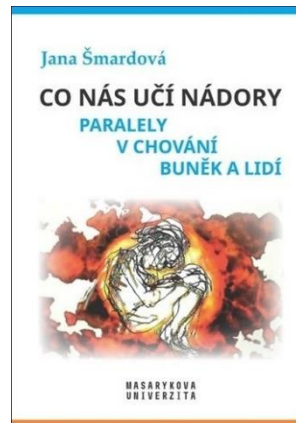
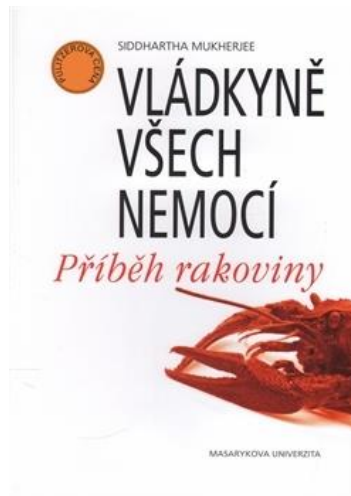
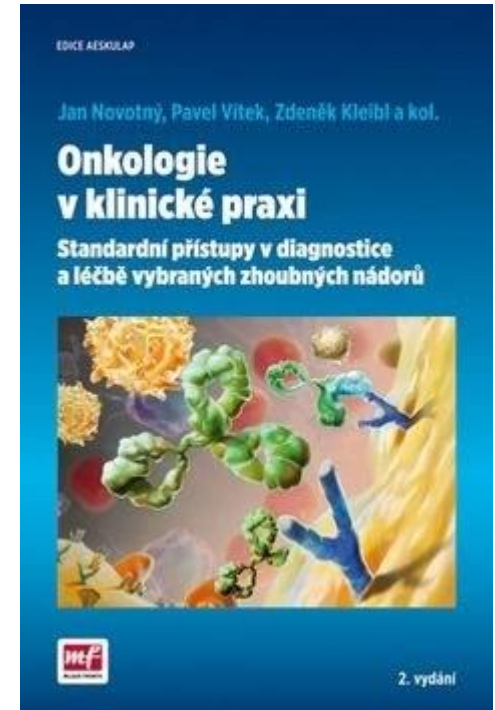
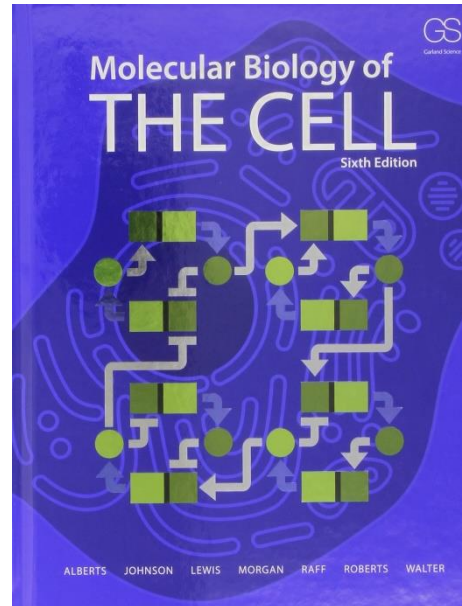
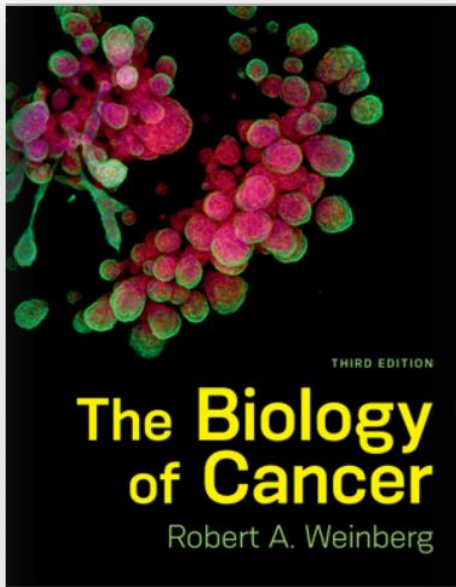


SIGNÁLNÍ DRÁHY A JEJICH DEREGULACE V PRŮBĚHU KARCINOGENEZE

Karel Souček

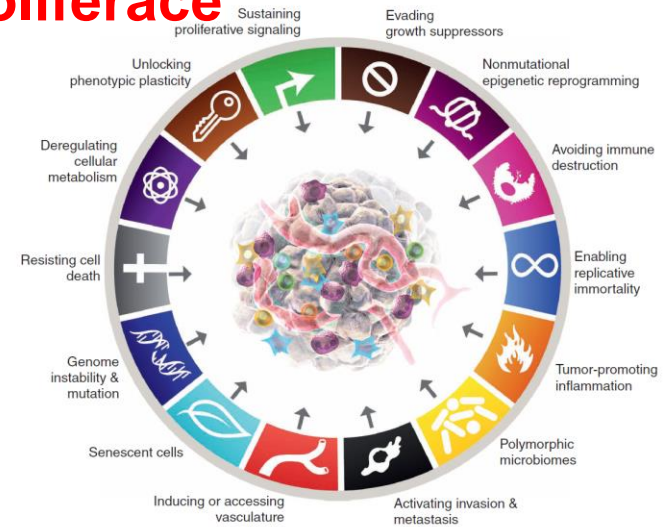
E-mail: ksoucek@ibp.cz, tel.: 541 517 166

Zdroje



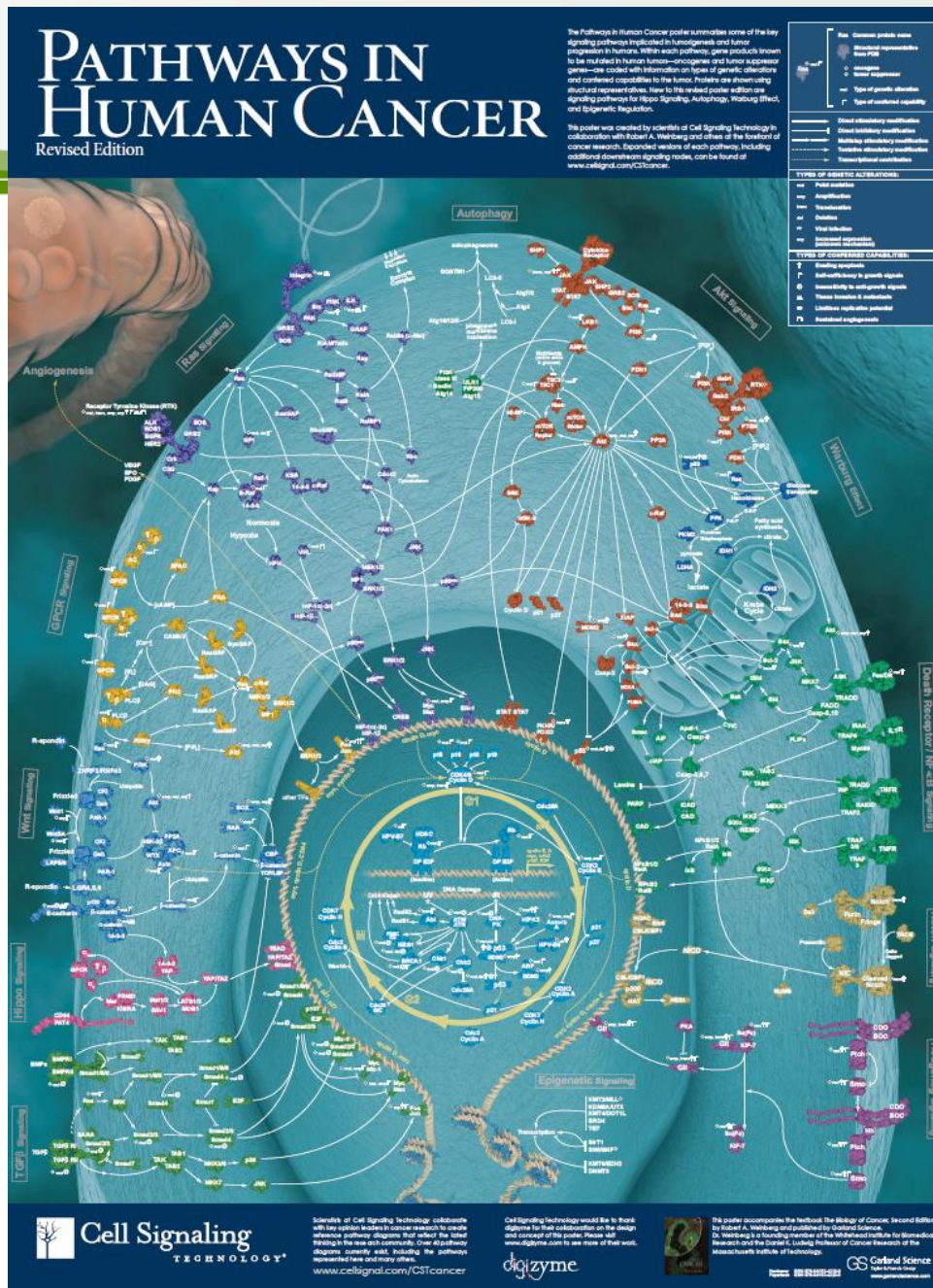
Typické znaky nádorové buňky

- **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

Mechanismy carcinogeneze



Podpůrné proliferační signály

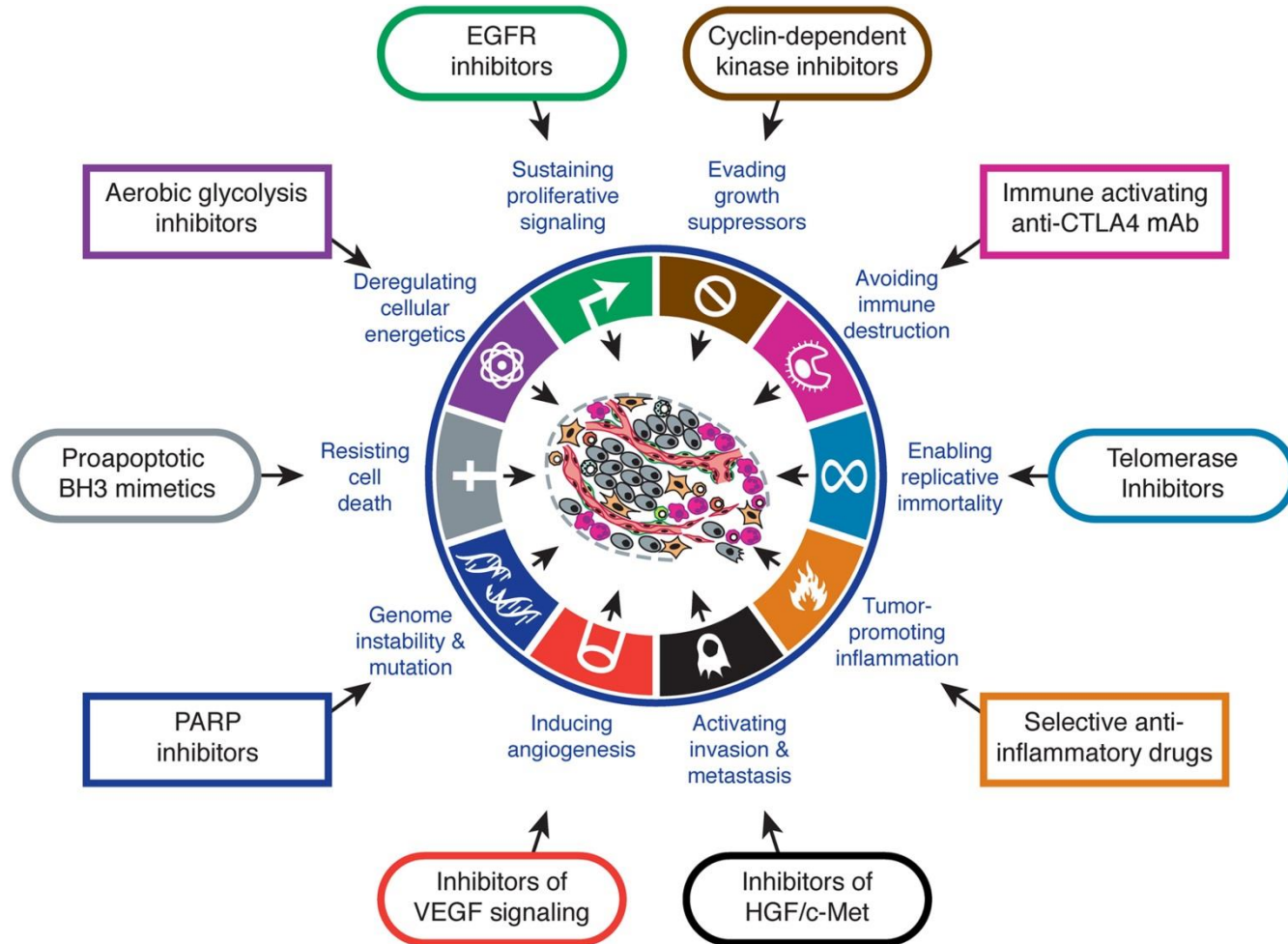
- ▶ Normální tkáně velice přesně kontrolují produkci růstových faktorů (RF) indukujících buněčné dělení
 - ▶ Klíčové pro udržení homeostázy, normální architektury a funkce tkáně
- ▶ Deregulace této kontroly propůjčuje nádorové buňce kontrolu nad svým osudem
 - ▶ Autokrinní produkce RF
 - ▶ Stimulace parakrinní produkce RF
 - ▶ Zvýšená citlivost k RF prostřednictvím zvýšené exprese receptorů
 - ▶ Konstitutivní aktivace receptorů pro RF bez závislosti na ligandech
 - ▶ Mutace
 - ▶ Ztráta negativní zpětné vazby
- ▶ *Otevřené otázky:*
 - ▶ *Jaké jsou mechanismy kontroly uvolňující RF v normální tkáni*
 - ▶ *Role parakrinní signalizace, úloha imobilizace RF v extracelulární matrix*



Deregulace supresorů růstu

- ▶ Stejně jako u pozitivních faktorů růstu i správná funkce negativních regulátorů růstu/proliferace je důležitá pro udržení tkáňové homeostázy
- ▶ Existují desítky negativních regulátorů proliferace, řada s nich patří mezi nádorové supresory.
 - ▶ RB protein – integruje signály z vnějšího i vnitřního prostředí buňky, klíčová molekula kontrolu buněčného cyklu
 - ▶ TP53 – integruje signály z vnitřního prostředí buňky, indukuje zástavu buněčného dělení nebo buněčnou smrt
 - ▶ Kontaktní inhibice – inhibiční dráha spočívající v mezibuněčné interakci proliferující tkáně (zapojení NF2, N-kadherinu, LKB1)
 - ▶ Deregulace signalizace cytokinu TGF- β
 - ▶ časté přepnutí funkce z inhibice proliferace na aktivaci plasticity a invazivity

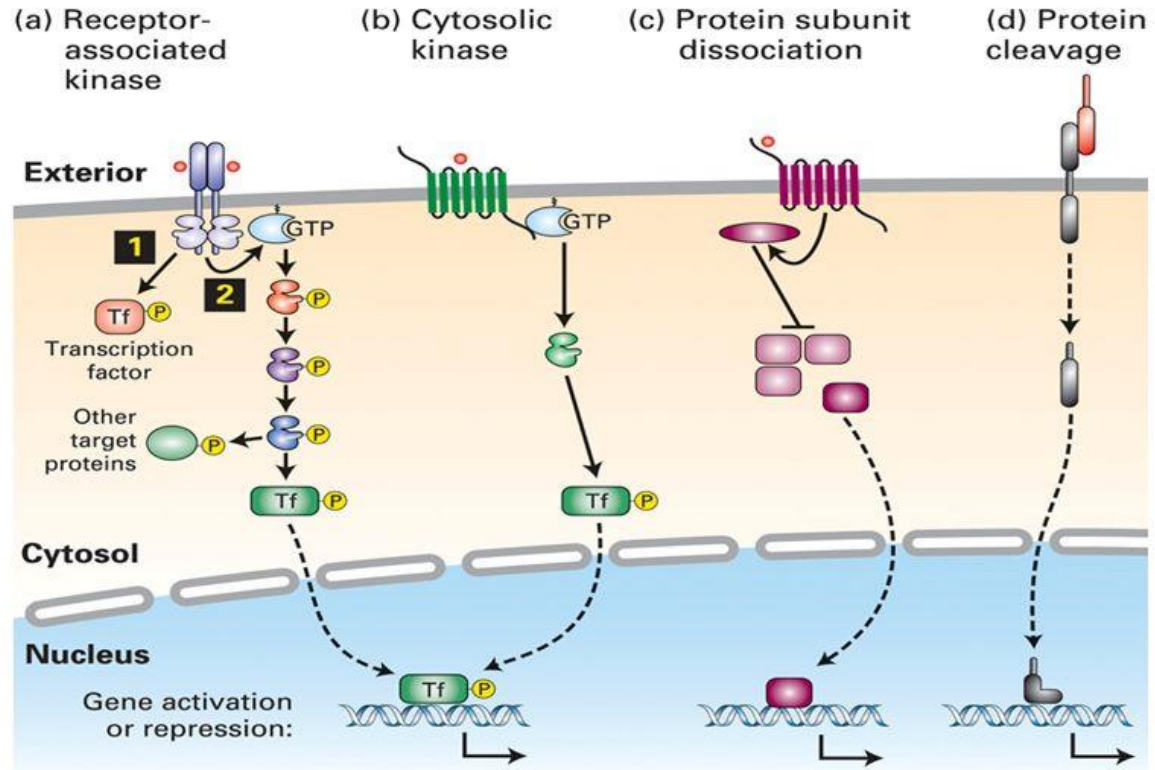
Typické znaky nádorové tkáně jako cíle protinádorové léčby



Růstové faktory a jejich receptory

- ▶ Onkoproteiny současně mění řadu odlišných regulačních drah
- ▶ Normální buňky získávají růstové signály ze svého okolí
- ▶ Jsou přenášeny a integrovány v komplexním okruhu, který rozhoduje zda dojde k dělení
- ▶ Přenos signálu přes lipidovou membránu představuje biochemický problém
 - ▶ Vnější a vnitřní prostor je oddělen lipidovou dvojvrstvou – bariérou
 - ▶ Různé koncentrace molekul včetně iontů
- ▶ Většina signálů je přenášena pomocí proteinů
 - ▶ Určité buňky sekretují proteiny do extracelulárního prostoru
 - ▶ Příjemci signálu musí být senzitivní k sekretované molekule a musí být v bezprostřední blízkosti
 - ▶ parakrinní
 - ▶ autokrinní
 - ▶ juxtakrinní

Základní principy buněčné signalizace



Representative receptors and pathways

RTKs
 TGF- β receptors
 Cytokine receptors
 JAK-STAT
 Ras/MAP Kinase

GPCRs
 cAMP/PKA/CREB

Wnt
 Hedgehog
 NF- κ B

Notch/Delta

ErbB signalizace – příklad buněčné komunikace

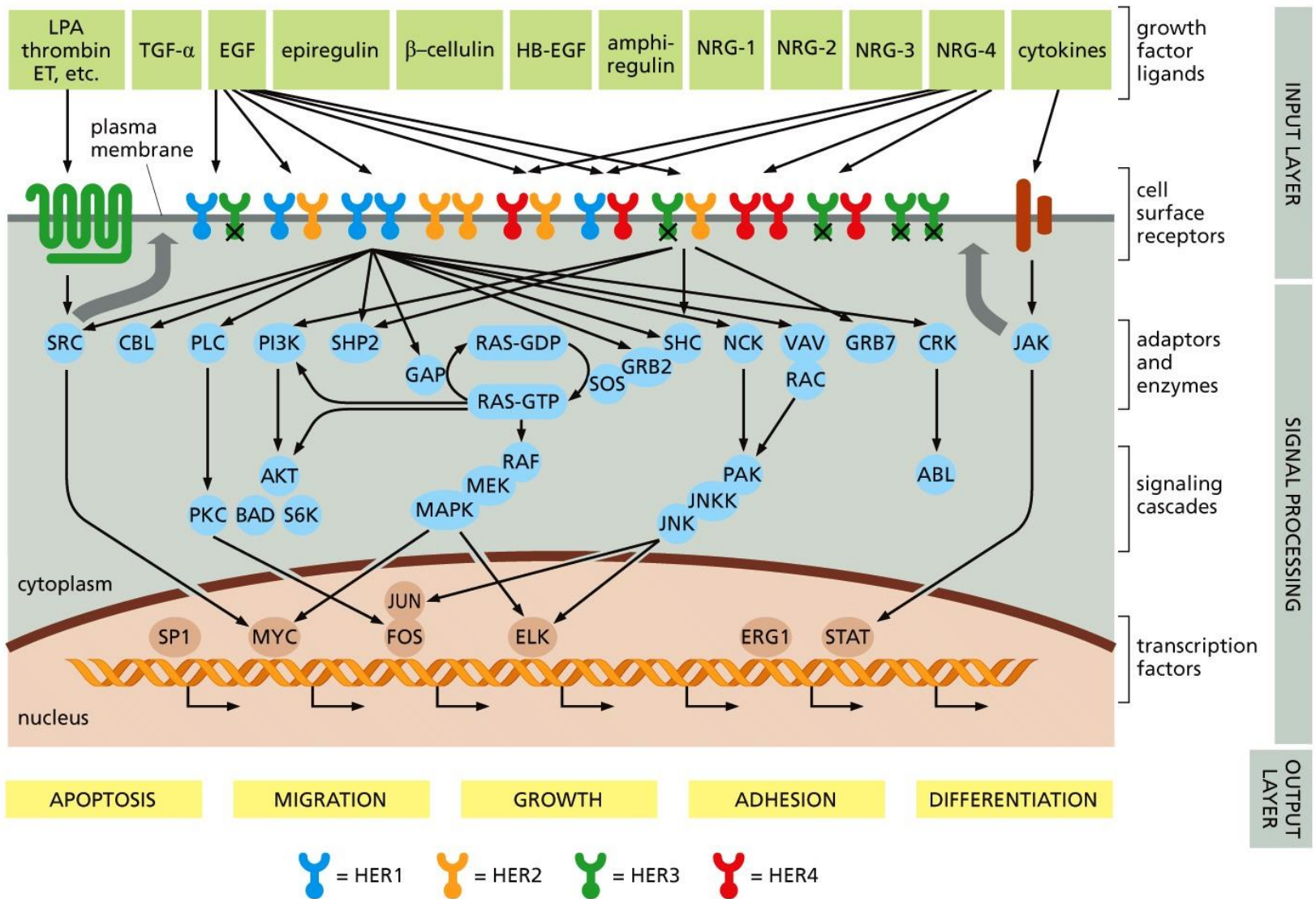


Figure 5.1 The Biology of Cancer (© Garland Science 2014)

Časná odpověď – okamžitá & opožděná

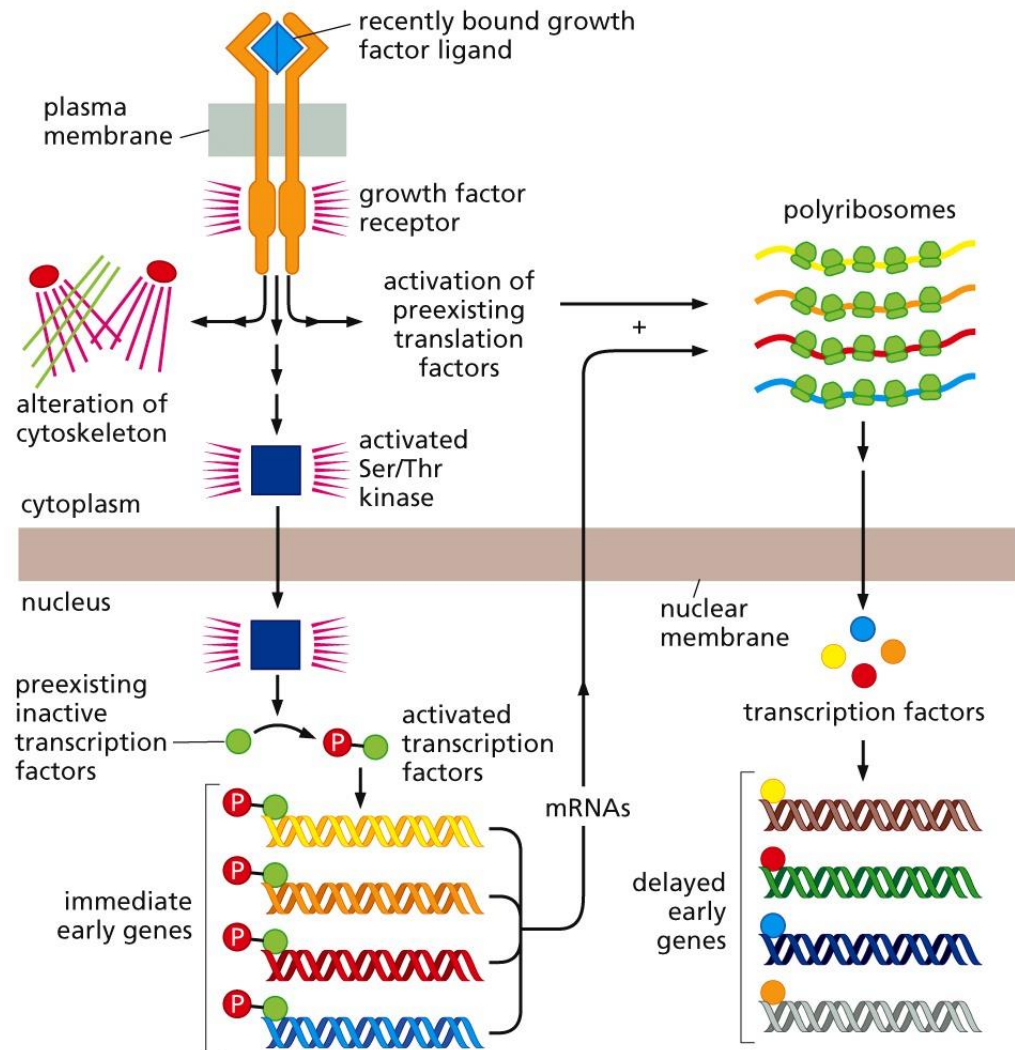


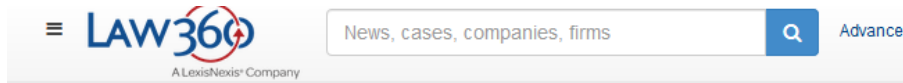
Figure 6.3 The Biology of Cancer (© Garland Science 2014)

Růstové faktory a jejich receptory

- Normální verze onkogen-kódujících proteinů jsou často zapojeny do regulačních drah zodpovědných za řízení buněčné proliferace
- Jeden ze základních principů udržení homeostázy a regenerace u mnohobuněčných organismů spočívá v kooperaci/komunikaci většího množství buněk
- Růstové faktory jsou relativně malé proteiny přenášející v extracelulárním prostoru určitou biologickou informaci
- Rozhodnutí dělit/nedělit se musí zohledňovat prospěch pro celý organismus, nikoliv pro samotnou buňku
 - Toto rozhodování neprovádí zdravá buňka autonomně a je pod kontrolou jejího okolí
 - Příklad – *in vitro* kultura normálních buněk vyžaduje sérum pro stimulaci proliferace

sérum

- frakce krve oddělená centrifugací po koagulaci
- hovězí fetální sérum (FBS) – aseptická srdeční punkce plodu (~ 150 - 550 ml/fetus, globálně 700.000 l/rok)
- batch-to-batch rozdíly
- regionální rozdíly

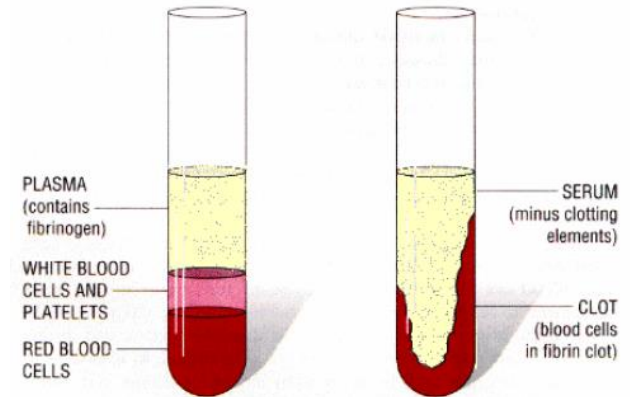


GE Unit Diluted Cell Growth Serum, Stole Buyers, Suit Says

By [John Kennedy](#)

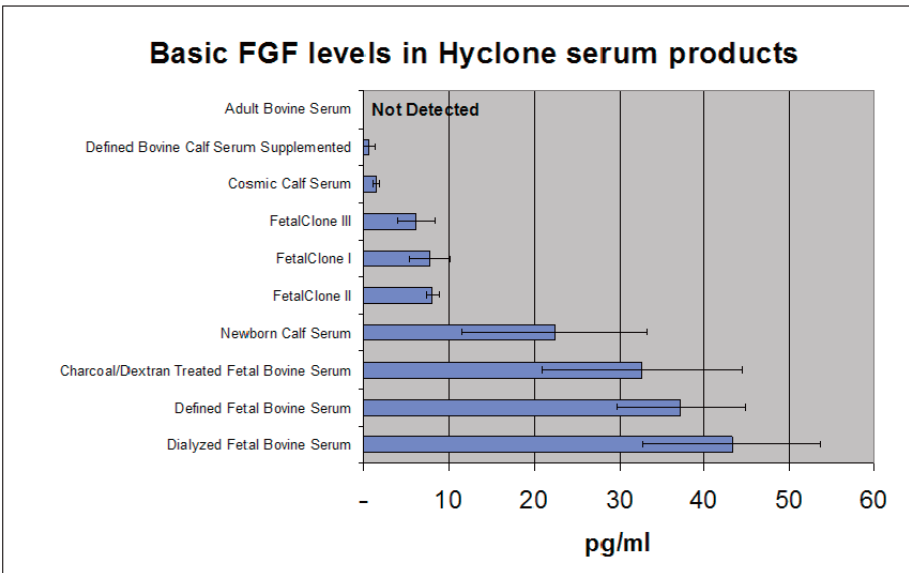
Law360, New York (June 24, 2016, 2:22 PM EDT) – A North Carolina company accused General Electric's health care and biosciences unit of stealing its customers and ruining its profits while also lying about the makeup of its own fetal bovine serum, a product used in laboratories to promote cell growth, in a complaint filed Thursday in federal court.

For six years, PAA Laboratories Inc., which continued its unfair and deceptive trade practices even after merging with GE Healthcare Bio-Sciences Corp., diluted the serum it sold to Serum Source International Inc. and other customers, misrepresented the...

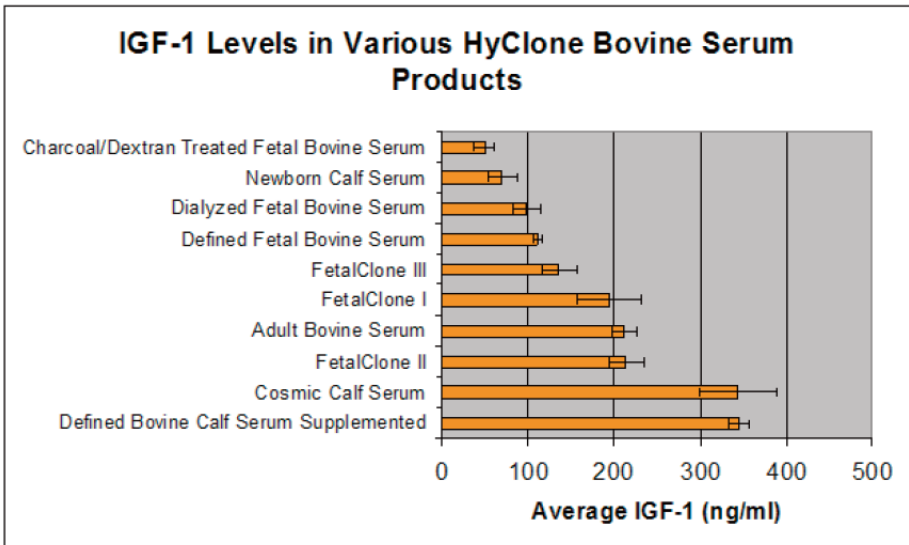


plasma: with anti-coagulating agent
 serum: without anti-coagulating agent

sérum



Comparison of average FGF-2 concentration in various HyClone Bovine Serum Products (n=3). Error bars show +/- one standard deviation.



sérum

- Krevní destičky jsou zdrojem řady faktorů
- Během srážení krve dochází k jejich uvolňování
- Příklad: **platelet-derived growth factor (PDGF)**
 - Stimulátor fibroblastů, mitogen

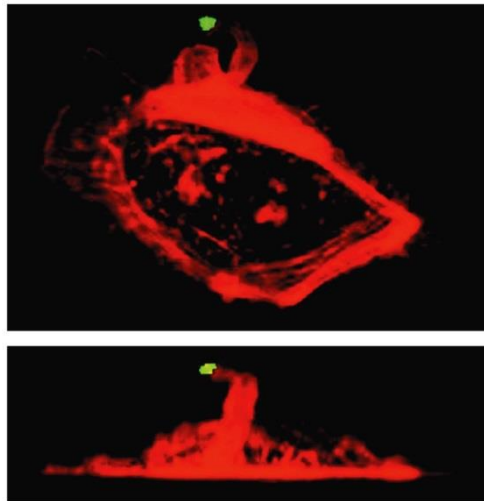


Figure 5.4b The Biology of Cancer (© Garland Science 2014)

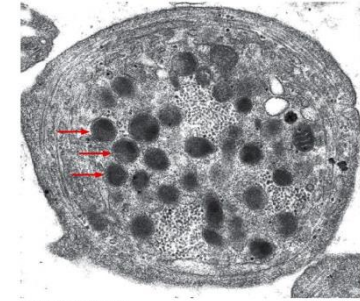


Figure 13 The Biology of Cancer (© Garland Science 2014)

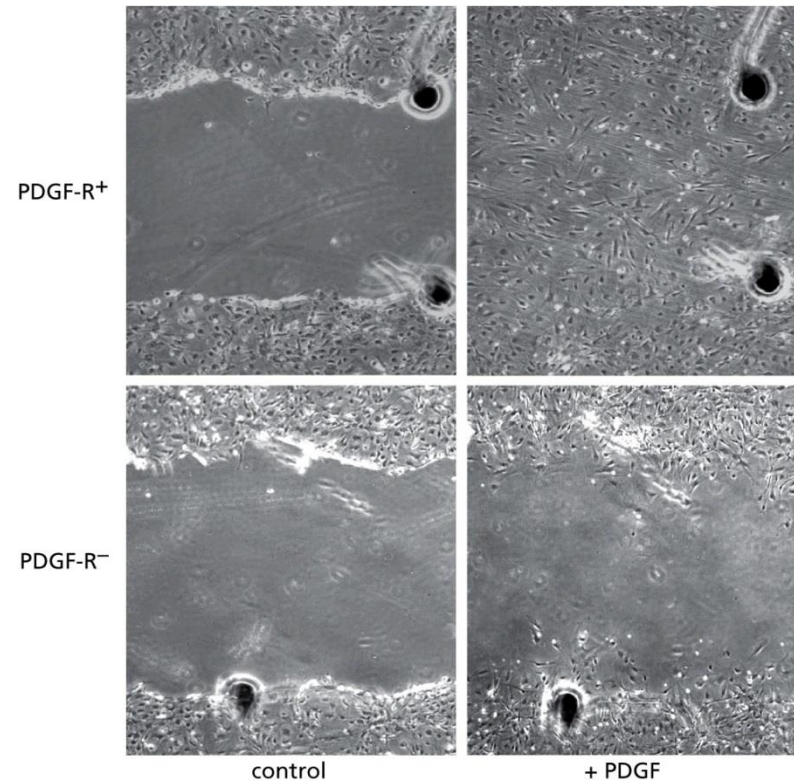


Figure 5.4a The Biology of Cancer (© Garland Science 2014)

Alternativy

- ▶ Chemicky definovaná média, kondiciovaná média, rekombinantní růstové faktory, kultivační kondice s definovanou maticí (simulace působení ECM) atp.
- ▶ Serum-free
- ▶ Xeno-free
- ▶ Chemically Defined (CD)
- ▶ Non-Animal Origin (NAO)
- ▶ Protein-free (PF)

Proto-oncogene tyrosine-protein kinase Src

- ▶ [sarc] sarcoma
- ▶ J. Michael Bishop a Harold E. Varmus – Nobelova cena, 1989
- ▶ Nereceptorová kináza aktivovatelná řadou transmembránových proteinů – adhezí, tyrozin kinázovými receptory, receptory pro cytokiny (PDGF, EGF)
- ▶ c-Src, Yes, Fyn, Fgr, Yrk, Lyn, Blk, Hck, and Lck
- ▶ změna u ~50% nádorů (zvýšená aktivita nebo exprese)
- ▶ Studium funkce v-Src (Rous sarcoma virus) onkoproteinu umožnilo pochopit některé základní principy transformace buněk
- ▶ Kináza s více než 50-ti substráty – pleiotropní účinek
- ▶ Regulace proliferace, přežití, angiogeneze, invaze
- ▶ Fosforyluje tyrosinová rezidua proteinů – typické pro mitogenní dráhy

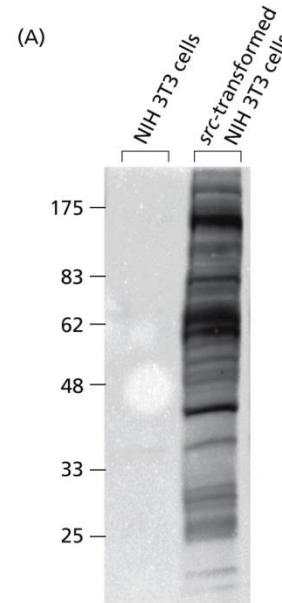


Figure 5.6 The Biology of Cancer (© Garland Science 2014)

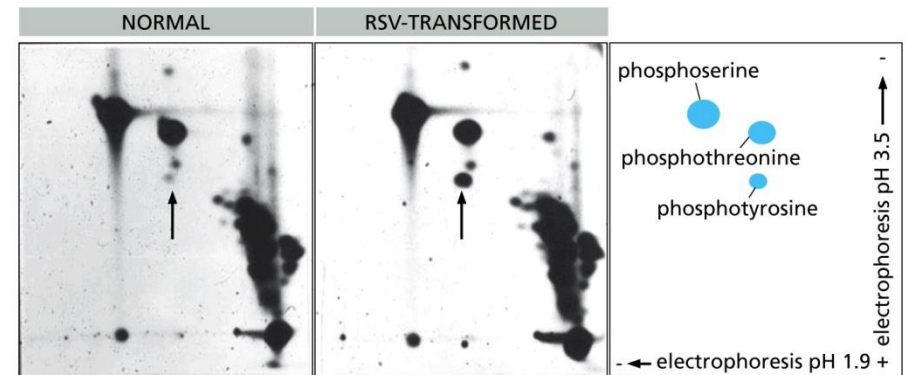
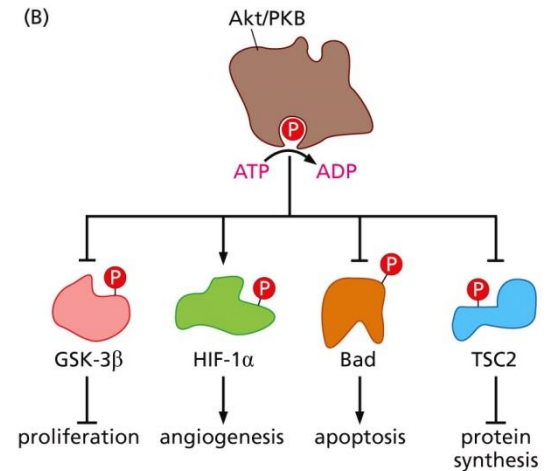


Figure 5.7 The Biology of Cancer (© Garland Science 2014)

Struktura Src proteinu

- SH1 – katalytická doména
- SH2, SH3 – rozpoznání substrátů „intracelulární receptory“
- „ligandy“ – krátké oligopeptidové sekvence s fofosfotyrosiny

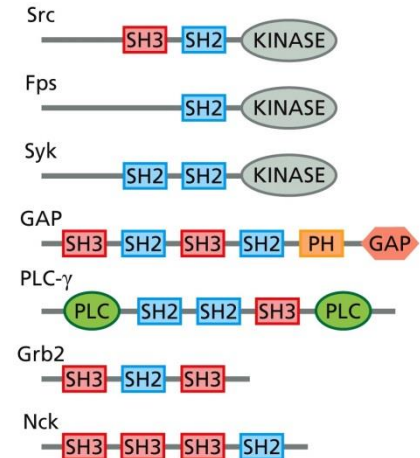


Figure 6.10a The Biology of Cancer © Garland Science 2014

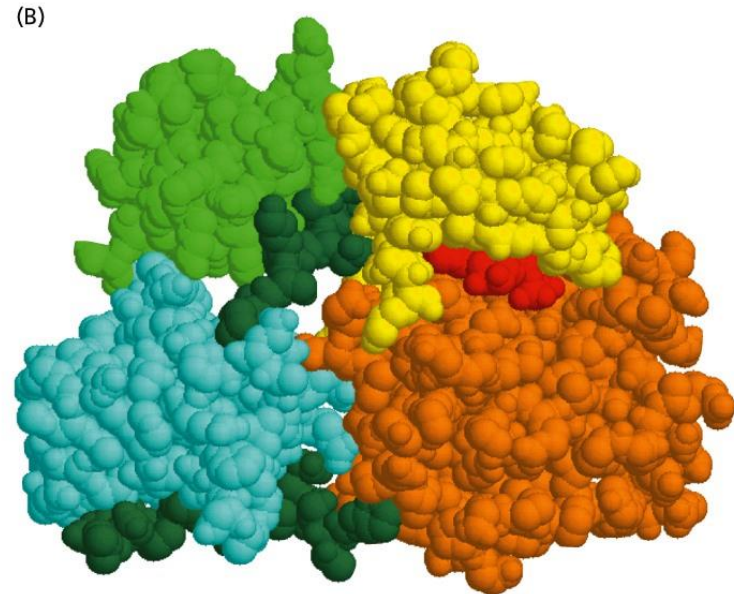
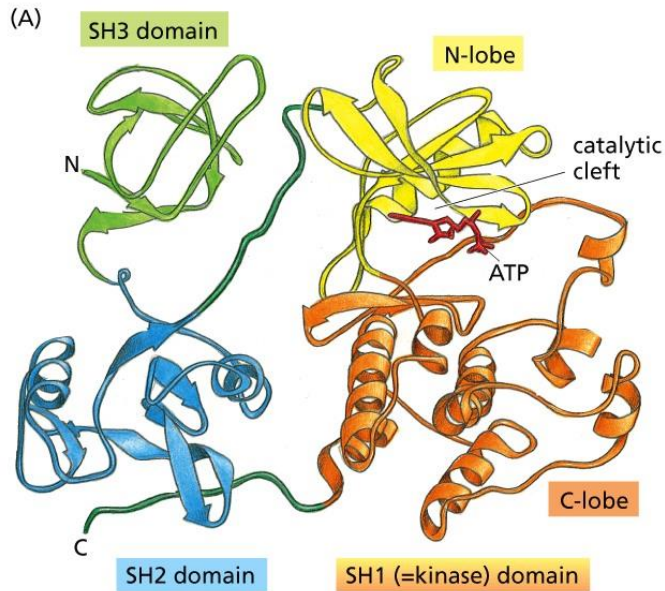


Figure 6.7 The Biology of Cancer © Garland Science 2014

Atrakce přenašečů signálu

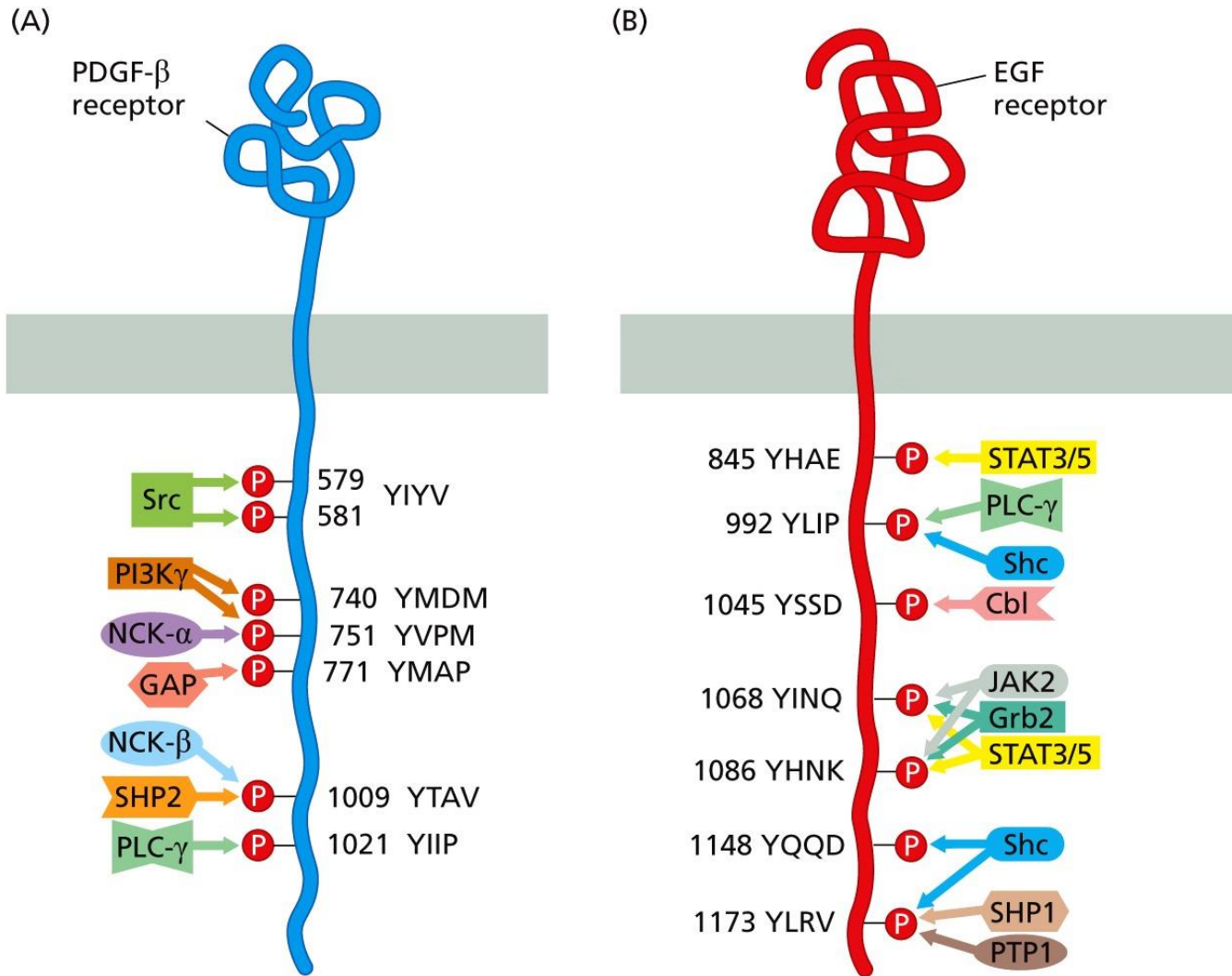


Figure 6.9 The Biology of Cancer (© Garland Science 2014)

Epidermal growth factor

- První objevený růstový faktor
- Mitogenní účinek na řadu typů epiteliálních buněk
- Receptor
 - N-konec – extracelulární doména – ektodoména, rozpoznává EGF ligand
 - Transmebránová doména, hydrofóbní rezidua
 - C-konec, intracelulární část
- Aktivace EGFR vede k aktivaci c-Src-like kináz

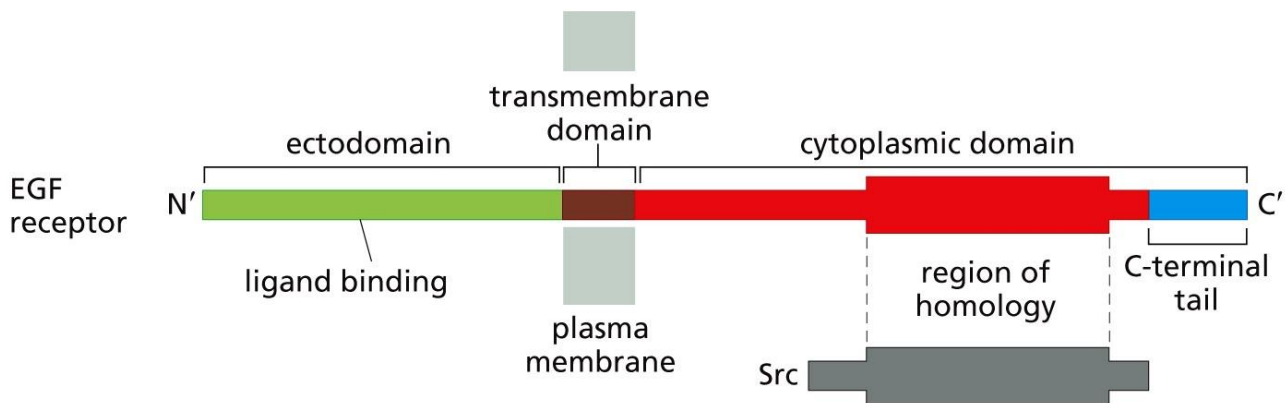


Figure 5.8a The Biology of Cancer (© Garland Science 2014)

Tyrozín kinázové receptory

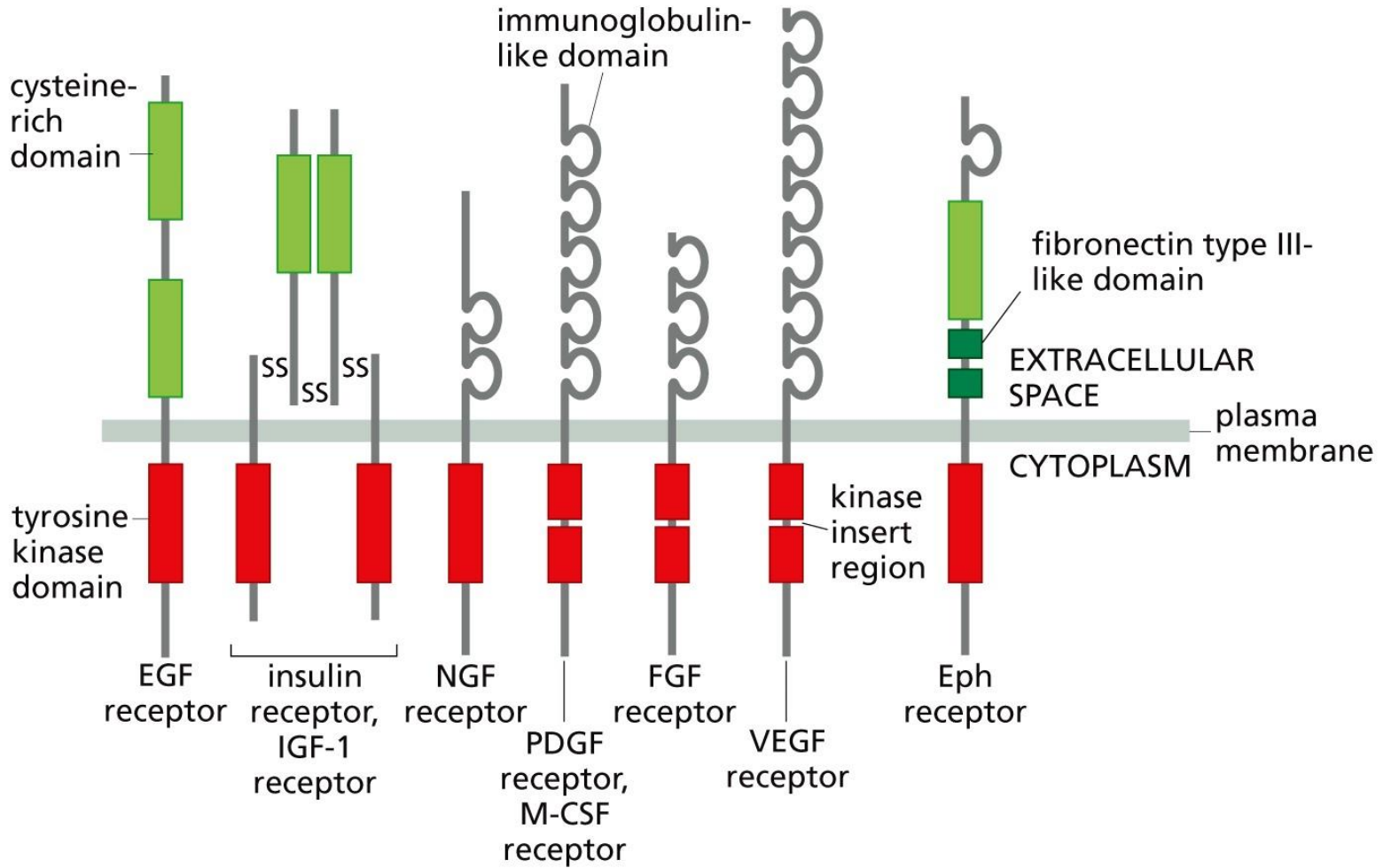


Figure 5.9 The Biology of Cancer (© Garland Science 2014)

Růstové faktory a jejich receptory v nádorové patogenezi

Name of receptor	Main ligand	Type of alteration	Types of tumor
EGF-R/ErbB1	EGF, TGF- α	overexpression	non-small cell lung cancer; breast, head and neck, stomach, colorectal, esophageal, prostate, bladder, renal, pancreatic, and ovarian carcinomas; glioblastoma
EGF-R/ErbB1		truncation of ectodomain	glioblastoma; lung and breast carcinomas
ErbB2/HER2/Neu	NRG, EGF	overexpression	30% of breast adenocarcinomas
ErbB3, 4	various	overexpression	oral squamous cell carcinoma
Flt-3	FL	tandem duplication	acute myelogenous leukemia
Kit	SCF	amino acid substitutions	gastrointestinal stromal tumor
Ret	GFL	fusion with other proteins; point mutations	papillary thyroid carcinomas; multiple endocrine neoplasias 2A and 2B
FGF-R2	FGF	amino acid substitutions	breast, gastric, endometrial carcinomas
FGF-R3	FGF	overexpression; amino acid substitutions; translocations	multiple myeloma; bladder and cervical carcinomas; acute myelogenous leukemia
PDGF-R β	PDGF	translocations	chronic myelomonocytic leukemia

^aSee also Figure 5.16.

Table 5.2 The Biology of Cancer (© Garland Science 2014)

Změněný receptor pro RF = onkoprotein

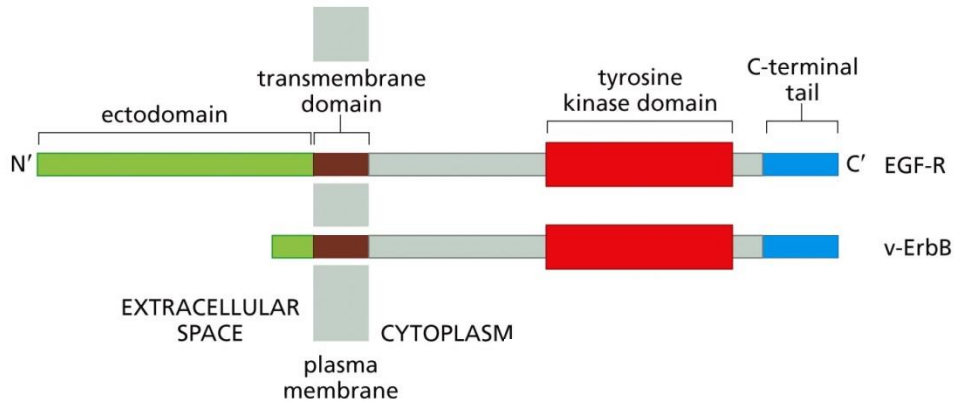


Figure 5.10 The Biology of Cancer (© Garland Science 2014)

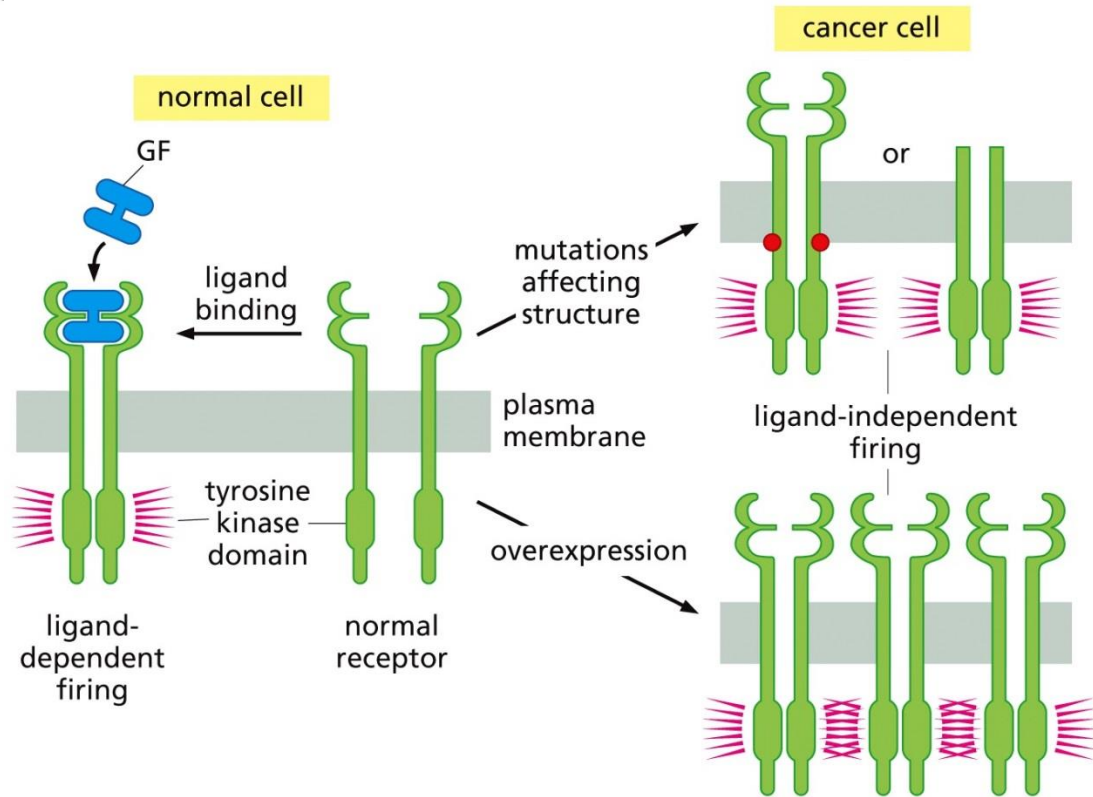


Figure 5.11a The Biology of Cancer (© Garland Science 2014)

Parakrinní signalizace

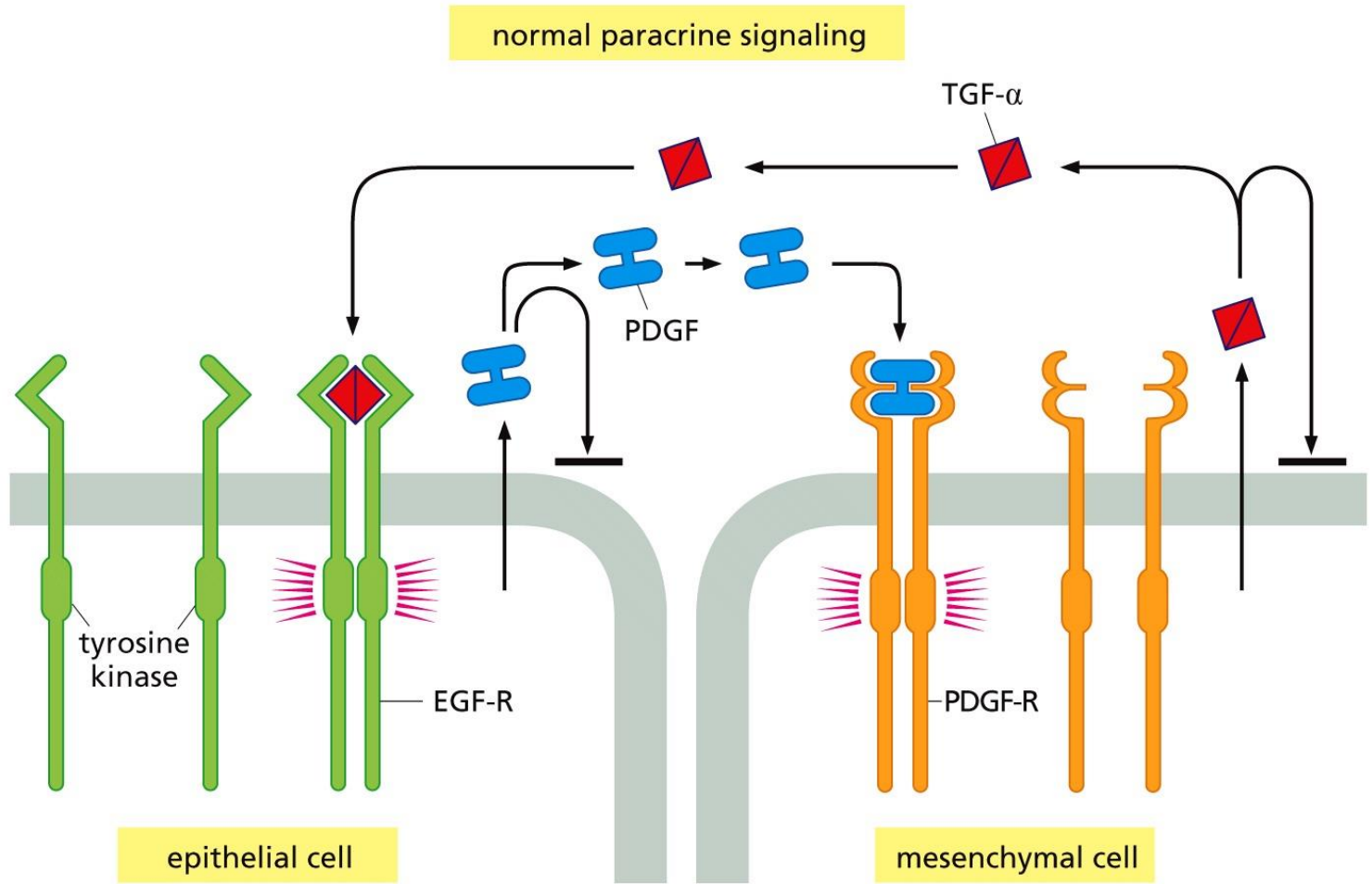


Figure 5.11b The Biology of Cancer (© Garland Science 2014)

Autokrinní signalizace nádorových buněk

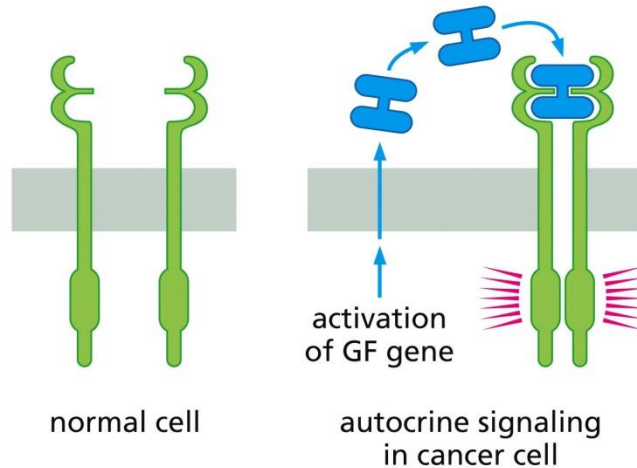


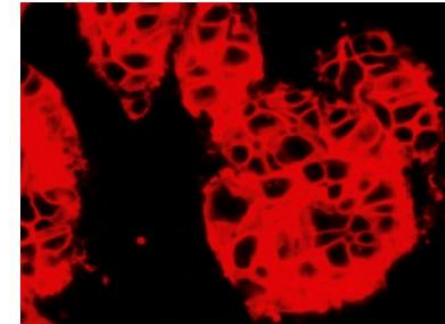
Figure 5.11c The Biology of Cancer (© Garland Science 2014)

Table 5.3 Examples of human tumors making autocrine growth factors

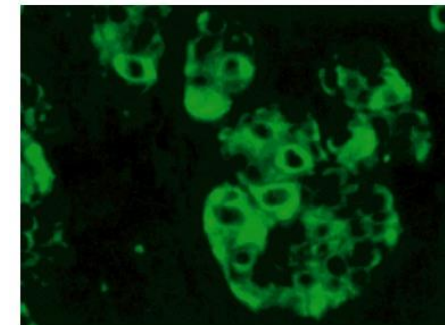
Ligand	Receptor	Tumor type(s)
HGF	Met	miscellaneous endocrinal tumors, invasive breast and lung cancers, osteosarcoma
IGF-2	IGF-1R	colorectal
IL-6	IL-6R	myeloma, HNSCC
IL-8	IL-8R A	bladder cancer
NRG	ErbB2 ^a /ErbB3	ovarian carcinoma
PDGF-BB	PDGF-R $\alpha\beta$	osteosarcoma, glioma
PDGF-C	PDGF-R $\alpha\beta$	Ewing's sarcoma
PRL	PRL-R	breast carcinoma
SCF	Kit	Ewing's sarcoma, SCLC
VEGF-A	VEGF-R (Flt-1)	neuroblastoma, prostate cancer, Kaposi's sarcoma
TGF- α	EGF-R	squamous cell lung, breast and prostate adenocarcinoma, pancreatic, mesothelioma
GRP	GRP-R	small-cell lung cancer

^aAlso known as HER2 or Neu receptor

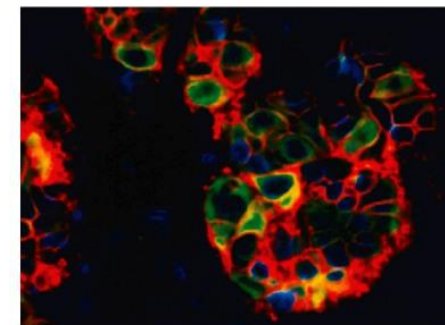
Table 5.3 The Biology of Cancer (© Garland Science 2014)



EGF-R



TGF- α



merged

Figure 5.11d The Biology of Cancer (© Garland Science 2014)

Autofosforylace tyrozin kinázových receptorů

- Při absenci signálu – ligandu – jsou receptory jako monomery
- Po vazbě ligandu dochází k dimerizaci receptorů
- Transfosforylace C-konců

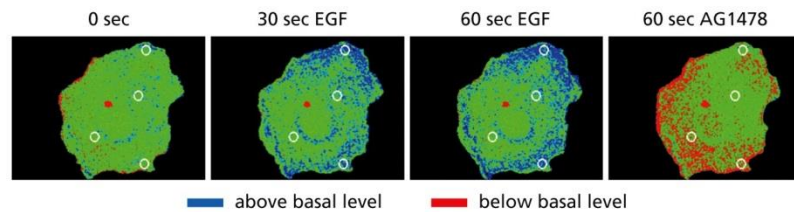


Figure 5.12 The Biology of Cancer (© Garland Science 2014)

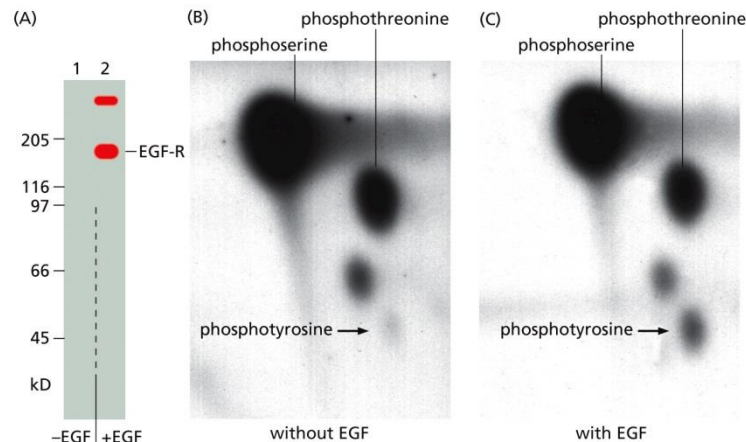


Figure 5.13 The Biology of Cancer (© Garland Science 2014)

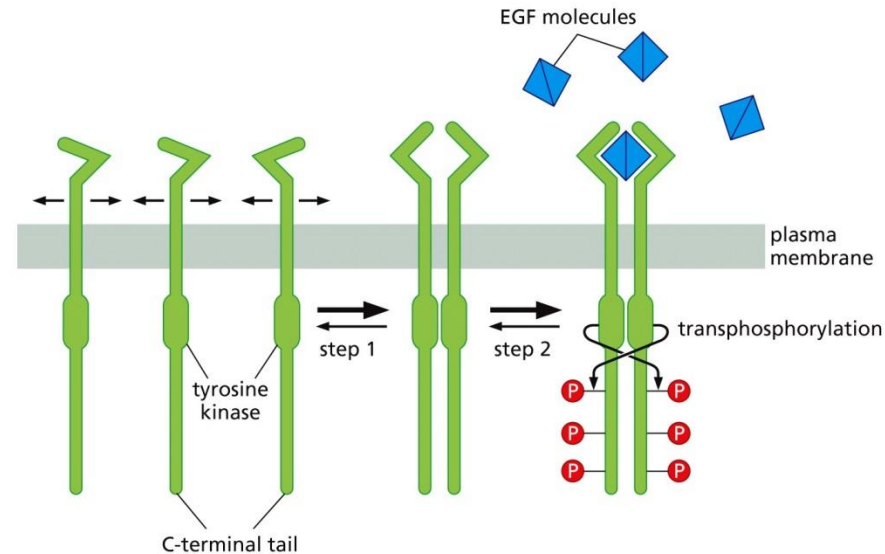


Figure 5.14a The Biology of Cancer (© Garland Science 2014)

Konstitutivní dimerizace receptorů způsobena fúzí genů

- Fúze genu pro RF s jiným genem jehož produkt může normálně dimerizovat nebo oligomerizovat
- Části takových hybridních receptorů (jejich ektodomény) jsou spojeny
- Stabilní změna struktury receptoru vedoucí k jeho trvalé aktivaci bez ligandu

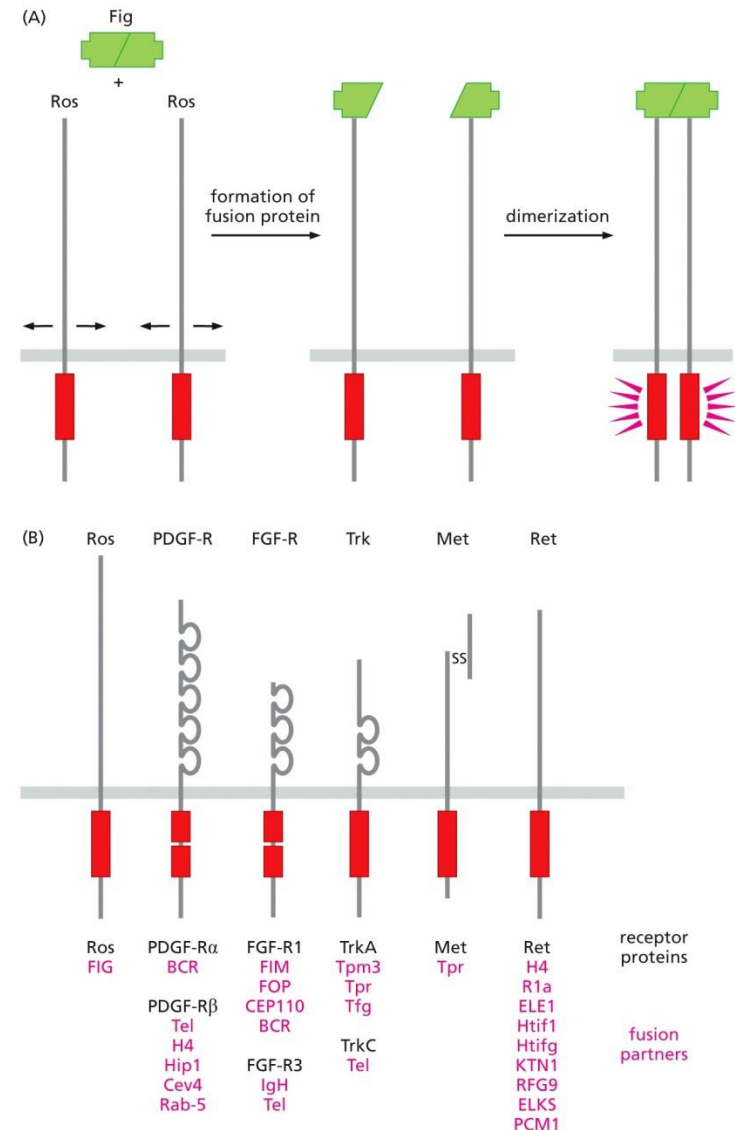
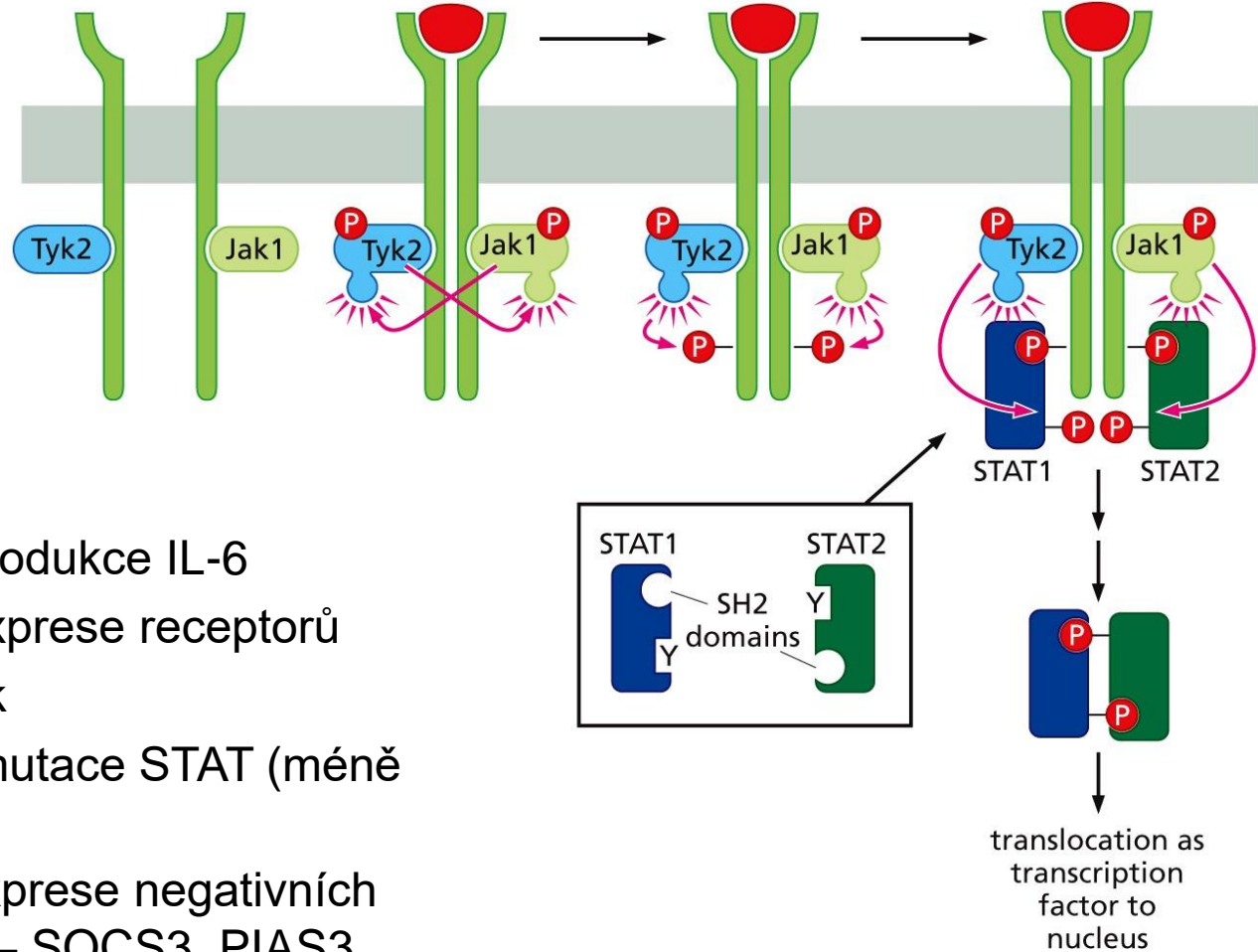


Figure 5.16 The Biology of Cancer (© Garland Science 2014)

Jak-STAT dráha



- Zvýšená produkce IL-6
- Zvýšená exprese receptorů
- Mutace Jak
- Aktivační mutace STAT (méně časté)
- Snížená exprese negativních regulátorů – SOCS3, PIAS3
- Aktivace STAT pomocí interakce s AR nebo BRCA1

STAT aktivace u solidních nádorů

Table 1. Summary of studies describing STAT activation and its clinical implications in solid tumours

Cancer type	Reference	STAT activation, tissue sample	Number of patients	Clinical implications of STAT activation
NSCLC	Xu and Lu, 2014	STAT3 and pSTAT3 detection with immunohistochemistry	1793 (meta-analysis of 17 studies)	Positivity for STAT3 or pSTAT3 associated with reduced overall survival (HR = 0.67, P < 0.0001)
Prostate	Mirtti et al, 2013	Nuclear STAT5A/B, immunohistochemistry on tissue microarrays from prostatectomy or TURP	562 radical prostatectomy 106 palliative treatment	Presence of nuclear STAT5 associated with early recurrence (HR = 1.6, P = 0.012) Presence of nuclear STAT5 associated with prostate cancer-specific death (HR = 1.59, P = 0.034)
	Sonnenblick et al, 2013	Immunohistochemistry for pSTAT3 on tissue microarrays	137 out of 375 positive (36%)	Presence of pSTAT3 associated with improved overall survival in patients receiving adjuvant chemotherapy (10 year survival 79% for pSTAT3 positive, vs 61.5% for pSTAT3 negative, HR = 0.48, P = 0.01)
Breast	Peck et al, 2011	Immunohistochemistry and immunofluorescence for nuclear pSTAT5 on tissue microarrays	208 out of 421 positive (49%). Node negative, with no adjuvant therapy	Absence of activated STAT5 associated with decreased cancer-specific survival (HR = 2.39, P = 0.023)
	Monnien et al, 2010	Immunohistochemistry for nuclear pSTAT3	39 out of 104 (37.5%) positive. 104 rectal, T3 or resectable T4M0	Presence of activated STAT3 associated with better overall survival (HR = 0.3, P = 0.01)
Rectal/colorectal	Kusaba et al, 2006	Immunohistochemistry for pSTAT3	62 out of 108 (57%) positive. Colorectal adenocarcinoma	Presence of activated STAT3 associated with worse overall survival (P < 0.001)
	Macha et al, 2011	Immunohistochemistry for nuclear pSTAT3	63 out of 94 (67%) positive (follow-up data for 71)	Nuclear pSTAT3 associated with shorter median disease-free survival (13 months vs 64 months, P = 0.019).
Oral squamous cell carcinoma	Pectasides et al, 2010	AQUA immunohistochemistry for nuclear STAT3		High nuclear STAT3 associated with improved overall survival (Mean 119 months vs 57.3 months, P = 0.009)
	Takemoto et al, 2009	Immunohistochemistry for nuclear pSTAT3	71 out of 125 (56.8%) positive	Nuclear pSTAT3 associated with reduced overall survival (5 year survival 79.2 months vs 95.3 months, P = 0.006)
Malignant melanoma	Messina et al, 2008	Immunohistochemistry for pSTAT1 and pSTAT3	6 out of 14 primary tumours positive for nuclear pSTAT3, 16 out of 26 lymph node metastases positive for pSTAT3, 6 out of 23 positive for STAT1	In patients with lymph node metastases, higher rates of recurrence with high pSTAT3 staining compared with low-grade staining (9 out of 16 vs 3 out of 10). Lower rates of recurrence with high pSTAT1 staining (8 out of 23 vs 2 out of 6) in lymph node and brain metastases
Renal cell carcinoma	Horiguchi et al, 2002	Immunohistochemistry for nuclear pSTAT3	24 out of 48 (50%) positive	Nuclear pSTAT3 associated with shortened cancer-specific survival (P = 0.0439)
Glioblastoma	Birner et al, 2010	Immunohistochemistry for pSTAT3 on tissue microarrays	58.8% of 111 positive	High or very high numbers of cells positive for pSTAT3 associated with reduced overall survival (P = 0.001)

Abbreviations: AQUA = automated quantitative analysis; HR = hazard ratio; NSCLC = non-small cell lung cancer; STAT = signal transducers and activators of transcription; TURP = transurethral resection of prostate.

TGF- β receptor

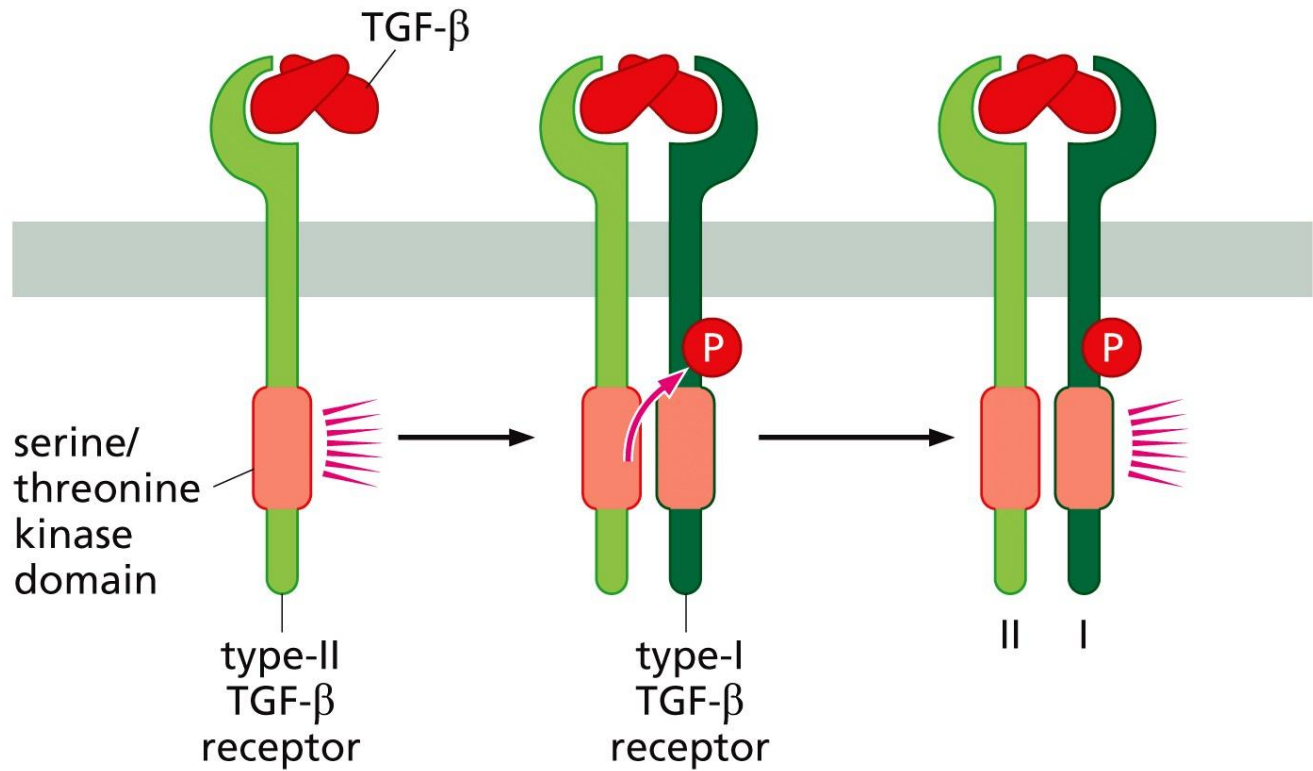
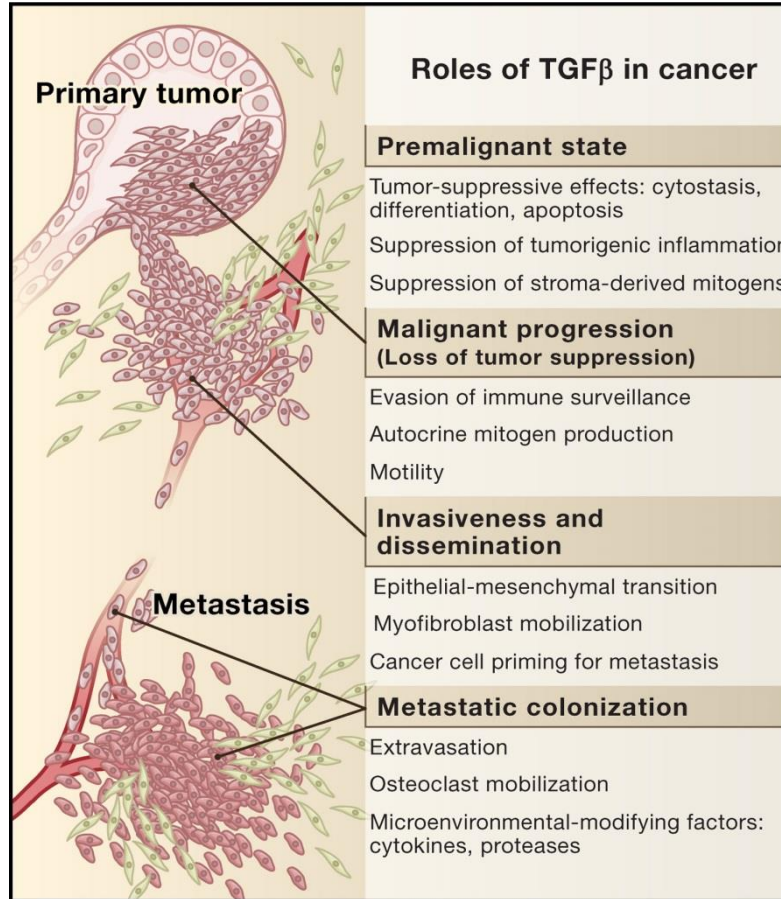
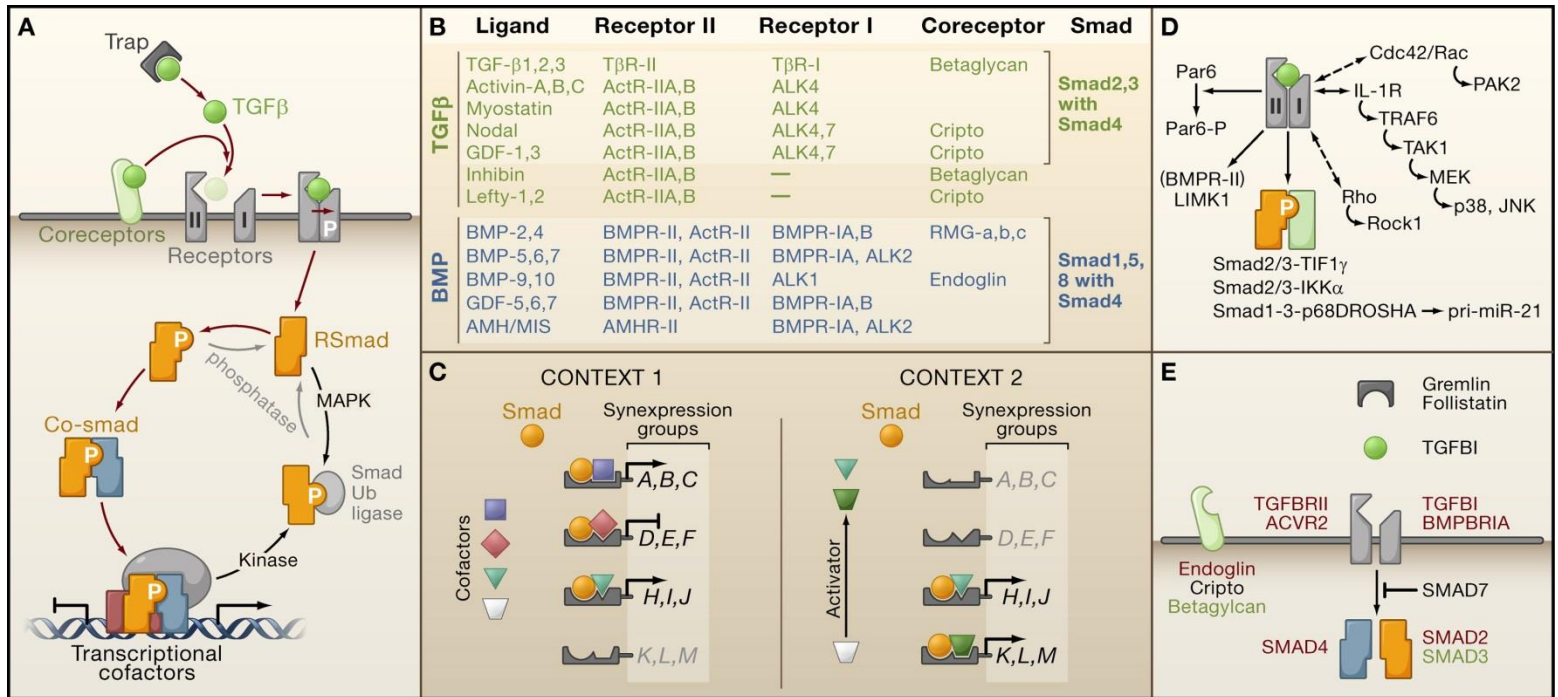


Figure 5.20 The Biology of Cancer (© Garland Science 2014)

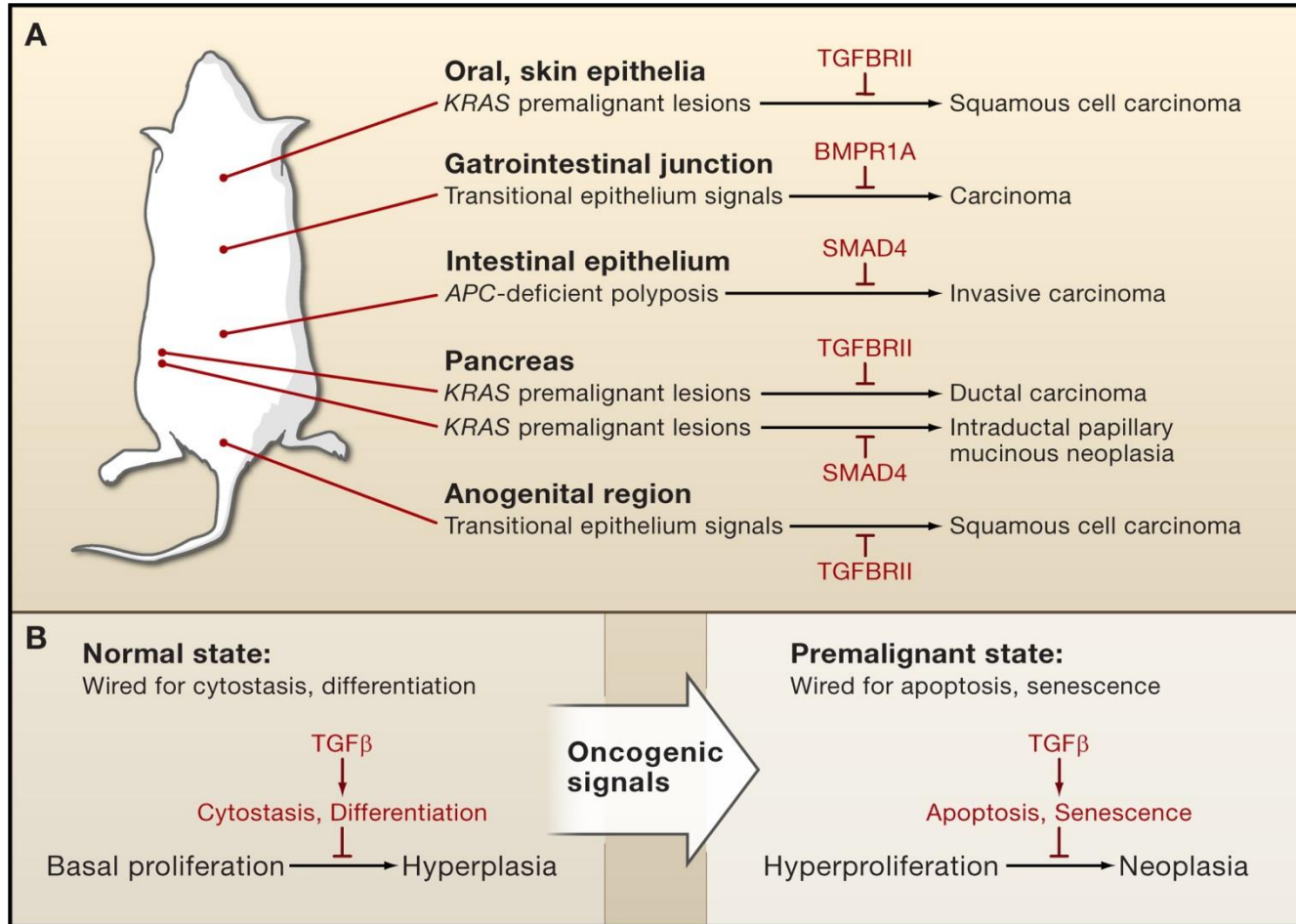
TGF- β v rakovině



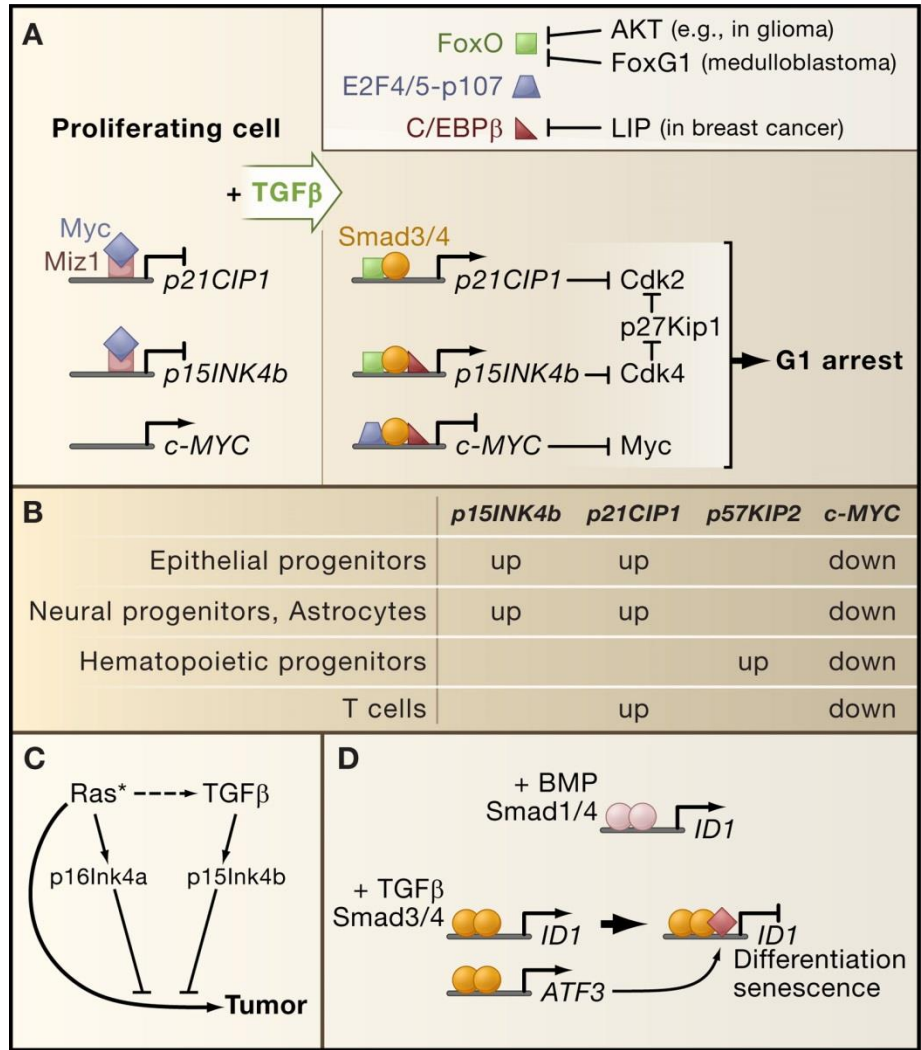
TGF-β v rakovině



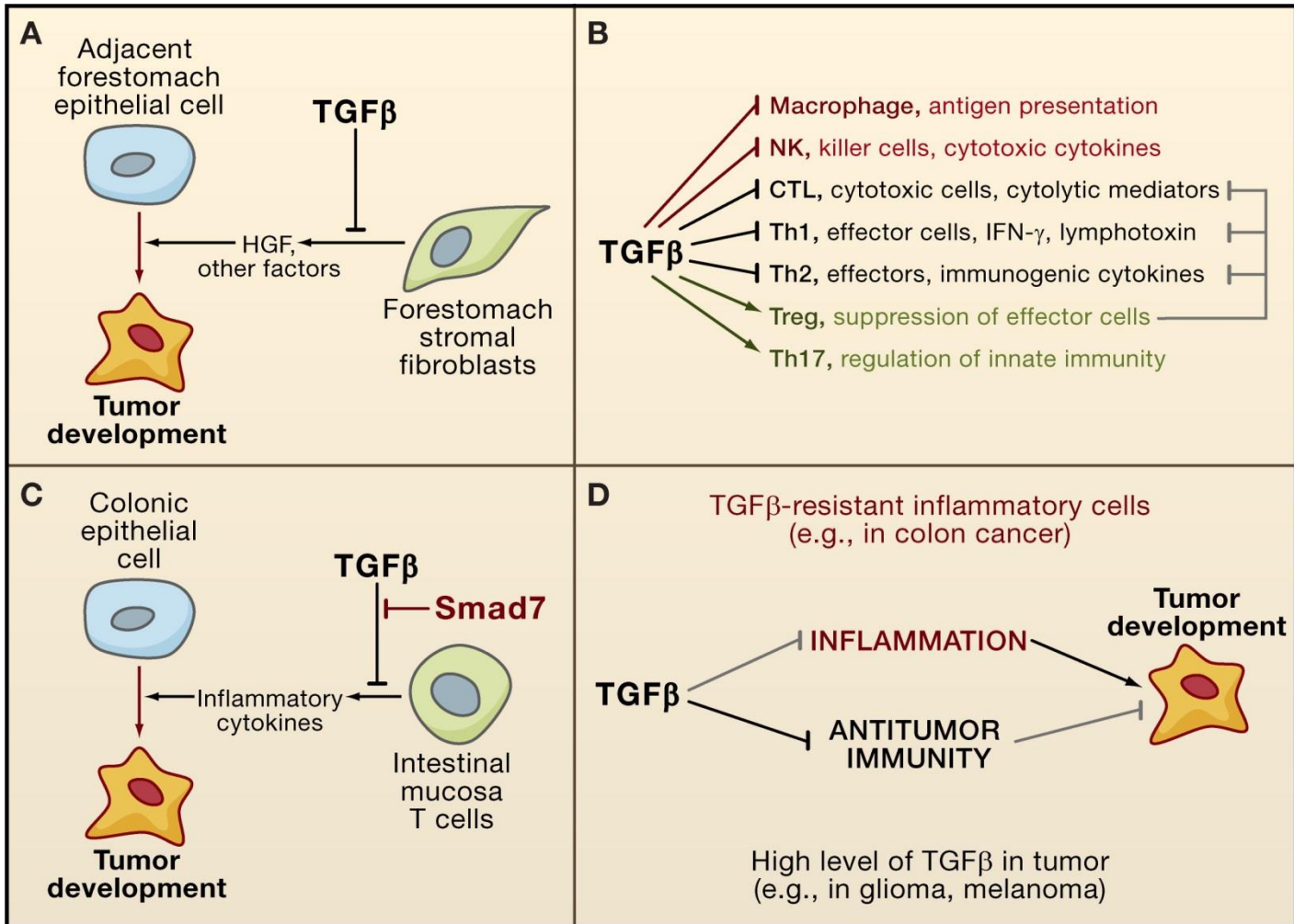
TGF- β v rakovině



TGF-β v rakovině



TGF- β a nádorové stroma



Notch

- 5 ligandů (NotchL, Delta, Jagged), 4 receptory
- Ligandy imobilizovány na povrchu buněk
- Juxtacrine signaling
- Proteolytické štěpení ectodomény -> jaderný kofaktor regulující genovou expresi
- Konstitutivně aktivní mutant Notch u 50% T-leukémií
- Nádorový supresor – hepatocelulární karcinom, dlaždicový karcinom
- Nejasná funkce - pankreas

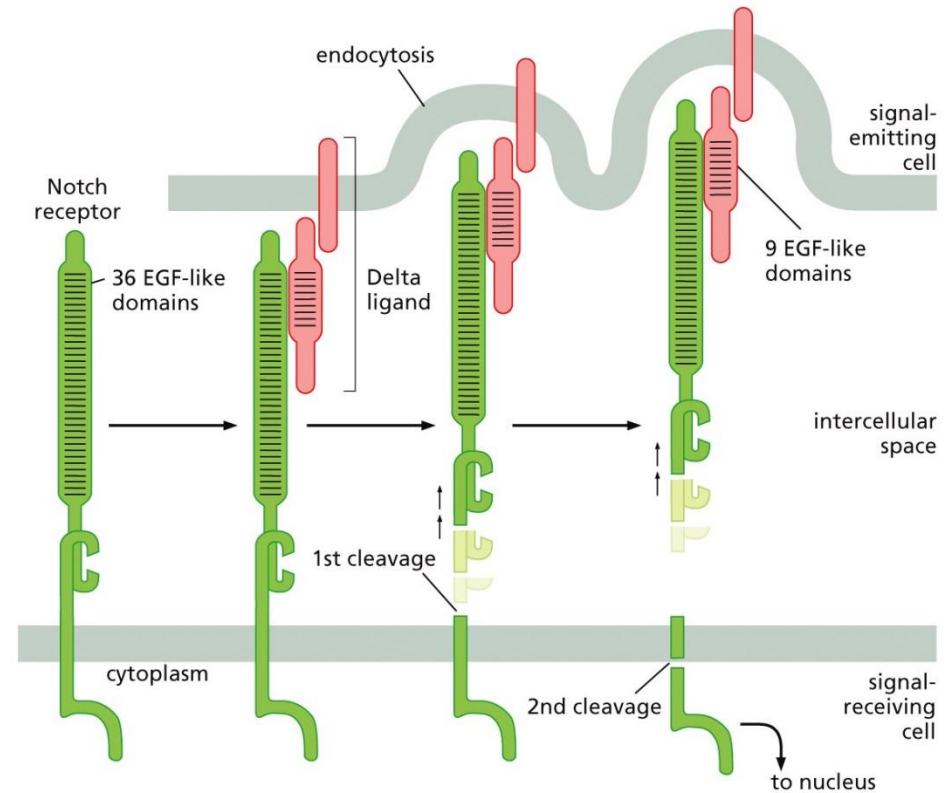
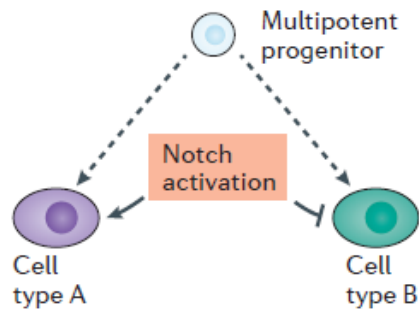


Figure 5.21 The Biology of Cancer (© Garland Science 2014)

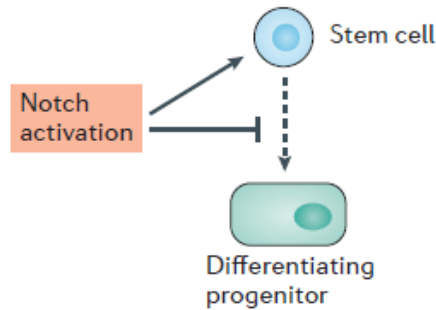
Úloha Notch

- Reguluje osud kmenových a progenitorových buněk
- Reguluje liniovou diferenciaci
- Inbibuje x indukuje diferenciaci

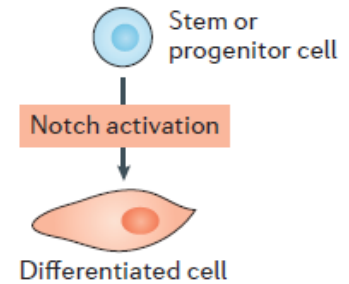
a Lineage specification, e.g. T cell commitment



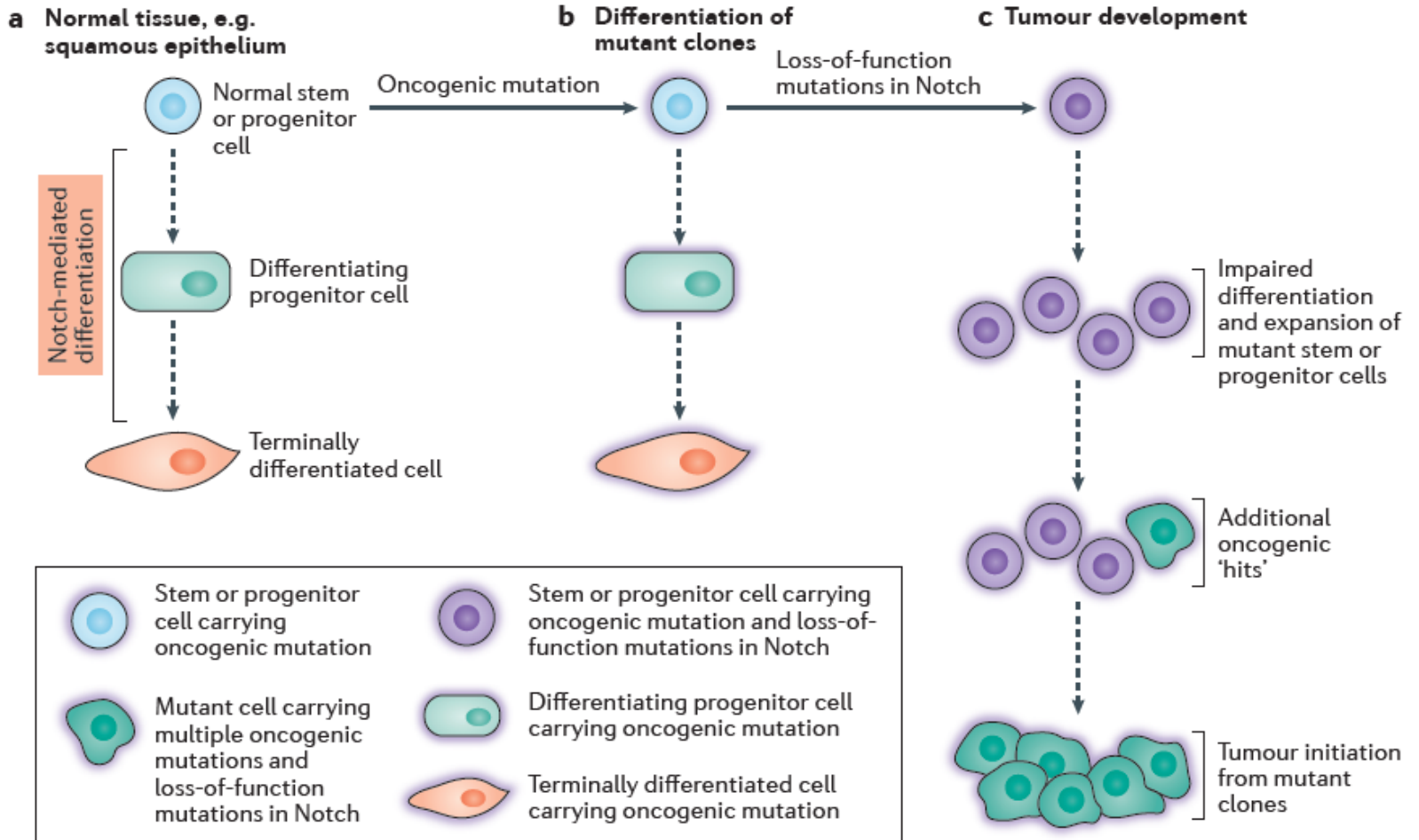
b Stem cell gatekeeper, e.g. intestinal epithelium



c Induction of differentiation, e.g. epidermis

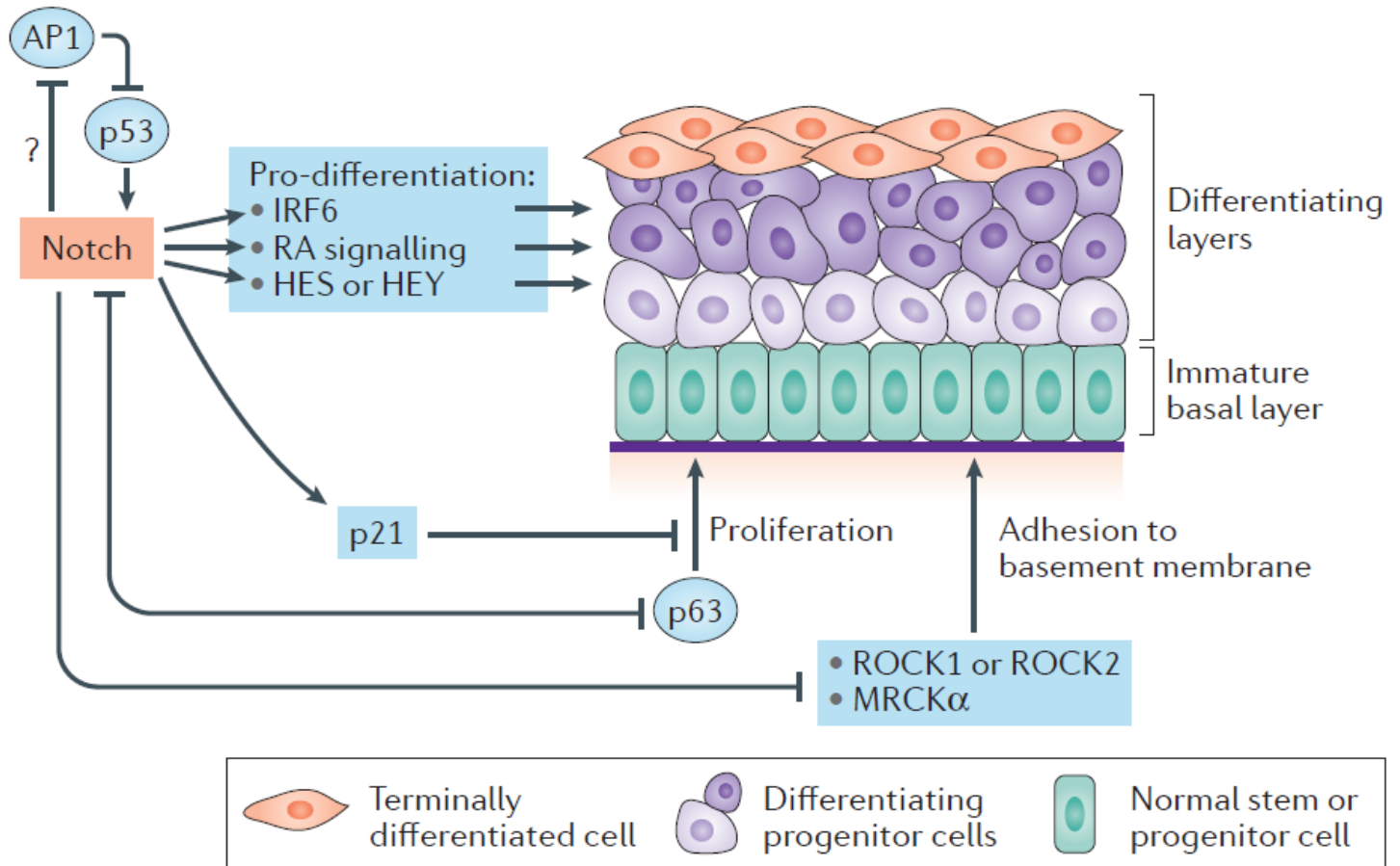


Notch jako nádorový supresor



Mechanismus nádorové suprese Notch

- Pozitivní regulace diferenciačních signálů – RA, IRF6
- Inhibice proliferace
- Inhibice adheze přes ROCK



Patched-Smoothened – Hedgehog dráha

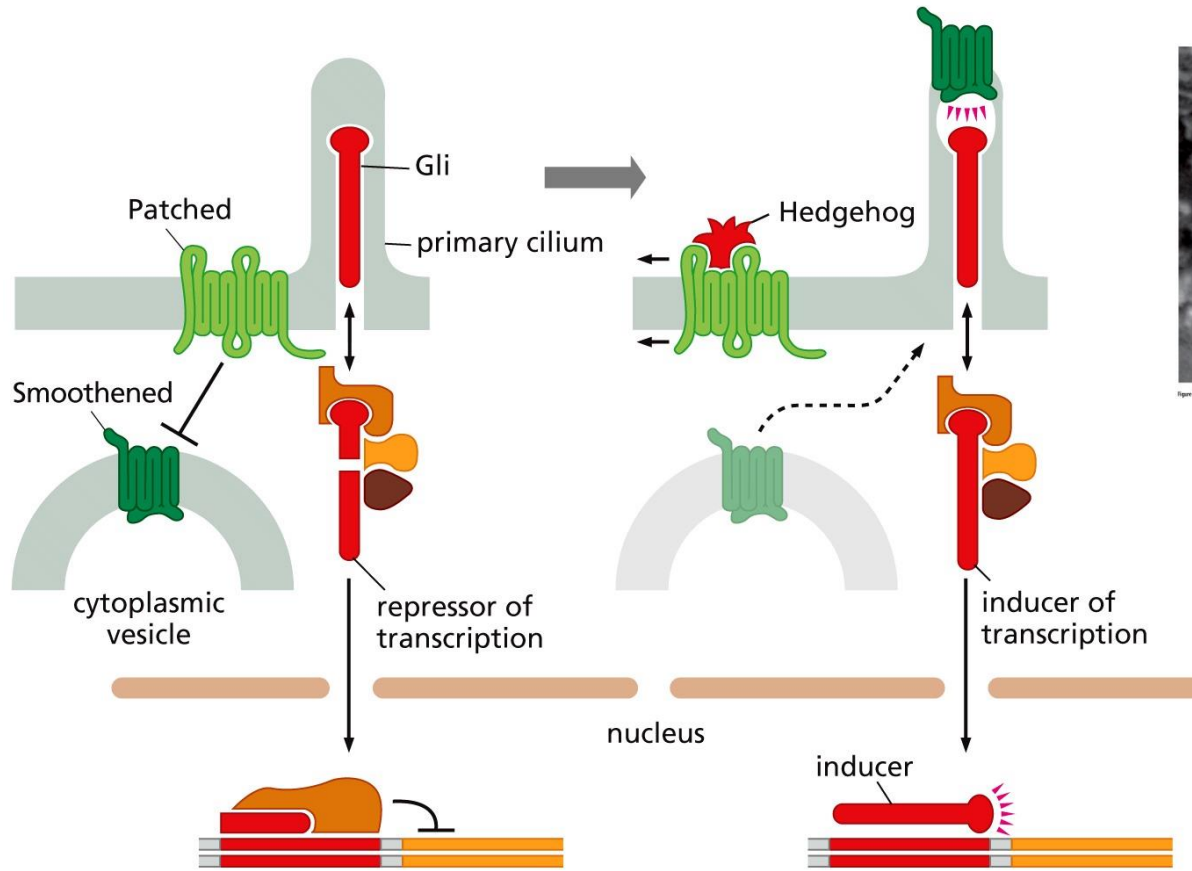


Figure 5.22a The Biology of Cancer (© Garland Science 2014)

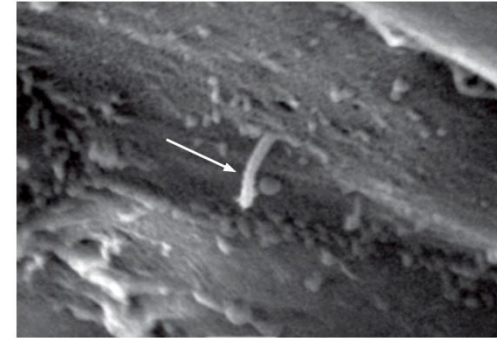


Figure 5.22b The Biology of Cancer (© Garland Science 2014)

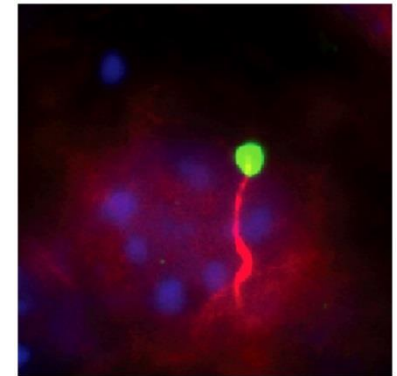
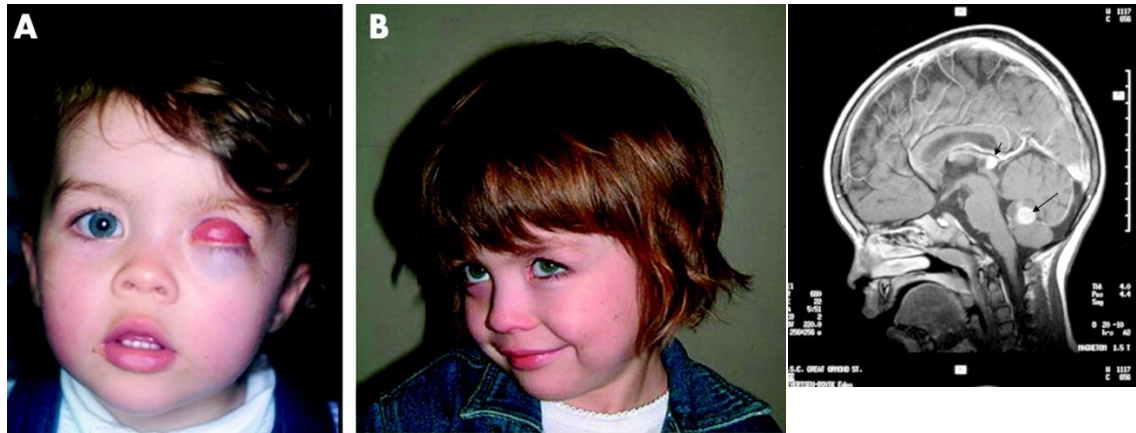


Figure 5.22c The Biology of Cancer (© Garland Science 2014)

Patched-Smoothened – Hedgehog dráha

- Gli – vysoká exprese u glioblastomů
- Záradečná inaktivační mutace genu *patched* (PTCH) = Gorlinův syndrom, vysoká incidence bazaliomů, meduloblastomu a dalších typů nádorů



SCIENTIFIC REPORT

Gorlin syndrome: the *PTCH* gene links ocular developmental defects and tumour formation

N K Ragge, A Salt, J R O Collin, A Michalski, P A Farndon

Br J Ophthalmol 2005;89:988–991. doi: 10.1136/bjo.2004.061390

Obr. 2. Bazocelulární karcinomy na zádech



Gorlin-Goltzův syndrom

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DERMATOLOGIE PRO PRAXI / Dermatol. praxi 2016; 10(2): 88–90 /

Frizzled receptor, kanonická Wnt signalizace

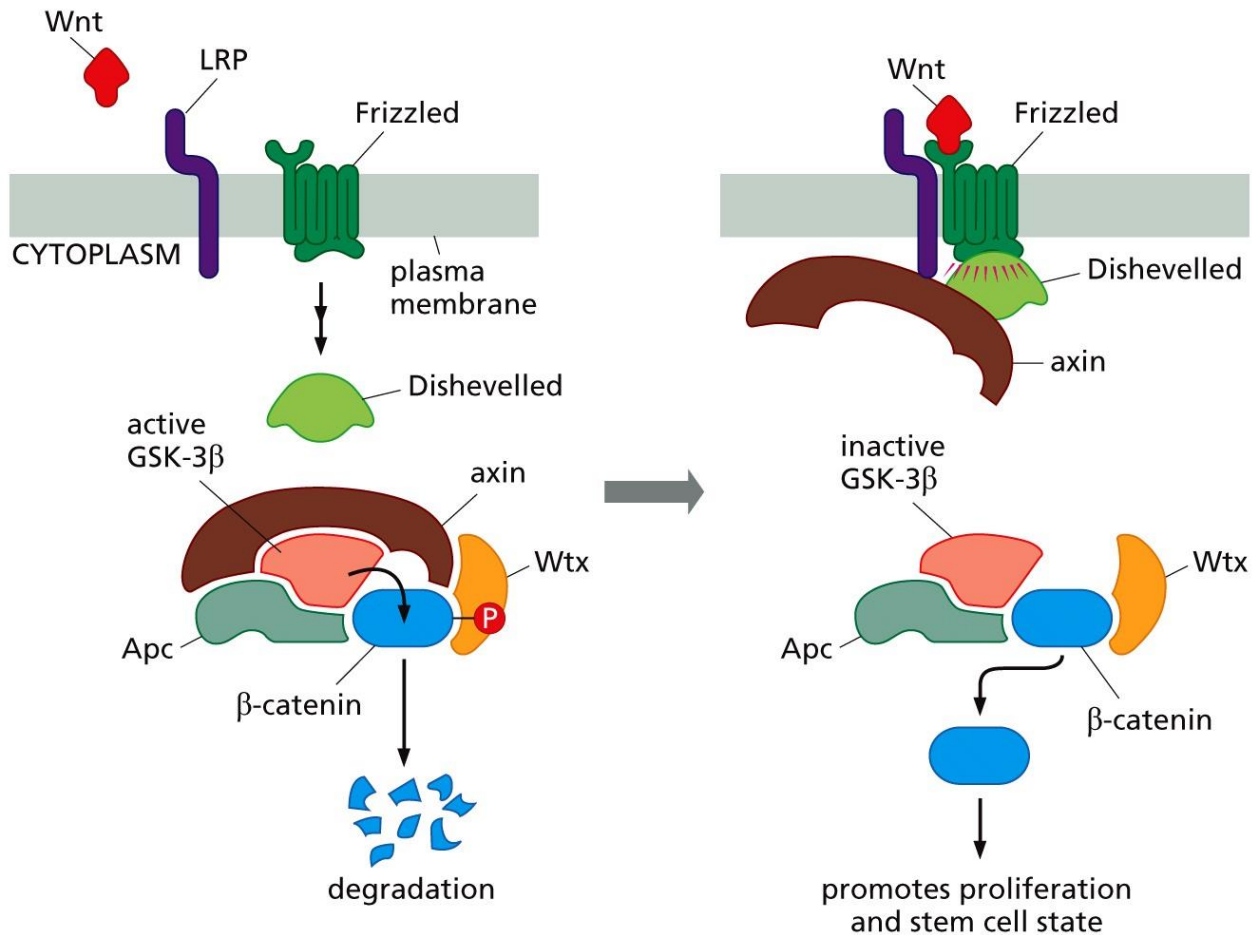


Figure 5.23 The Biology of Cancer (© Garland Science 2014)

Frizzled receptor, nekanonická Wnt signalizace

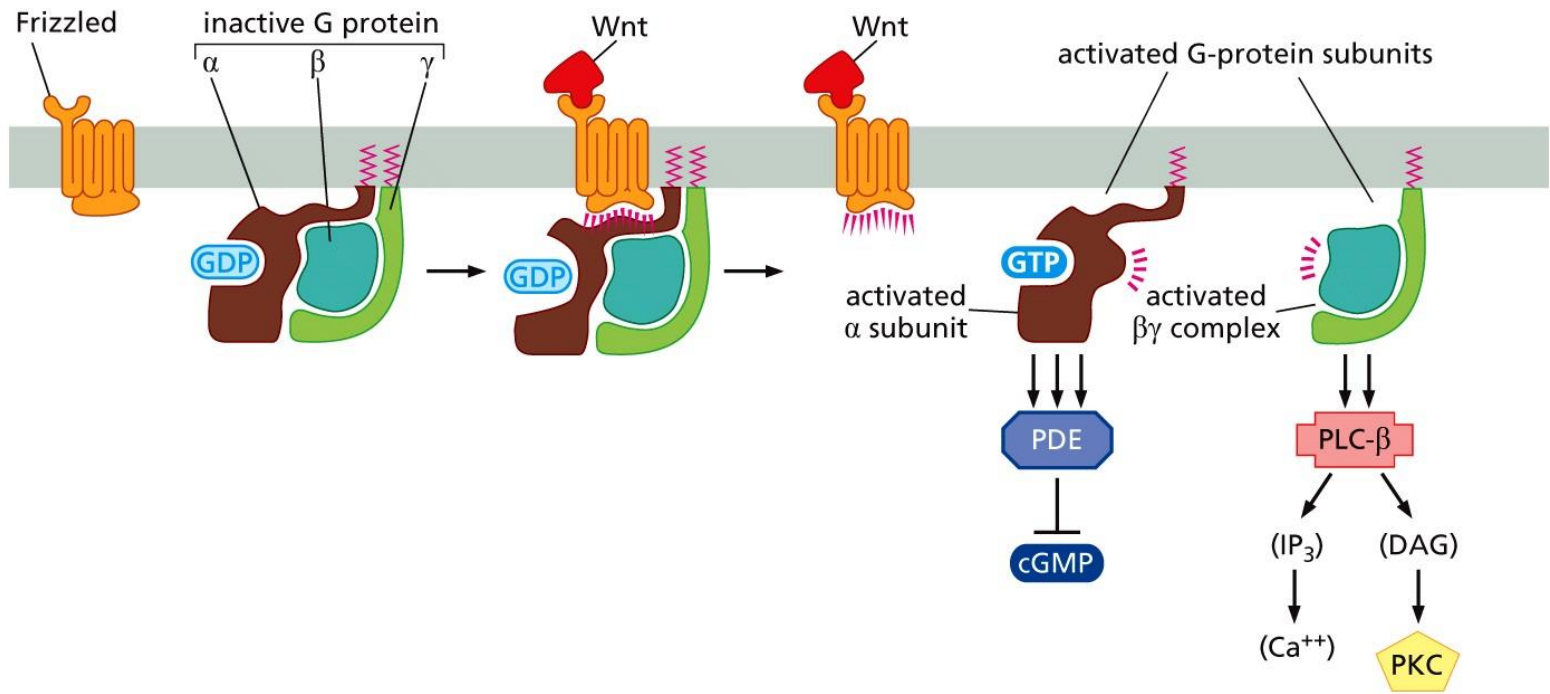
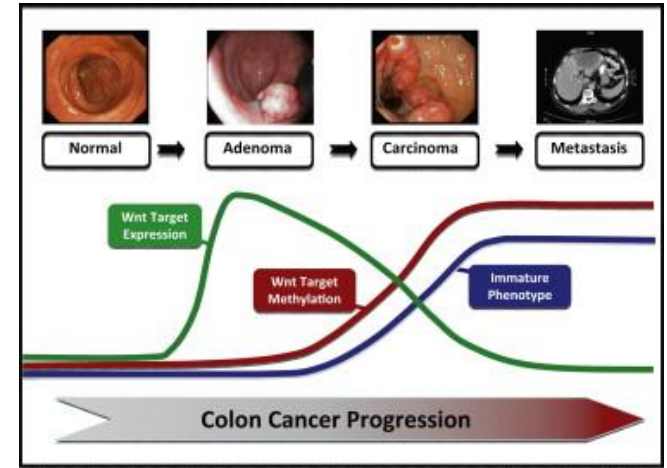
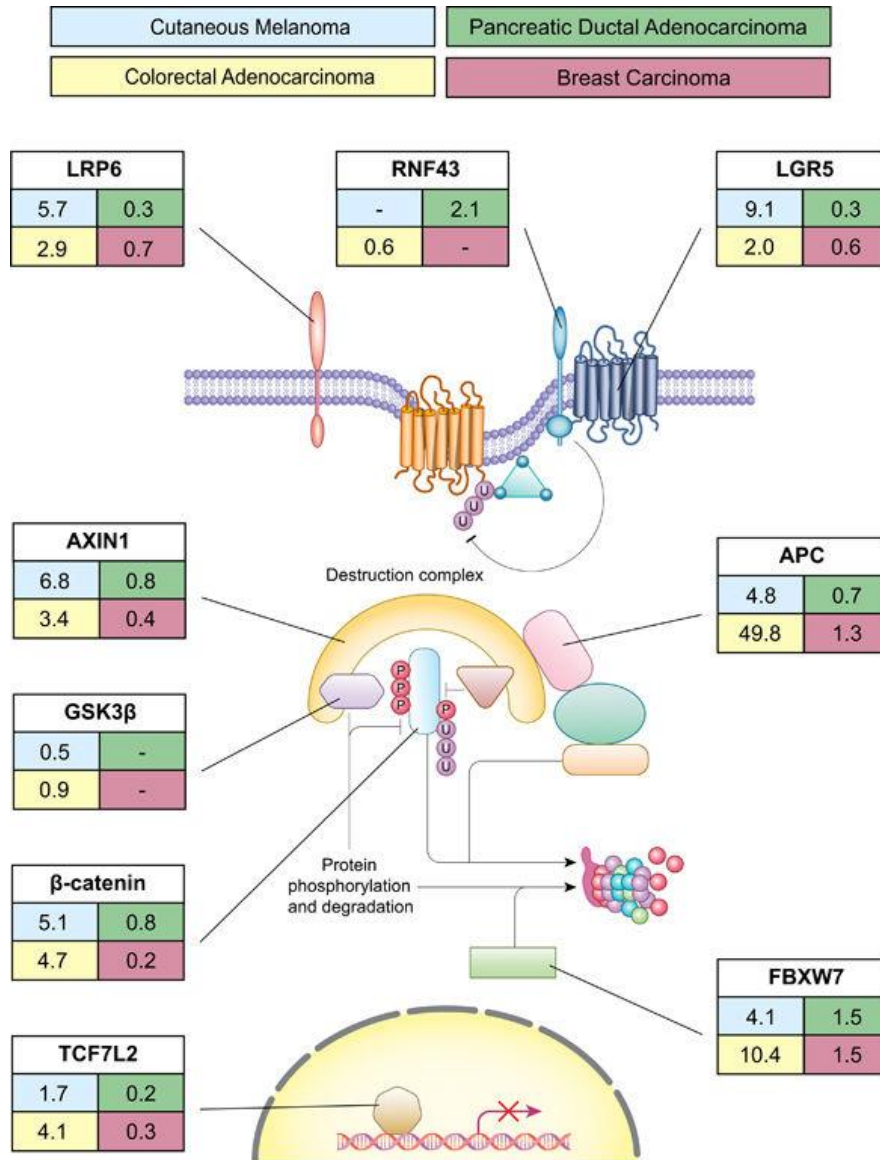


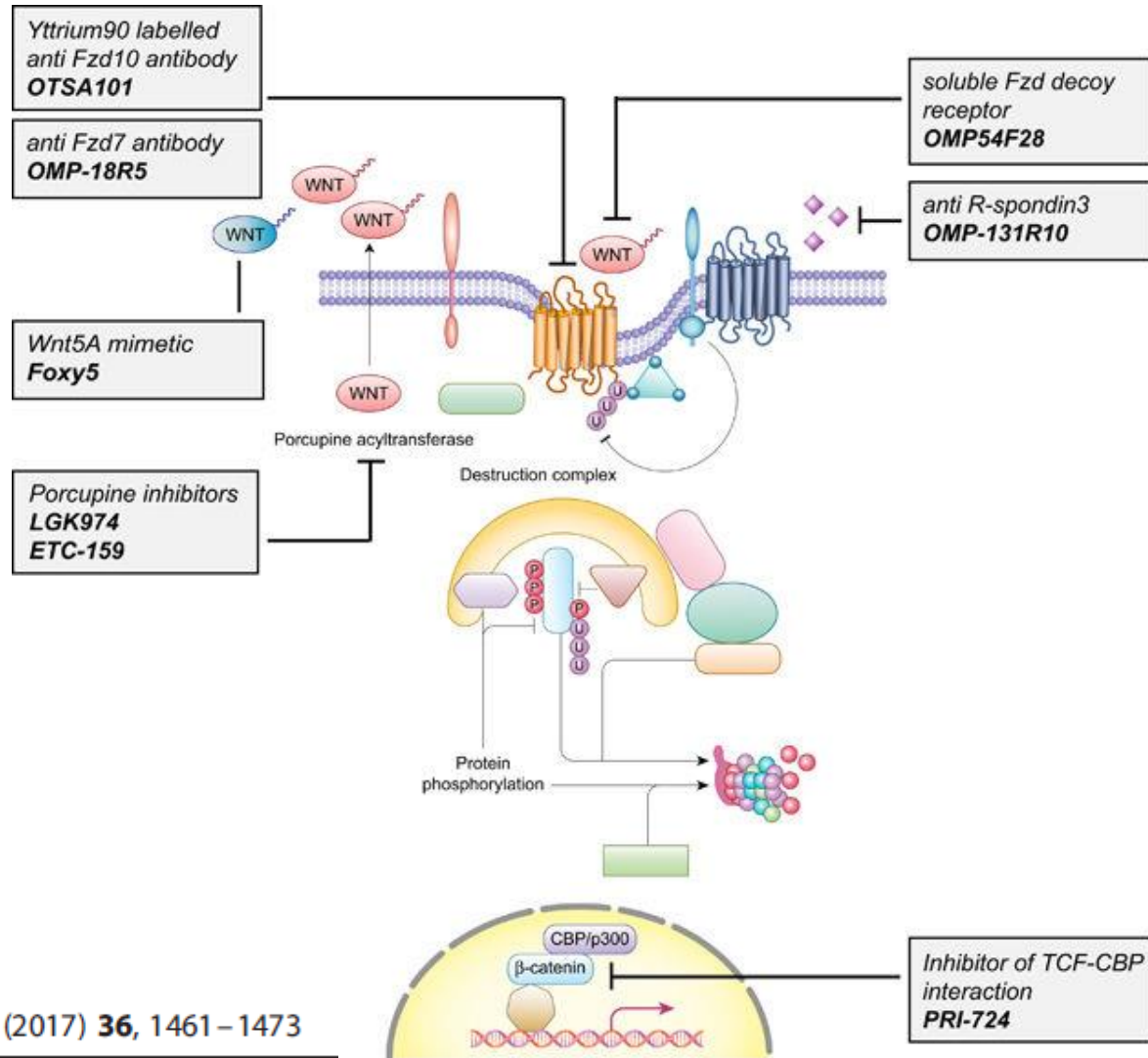
Figure 5.24a The Biology of Cancer (© Garland Science 2014)

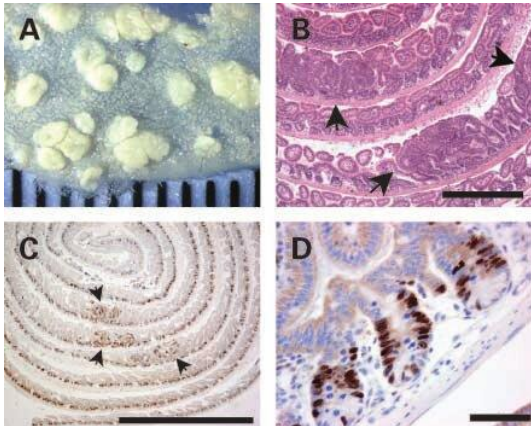
Wnt signalizace a rakovina



Cell Stem Cell 9, 476–485, November 4, 2011

Wnt signalizace a rakovina





Integriny

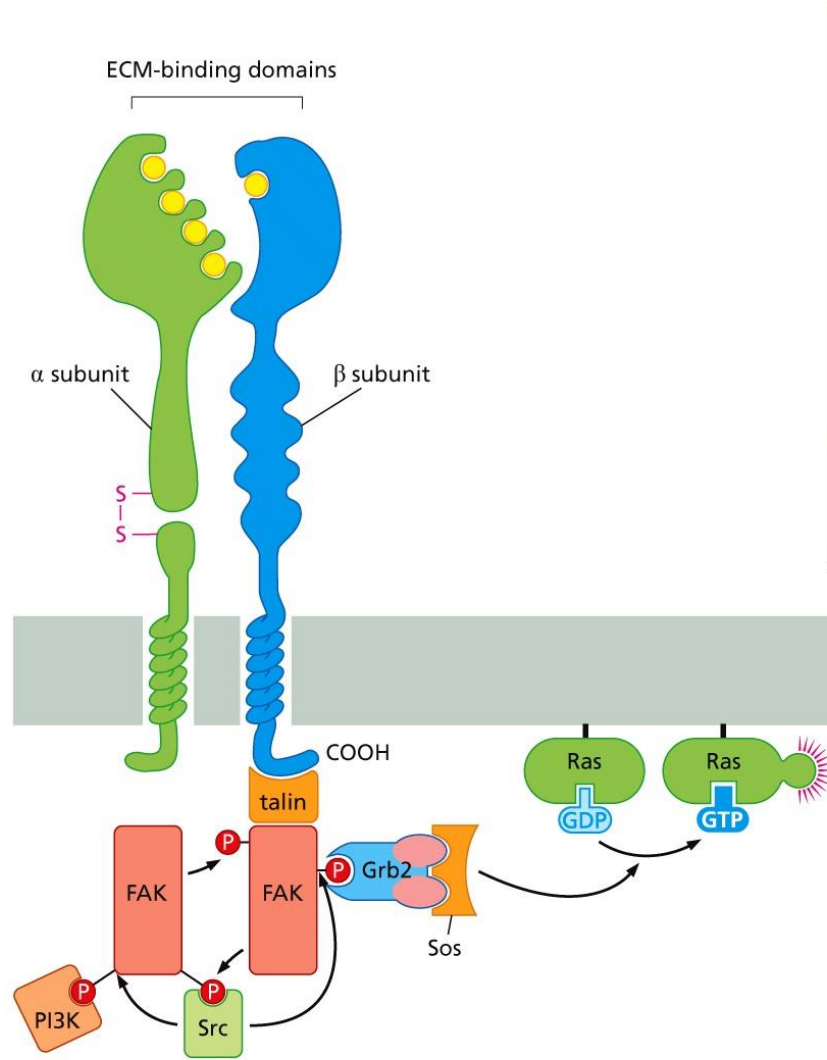


Figure 6.24a The Biology of Cancer (© Garland Science 2014)

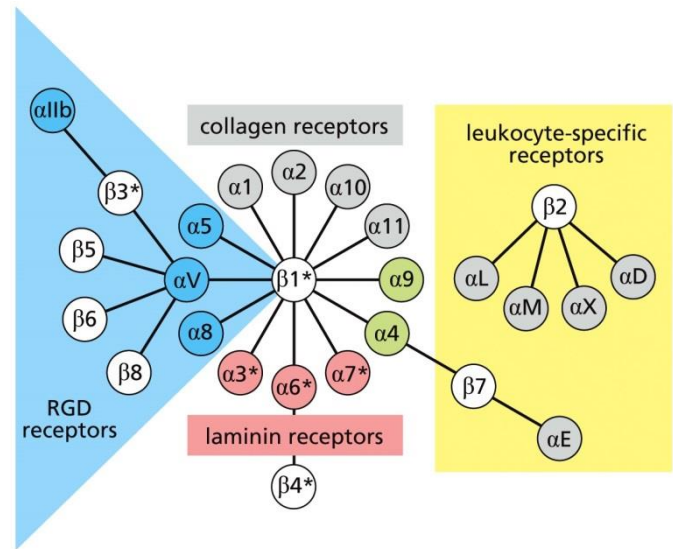


Figure 5.27b The Biology of Cancer (© Garland Science 2014)

Table 5.4 Examples of integrins and their extracellular matrix ligands

Integrin	ECM ligand
$\alpha 1 \beta 1$	collagens, laminin
$\alpha v \beta 3$	vitronectin, fibrinogen, thrombospondin
$\alpha 5 \beta 1$	fibronectin
$\alpha 6 \beta 1$	laminin
$\alpha 7 \beta 1$	laminin
$\alpha 2 \beta 3$	fibrinogen
$\alpha 6 \beta 4$	laminin—epithelial hemidesmosomes

Adapted in part from B. Alberts et al., Molecular Biology of the Cell, 5th ed. New York: Garland Science, 2008; and from H. Lodish et al., Molecular Cell Biology. New York: W.H. Freeman, 1995.

Table 5.4 The Biology of Cancer (© Garland Science 2014)

Integriny

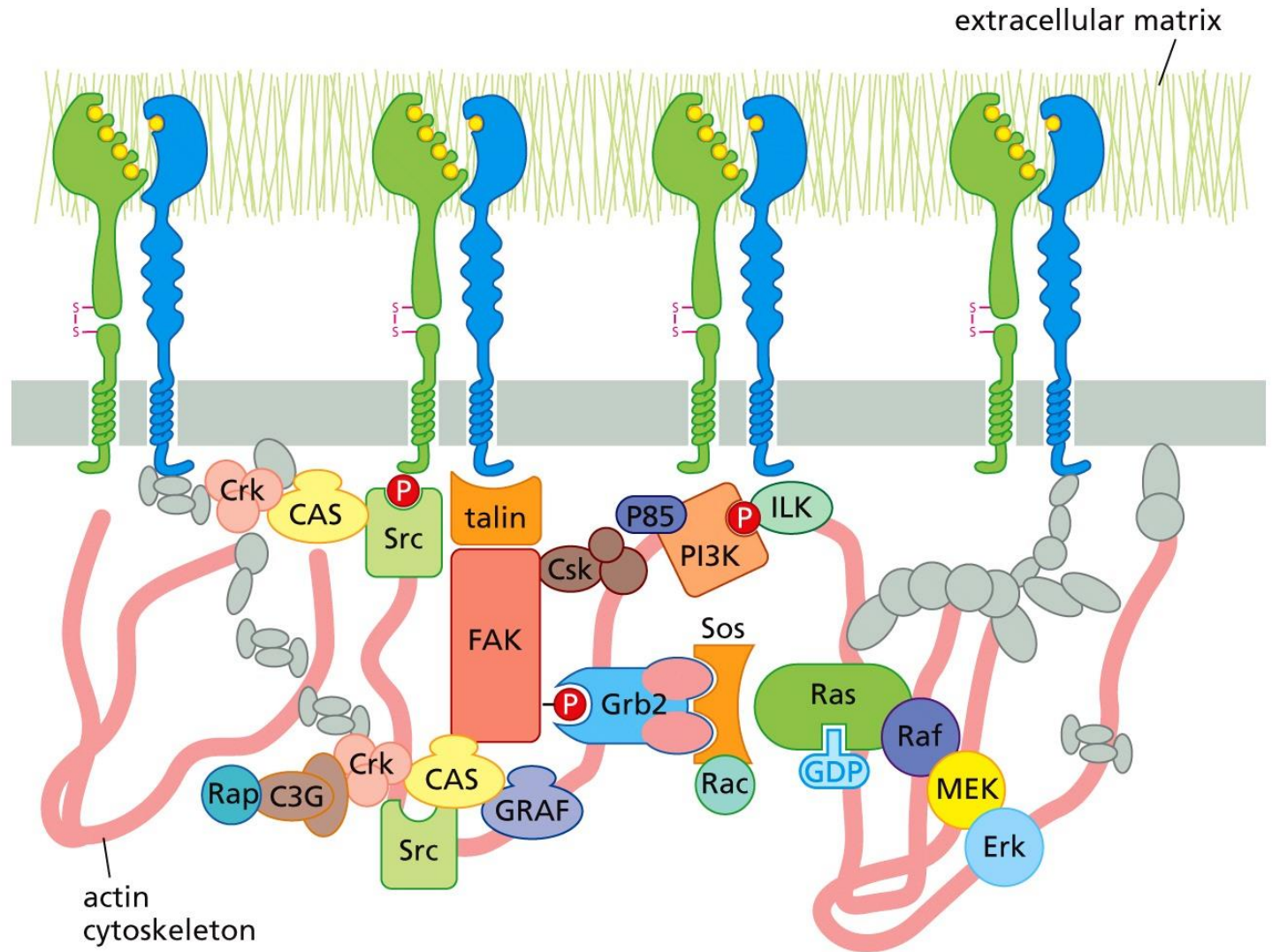
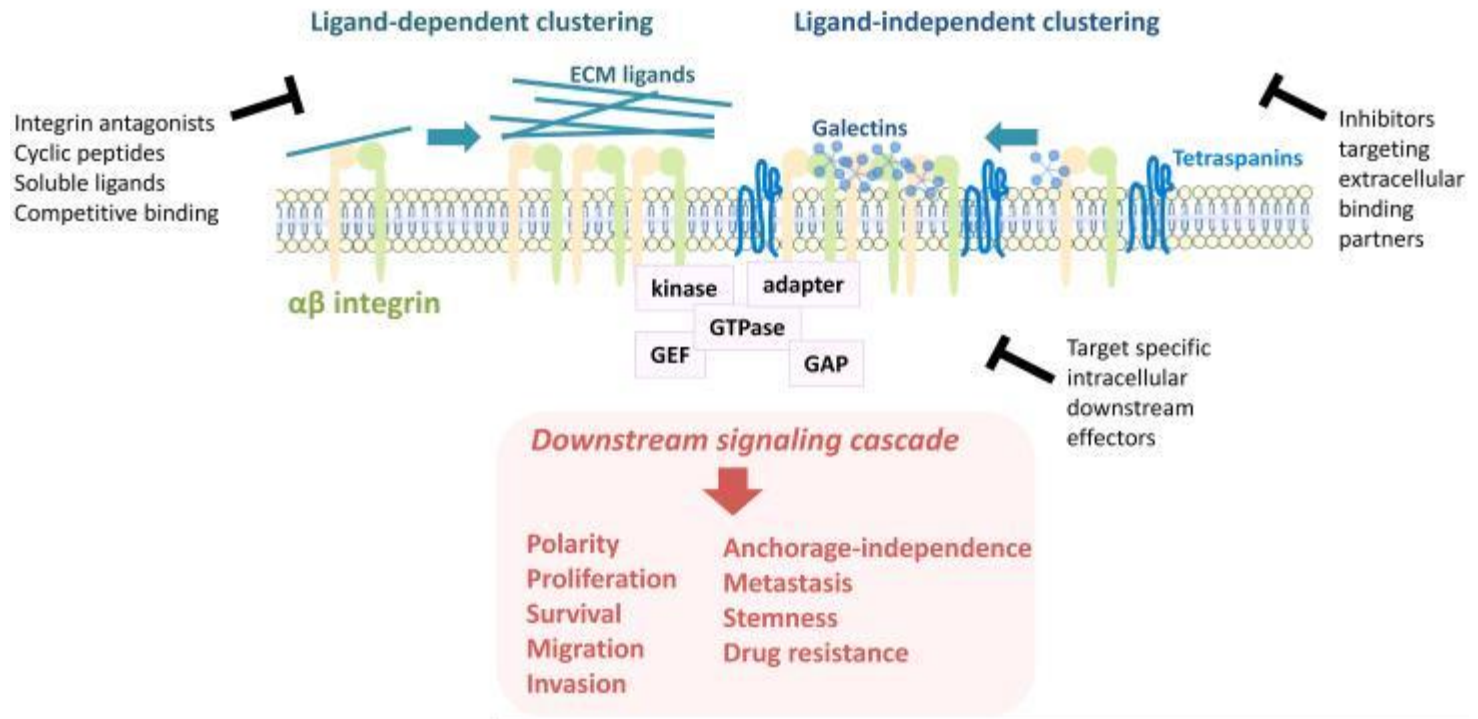


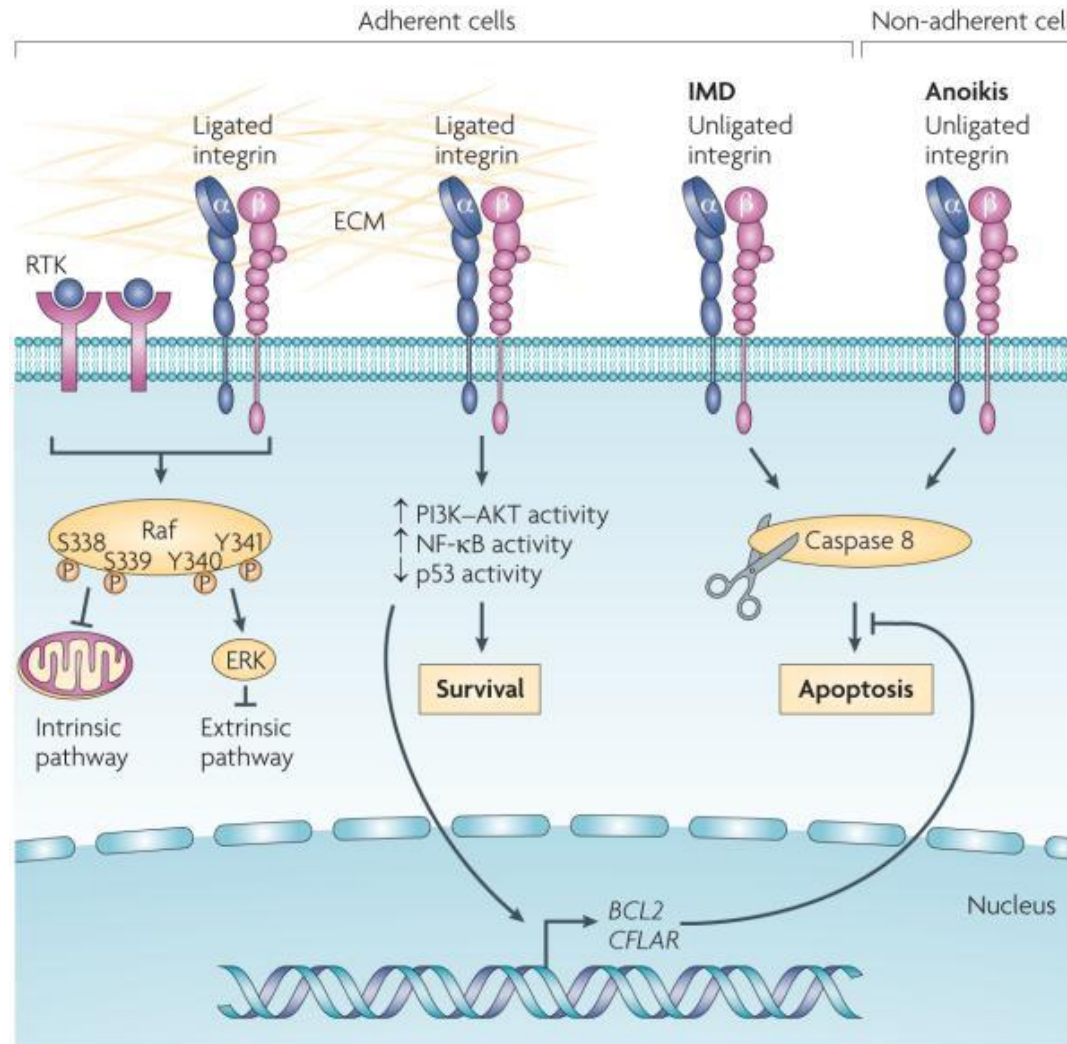
Figure 6.24b The Biology of Cancer (© Garland Science 2014)

Integriny a rakovina

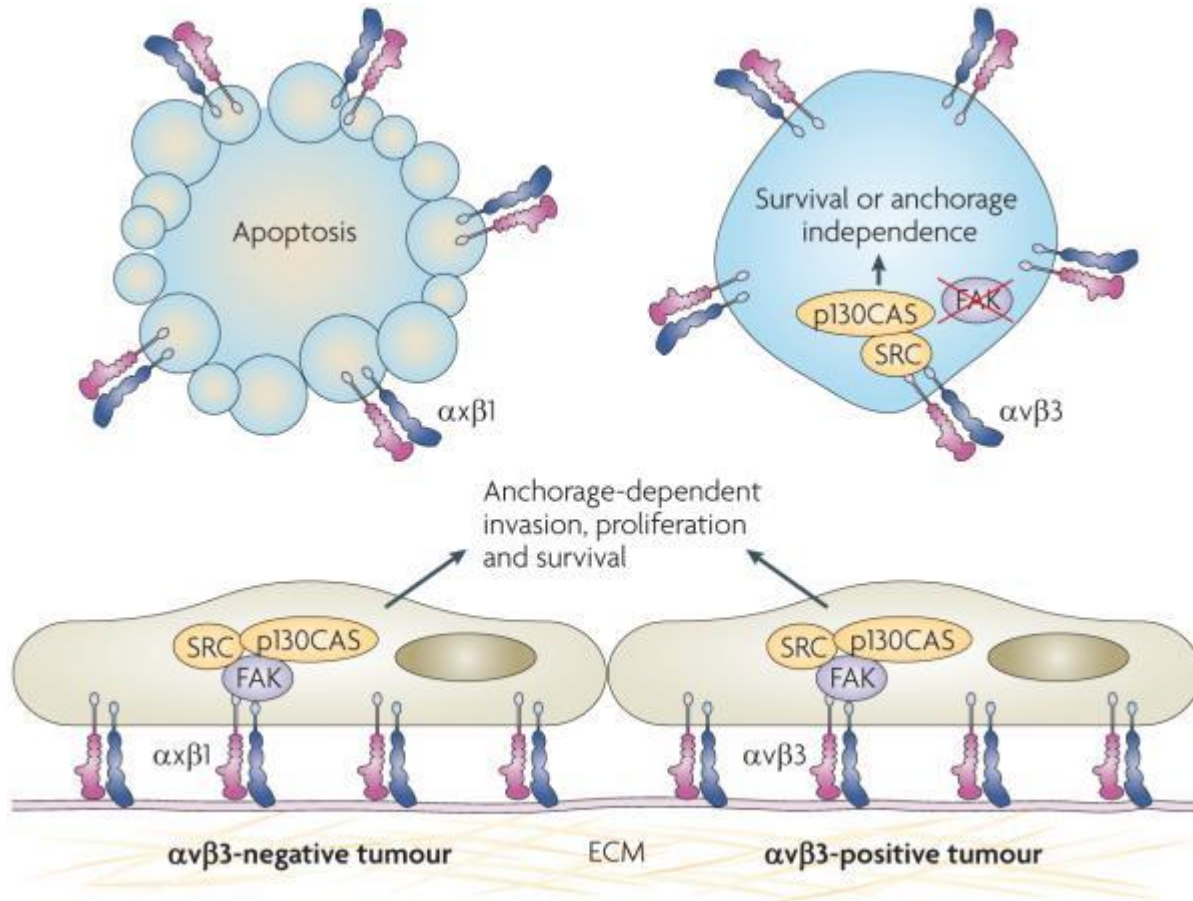
Targeting integrin function



Integriny

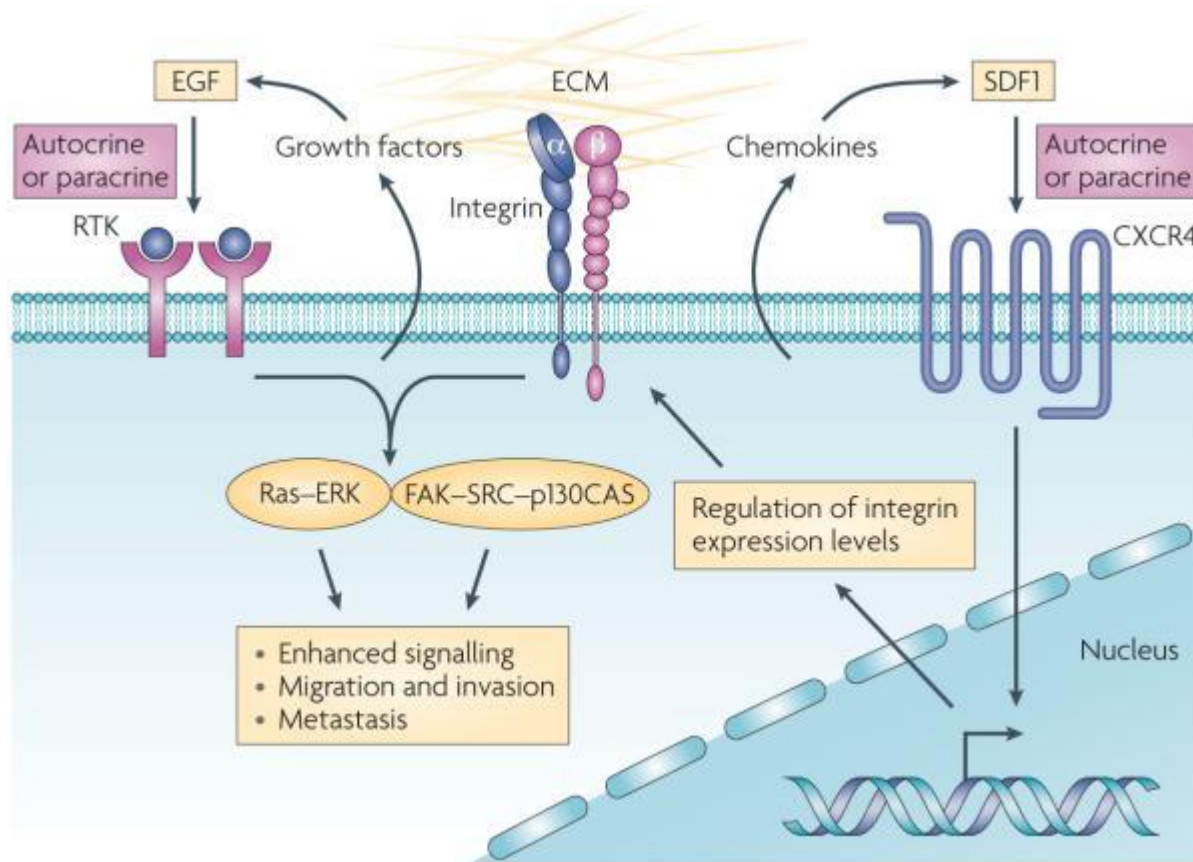


Integriny a rakovina



p130Cas/BCAR1 belongs to the Cas family of adaptor proteins and can act as a docking protein for several signalling partners

Integriny a rakovina



Ras (GTPása, spolu s Rho, Rac, Cdc42)

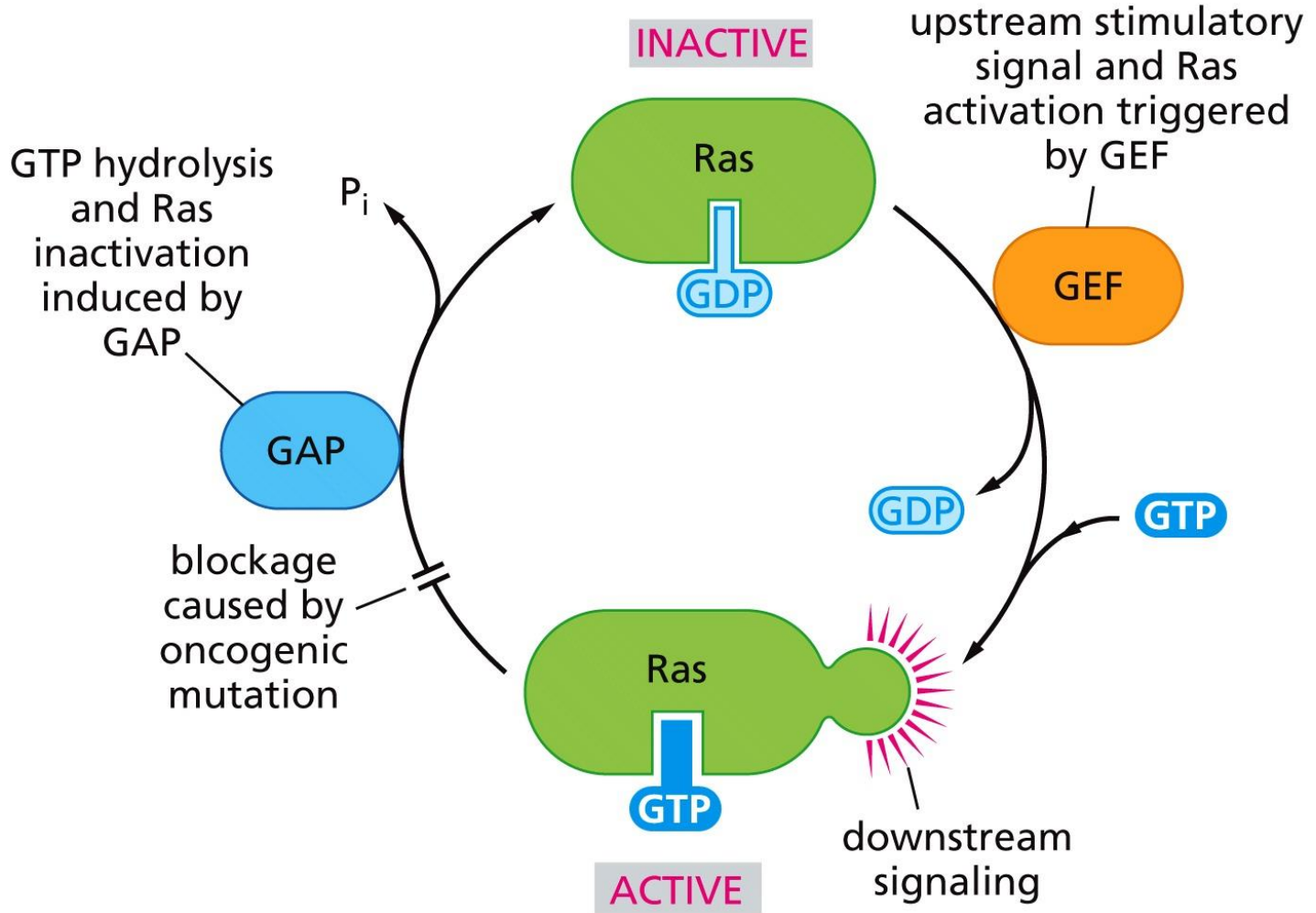
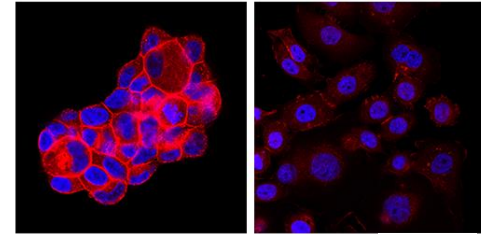


Figure 5.30 The Biology of Cancer (© Garland Science 2014)

Ras aktivace pomocí RF

- Receptor -> Grb2 -> Sos -> Ras
- Receptor -> Shc -> Grb2 -> Sos -> Ras



Cell Signaling Technology

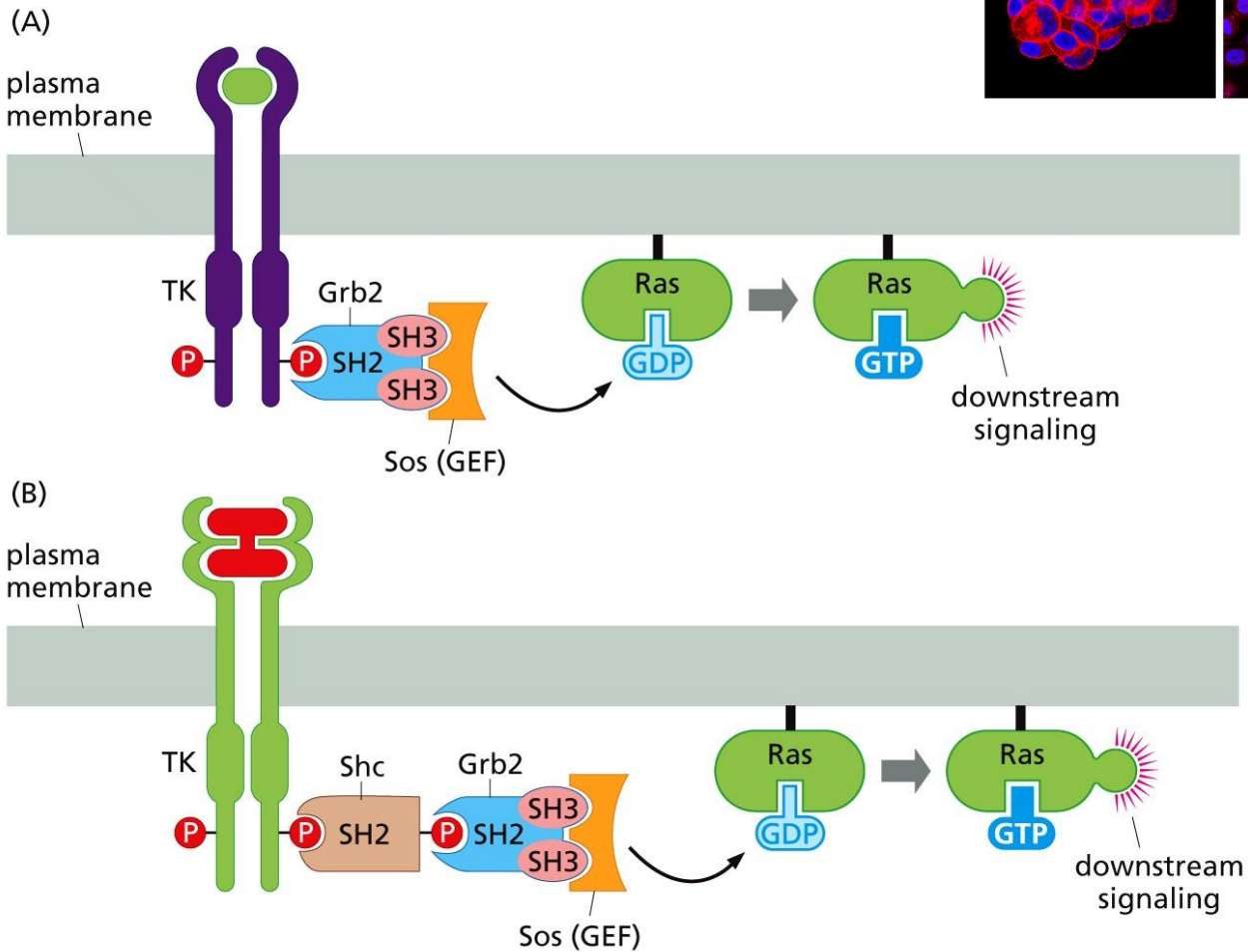


Figure 6.12 The Biology of Cancer (© Garland Science 2014)

Ras – alternativní mechanismus transformace

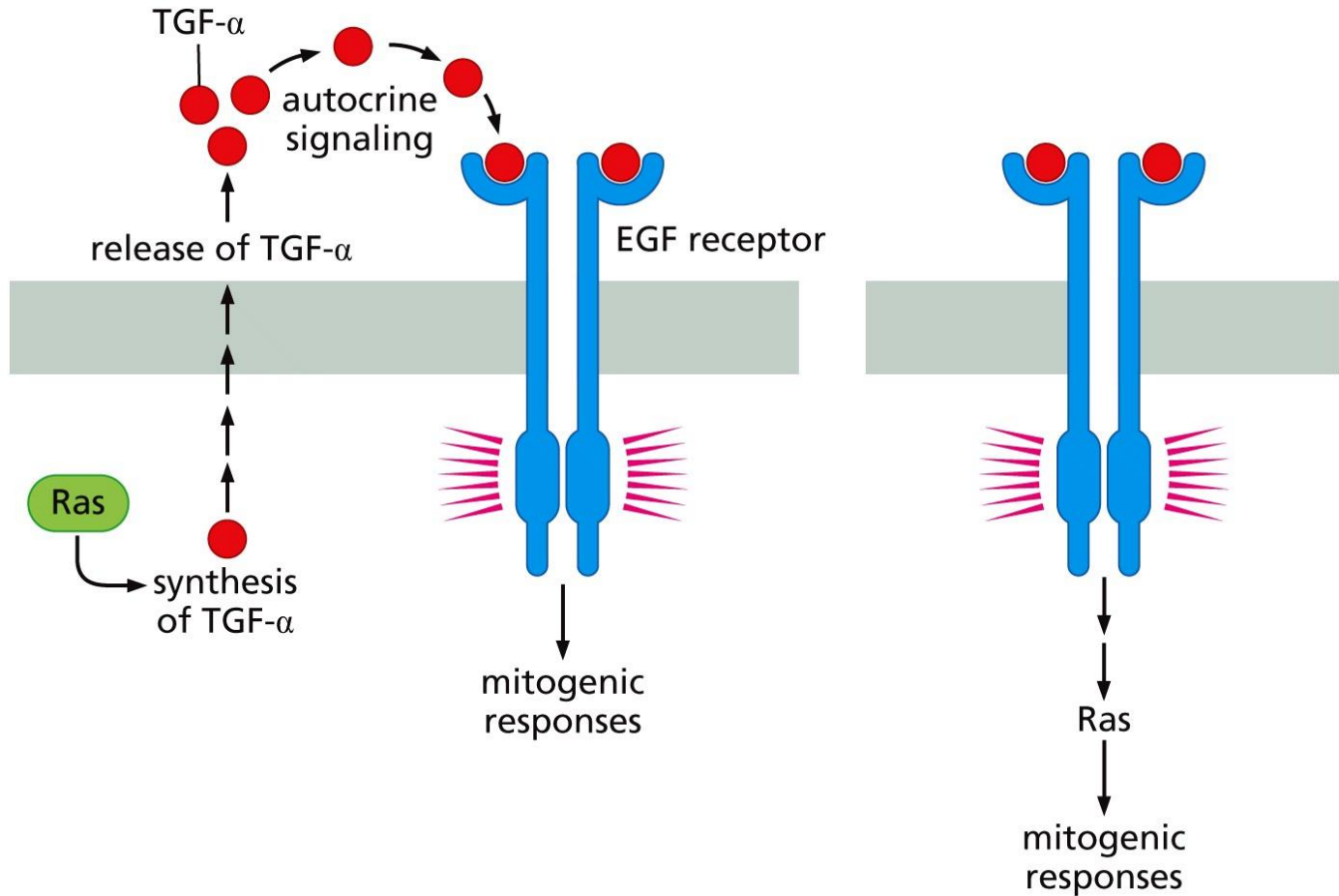


Figure 5.32a The Biology of Cancer (© Garland Science 2014)

Ras-Raf-MAP kinázová dráha

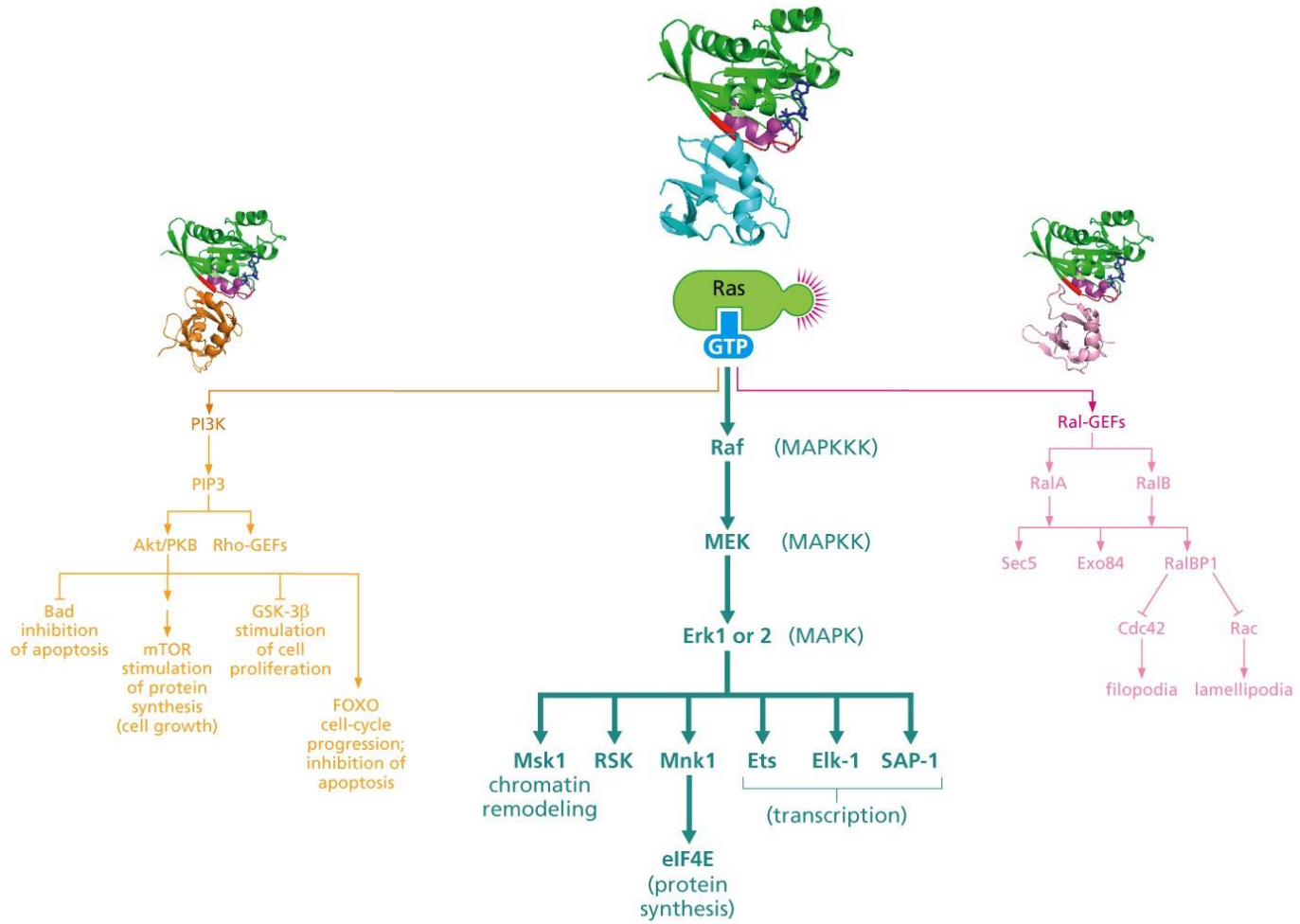


Figure 6.14 The Biology of Cancer (© Garland Science 2014)

PI3K/Akt/PKB dráha

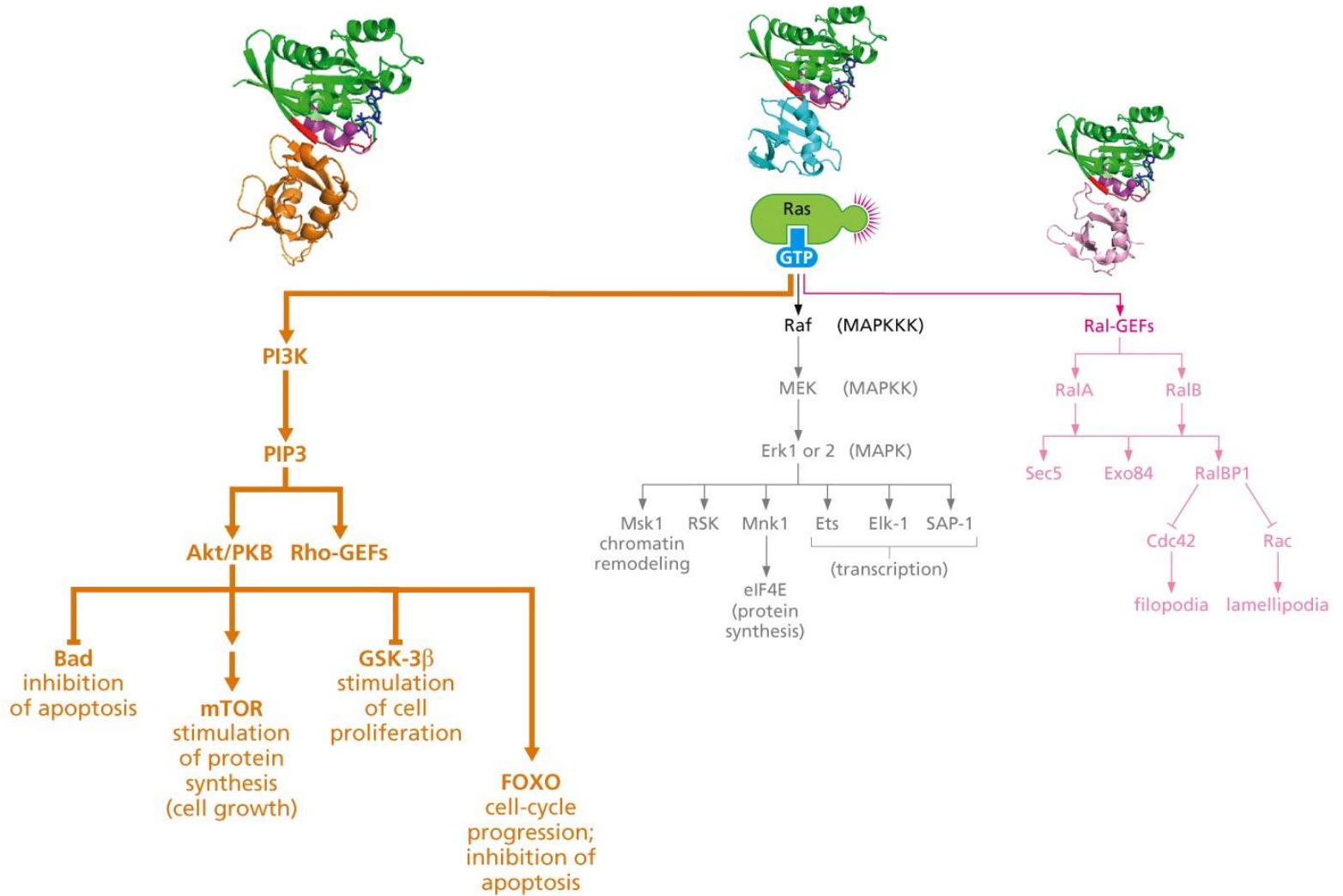


Figure 6.15 The Biology of Cancer (© Garland Science 2014)

PI3K/Akt/PKB dráha

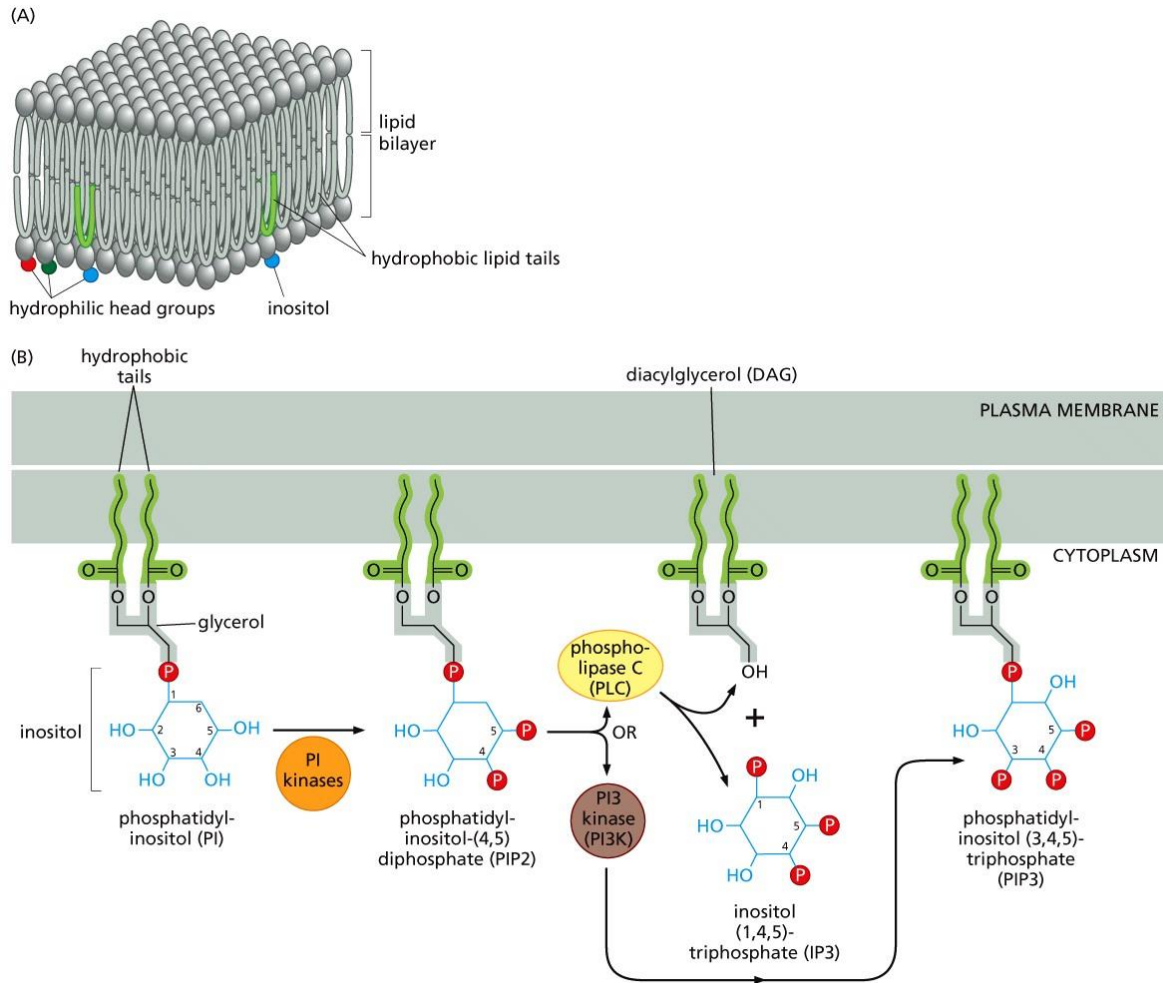


Figure 6.16 The Biology of Cancer (© Garland Science 2014)

PTEN

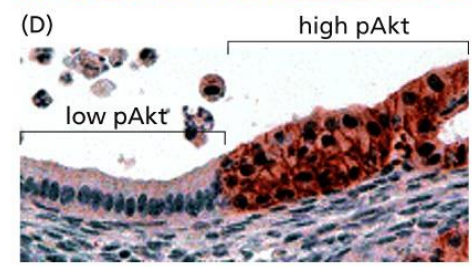
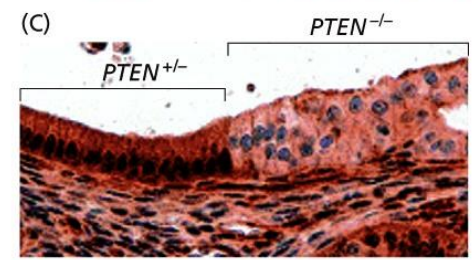
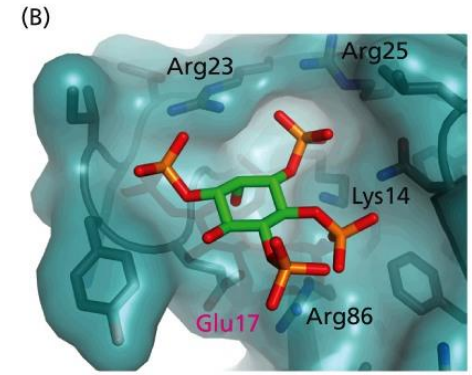
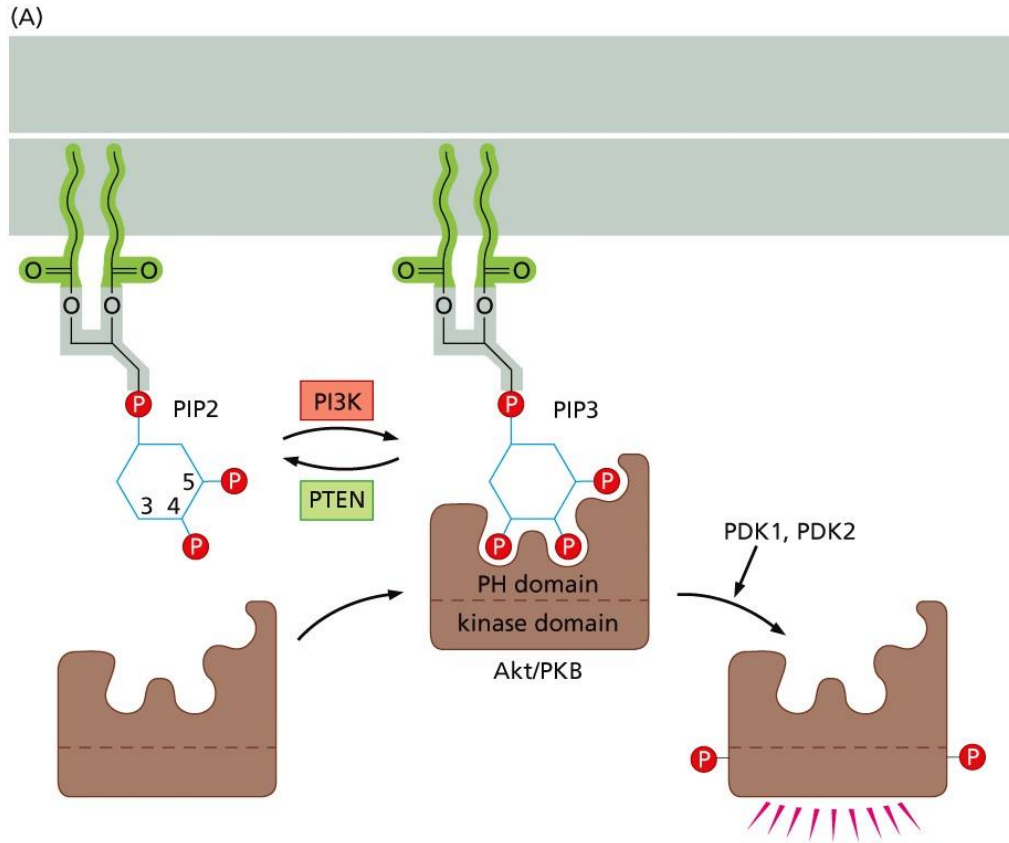


Figure 6.19 The Biology of Cancer (© Garland Science 2014)

Funkce Akt/PKB dráhy

Table 6.3 Effects of Akt/PKB on survival, proliferation, and cell growth

Biological effect	Substrate of Akt/PKB	Description	Functional consequence
<i>Anti-apoptotic</i>			
	Bad (pro-apoptotic)	Bcl-X antagonist; like Bad, belongs to Bcl-2 protein family controlling mitochondrial membrane pores (Section 9.13).	inhibition
	caspase-9 (pro-apoptotic)	Component of the protease cascade that affects the apoptotic program (Section 9.13).	inhibition
	IκB kinase, abbreviated IKK (anti-apoptotic)	Activated by Akt/PKB phosphorylation (Section 6.12).	activation
	FOXO1 TF, formerly called FKHR TF (pro-apoptotic)	Phosphorylation prevents its nuclear translocation and activation of pro-apoptotic genes.	inhibition
	Mdm2 (anti-apoptotic)	Activated via phosphorylation by Akt/PKB; it triggers destruction of p53 (Section 9.7).	activation
<i>Proliferative</i>			
	GSK-3β (anti-proliferative)	Phosphorylates β-catenin, cyclin D1, and Myc (Sections 7.11, 8.3, 8.9), causing their degradation; inactivated via phosphorylation by Akt/PKB.	inhibition
	FOXO4, formerly called AFX (anti-proliferative)	Induces expression of the CDK inhibitor p27 ^{Kip1} (Section 8.4) gene and some pro-apoptotic genes; exported from the nucleus when phosphorylated by Akt/PKB.	inhibition
	p21 ^{Cip1} (anti-proliferative)	CDK inhibitor, like p27 ^{Kip1} (Section 8.4). Exits the nucleus upon phosphorylation by Akt/PKB; in the cytoplasm, phosphorylated p21 ^{Cip1} inhibits caspases, thereby acquiring anti-apoptotic functions (Section 9.13).	inhibition
<i>Growth</i>			
	Tsc2 (anti-growth)	Phosphorylation by Akt/PKB causes Tsc1/Tsc2 complex to dissociate, allowing activation of mTOR, which then up-regulates protein synthesis (Section 16.15).	inhibition

Table 6.3 The Biology of Cancer (© Garland Science 2014)

Změny PI3K dráhy

Table 6.4 Alteration of the PI3K pathway in human tumors^a

Cancer type	<i>Akt/PKB</i> hyperactive	<i>PIK3A</i> hyperactive ^b	<i>p85α</i> ^c	<i>PTEN</i> -mutant or repressed ^d
Glioblastoma		6–27%	8%	20%
Ovarian carcinoma	~2%	4–12%	4%	8%
Endometrial carcinoma		22%		42–54%
Hepatocellular carcinoma		6–36%		5%
Melanoma	~80%	~9%		40–50%
Lung carcinoma		3–4%		9%
Renal cell carcinoma		3%		4%
Thyroid carcinoma		5%		5%
Lymphoid		3%		8%
Prostate carcinoma		2%		10%
Colon carcinoma	~6%	14–32%	2–8%	13–54%
Breast carcinoma	~8%	18–40%	2%	20–33%
Bladder		23%		8%
Pancreatic		25%	17%	
Gastric		8%		

^aThe percentages in this table are approximate, since the proportion of tumors bearing the indicated alteration increases progressively as tumor progression proceeds, often dramatically, and because many reports do not distinguish between inactivation by mutation and inactivation by promoter methylation.

^b*PIK3A* appears to be the only gene of the 16 members of the PI3K-encoding gene family to undergo somatic mutation during tumor development. These mutations affect the p110 catalytic subunit of PI3 kinase; frequently occurring amplifications of this gene are not registered in this table.

^c*PI3KR1* mutations affect the regulatory subunit of PI3K kinase and are most commonly observed in human cancers; alterations of the four other members of this family of PI3K regulatory subunits are not registered here. Alterations of the encoded p85α subunit cited here were few in number and the indicated percentages are likely to change dramatically as more data are collected.

^d*PTEN* nonsense mutations and deletions are registered here and, in many cases, the even more frequent shutdown of expression through promoter methylation or the actions of microRNAs. (Promoter methylation often results in shutdown of transcription of a gene; see Section 7.8.)

From www.sanger.ac.uk/perl/genetics/CGP/cosmic; T.L. Yuan and L.C. Cantley, *Oncogene* 27:5497–5510; B.S. Jaiswal et al., *Cancer Cell* 16:463–474, 2009; D.W. Parsons et al., *Science* 321:1807–1812, 2008; and Y. Samuels and K. Ericson, *Curr. Opin. Oncol.* 18:77–82, 2006.

Table 6.4 The Biology of Cancer (© Garland Science 2014)

Ral (Ras-Like) signalizace

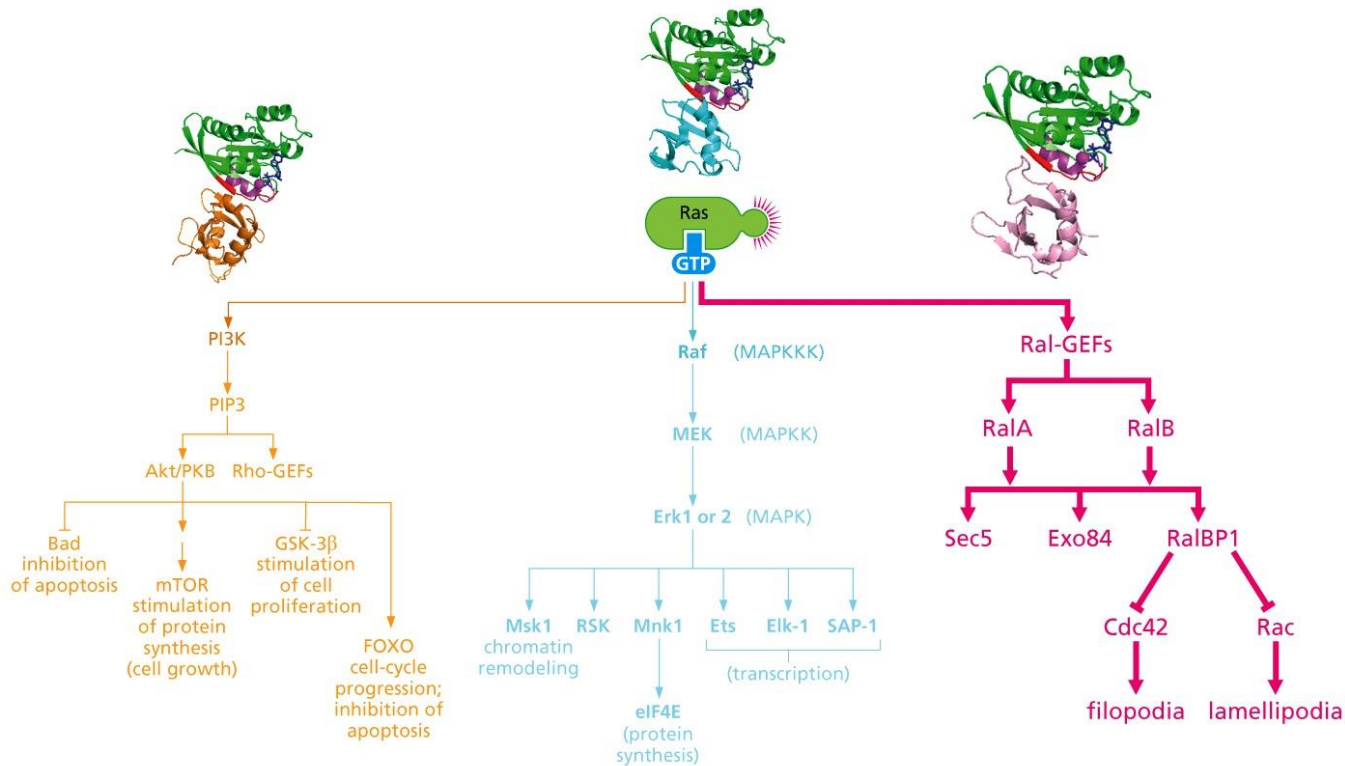


Figure 6.21 The Biology of Cancer (© Garland Science 2014)

- Ral-A, Ral-B – 58% identita s Ras
- Sec5, Exo84 - Ras zprostředkovaná aktivace neadherentního růstu
- Inaktivace Cdc42 a Rac

Shrnutí

- Deregulace buněčné signalizace je klíčová pro vznik a rozvoj rakoviny
- Fosforylace tyrosinu je preferovaná u řady mitogenních signálů
- zvýšená exprese růstových receptorů u nádorových buněk vede k jejich časté kolizi, dimerizaci a oligomerizaci – aktivaci bez ligandu
- Mutace receptorových tyrozin kinázových domén vede ke konstitutivní aktivaci receptoru bez ligandu
- Další dráhy zapojené v karcinogenezi
 - JAK/STAT, Wnt, Notch, Hedgehog
- Integriny – transmembránové receptory propojující ECM a buněčný cytoskelet, formování fokálních adhezí, klíčová role v rakovině
- Ras aktivuje tři hlavní signálové kaskády
 - Raf, PI3K/Akt, Ral-GEF