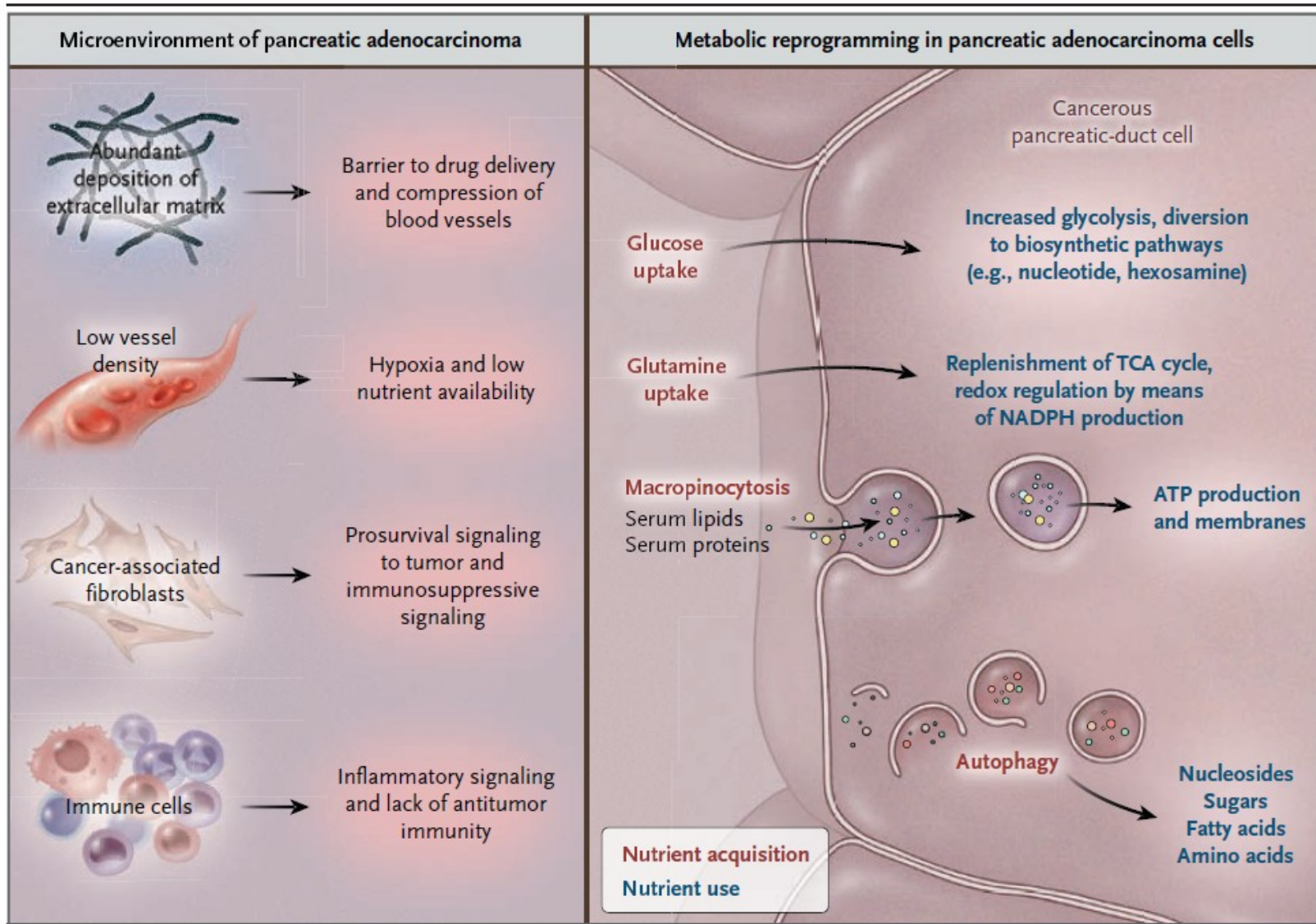
Léčba metastazujícího adenokarcinomu slinivky


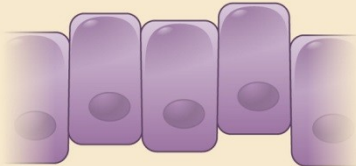

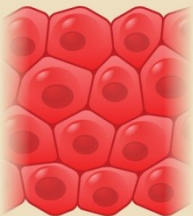

Table 3. Key Clinical Trials in Metastatic Pancreatic Cancer.*

Trial	No. of Patients	Treatment	Median Survival <i>mo</i>	P Value
Burris et al. ⁷⁰	126	Fluorouracil Gemcitabine	4.4 5.6	0.002
NCIC ⁷¹	569	Gemcitabine Gemcitabine plus erlotinib	5.9 6.2	0.04
Ueno et al. ⁷²	834	Gemcitabine S-1	8.8 9.7	<0.001 for non-inferiority
Conroy et al. ⁷³	342	Gemcitabine FOLFIRINOX	6.8 11.1	<0.001
Von Hoff et al. ⁷⁴	861	Gemcitabine Gemcitabine plus nab-paclitaxel	6.7 8.5	<0.001

* FOLFIRINOX denotes fluorouracil, irinotecan, oxaliplatin, and leucovorin; and NCIC National Cancer Institute of Canada.

Biologické vlastnosti nádoru slinivky



Metastasis in Pancreatic Cancer		
 <p>Stationary normal cells</p>	 <p>Migratory preneoplastic cells (PanIN)</p>  <p>Invading EMT cells</p>	 <p>Colonizing neoplastic cells (PDAC)</p> 
Extrinsic factors:	Inflammation	Inflammation, ?hypoxia
Intrinsic factors:	KRAS*	KRAS LOH, Ink4a/ARF, TP53*, SMAD4
Competency to colonize:	Nil or low	High

Shrnutí

- Nádor je komplexní tkáň závislá na komunikaci mezi různými buněčnými typy
- Karcinomy zahrnují neoplastické buňky a buňky stromatu – fibroblasty, myofibroblasty, zánětlivé buňky, endoteliální buňky, pericity
- Většina nádorů je na stromatu závislá s výjimkou ascitických nádorů
- Formování nových cév je kritickým faktorem determinující růst solidních nádorů
- Antiangiogenní léčba může vést k paradoxním výsledkům
- Rakovina jako nikdy se nehojící rána
- Zánět – jeden z rizikových faktorů pro vznik nádorů slinivky
- EMT předchází metastázování nádorových buněk slinivky