INVAZIVITA A METASTÁZOVÁNÍ - dokončení

Karel Souček
E-mail: ksoucek@ibp.cz, tel.: 541 517 166

Mechanismy karcinogeneze

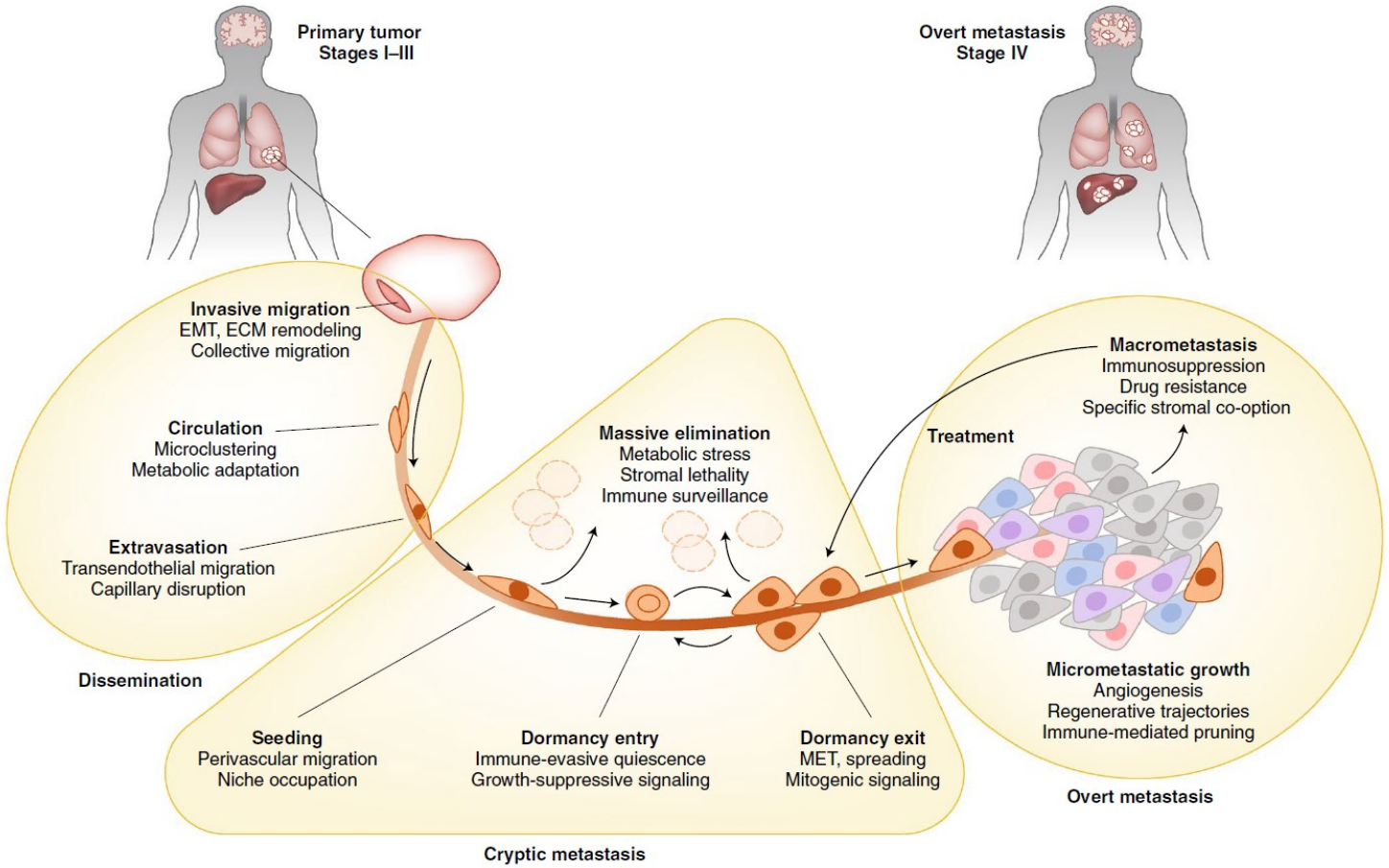


Fig. 1 | Steps, biological functions and cancer cell vulnerabilities in the metastasis cascade. Local surgery or radiation and systemic approaches including chemotherapy, targeted therapy and immunotherapy are currently the mainstay of metastasis prevention and treatment and are frequently effective at reducing metastatic tumor mass. However, these treatments do not specifically target the cryptic phase of metastasis or regenerative progenitors that persist following therapeutic debulking of macrometastatic disease. Cancer cells disseminating from a primary tumor via the blood or lymphatic system require specific functions (as listed under each boldface step) to adapt to a number of stresses in order to invade vessels, survive the loss of niche factors from the originating organ and survive in the circulation. On reaching distant organs (gray area), cancer cells enter and exit proliferative dormancy, evade immunity and acquire mitogenic signals by co-opting the stroma of the distant organs. The majority of cancer cells leaving a primary tumor are unable to survive these stresses and are cleared. Cancer cells that survive and retain the ability to regenerate the tumor during the cryptic phase of metastasis are called metastasis-initiating cells (MICs). MICs launch overt metastatic growth in distant organs, develop along tissue-regenerative trajectories and deploy organ-specific stromal co-option functions. Clinically overt macrometastases may be effectively debulked by classic therapies, but resistance and relapse are driven by the plasticity and persistence of MIC states within macrometastases. ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; MET, mesenchymal–epithelial transition.

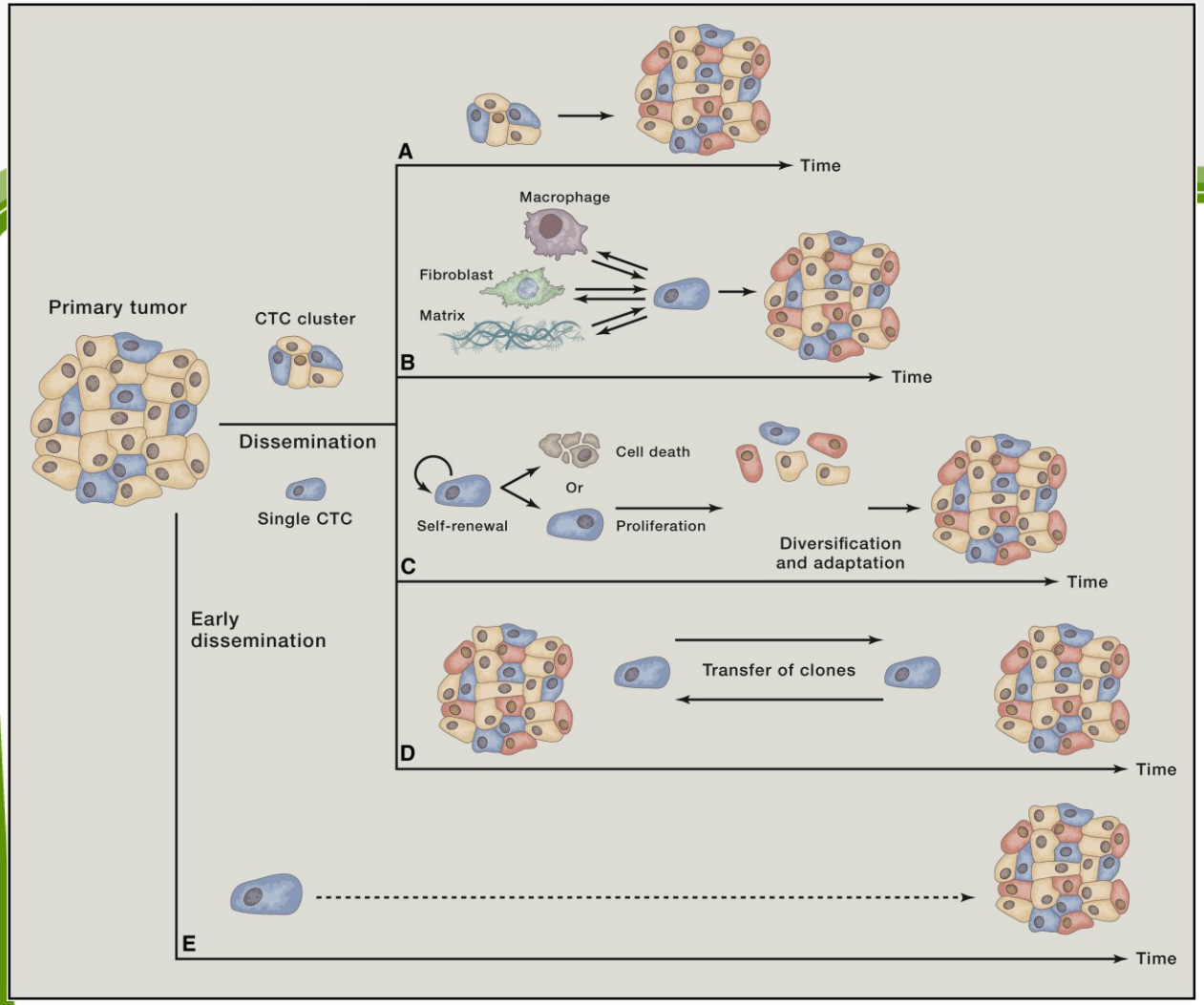
REVIEW ARTICLE
https://doi.org/10.1038/s41591-020-01195-4

Targeting metastatic cancer

Karuna Ganesh[1,2] and Joan Massagué[3]

Mechanismy karcinogeneze

Cell 2017 168670-691DOI:
(10.1016/j.cell.2016.11.037)



The progression and evolution of metastatic disease is highly variable, manifesting in ways that must affect the kinetics of metastatic colonization. Five hypothetical alternatives are presented here.
(A) The dissemination of CTC clusters to distant sites may generate overt metastases with a relatively short latency, since such clusters are highly efficient at spawning metastatic growths. Their efficiency in forming metastases may derive from advantages during transit in the circulation or because they benefit from homotypic cell-cell interactions in a foreign tissue environment.
(B) Solitary disseminated carcinoma cells that are adept at recruiting and establishing a supportive metastatic niche, or that are able to generate a microenvironmental niche themselves, may be better able to survive and initiate programs of proliferation.
(C) While the dissemination of tumor-initiating cancer stem cells may be a prerequisite for metastasis, the generation and evolution of progeny that are well adapted to the local microenvironment could take many months or years.
(D) At later stages of metastatic progression, other dynamics come into play, such as the exchange of metastatic cell clones between different metastatic lesions in the same patient. The biological and clinical impact of such transfer, however, remains to be firmly established.
(E) Tumor cells may disseminate during the early stages of tumorigenesis and even from pre-malignant lesions, but it remains unclear how such cells are able to evolve, in parallel with the primary tumor, the full complement of genetic mutations and malignant traits required for successful metastatic colonization.

EMT & nádory

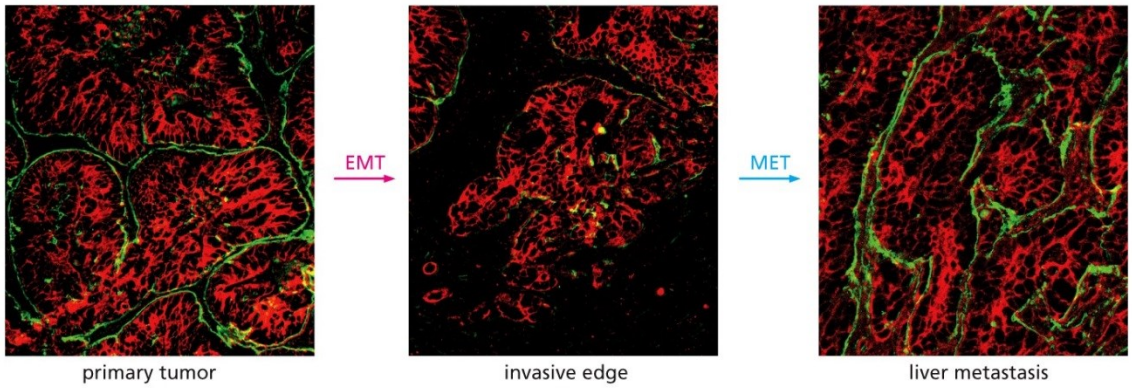


Figure 14.18a The Biology of Cancer (© Garland Science 2014)

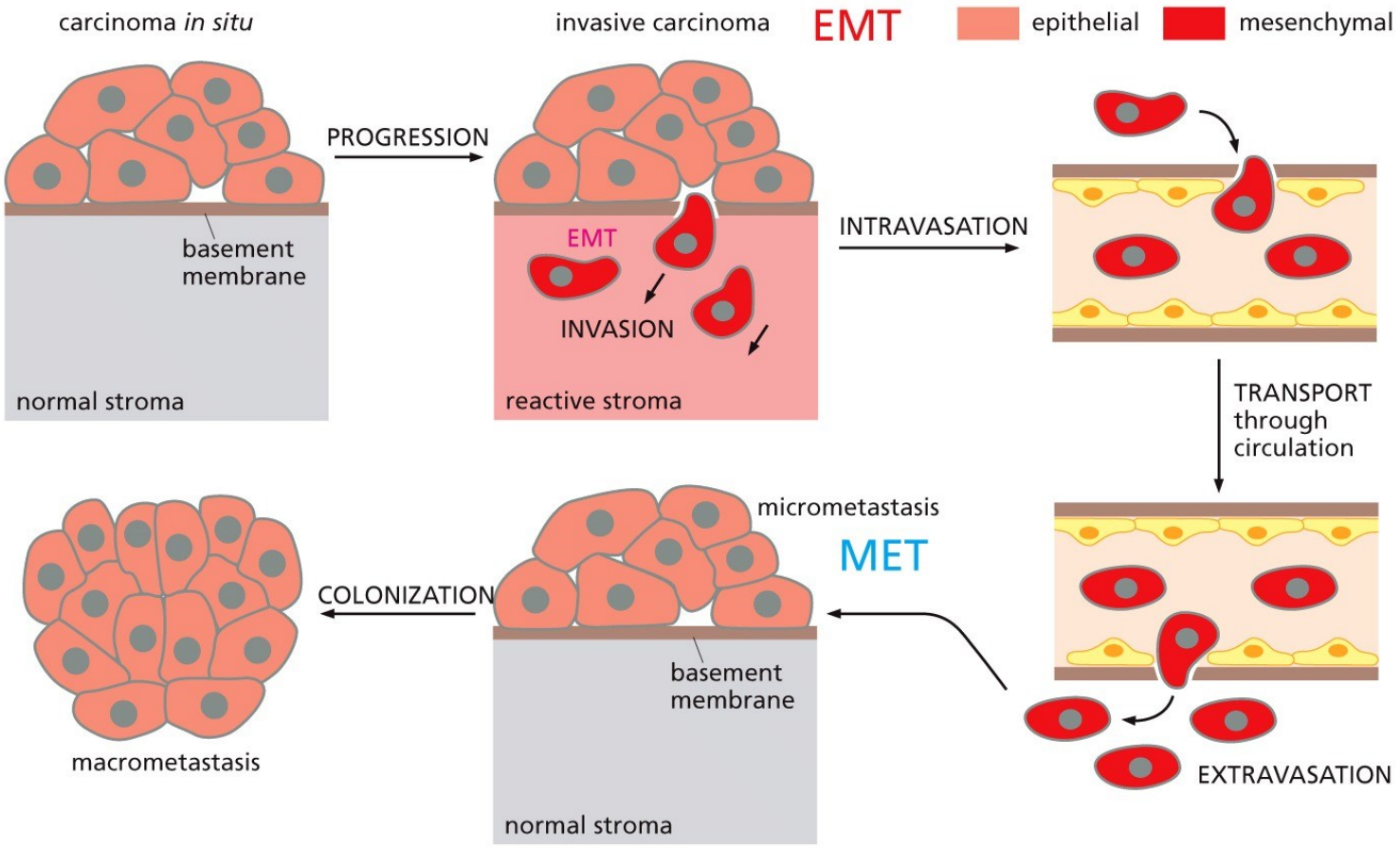
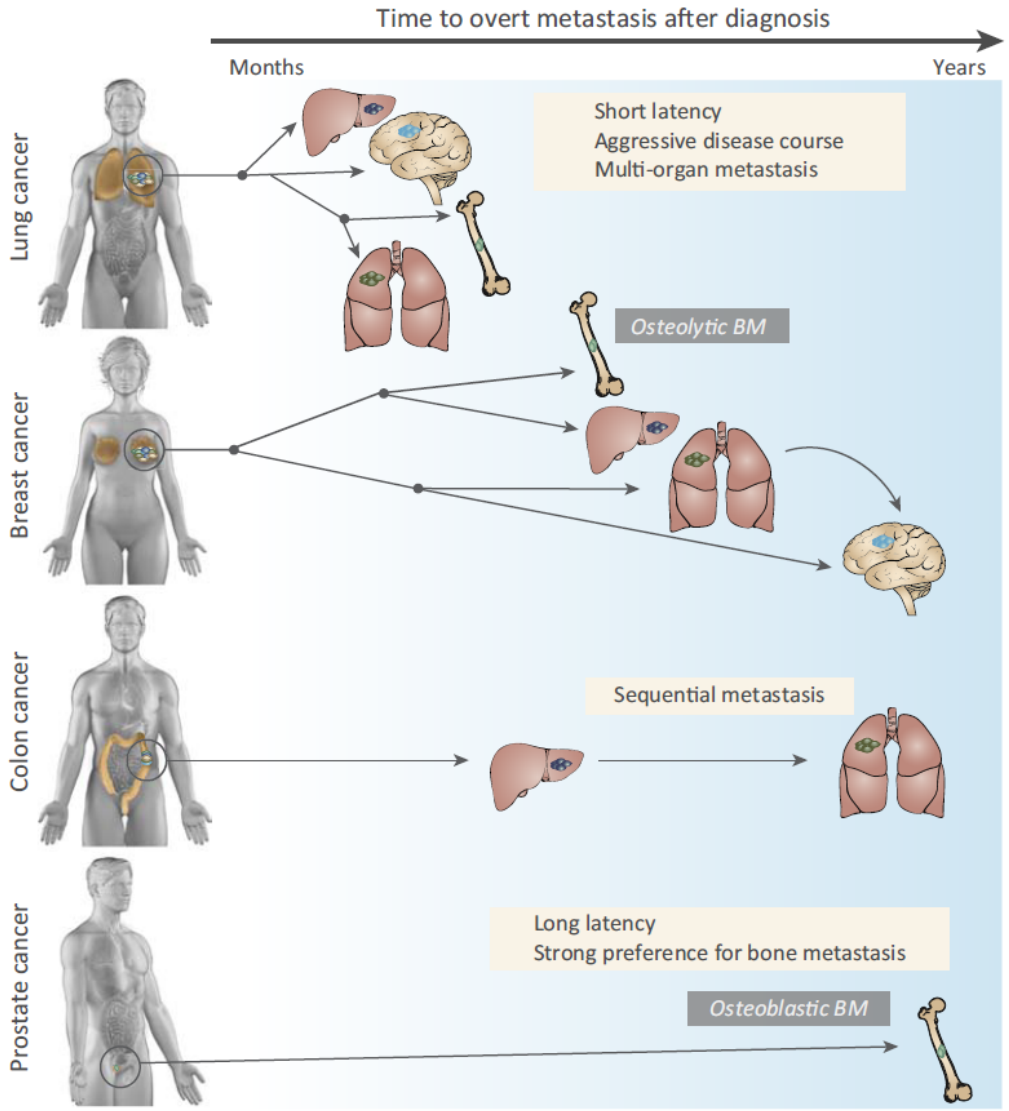


Figure 14.18b The Biology of Cancer (© Garland Science 2014)

Diseminace solidních nádorů



Metastatický tropismus

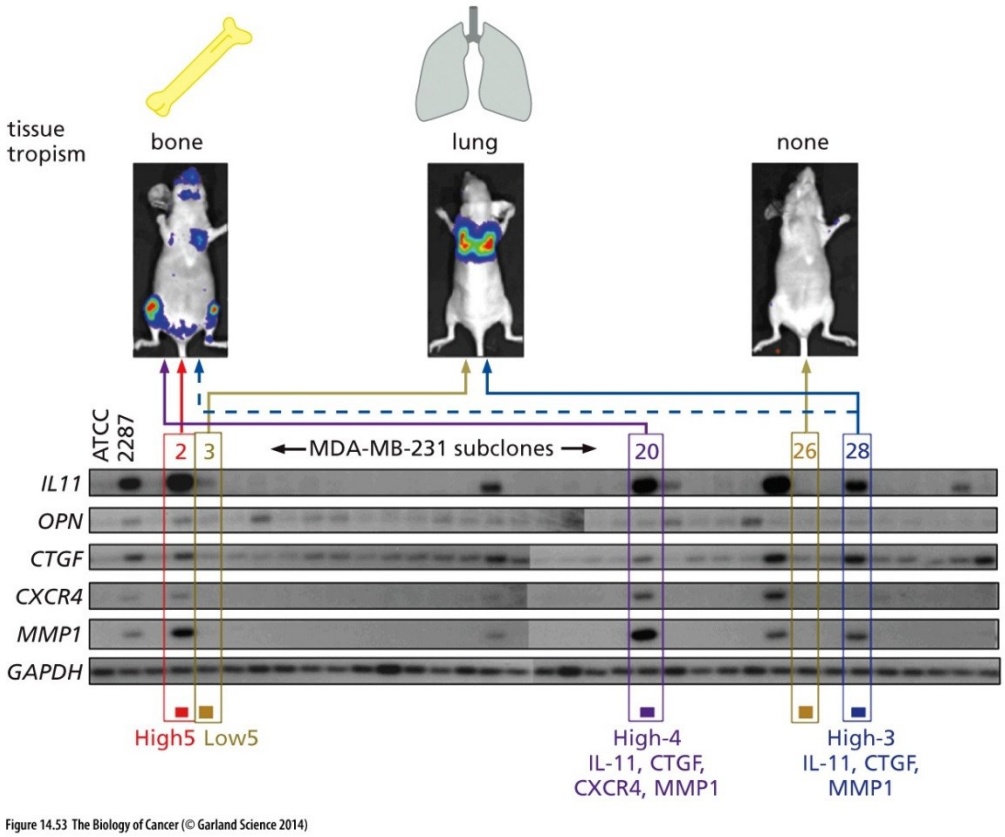
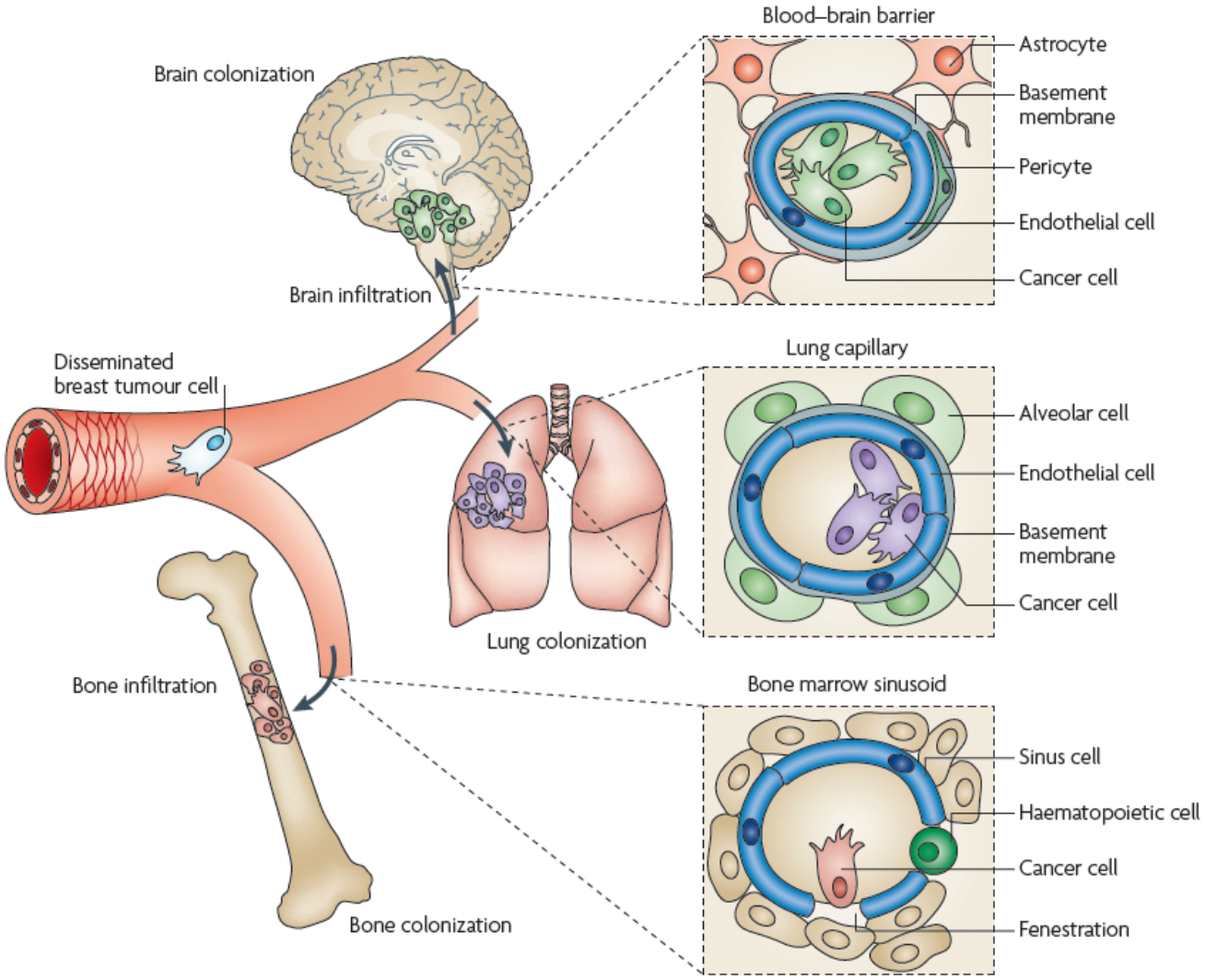


Figure 14.53 The Biology of Cancer (© Garland Science 2014)

- 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

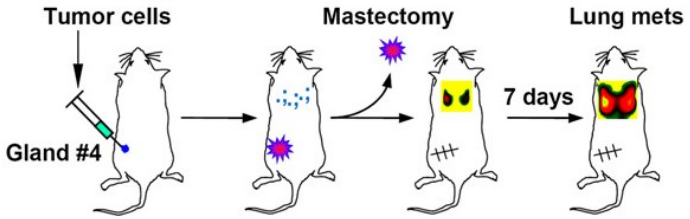


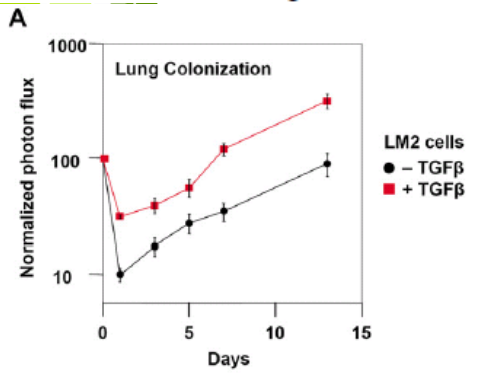
Cell

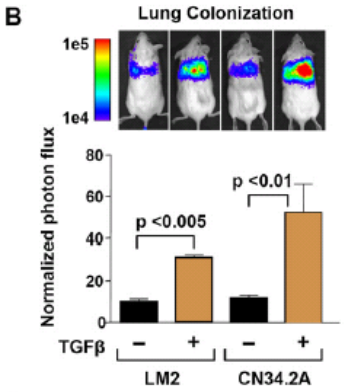
Cell 133, 66–77, April 4, 2008

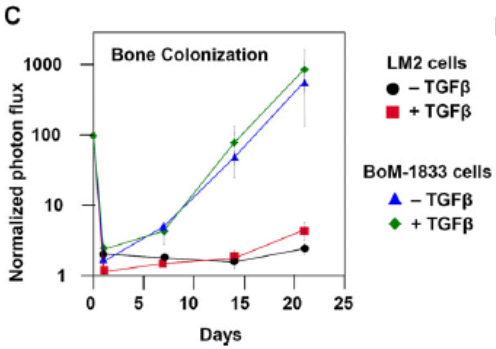
TGFβ Primes Breast Tumors for Lung Metastasis Seeding through Angiopoietin-like 4

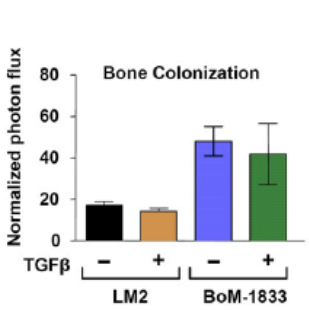
David Padua,[1] Xiang H.-F. Zhang,[1] Qiongqing Wang,[1] Cristina Nadal,[5] William L. Gerald,[2] Roger R. Gomis,[4] and Joan Massagué[1,3,*]

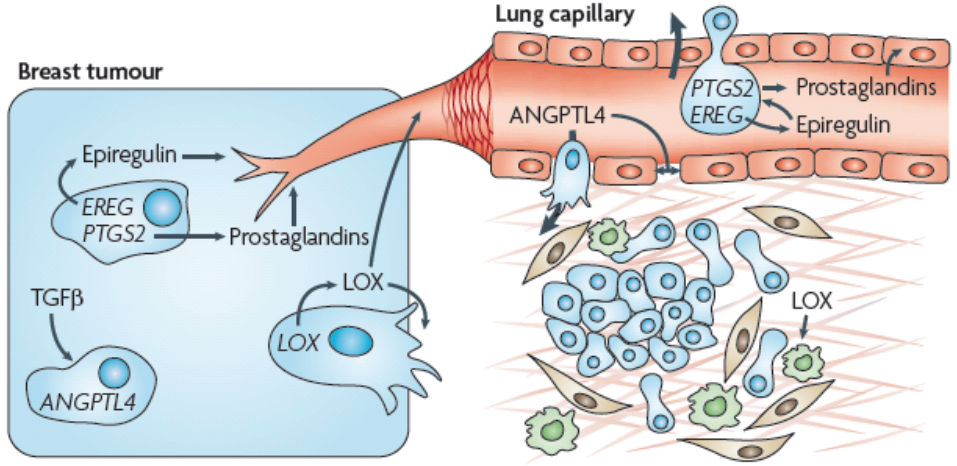












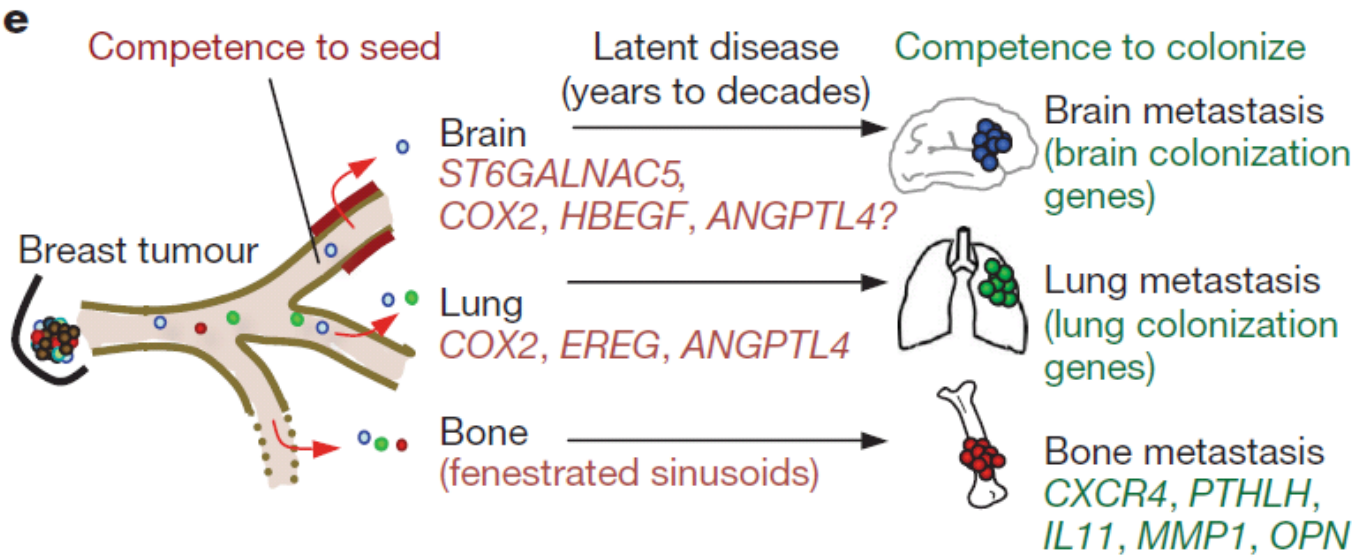
Angiopoietin-like 4 ~ *ANGPTL4*
Epiregulin (EPR) ~ *EREG*, EGF family member

Vol 459|18 June 2009|doi:10.1038/nature08021 nature

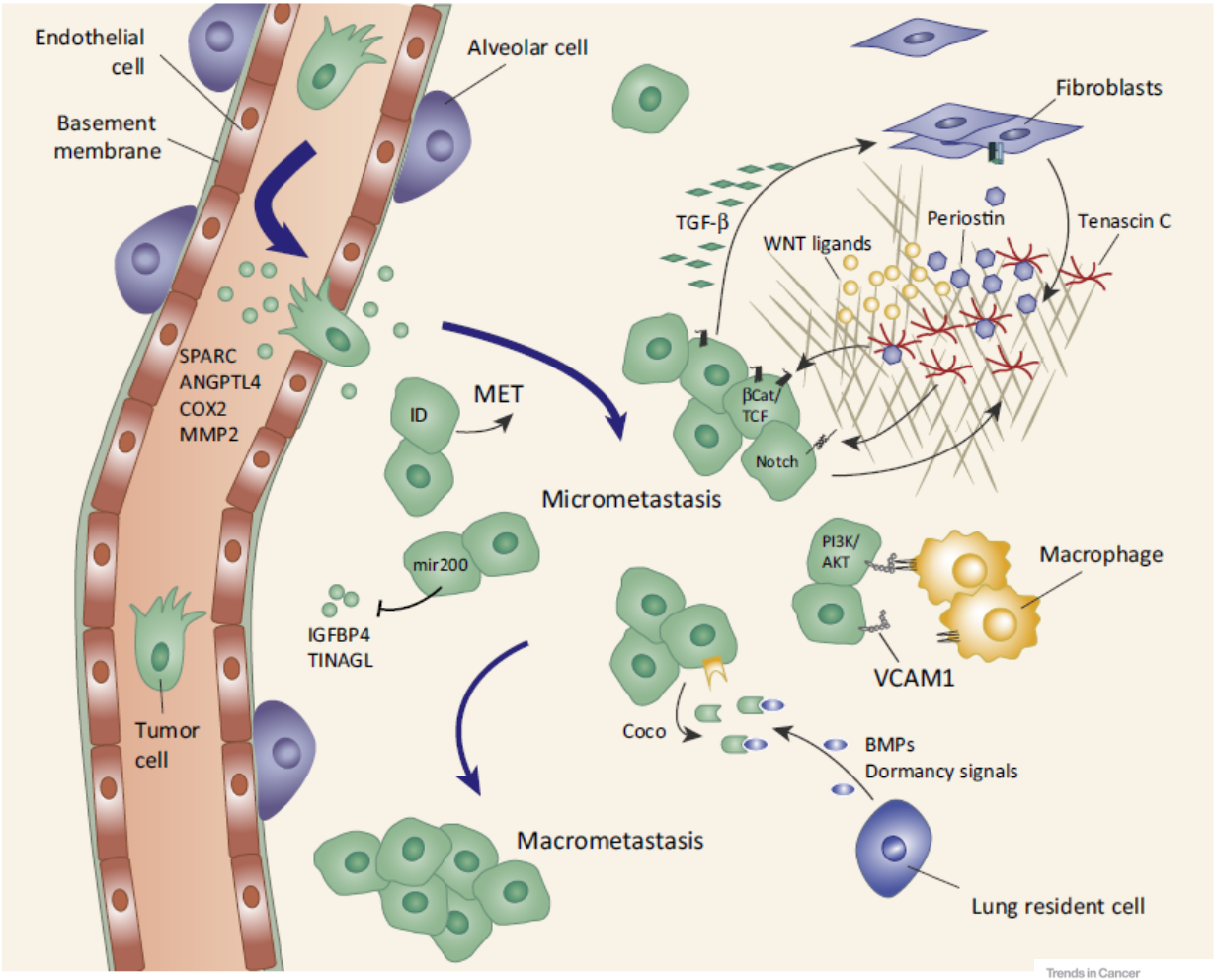
LETTERS

Genes that mediate breast cancer metastasis to the brain

Paula D. Bos[1], Xiang H.-F. Zhang[1], Cristina Nadal[1]†, Weiping Shu[1], Roger R. Gomis[1]†, Don X. Nguyen[1], Andy J. Minn[2], Marc J. van de Vijver[3], William L. Gerald[4], John A. Foekens[5] & Joan Massagué[1,6]

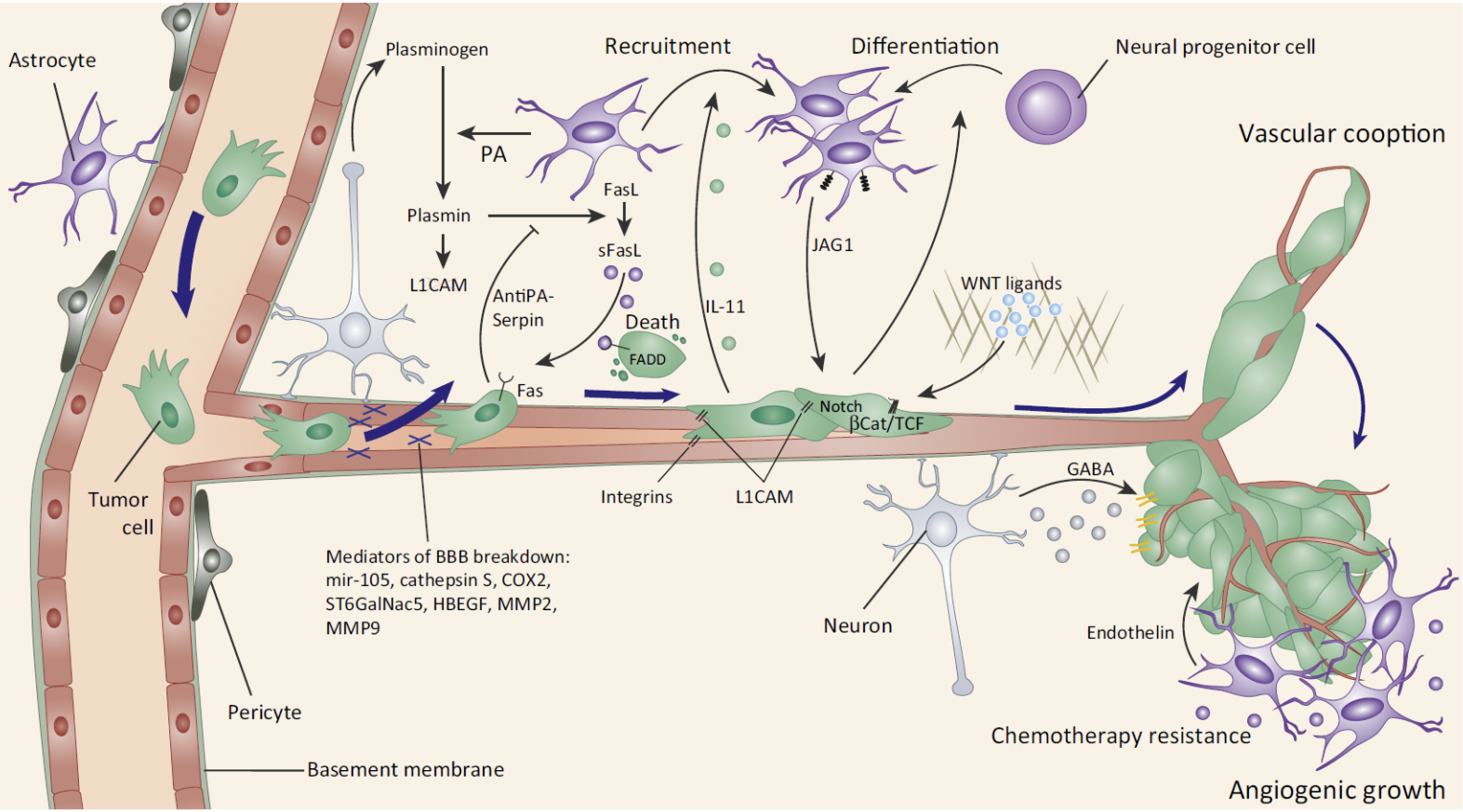


Metastatická kolonizace plic



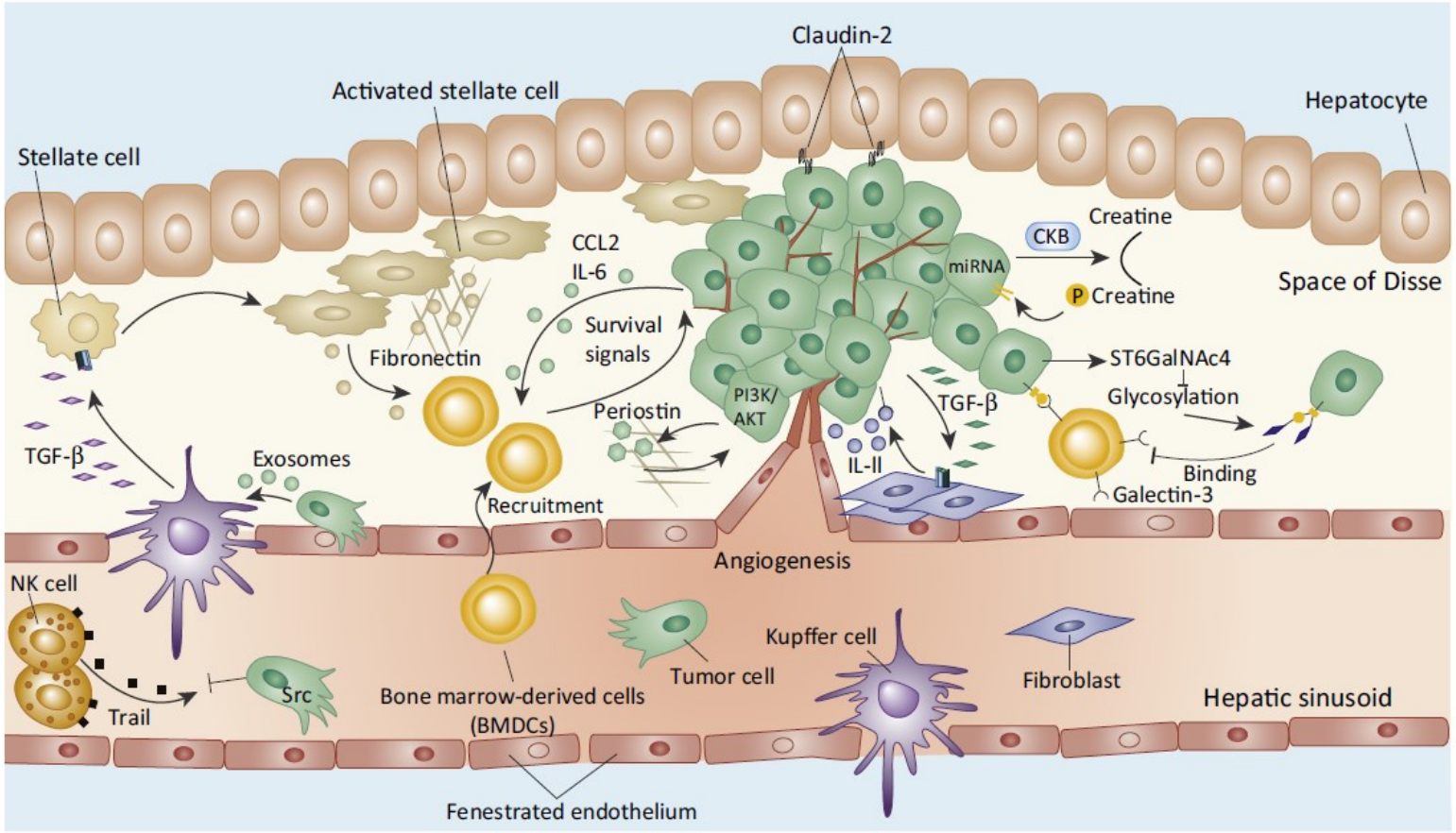
Trends in Cancer
CellPress
Review
Surviving at a Distance: Organ-Specific Metastasis
Anna C. Obenauf[1] and Joan Massagué[1,*]

Metastatická kolonizace mozku



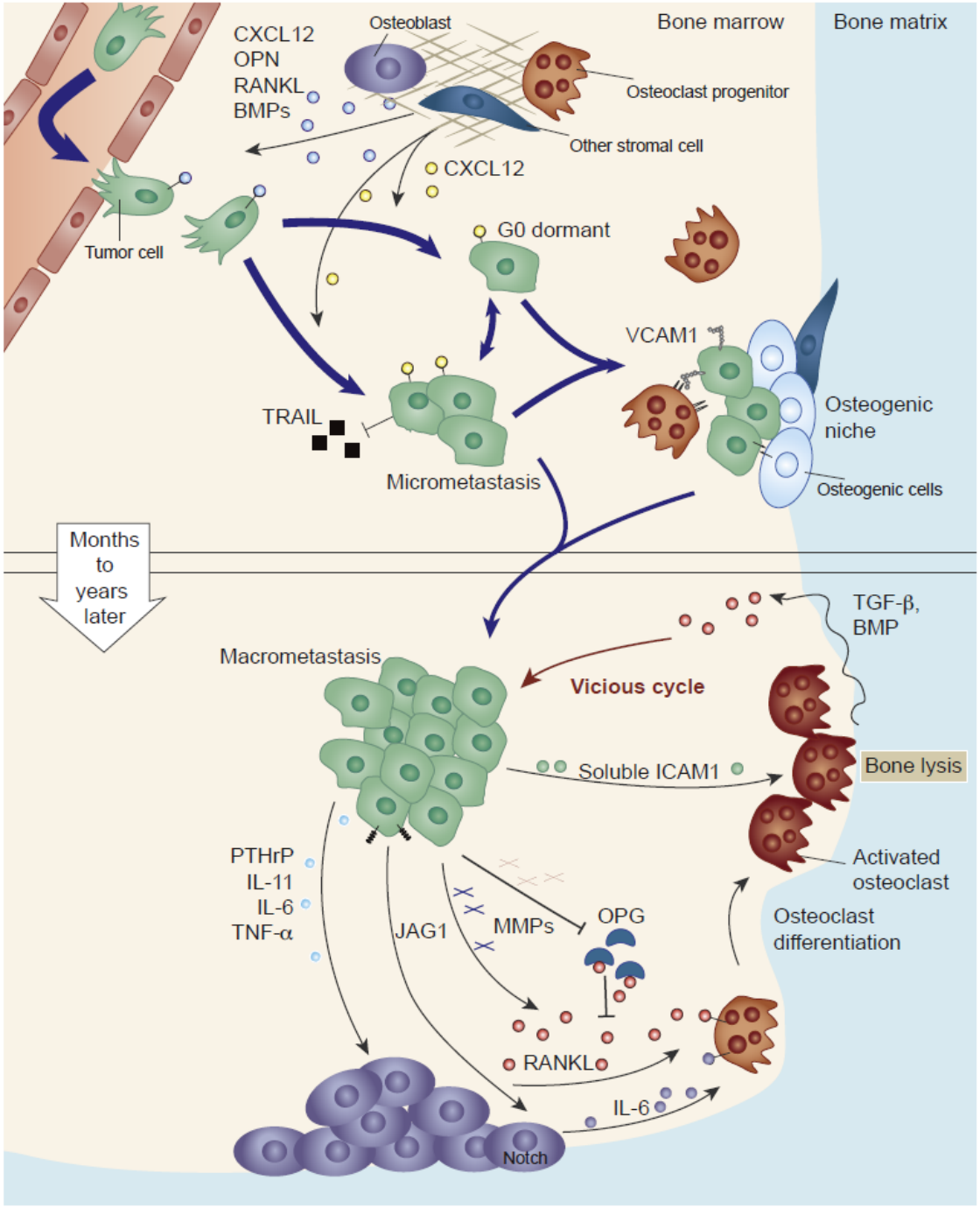
Trends in Cancer

Metastatická kolonizace jater



Trends in Cancer

Osteotropní metastáze



Trends in Cancer

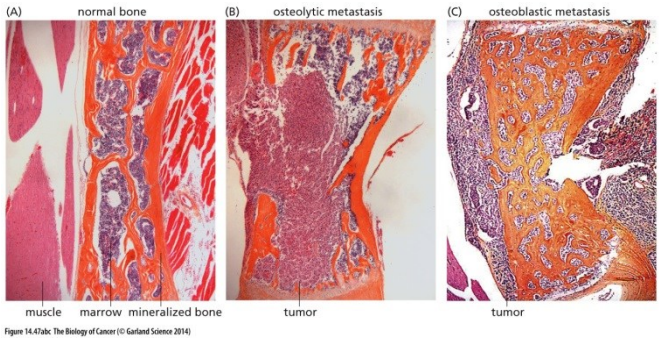


Figure 14.47abc The Biology of Cancer (© Garland Science 2014)

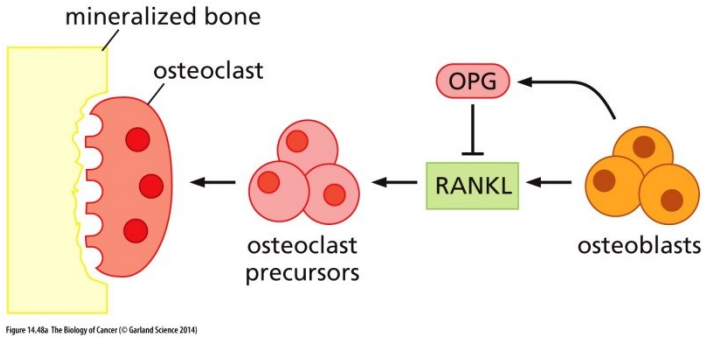


Figure 14.48a The Biology of Cancer (© Garland Science 2014)

Osteotropní metastáze

- Parathyroid hormone-related peptide (PTHrP)
- Během 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

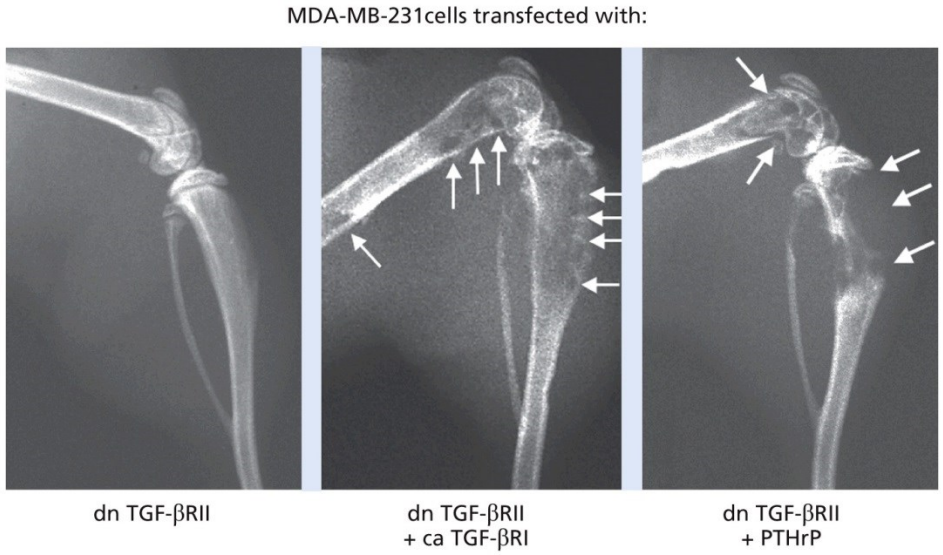


Figure 14.49 The Biology of Cancer (© Garland Science 2014)

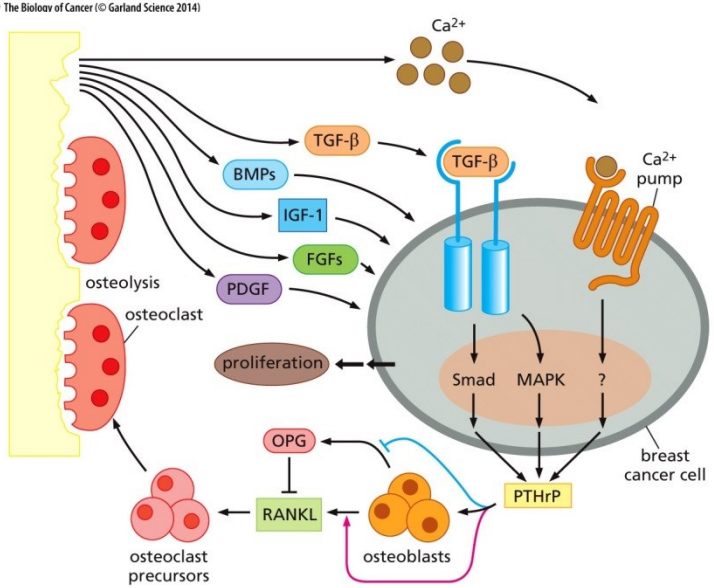
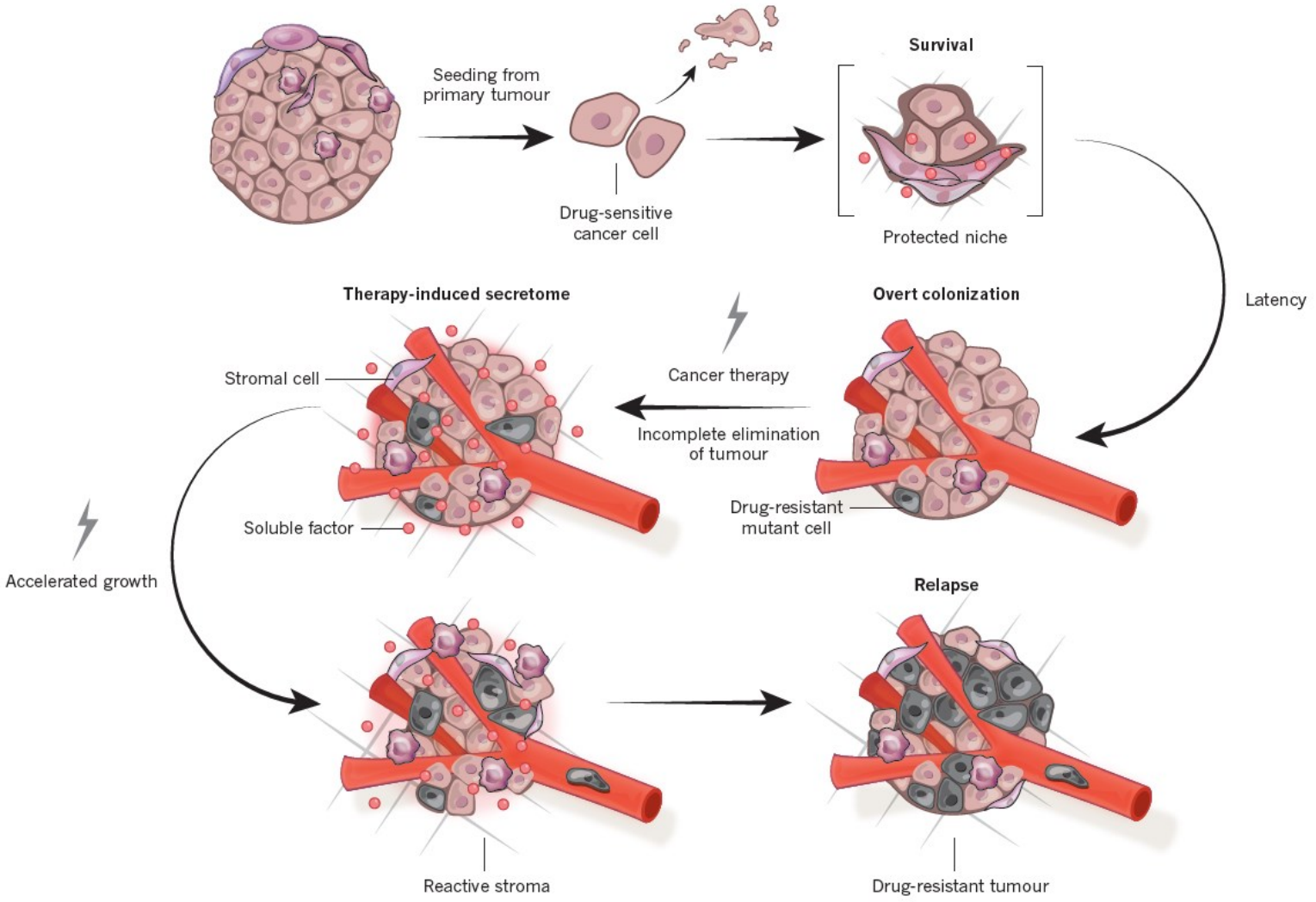


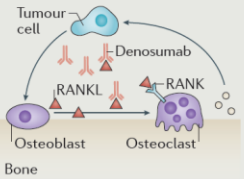
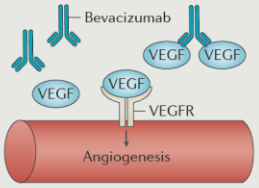
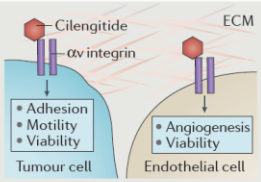
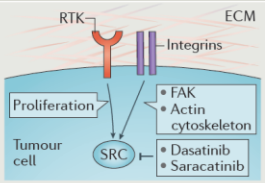
Figure 14.48b The Biology of Cancer (© Garland Science 2014)

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
Denosumab				
Monoclonal antibody to RANKL		RANKL activates osteoclasts and promotes bone destruction; denosumab reduced bone resorption in mice expressing human RANKL[29]	SREs* in metastatic setting; adjuvant trials used time to first bone metastasis or fracture[30–33]	FDA approved for prevention of SREs in solid tumours; approved as adjuvant therapy in prostate cancer
Bevacizumab				
Monoclonal antibody to VEGF		• Bevacizumab inhibited corneal angiogenesis and lymphangiogenesis[244] • In multiple cancer xenograft models, bevacizumab reduced primary tumour growth rates and, in some studies, enhanced survival. Reduced angiogenesis and vessel normalization was observed[245] • Prevention or, less frequently, abrogation of metastasis[246,247]	• Recurrent ovarian cancer, PFS[35,36] • Metastatic colorectal cancer, OS[260,261] • Metastatic or resistant HER2⁺ breast cancer, PFS[38] • Metastatic renal cancer, PFS[262] • Glioblastoma, OS, PFS[263] • Advanced lung cancer, OS[37] • Adjuvant therapy in triple-negative breast cancer, DFS[41]	• 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
Cilengitide				
αvβ3 and αvβ5 integrin peptide inhibitor		• Stabilization of glioma growth and angiogenesis. Synergistic inhibition of glioma with TMZ[61–64] • Synergy with therapeutics in melanoma primary tumour growth[63], synergy with radio-immunotherapy in breast cancer tumour growth[248] • Inhibition of metastasis[62] • Synergy with verapamil increased angiogenesis and reduced metastasis[249]	• Phase III CENTRIC EORTC, with radiation therapy and TMZ, for glioma, OS. Newly diagnosed glioma, same combination, recurrence[65] • Phase II trials in melanoma and lung and prostate cancers, PFS[66–68]	All advanced trials were negative
Dasatinib and saracatenib				
SRC kinase and BCR–ABL kinase inhibitor		• Inhibition of CML models[250] • Inhibition of primary tumour growth in multiple model systems, as monotherapy or in combination[251–253] • Prevention of metastasis in multiple cancer model systems[254–258], but not osteosarcoma[259] • Inhibition of prostate cancer growing in bone and bone remodelling[82,83]	• Cytogenetic response end points for CML • Response for advanced solid tumours[71–80] • OS in Phase III prostate cancer[87]	• 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-κB; 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.

NATURE REVIEWS | CANCER

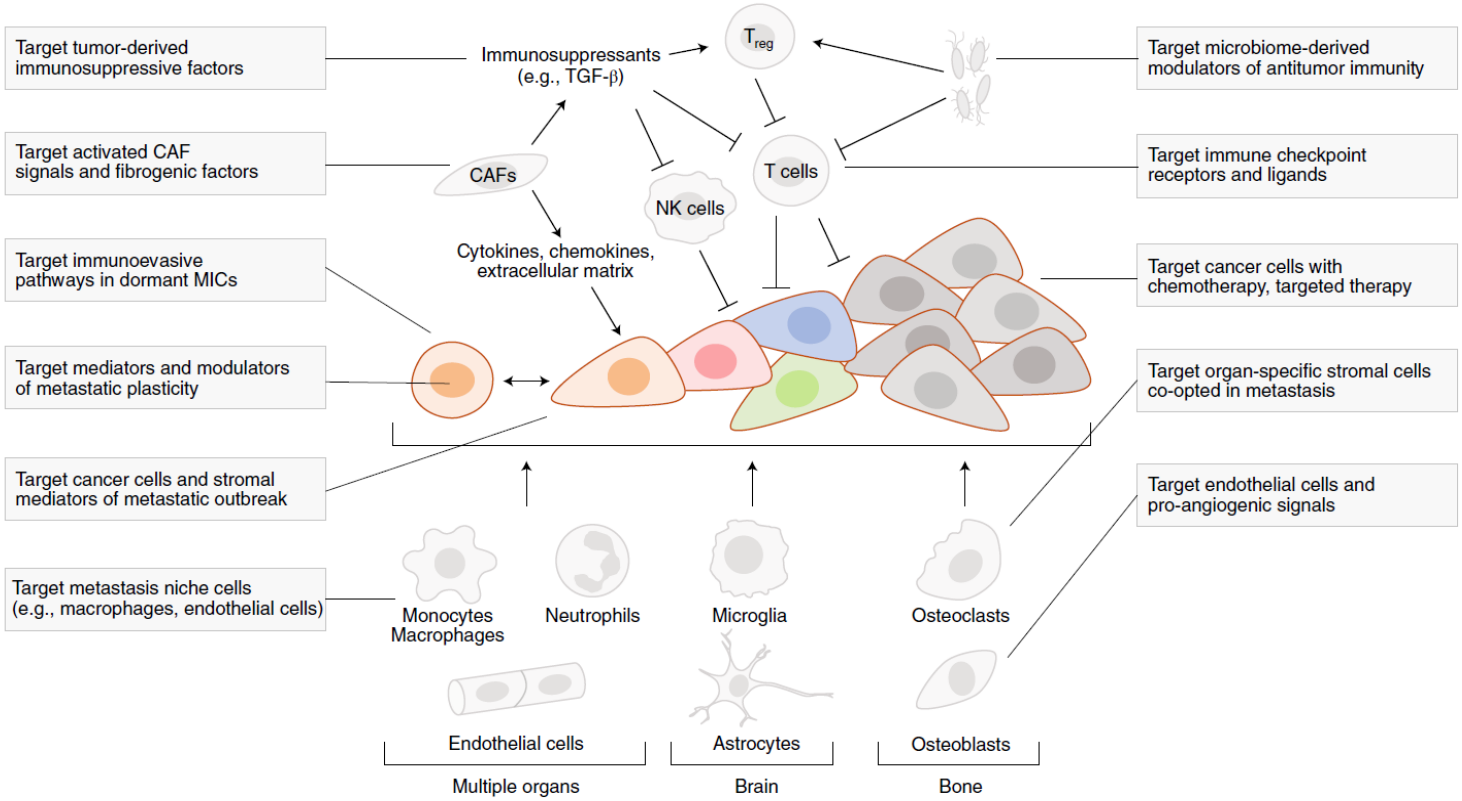


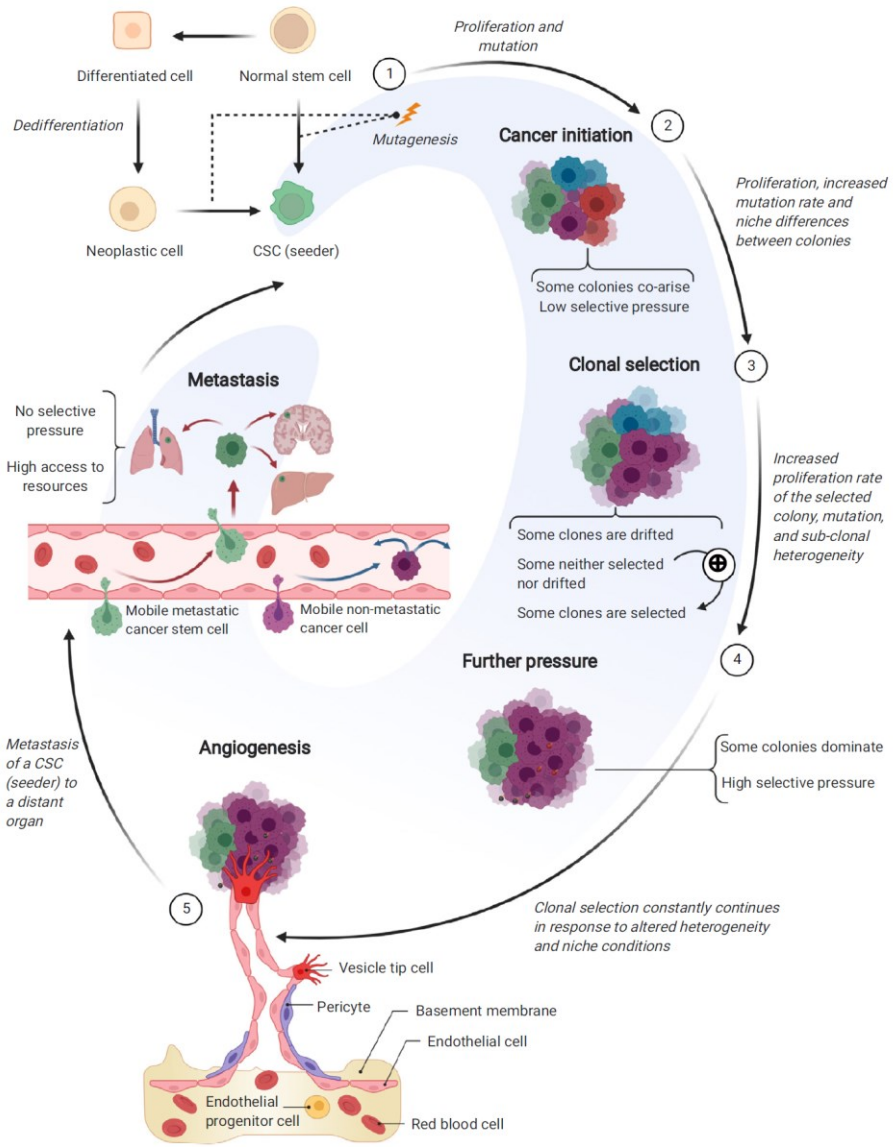
Fig. 3 | Classic and new opportunities for the treatment of metastatic cancer. Targeting cancer cells with chemotherapy and targeted therapies is a mainstay of metastasis prevention and treatment. However, the recent success of ICI therapy demonstrates the value of targeting specific components of the tumor stroma (T cells) to treat metastasis. Leveraging recent insights into the regenerative origins, phenotypic plasticity, immune evasion and organ-specific colonization strategies of MICs could yield more potent approaches to prevent metastasis by targeting its cryptic phase during dormancy and micrometastasis and to augment the efficacy of ICI and other therapies by more effective elimination of drug-resistant macrometastatic disease. CAFs, cancer-associated fibroblasts; T_{reg}, regulatory T cells; NK, natural killer cells; TGF-β, transforming growth factor-β.

REVIEW ARTICLE
https://doi.org/10.1038/s41591-020-01195-4

Targeting metastatic cancer

Karuna Ganesh[1,2] and Joan Massagué[3]

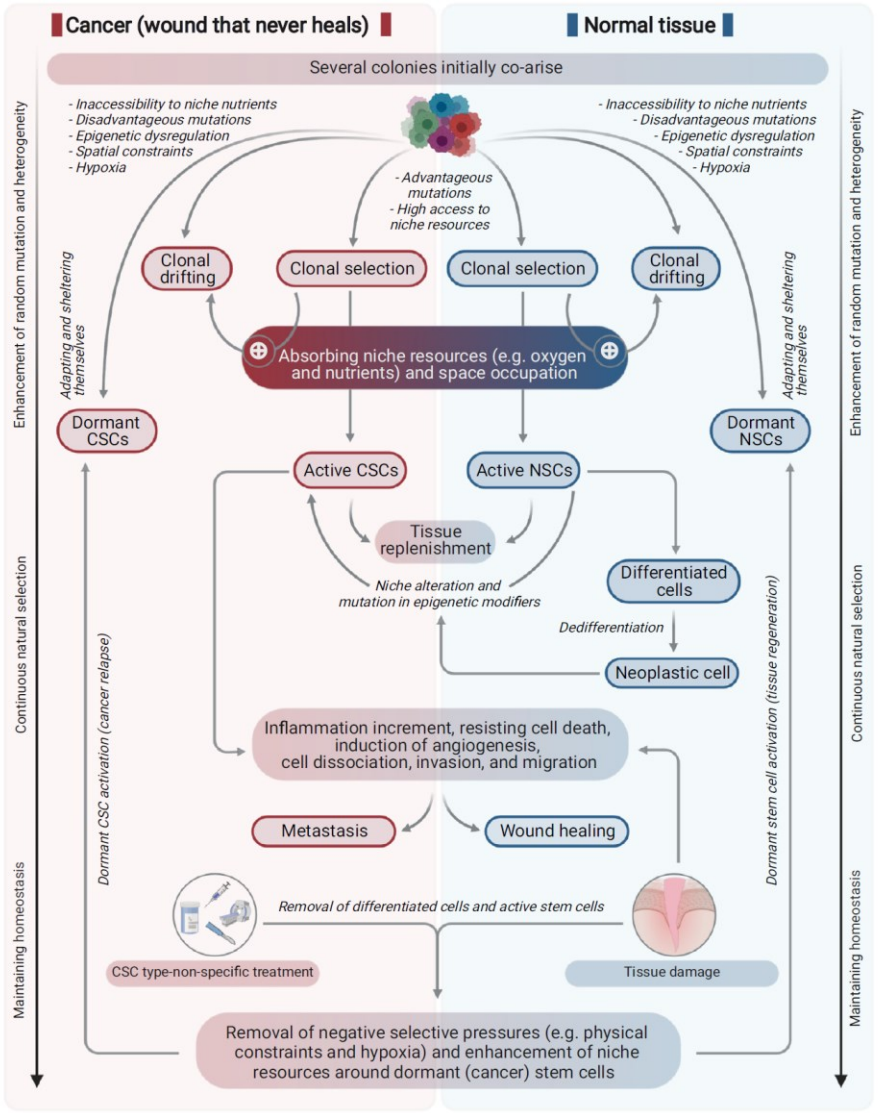
Selektivní tlak řídí proces selekce a driftingu během vývoje rakoviny



Trends in Genetics

https://doi.org/10.1016/j.tig.2023.01.007

Paralely v klonální selekci/driftu mezi vývojem rakoviny a normální tkáně a jejich přechodem.



https://doi.org/10.1016/j.tig.2023.01.007

Shrnutí

- 90% úmrtí na nádorová onemocnění souvisí s metastázováním
- Invazivní kaskáda zahrnuje: lokální invazi, intravazaci, transport, extravazaci, formovaní 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 a specifikými molekulárními mechanismy

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 iniciální 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?

Science Spotlight lecture: Joan Massagué, PhD

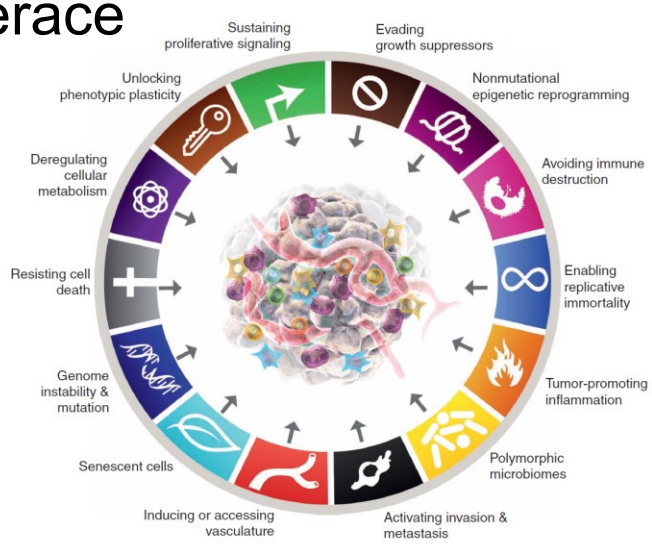
- https://www.youtube.com/watch?v=SWzcAND9f5A

ZÁNĚT, NÁDOROVÉ MIKROPROSTŘEDÍ A NEOANGIOGENEZE

Karel Souček
E-mail: ksoucek@ibp.cz, tel.: 541 517 166

Typické znaky nádorové buňky

- podpůrné proliferační signály
- deregulace supresorů růstu/proliferace
- odolnost k buněčné smrti
- neomezená replikace
- neoangiogeneze
- invaze a metastázování
- mutace a genomická nestabilita
- zánět
- přestavba energetického metabolismu
- únik před zničením imunitním systémem
- *senescence*
- *plasticita*
- *epigenetika*
- *mikrobiom*



Douglas Hanahan & Robert A. Weinberg: Hallmarks of Cancer: Next Generation, Cell, 2011
Douglas Hanahan: Hallmarks of Cancer: New Dimension, Cancer Discovery, 2022

Stromální komponenta karcinomu

duktální karcinom prsu

karcinom střeva

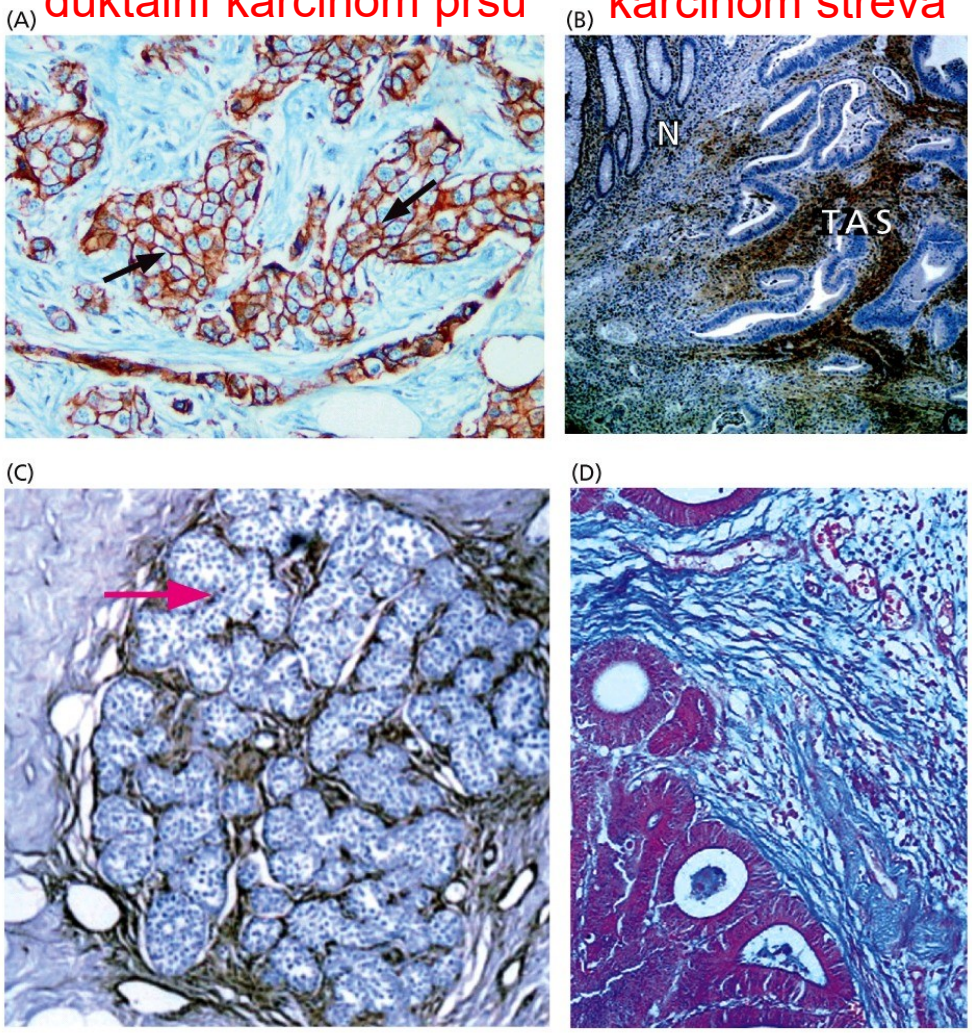


Figure 13.1 The Biology of Cancer (© Garland Science 2014)

lobulární karcinom prsu

adenokarcinom žaludku

Variabilita poměru neoplastických buněk a stromatu

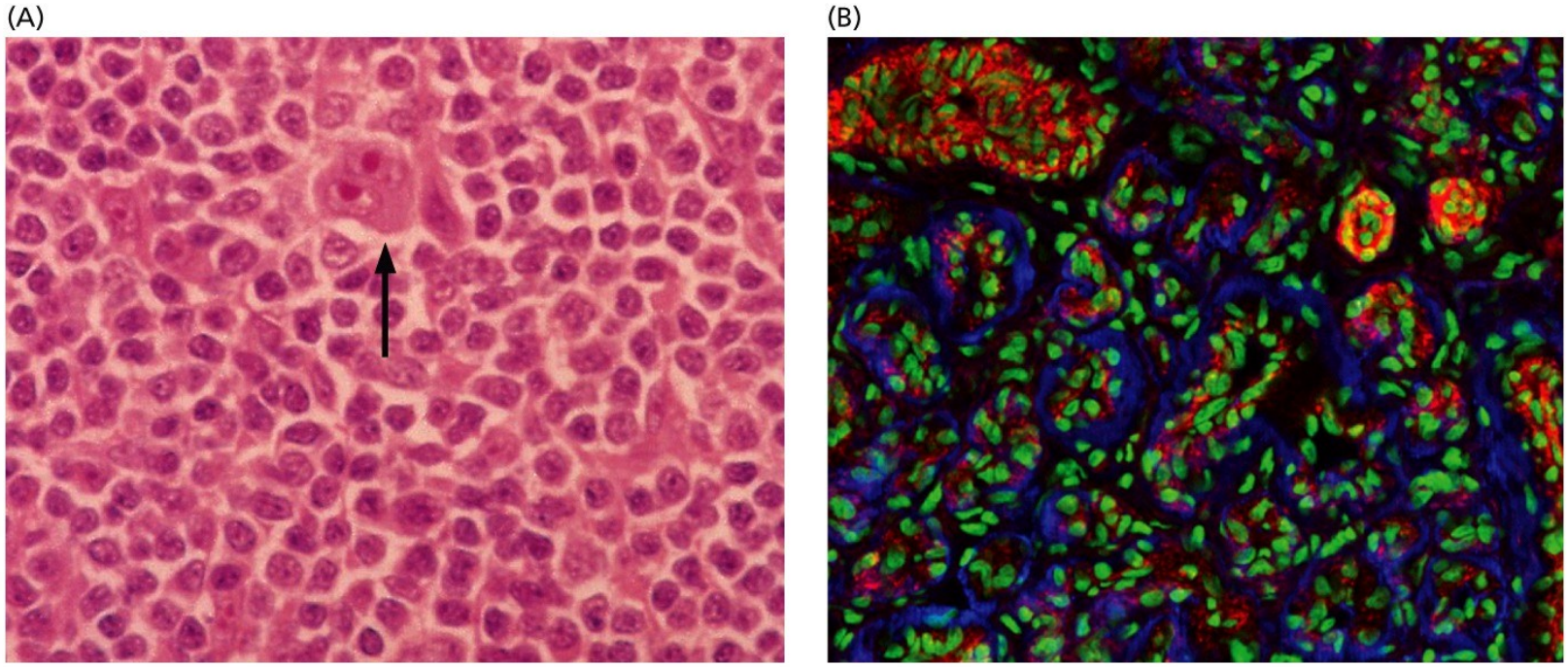


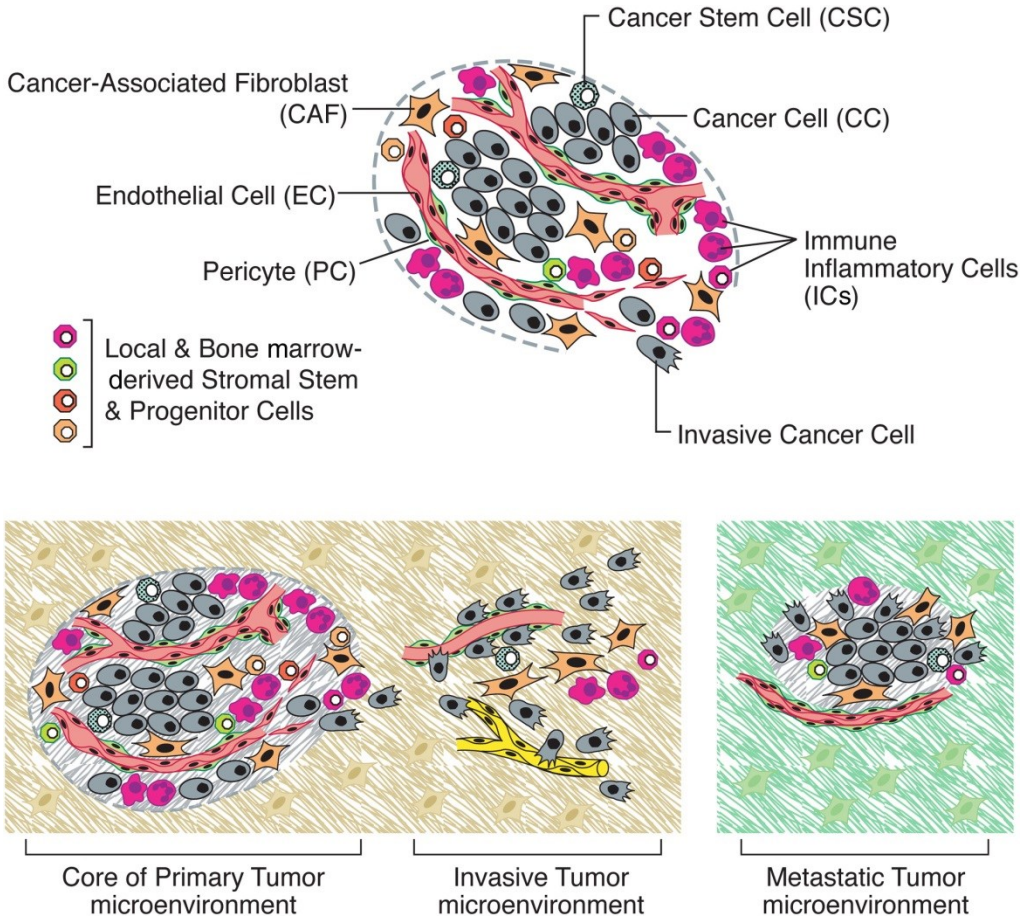
Figure 13.2 The Biology of Cancer (© Garland Science 2014)

Příklad:

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

Základní principy a znaky karcinogeneze

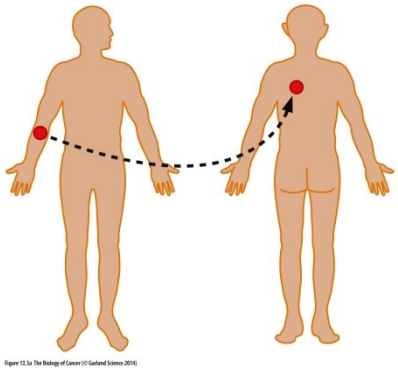
- Rakovina není onemocnění jedné buňky

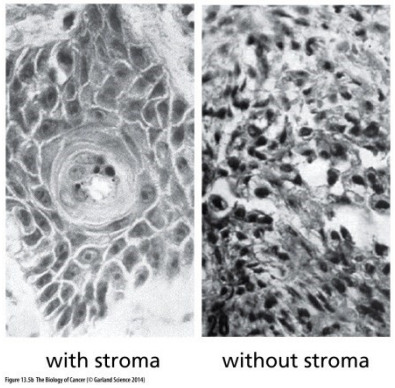


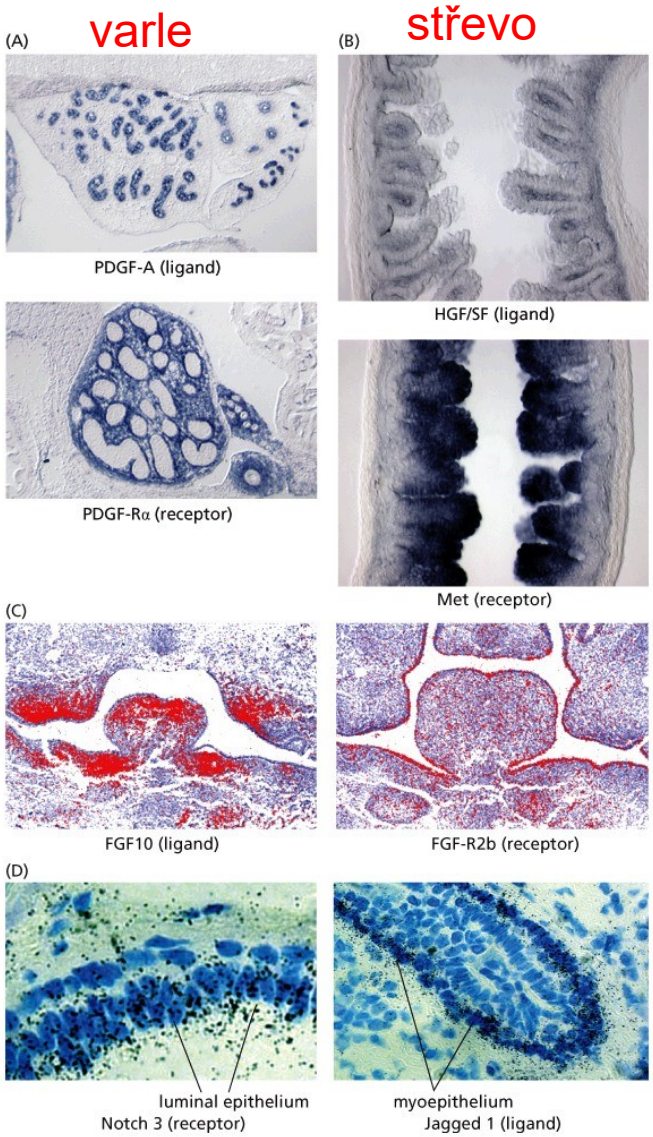
Cell 2011 144, 646-674DOI: (10.1016/j.cell.2011.02.013)

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







Ústní dutina

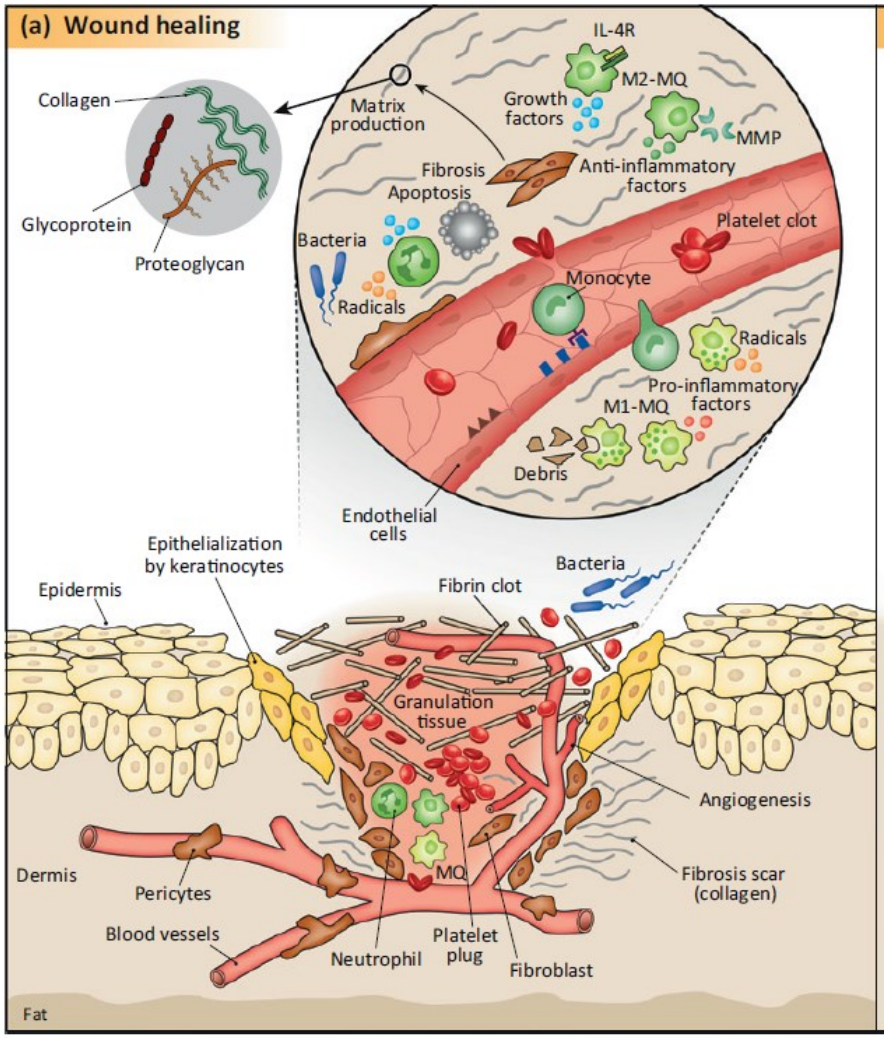
Prsní žláza

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

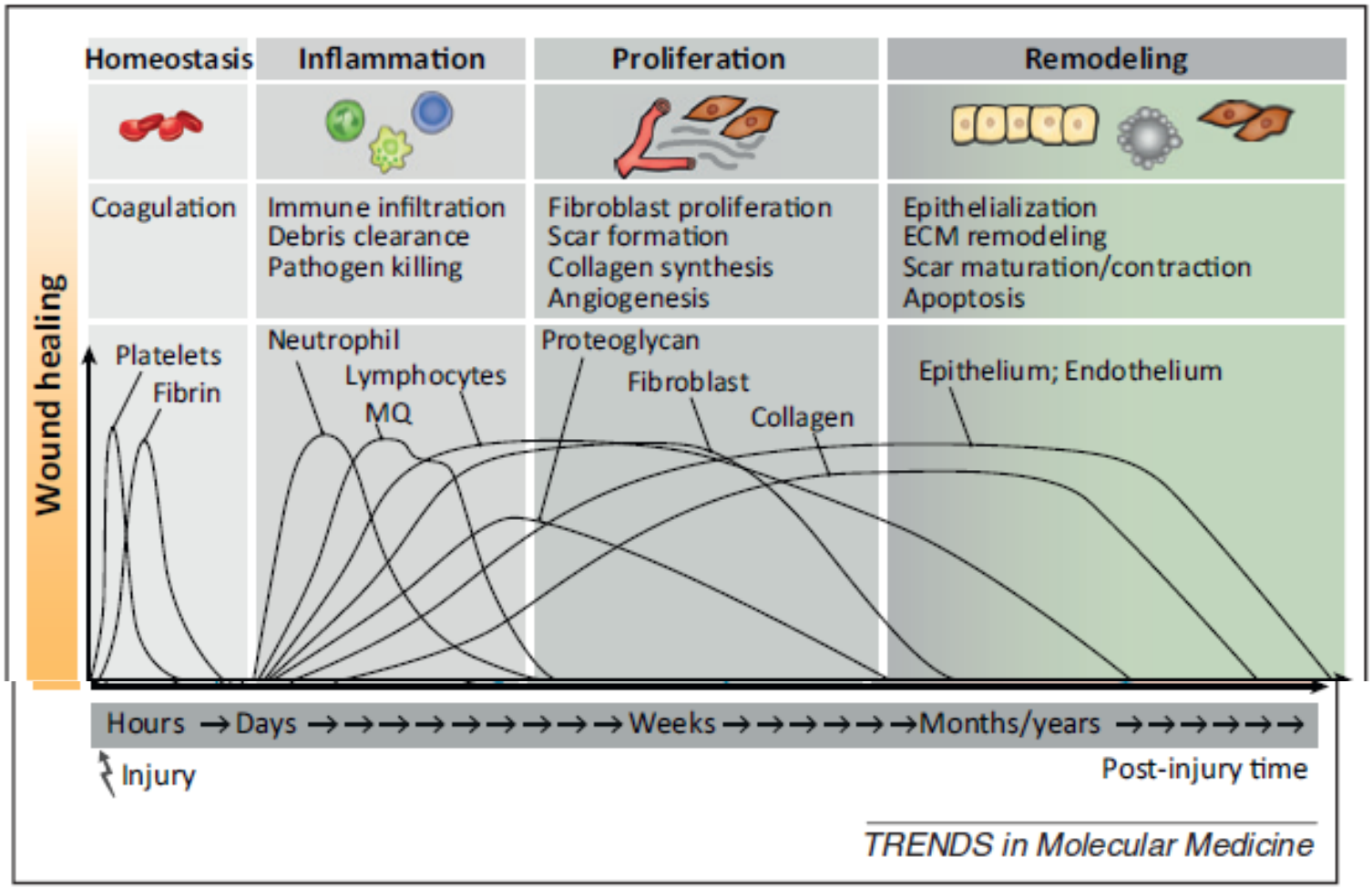
Hojení rány

- 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 endoteliáních 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


(a) Wound healing
Collagen
Glycoprotein
Proteoglycan
Matrix production
IL-4R
M2-MQ
Growth factors
MMP
Fibrosis
Apoptosis
Anti-inflammatory factors
Bacteria
Radicals
Platelet clot
Monocyte
Radicals
Pro-inflammatory factors
M1-MQ
Debris
Endothelial cells
Epithelialization by keratinocytes
Epidermis
Bacteria
Fibrin clot
Granulation tissue
Angiogenesis
Dermis
Pericytes
Blood vessels
MQ
Neutrophil
Platelet plug
Fibroblast
Fibrosis scar (collagen)
Fat

Hojení rány


Homeostasis
Inflammation
Proliferation
Remodeling
Coagulation
Immune infiltration
Debris clearance
Pathogen killing
Fibroblast proliferation
Scar formation
Collagen synthesis
Angiogenesis
Epithelialization
ECM remodeling
Scar maturation/contraction
Apoptosis
Wound healing
Platelets
Fibrin
Neutrophil
Lymphocytes
MQ
Proteoglycan
Fibroblast
Collagen
Epithelium; Endothelium
Hours → Days → → → → → → → → → Weeks → → → → → → Months/years → → → → → →
Injury
Post-injury time
TRENDS in Molecular Medicine

Nádor – nehojící se rána

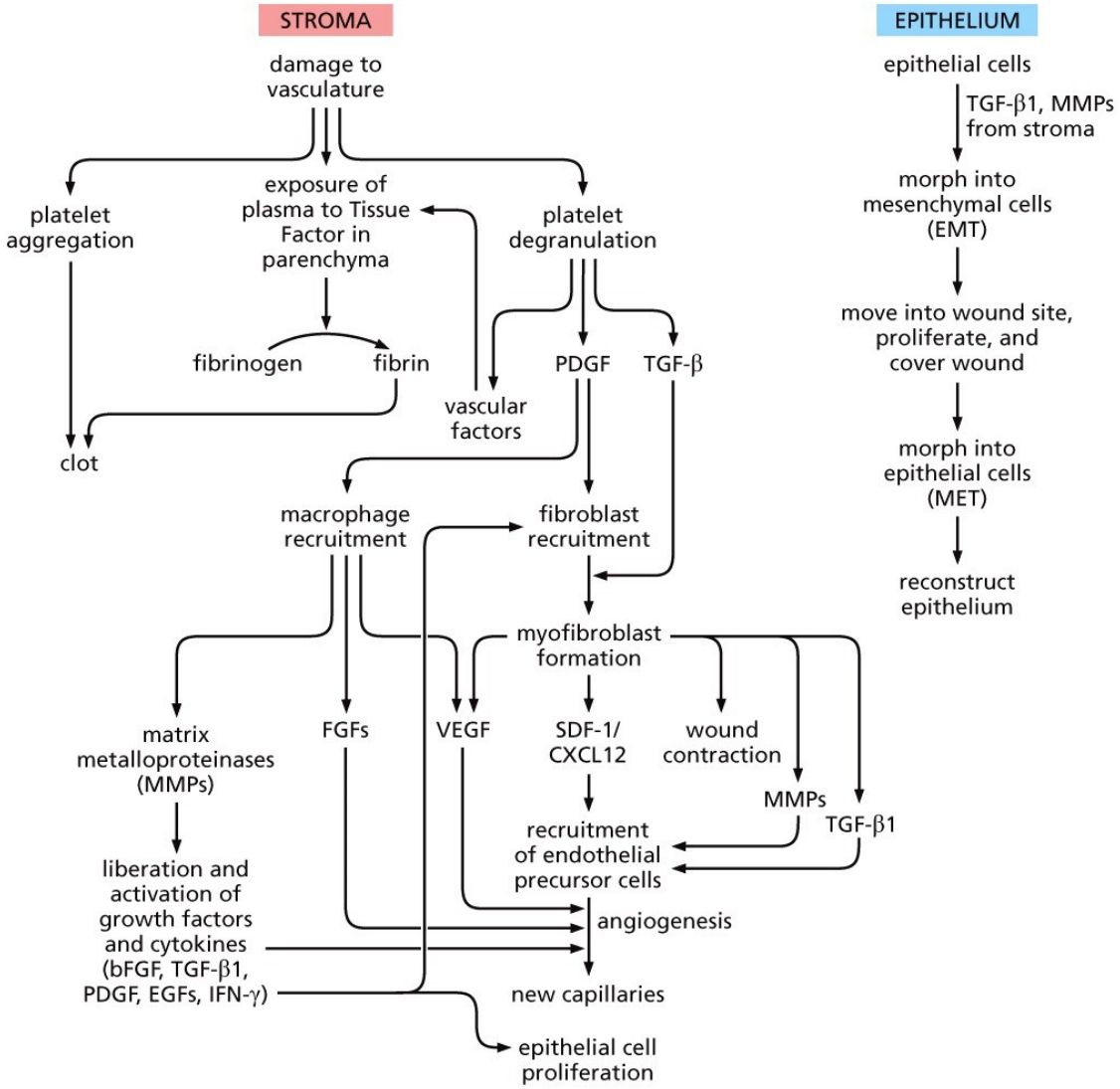
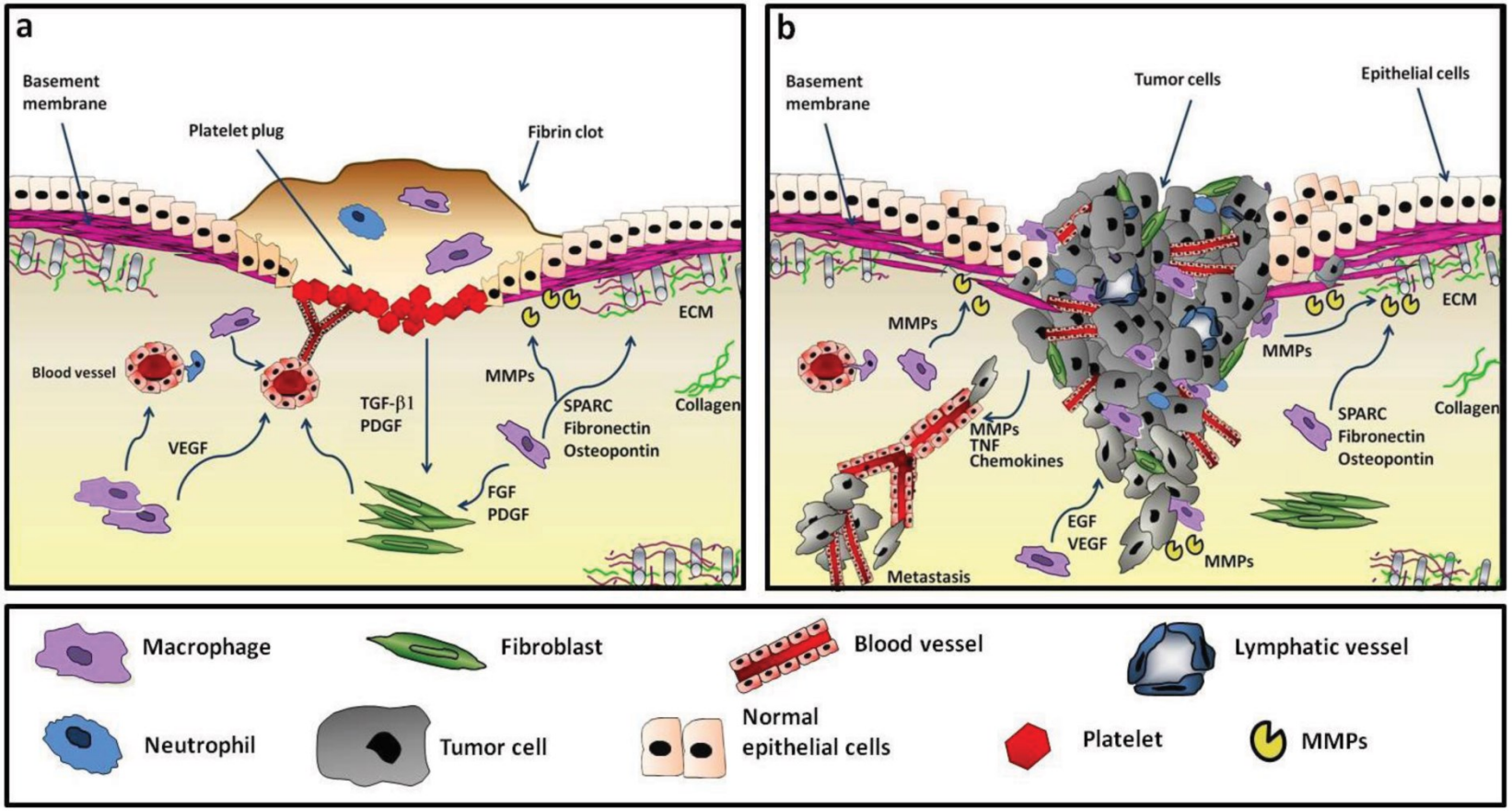


Figure 13.11 The Biology of Cancer (© Garland Science 2014)

Nádor – nehojící se rána



Remodelace epiteliální tkáně během hojení, EMT, MET

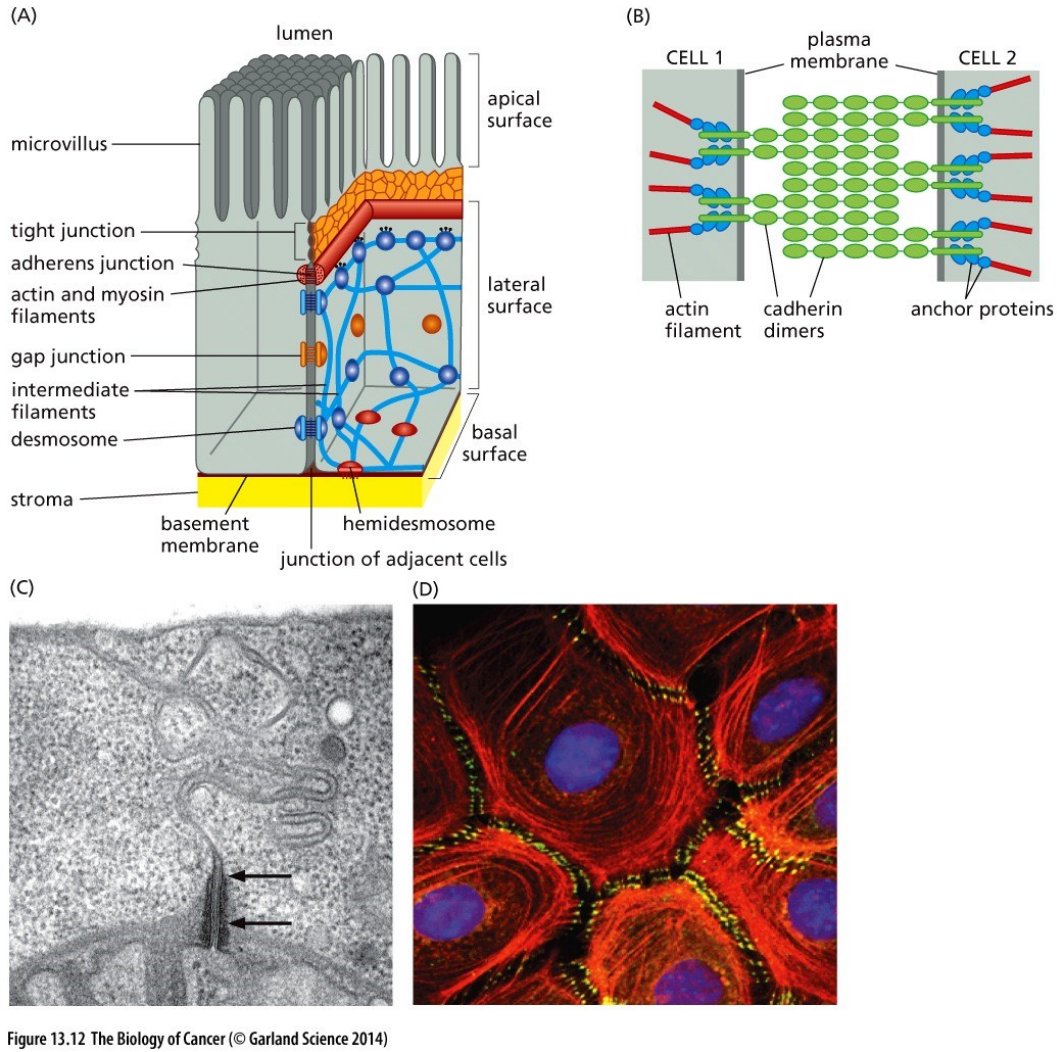


Figure 13.12 The Biology of Cancer (© Garland Science 2014)

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

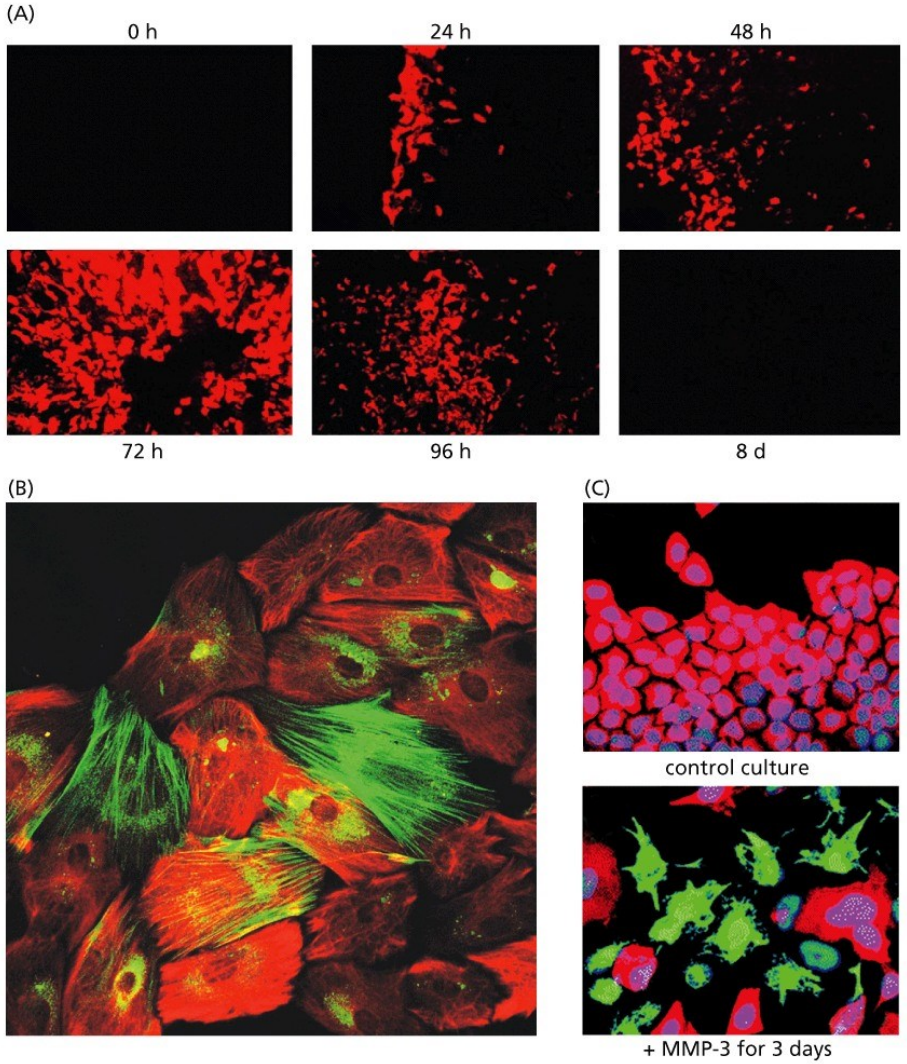
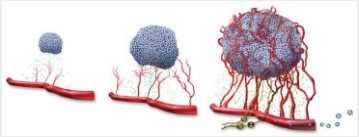


Figure 13.13 The Biology of Cancer (© Garland Science 2014)

Neoangiogeneze



- nádor, stejně jako zdravá tkáň, vyžaduje přísun živin a kyslíku a odvod metabolitů a CO_2
- 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

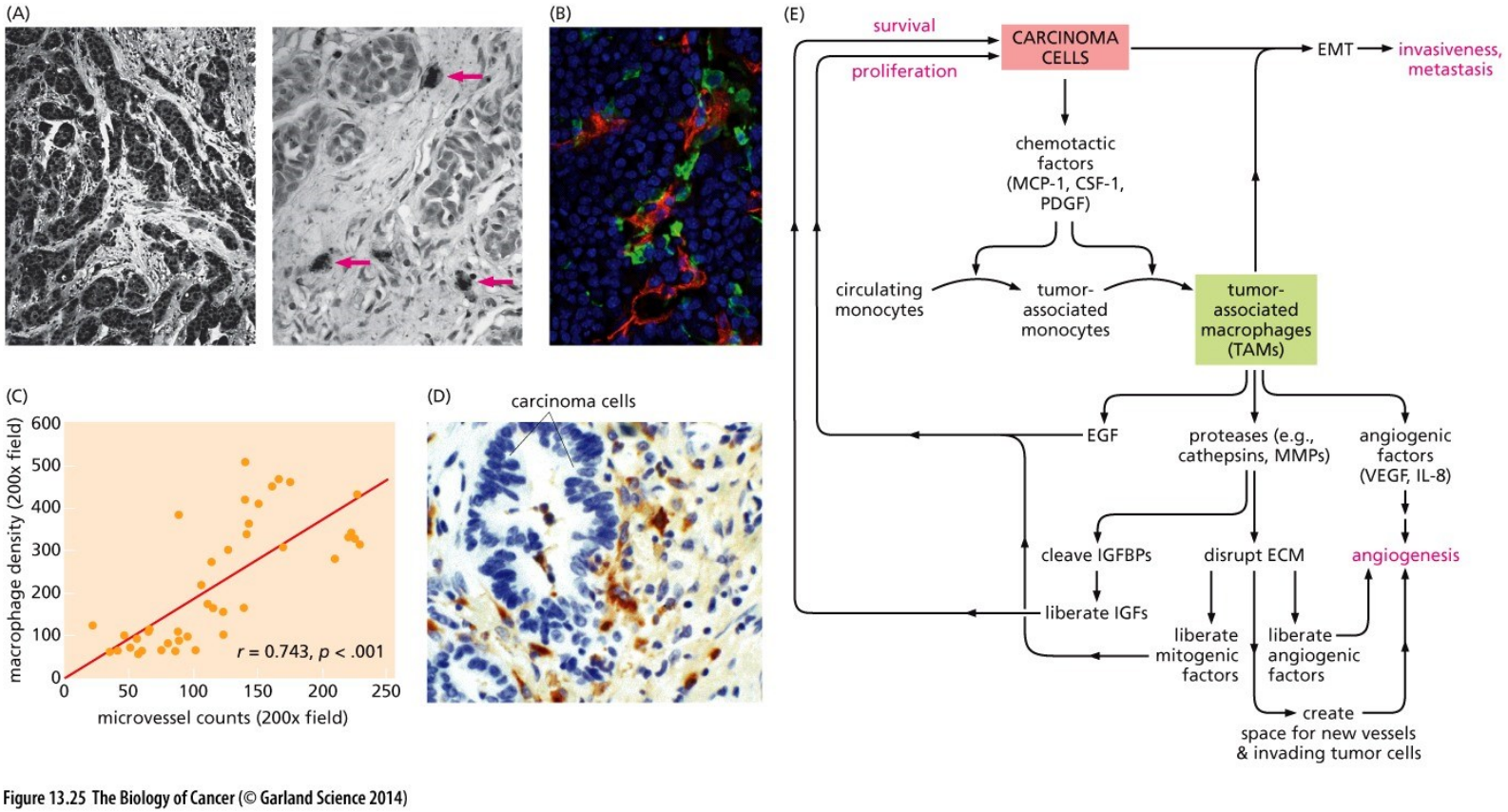


Figure 13.25 The Biology of Cancer (© Garland Science 2014)

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

Hypoxie, neoangiogeneze

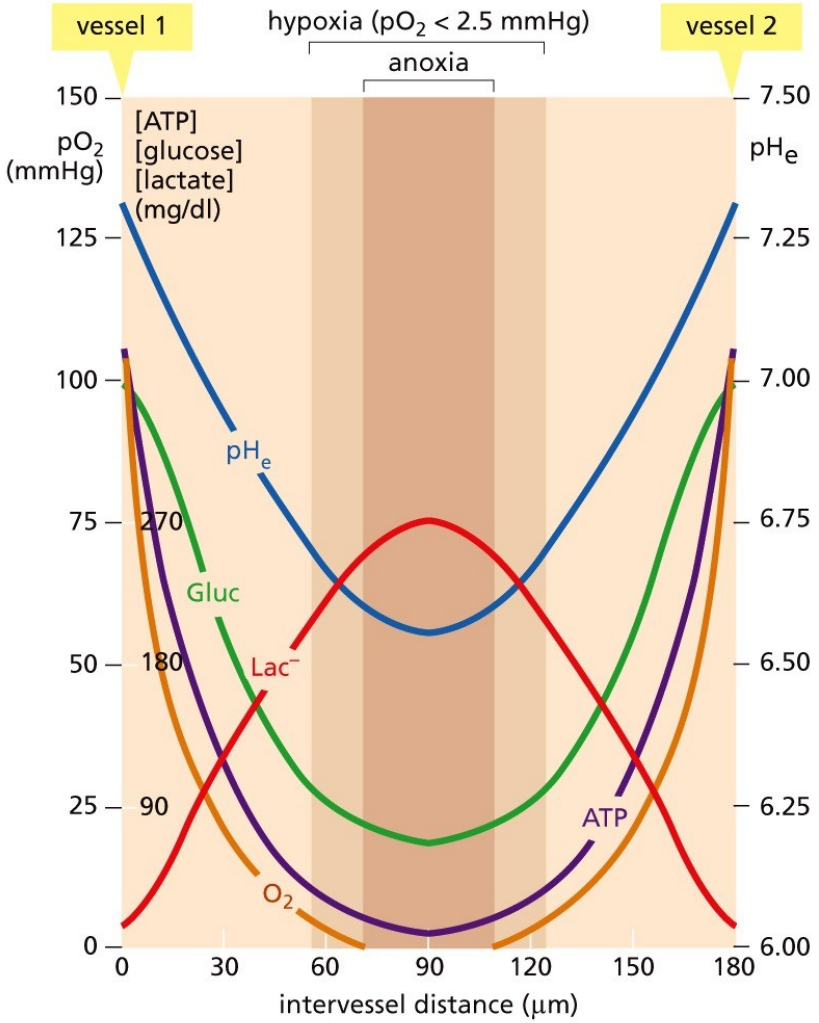


Figure 13.27d The Biology of Cancer (© Garland Science 2014)

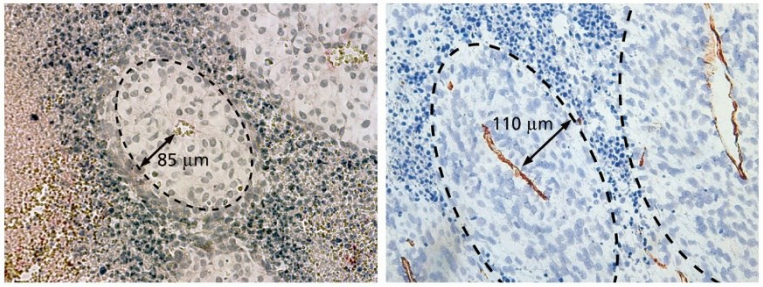


Figure 13.27b The Biology of Cancer (© Garland Science 2014)

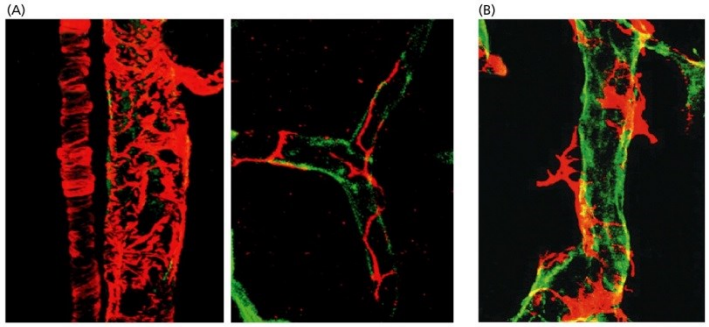


Figure 13.32 The Biology of Cancer (© Garland Science 2014)

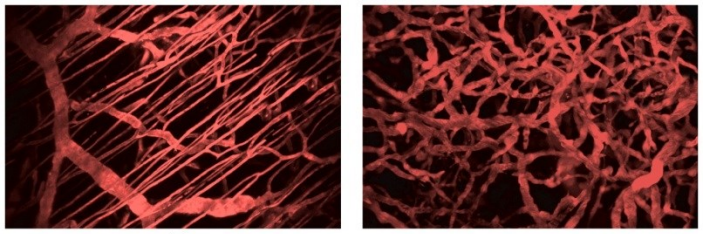


Figure 13.33b The Biology of Cancer (© Garland Science 2014)

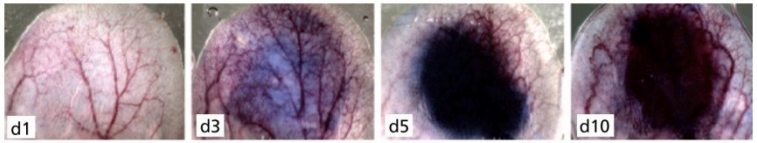


Figure 13.34c The Biology of Cancer (© Garland Science 2014)

Angiogeneze a klinická prognóza

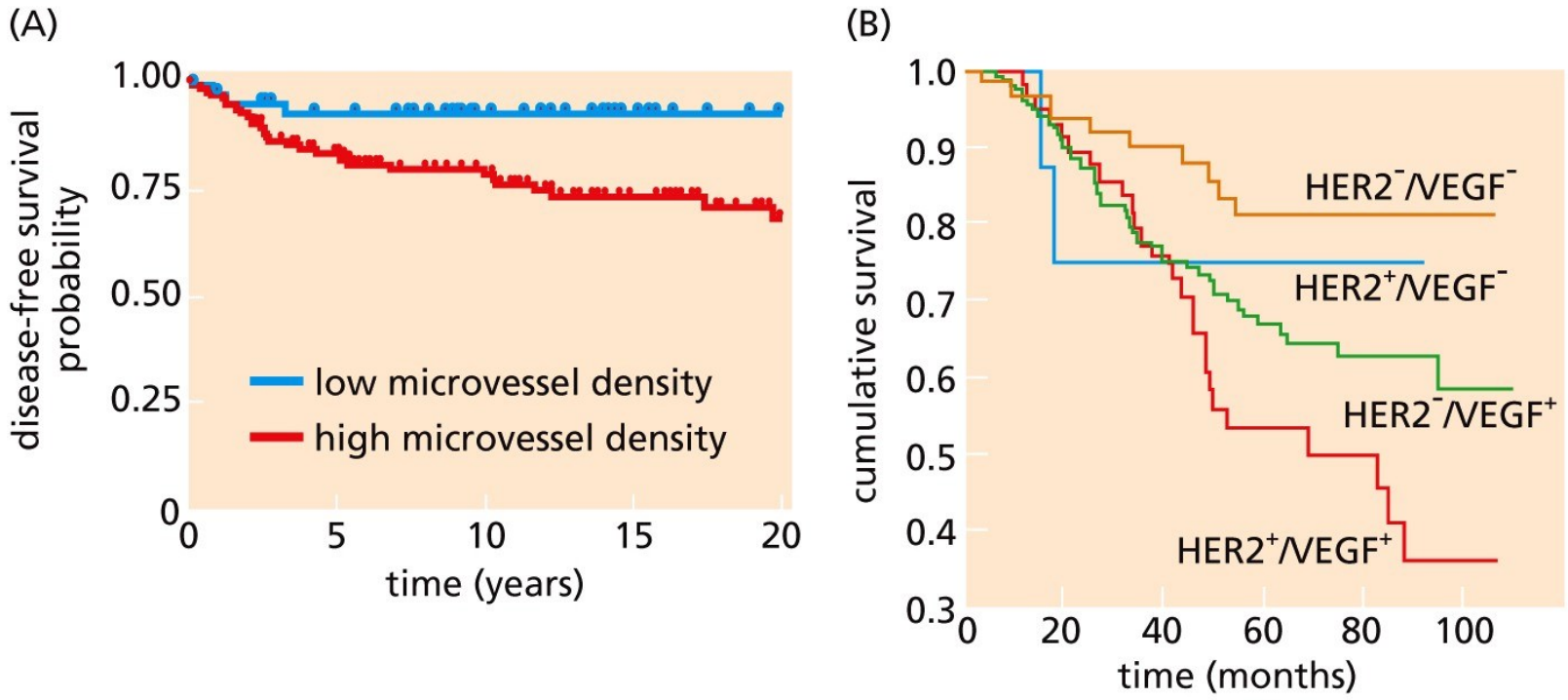


Figure 13.41 The Biology of Cancer (© Garland Science 2014)

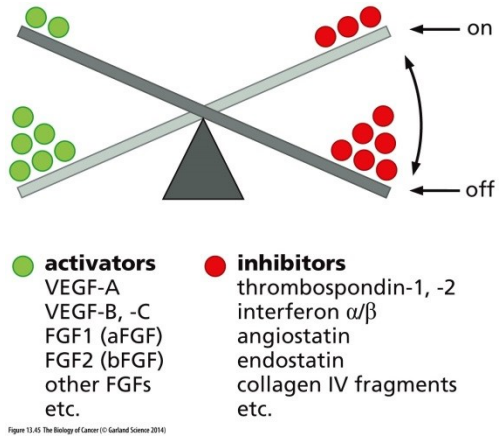


Figure 13.45 The Biology of Cancer (© Garland Science 2014)

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)
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.
[b] Improvement relative to standard treatment.
[c] FDA approval for use against breast cancer was revoked in 2011.
[d] First-line therapy.
[e] Second-line therapy. Axitinib was approved because PFS was 2.0 months longer than existing Sorafenib treatment.
[f] Monotherapy.
[g] Inhibitor of VEGF-R, PDGF-R, FLT-3, Ret, and Kit TKs; Raf/B-Raf.
[h] Low–molecular-weight inhibitor of VEGF-Rs and PDGF-Rs.
[i] Inhibitor 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

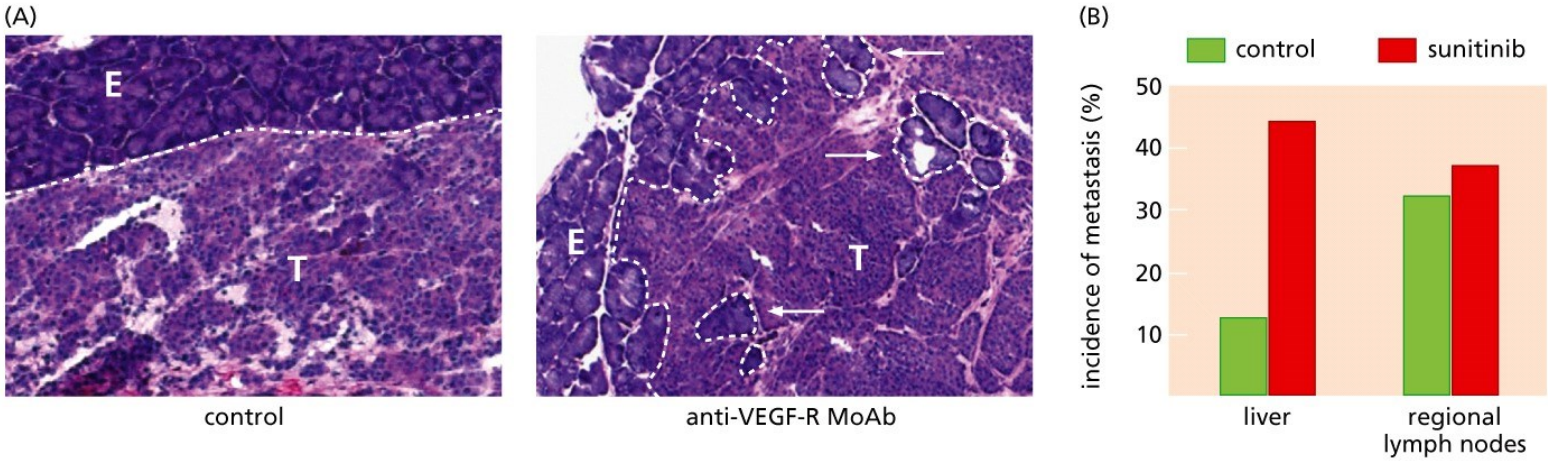


Figure 13.48 The Biology of Cancer (© Garland Science 2014)

Heterotypické interakce jako cíl protinádorové léčby

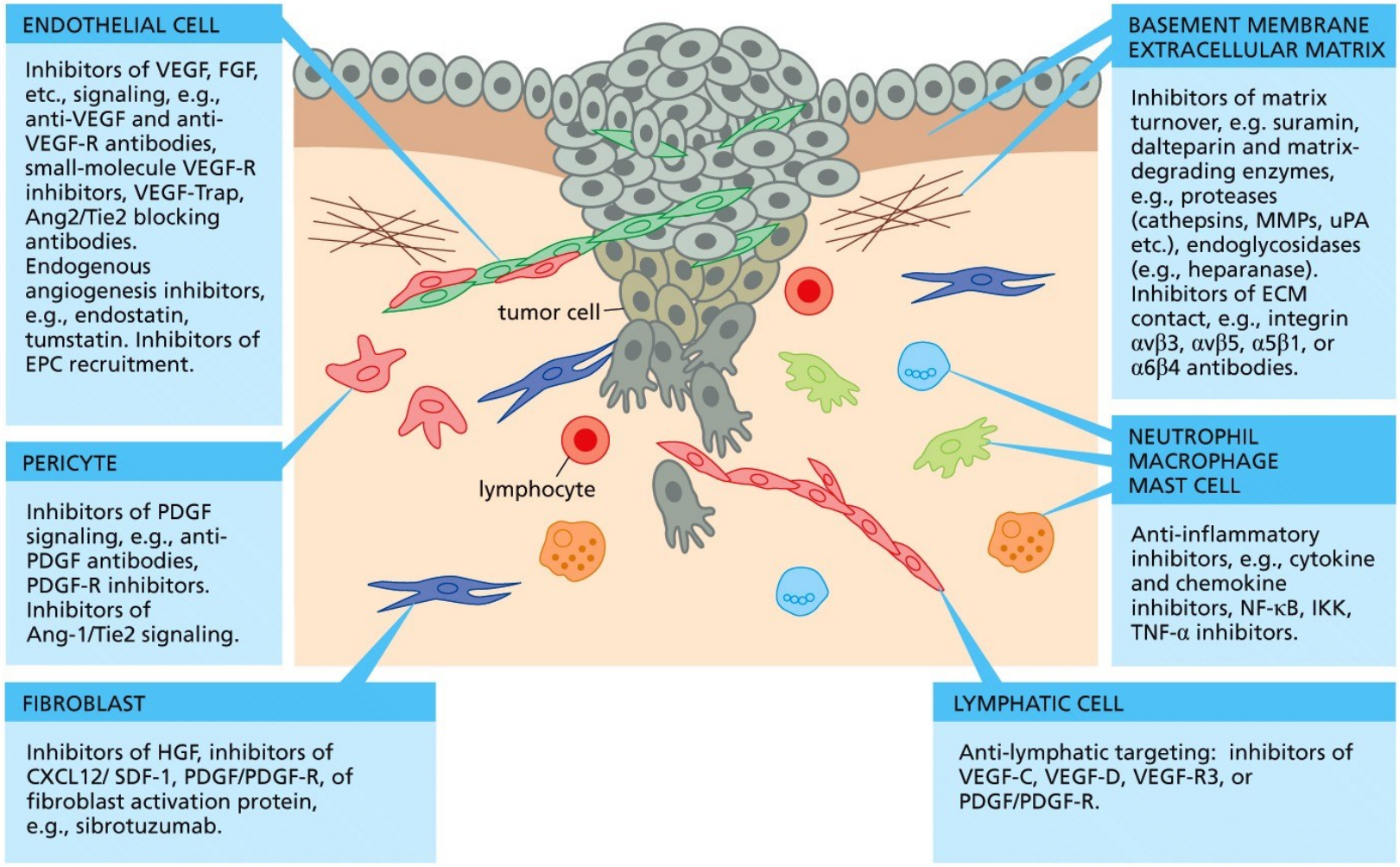
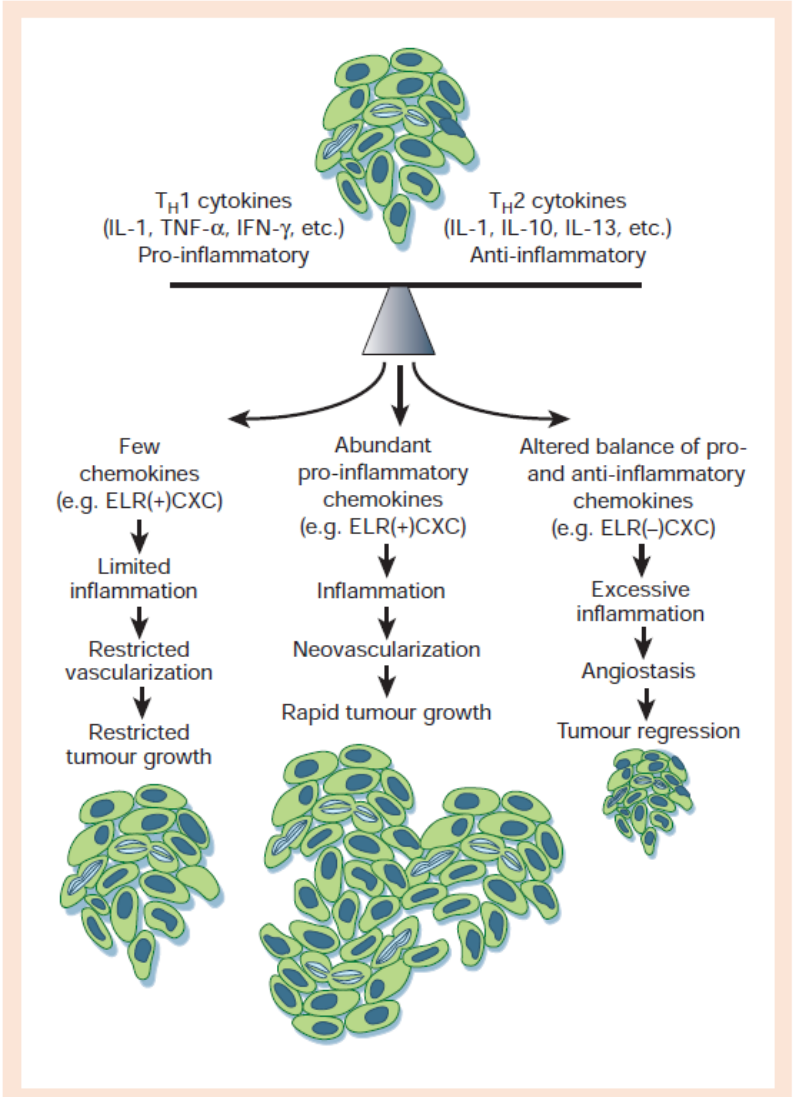


Figure 13.49 The Biology of Cancer (© Garland Science 2014)

Cytokiny a nádorová progrese



NATURE | VOL 420 | 19/26 DECEMBER 2002 |

Zánět a nádorová progrese

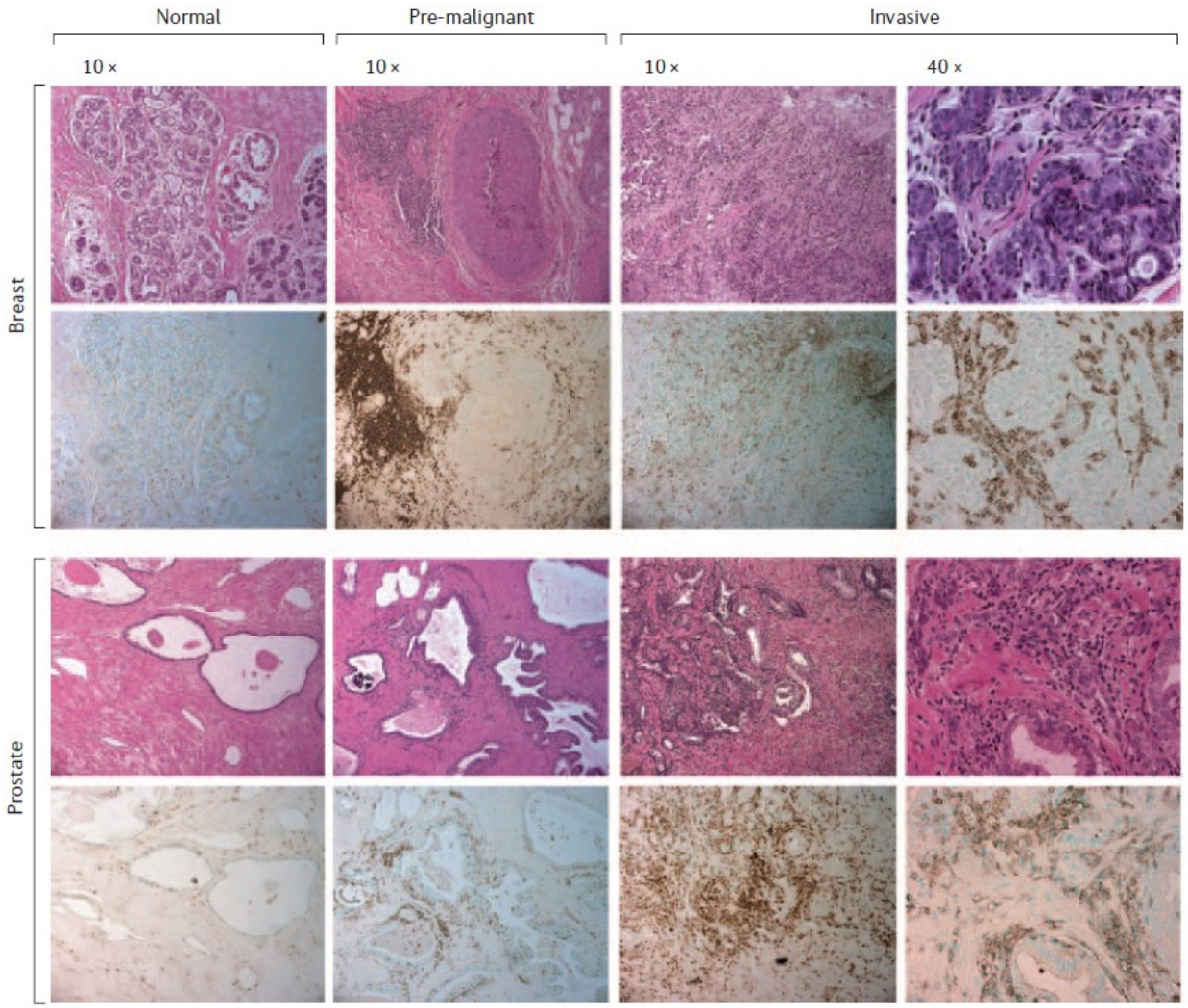
Table 1 **Chronic inflammatory conditions associated with neoplasms**

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 sclerosus	Vulvar squamous cell carcinoma	
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma	Alcholism, 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

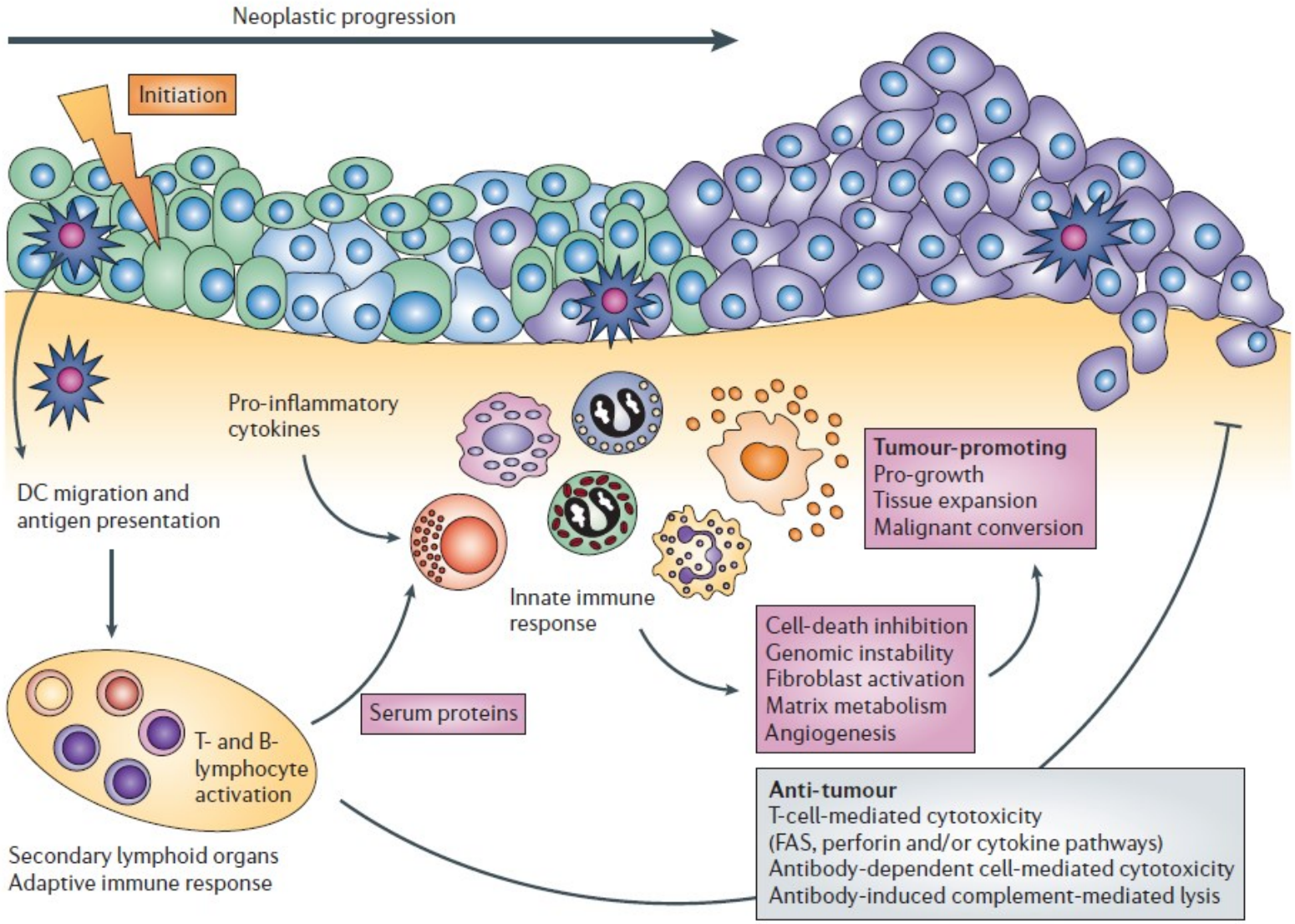
Zánět a nádorová progrese

Cancers associated with infectious agents		
Opisthorchis, Cholangitis	Cholangiosarcoma, colon carcnoma	Liver flukes (*Opisthorchis viverrini*), bile acids
Chronic cholecystitis	Gall bladder cancer	Bacteria, gall bladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	*Helicobacter pylori*
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	Gonnorrhoea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen	Schistosomiasis
Pathologic condition	Associated neoplasm(s)	Aetiologic agent

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.

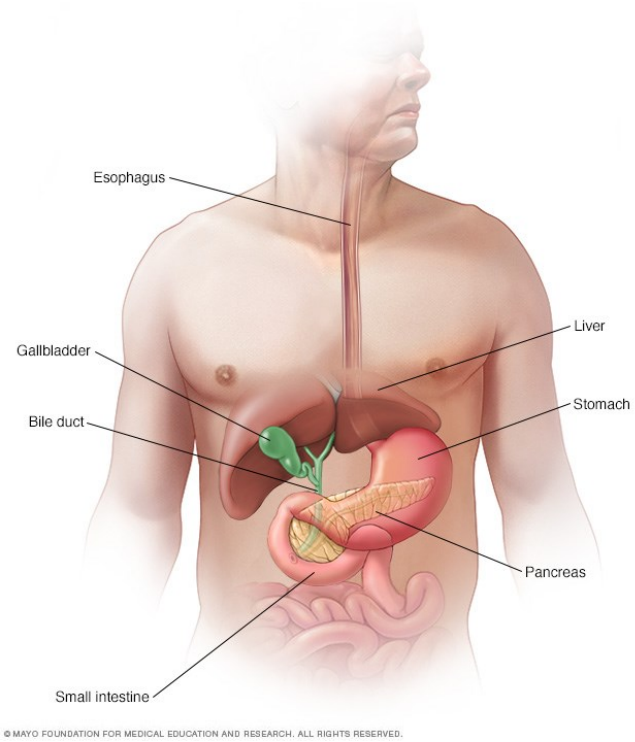
Diabetes

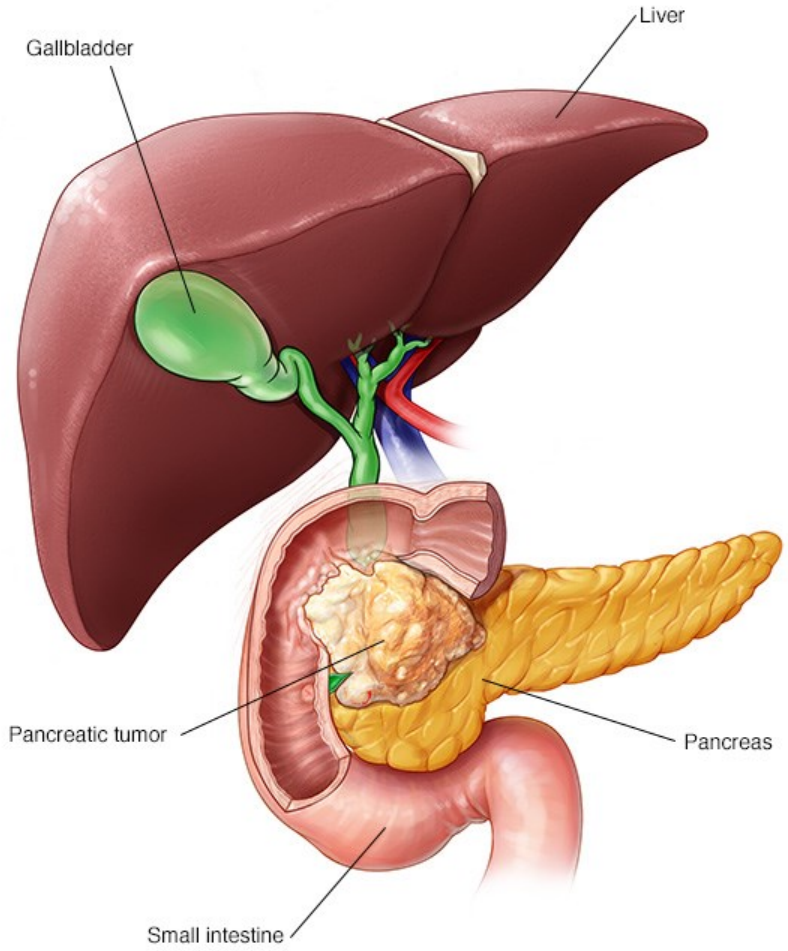
Long standing (over 5 years) diabetes increases risk.

Pancreatitis

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

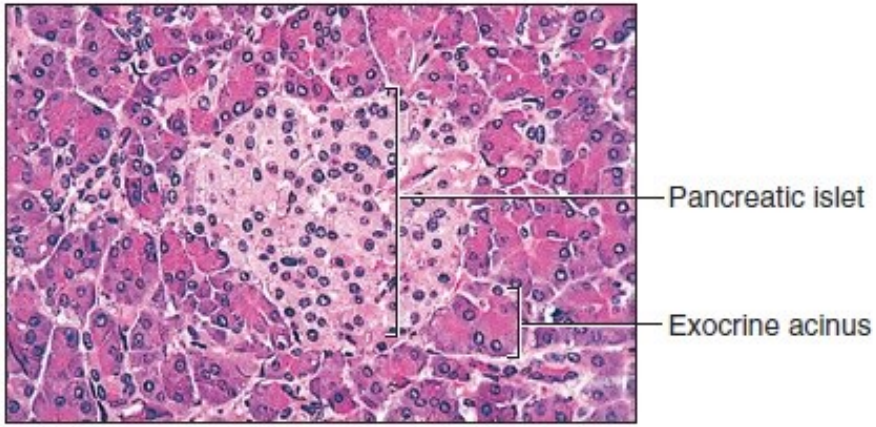
Slinivka břišní, pankreas



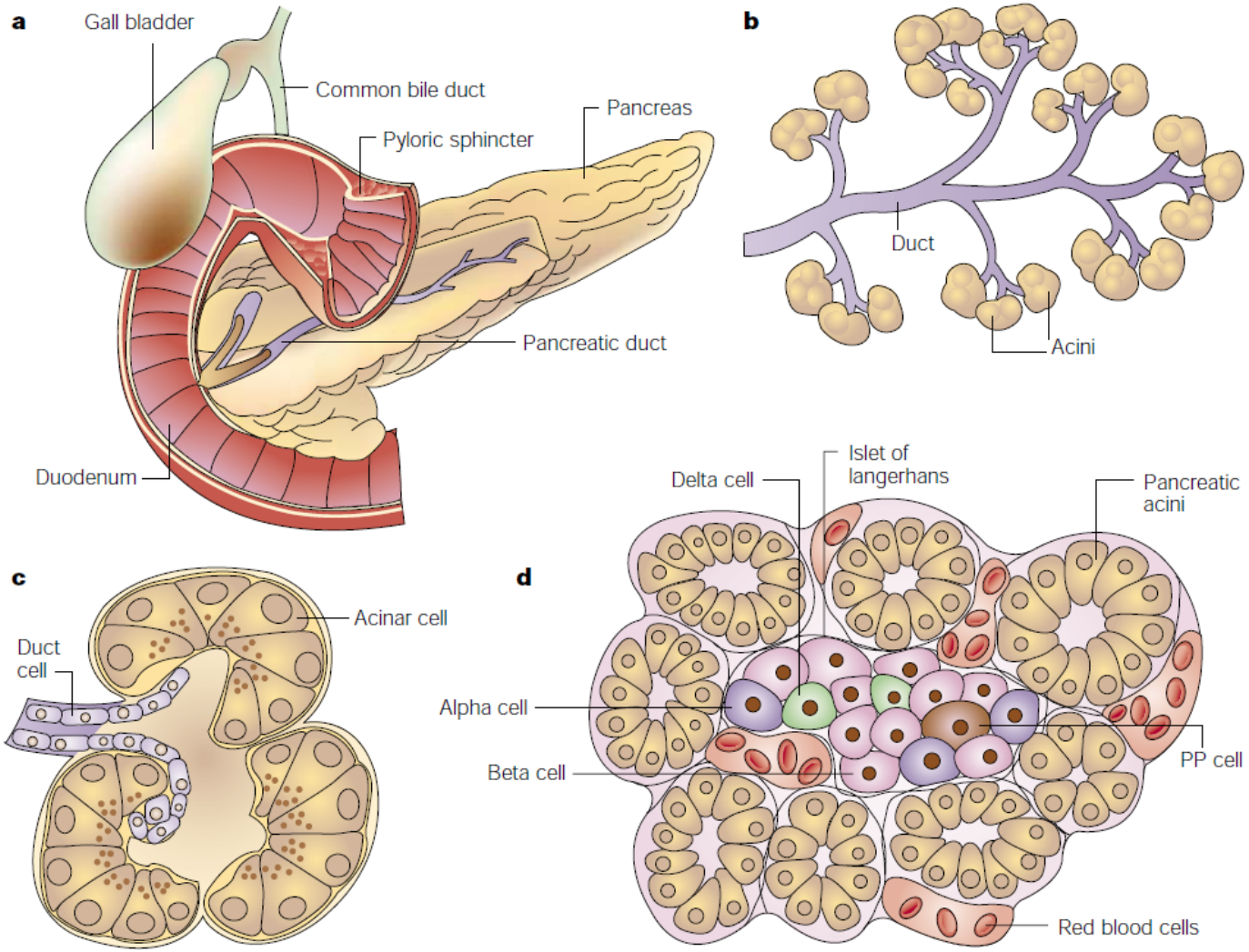


Slinivka břišní, pankreas

- 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)



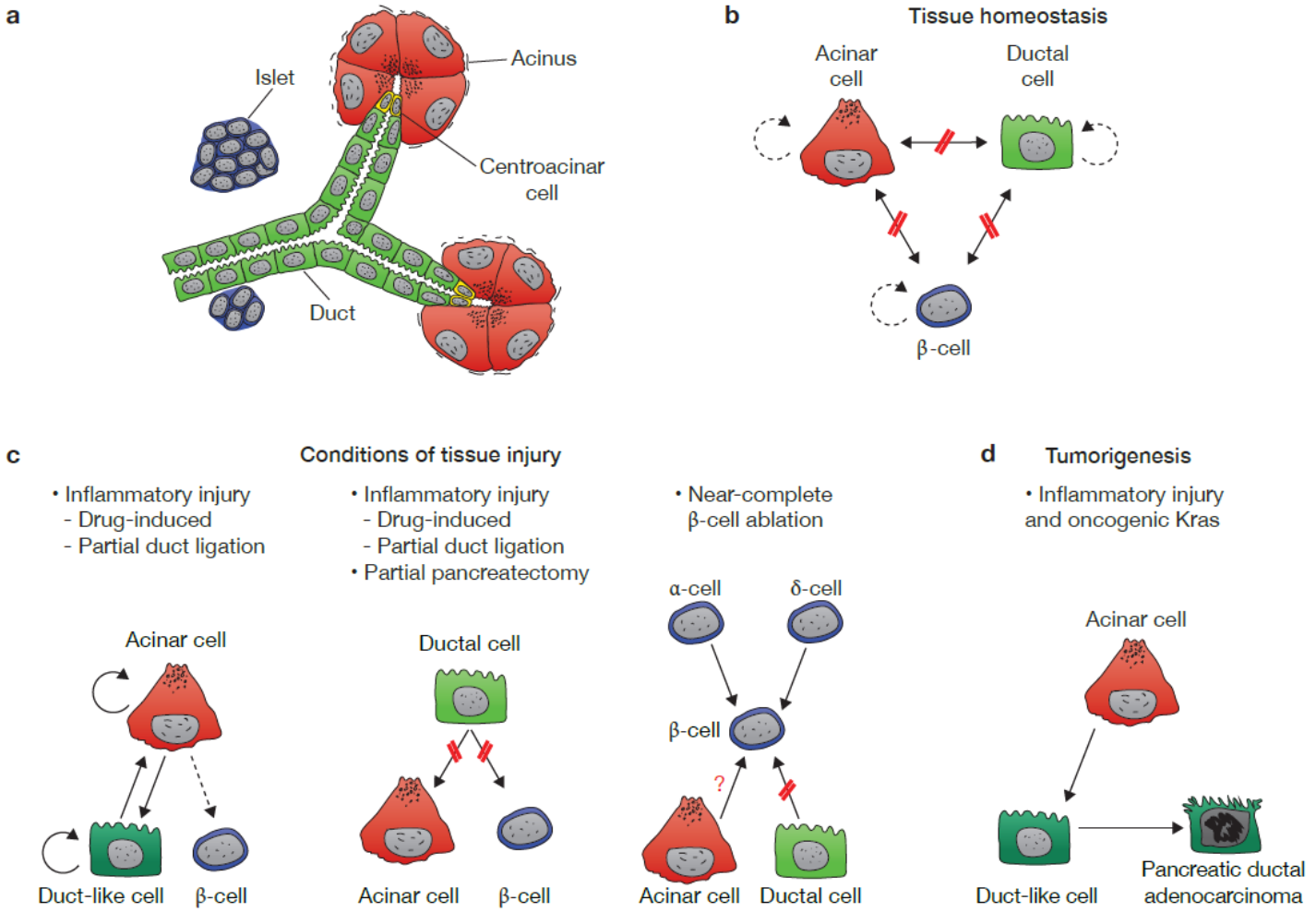
Pankreas


a
Gall bladder
Common bile duct
Pancreas
Pyloric sphincter
Pancreatic duct
Duodenum
b
Duct
Acini
c
Acinar cell
Duct cell
d
Delta cell
Islet of langerhans
Pancreatic acini
Alpha cell
Beta cell
PP cell
Red blood cells

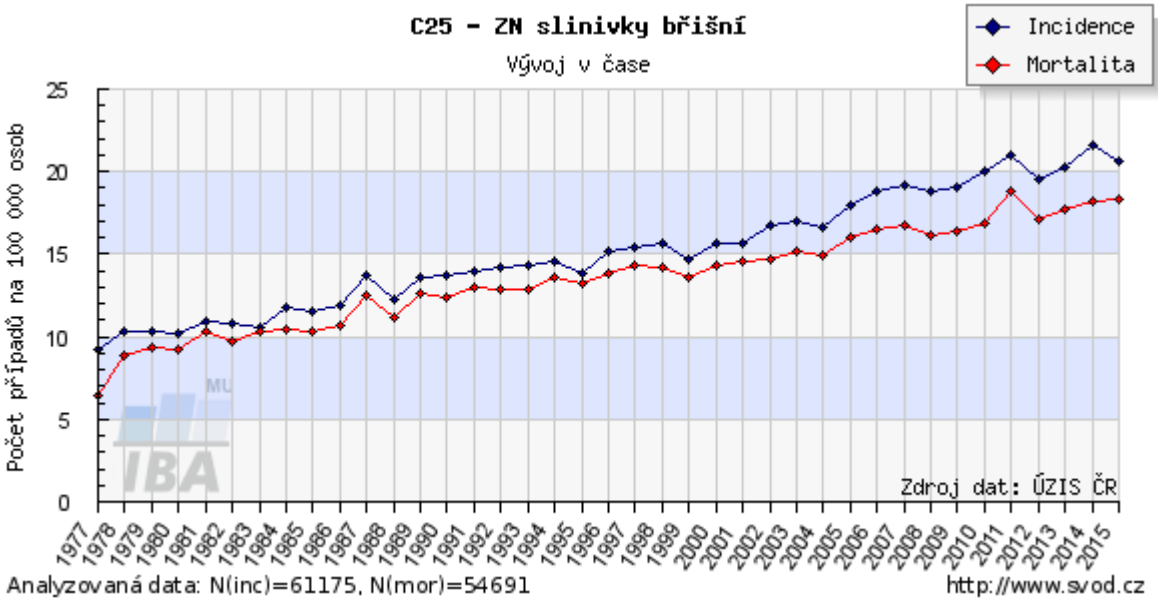
Regenerace pankreatu

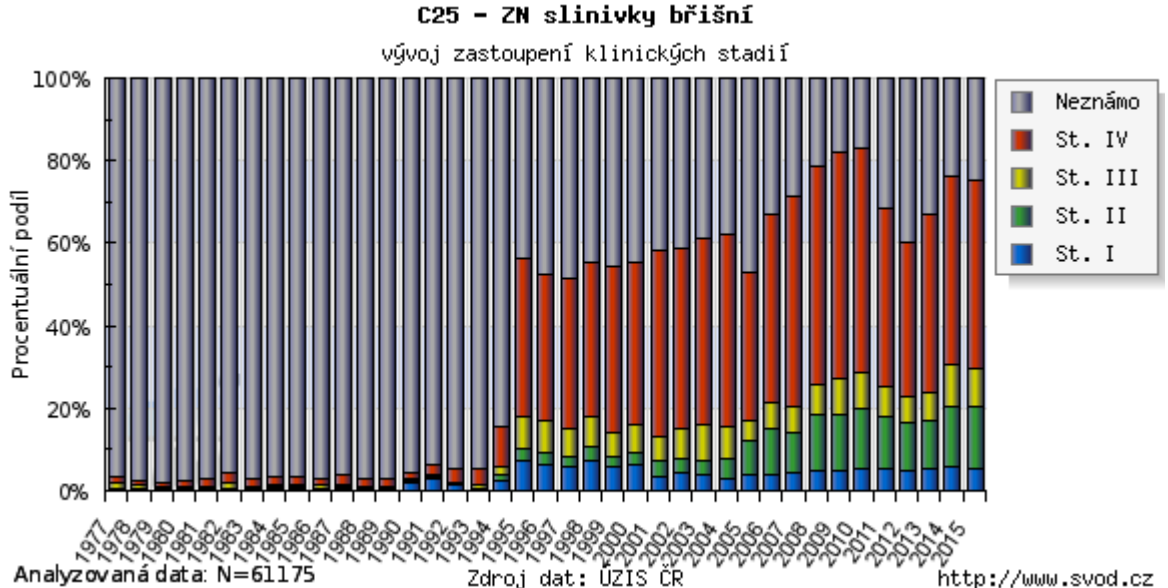
- Nízká intenzita proliferace
- Nízká klonogenní kapacita
- Délka života u myších buněk ~ 1 rok (podobně jako u jater)
- Regenerační kapacita odlišná od jaterní
  - Buňky zvýší svoji proliferační kapacitu, ale k úplné obnově poškozené tkáně nedojde
  - Lgr5+ buňky nejsou přítomny, jsou indukovány při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

Regenerace pankreatu

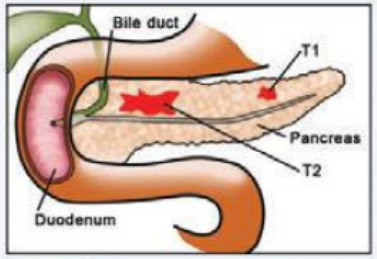


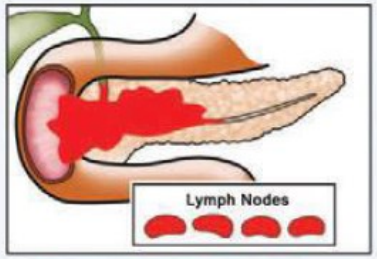
Rakovina slinivky

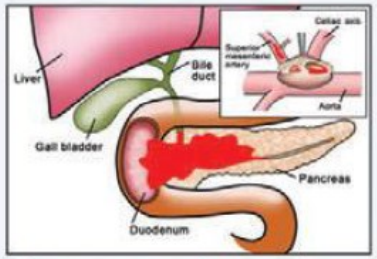


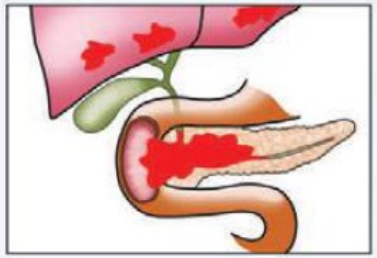


Rakovina slinivky



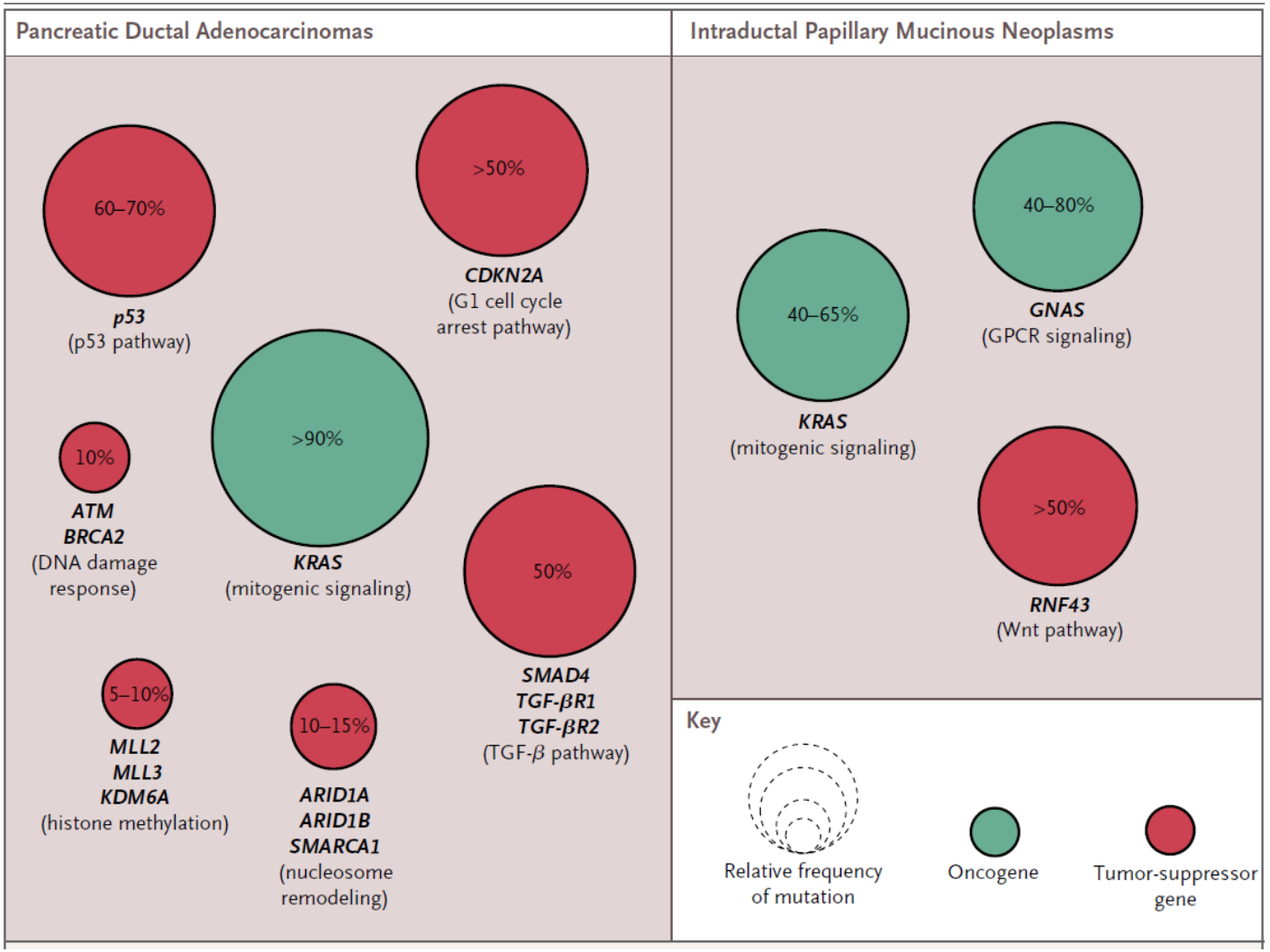






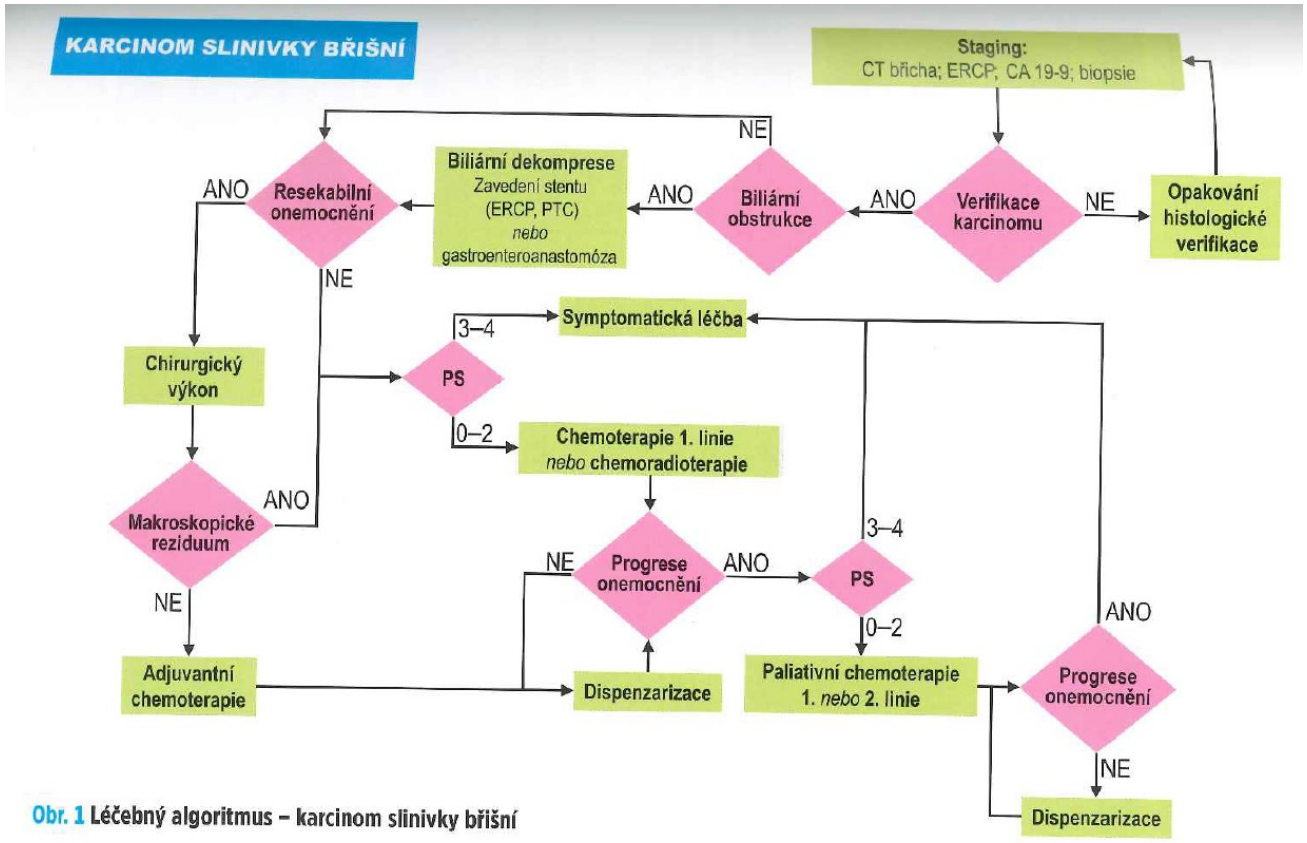
AJCC Stage	TNM Stage	Extent of Tumor	5 year Survival	Stage at Presentation (14% Unknown)
I	T1/N0	Limited to pancreas ≤ 2cm	20%	7%
	T2/N0	Limited to pancreas > 2cm		
II	T3 or N1	Beyond pancreas or regional lymph node metastases	8%	26%
III	T4 any N	Involves celiac axis or superior mesenteric artery		
IV	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 Fluorouracil plus radiotherapy	10% at 2 yr 20% at 2 yr	0.007
EORTC[59]	218	Observation Fluorouracil plus radiotherapy	26% at 2 yr 34% at 2 yr	0.10
ESPAC-1[60]	289	Observation Chemoradiotherapy	16.9 mo (median)† 13.9 mo	
		Fluorouracil Chemoradiotherapy plus fluorouracil	21.6 mo 19.9 mo	
CONKO-01[61]	368	Observation Gemcitabine	10.4% at 5 yr 20.7% at 5 yr	0.01
ESPAC 3[62]	1088	Fluorouracil Gemcitabine	23.0 mo (median) 23.6 mo	0.39
RTOG 9704[63]	451	Fluorouracil plus radiotherapy Gemcitabine plus radiotherapy	22% at 5 yr 18% at 5 yr	0.12
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).

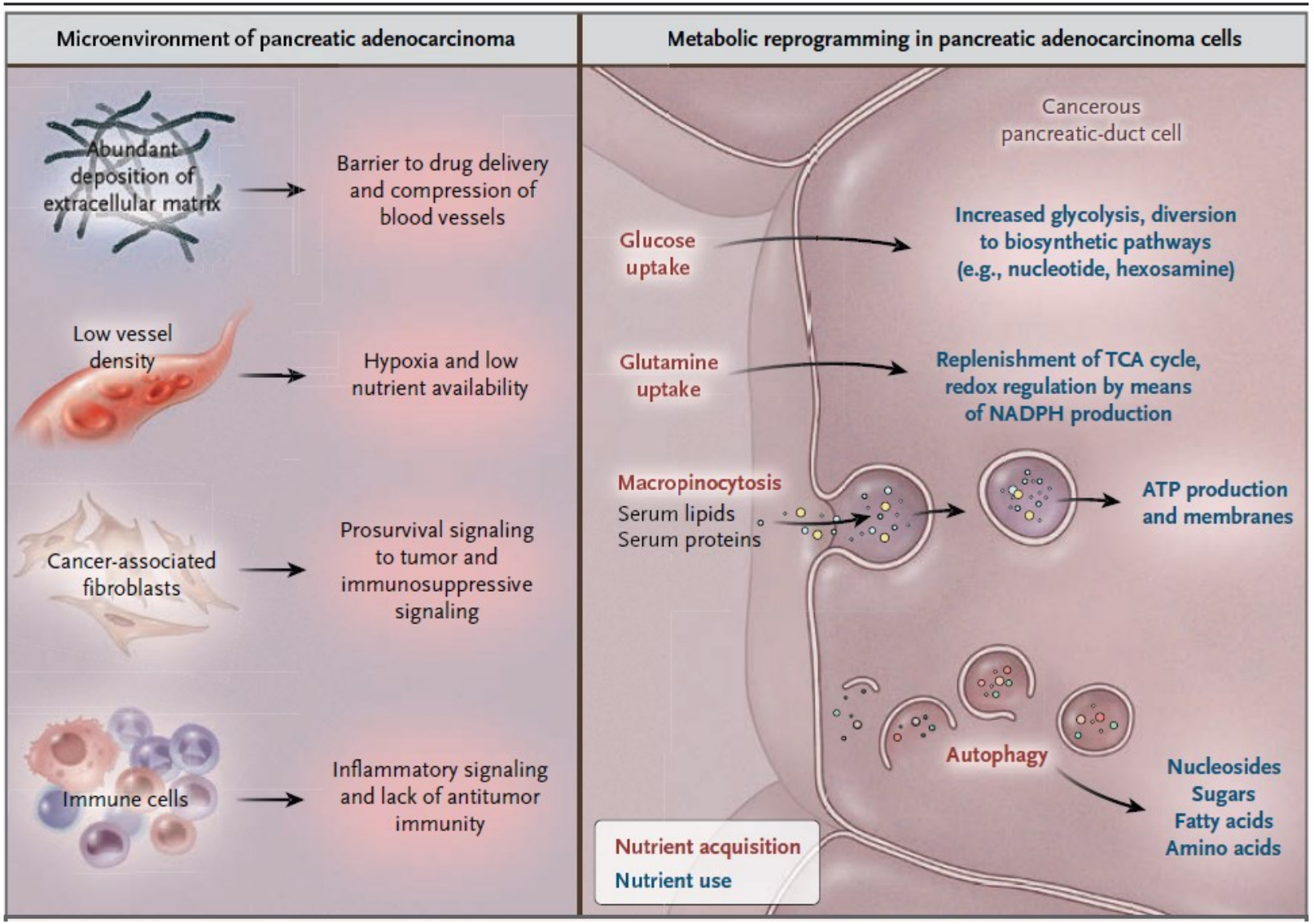
Léčba metastazujícího adenokarcinomu slinivky

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

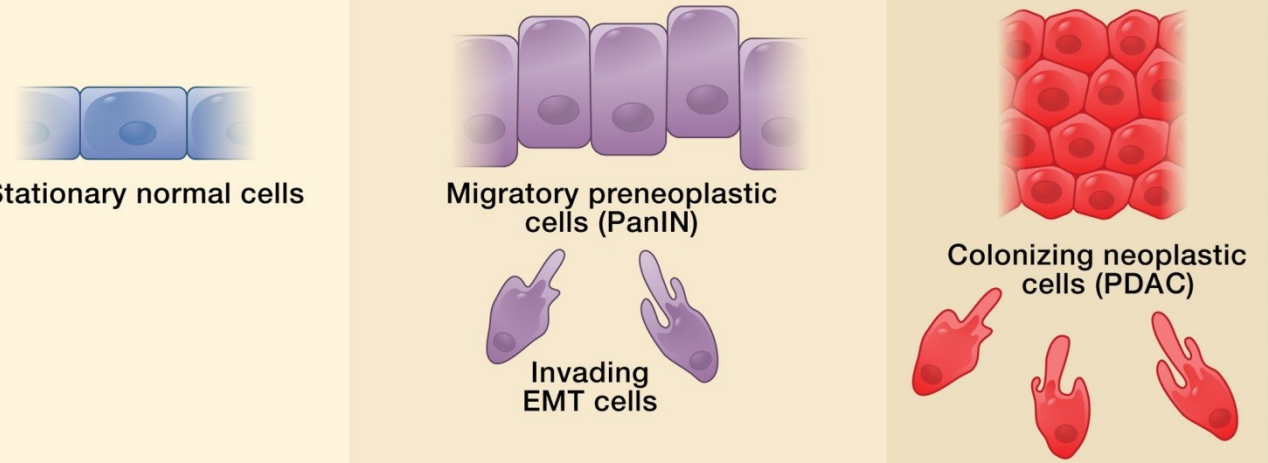
Trial	No. of Patients	Treatment	Median Survival	P Value
			mo	
Burris et al.[70]	126	Fluorouracil Gemcitabine	4.4 5.6	0.002
NCIC[71]	569	Gemcitabine Gemcitabine plus erlotinib	5.9 6.2	0.04
Ueno et al.[72]	834	Gemcitabine S-1	8.8 9.7	<0.001 for non-inferiority
Conroy et al.[73]	342	Gemcitabine FOLFIRINOX	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



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