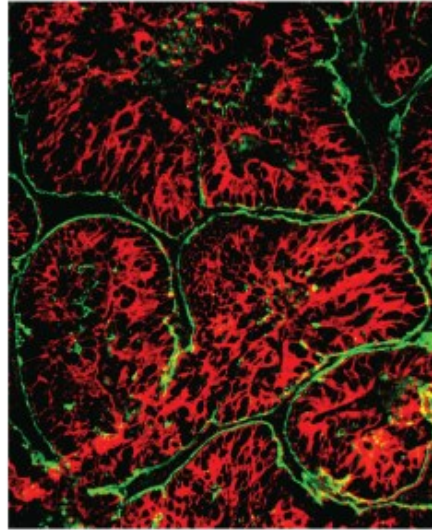


Plasticita nádorových buněk

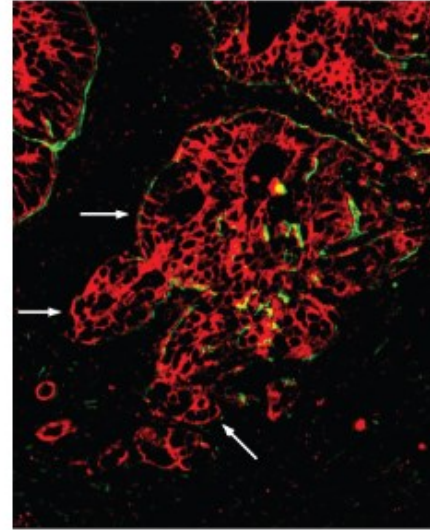
Karel Souček

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

Porušení bazální membrány



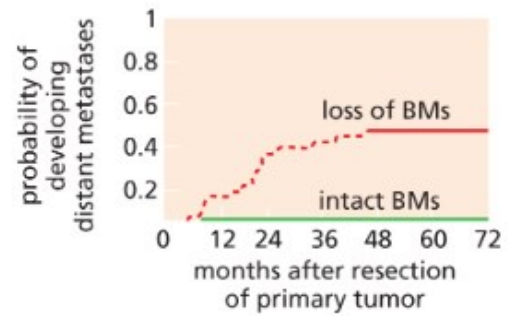
(A)



(B)

Cytokeratin

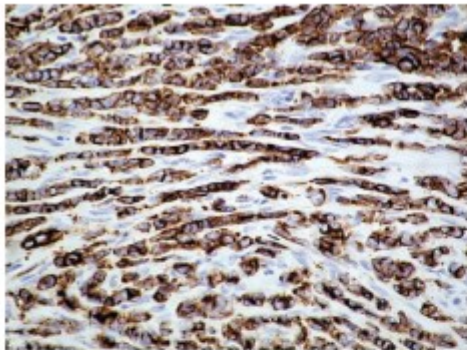
Laminin (basal lamina)



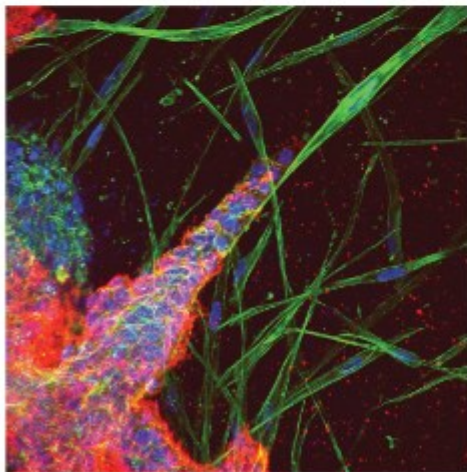
(C)

Typy nádorové invaze

Invazivní lobulární karcinom



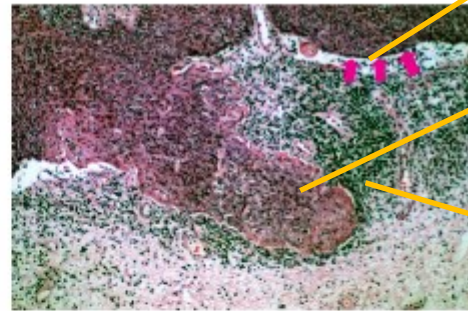
(A)
Kolektivní invaze, 3D



E-cadherin
Phalloidin
DAPI

(C)

Kolektivní invaze



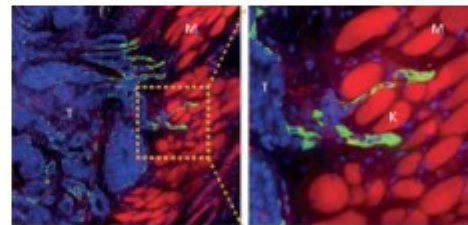
(B)

bazální l.

nádor

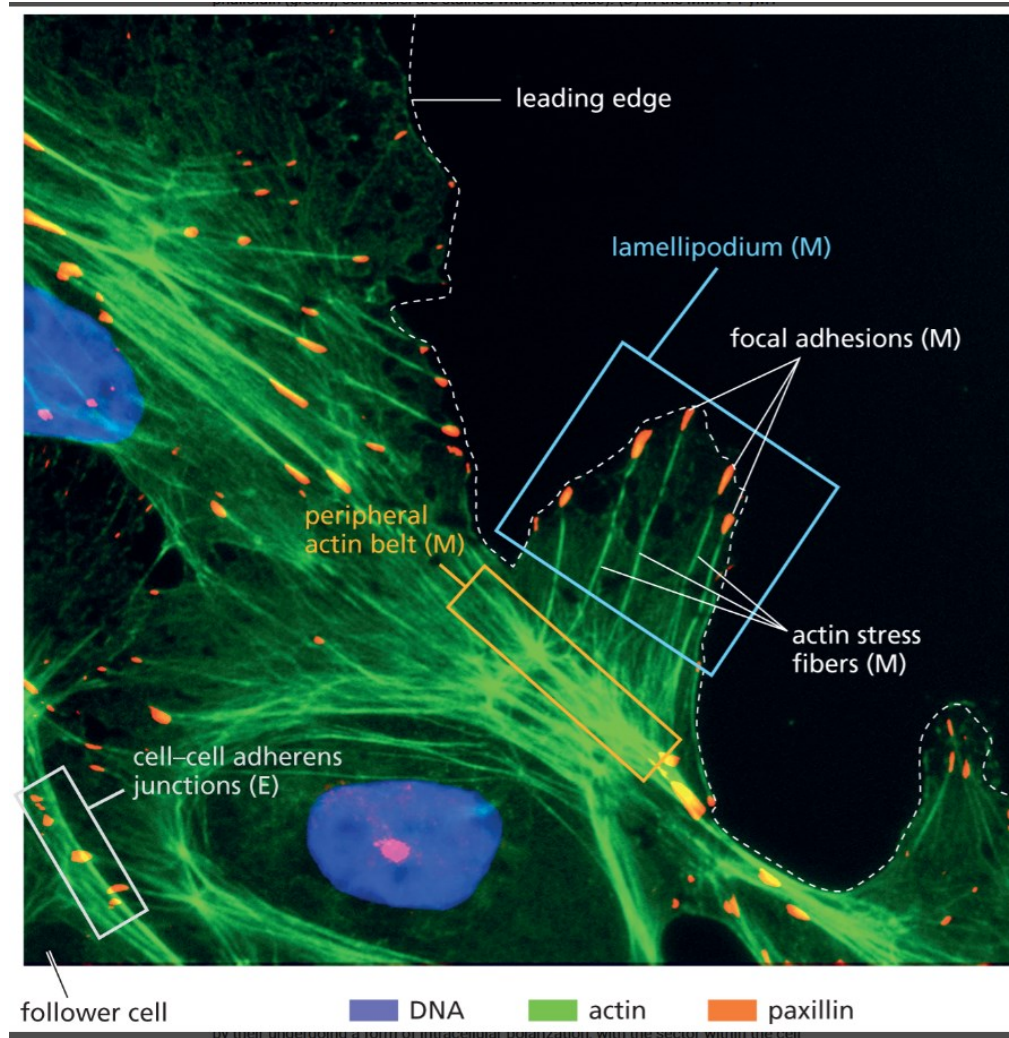
stroma

MMTV-PyMT, in vivo

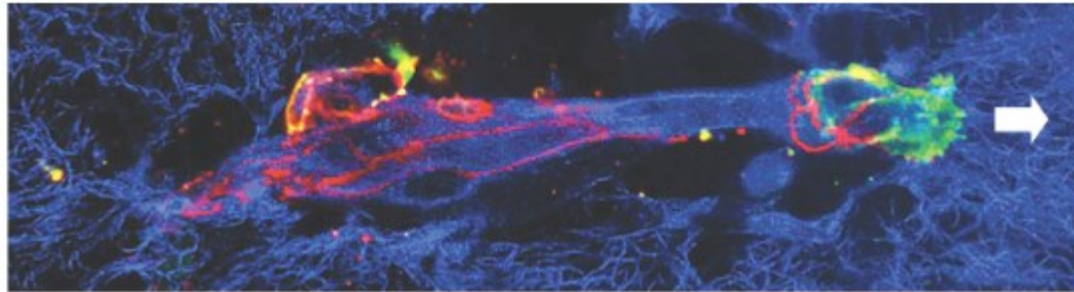


(D)

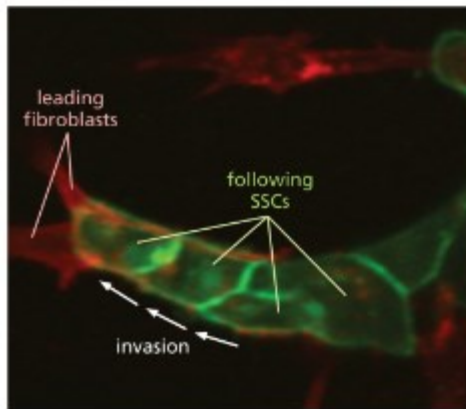
Buněčná polarizace



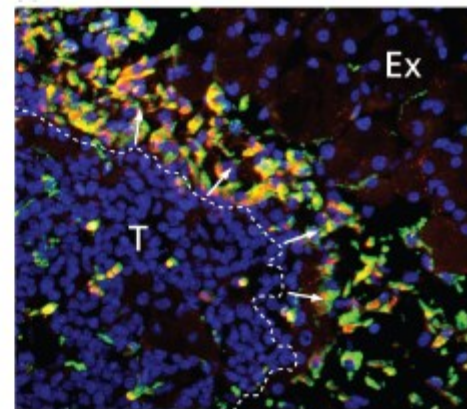
Invaze přes ECM a role stromálních buněk



(A)

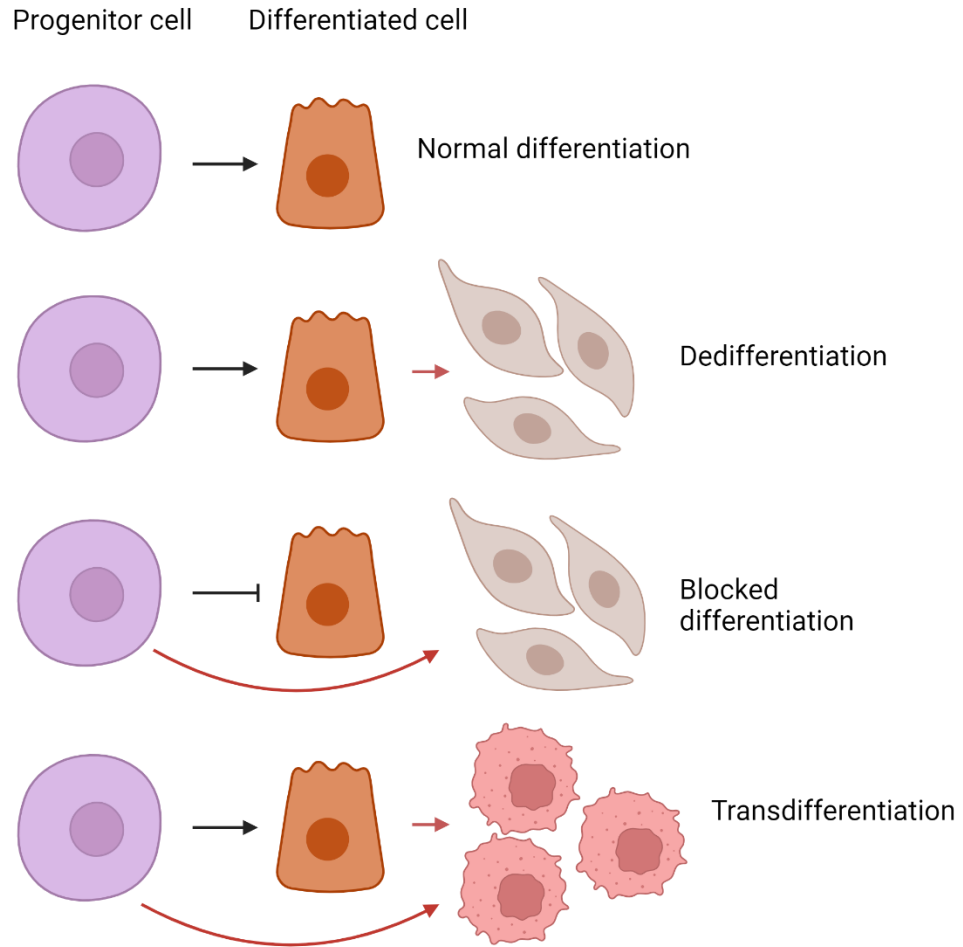


(B)

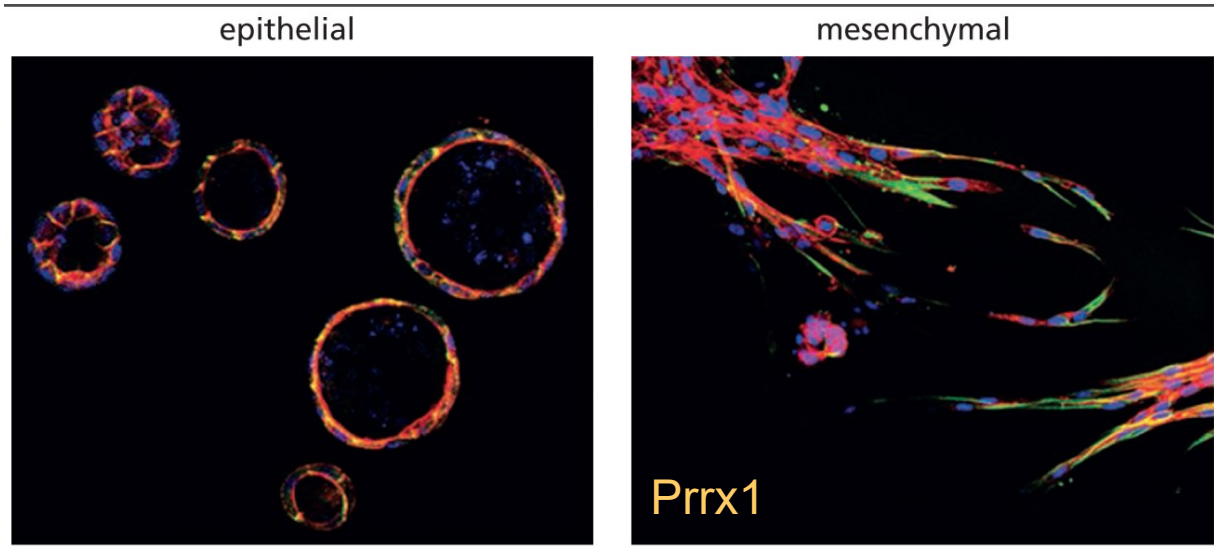


(C)

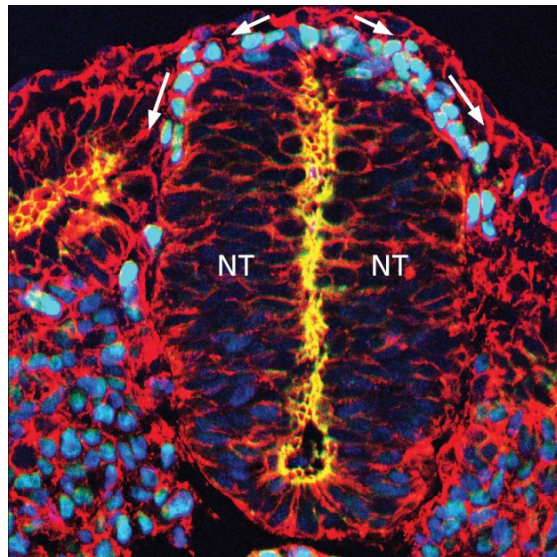
Buněčná plasticita



EMT a motilita/invazivita



E-kadherin
 Vimentin
 Actin
 DAPI



N-kadherin
 Actin
 DAPI
 Sox9

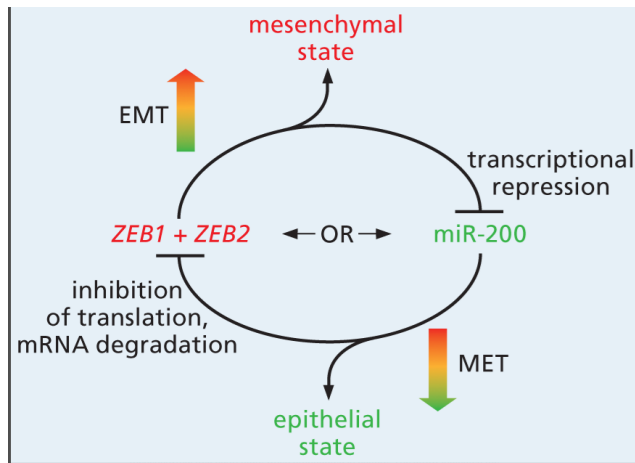
Table 14.1 Examples of EMTs during mouse embryonic development

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

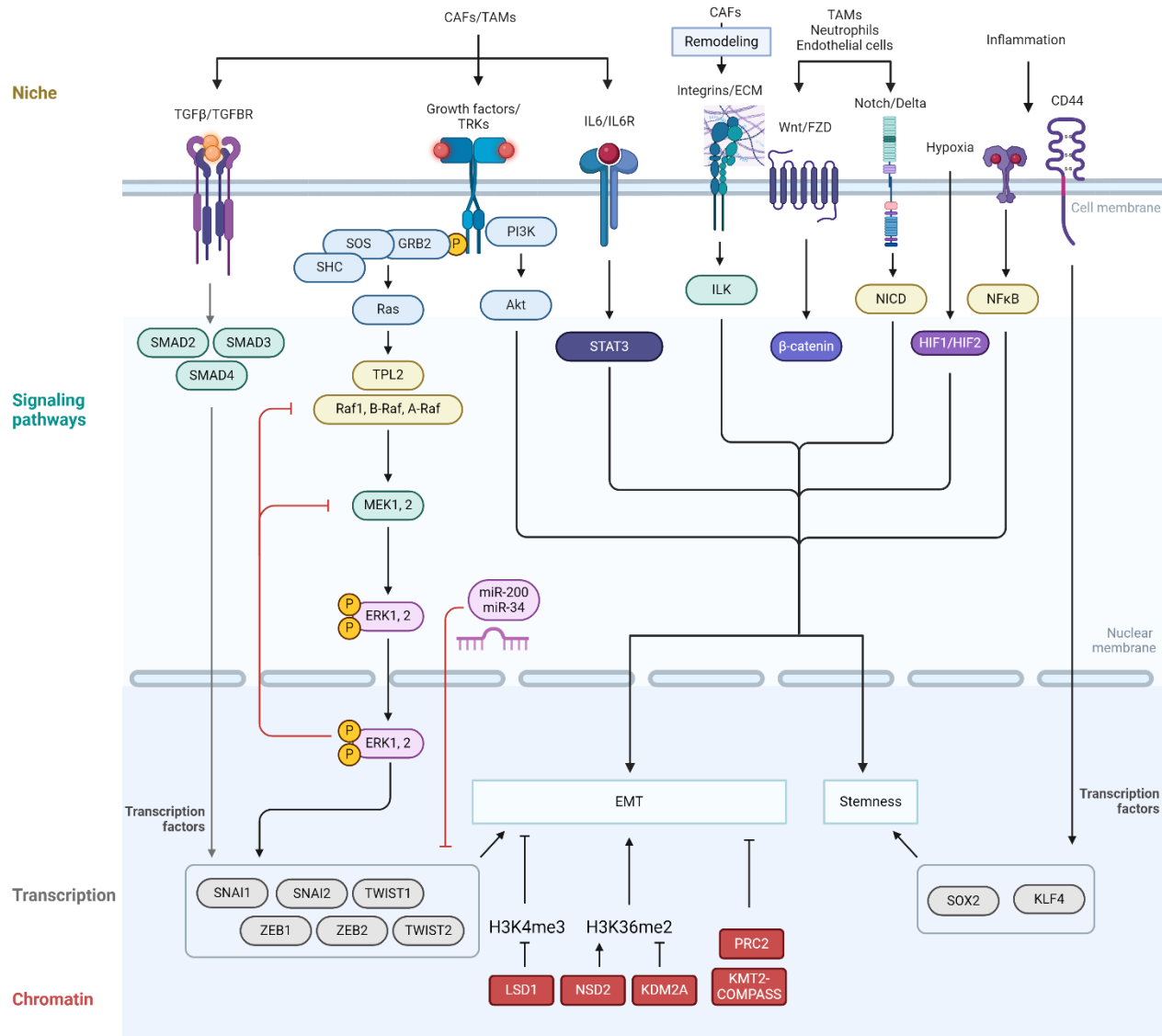
Adapted from P. Savagner, *BioEssays* 23:912–923, 2001.

Table 14.4 Transcription factors orchestrating an EMT

Name	Where first identified	Type of transcription factor	Cancer association
Snail (SNAI1)	mesoderm induction in <i>Drosophila</i> ; neural crest migration in vertebrates	C2H2-type zinc finger	invasive ductal carcinoma
Slug (SNAI2)	delamination of the neural crest and early mesoderm in chicken	C2H2-type zinc finger	breast cancer cell lines, melanoma
Twist	mesoderm induction in <i>Drosophila</i> ; emigration from neural crest	bHLH	various carcinomas, high-grade melanoma, neuroblastoma
Goosecoid	gastrulation in frog	paired homeodomain	various carcinomas
FOXC2	mesenchyme formation	winged helix/forkhead	basal-like breast cancer
ZEB1 (δEF1)	postgastrulation mesodermal tissue formation	2-handed zinc finger/homeodomain	wide variety of cancers
ZEB2 (SIP1)	neurogenesis	2-handed zinc finger/homeodomain	ovarian, breast, liver carcinomas
E12/E47 (Tcf3) ^a	associated with E-cadherin promoter	bHLH	gastric cancer
Prrx 1	chick mesoderm formation	paired homeobox	various carcinomas

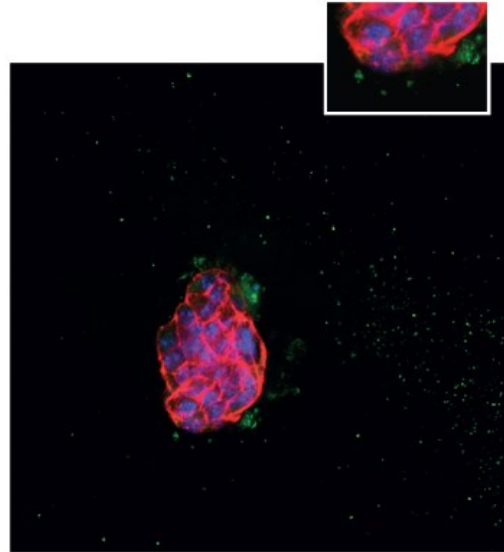


Buněčná signalizace a plasticita



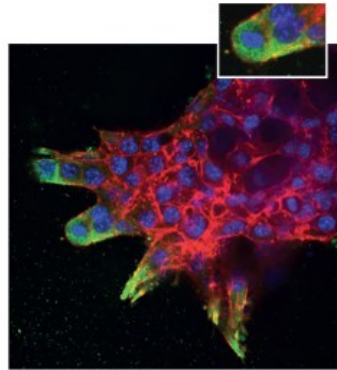
TGF- β a tuhá extracelulární matrix společně aktivují markery EMT

Kolagen I



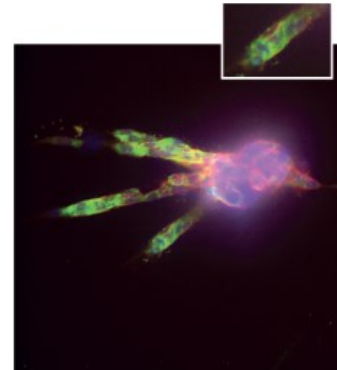
Snail

(A)



(B)

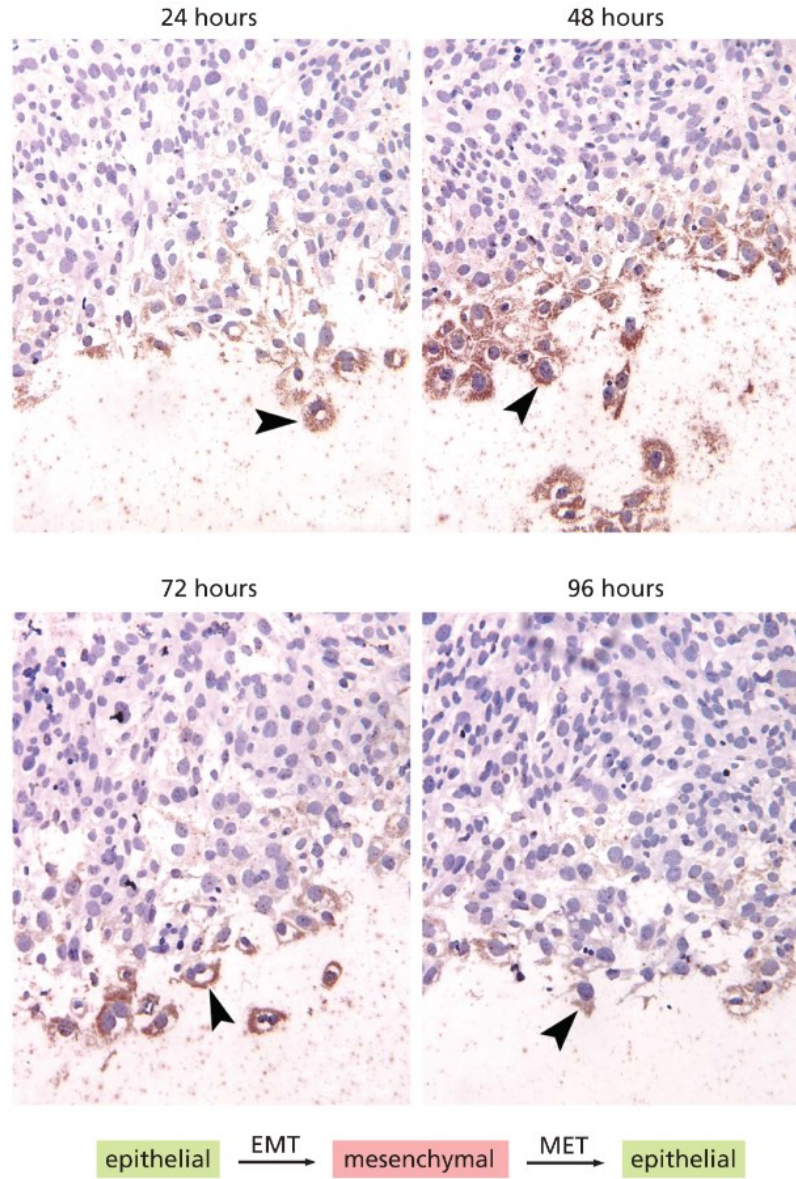
Tuhá ECM



(C)

Tuhá ECM + TGFbeta

Přechodná exprese transkripčního faktoru Slug indukujícího EMT při hojení ran



Epiteliálně-mezenchymální přechod (EMT)

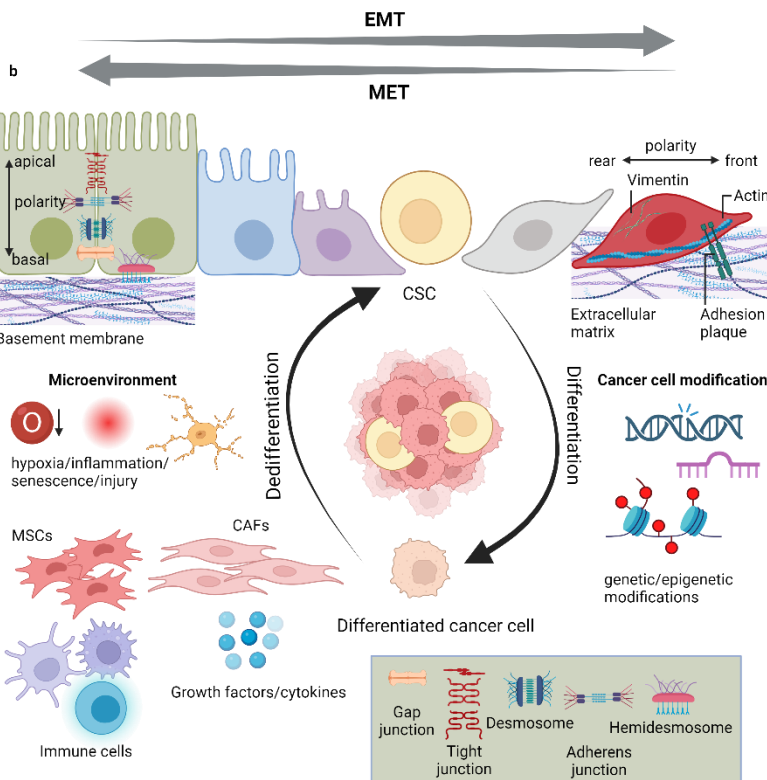
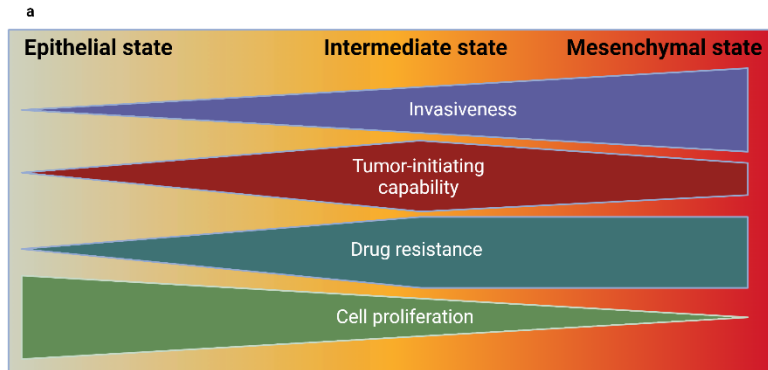
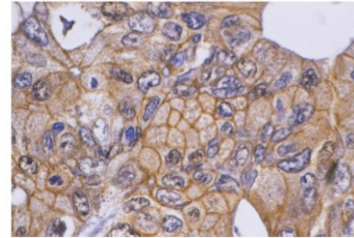
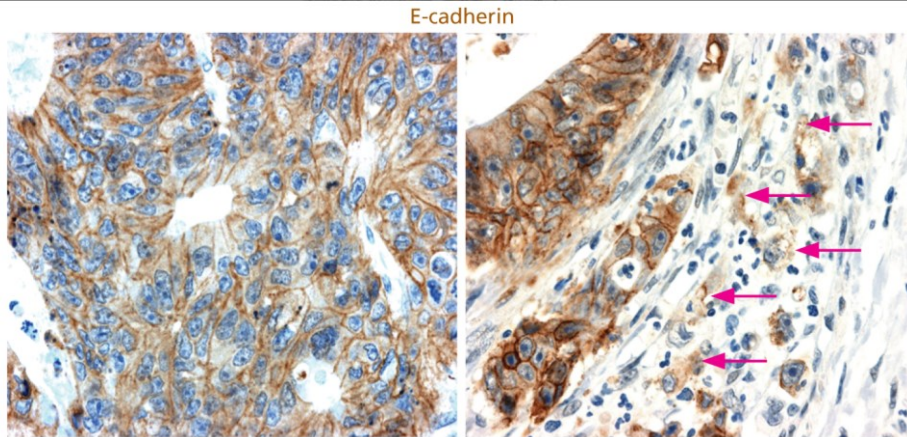


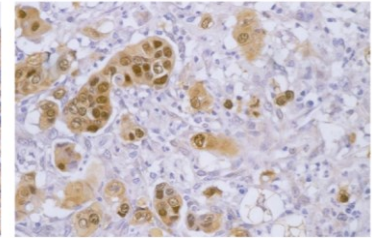
Table 14.3 Contextual signals inducing EMT programs

TGF- β
canonical and non-canonical Wnts
Notch ligands
RTKs such as EGF-R, FGF-R, Met
various cytokines
stiff extracellular matrix
absence of epithelial neighbors
periostin
collagen type 1

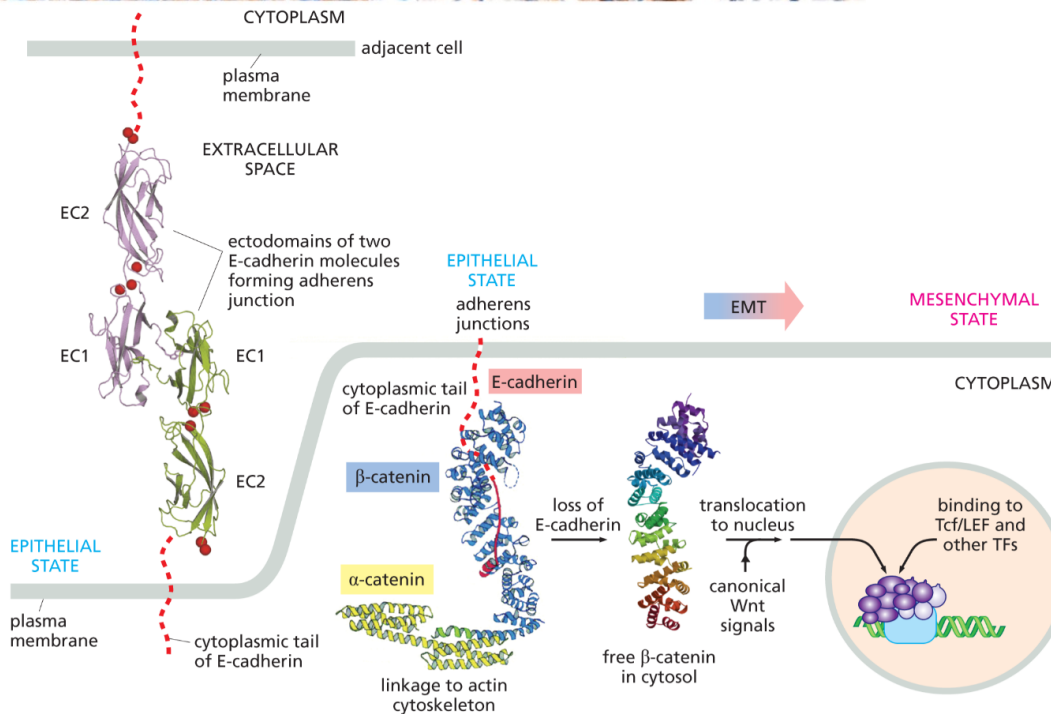
EMT a invazivní přechod nádoru



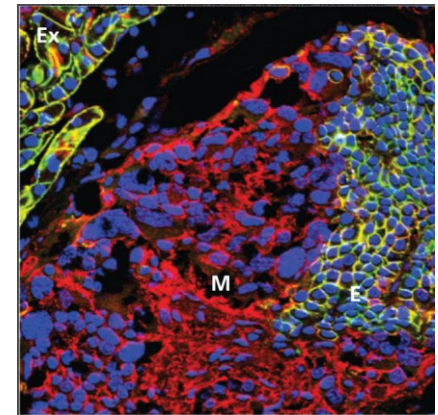
center of tumor
(membranous β -catenin)



invasive front
(nuclear β -catenin)



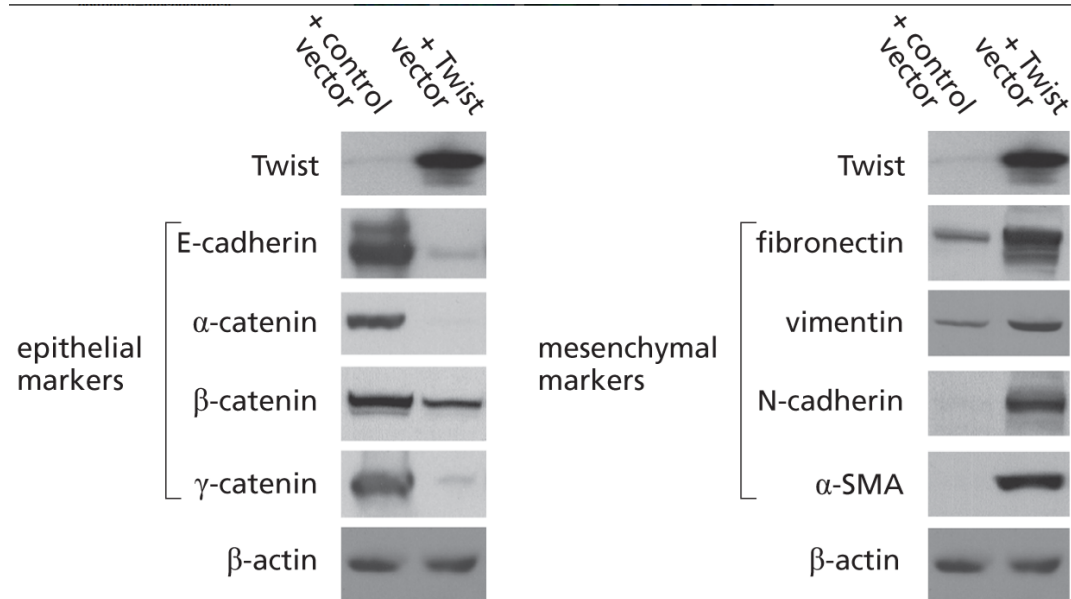
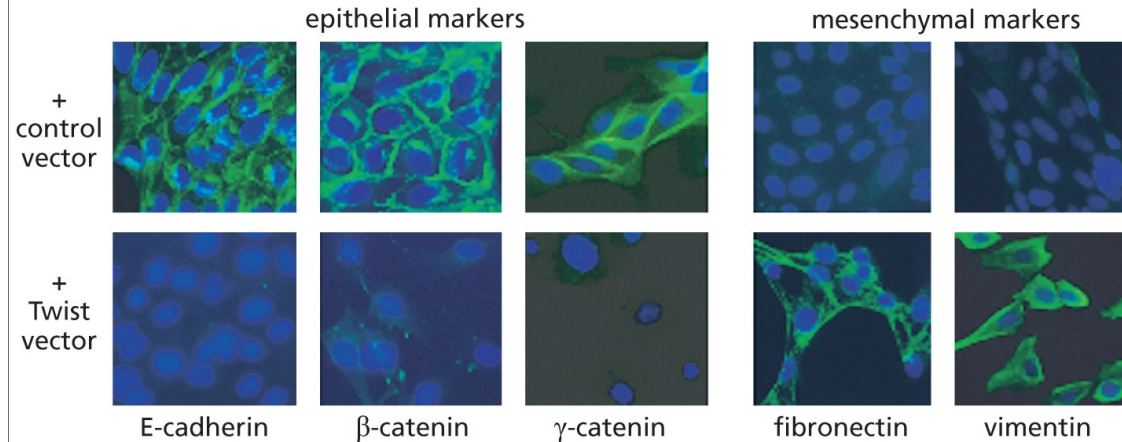
E-cadherin
 β -catenin
DAPI



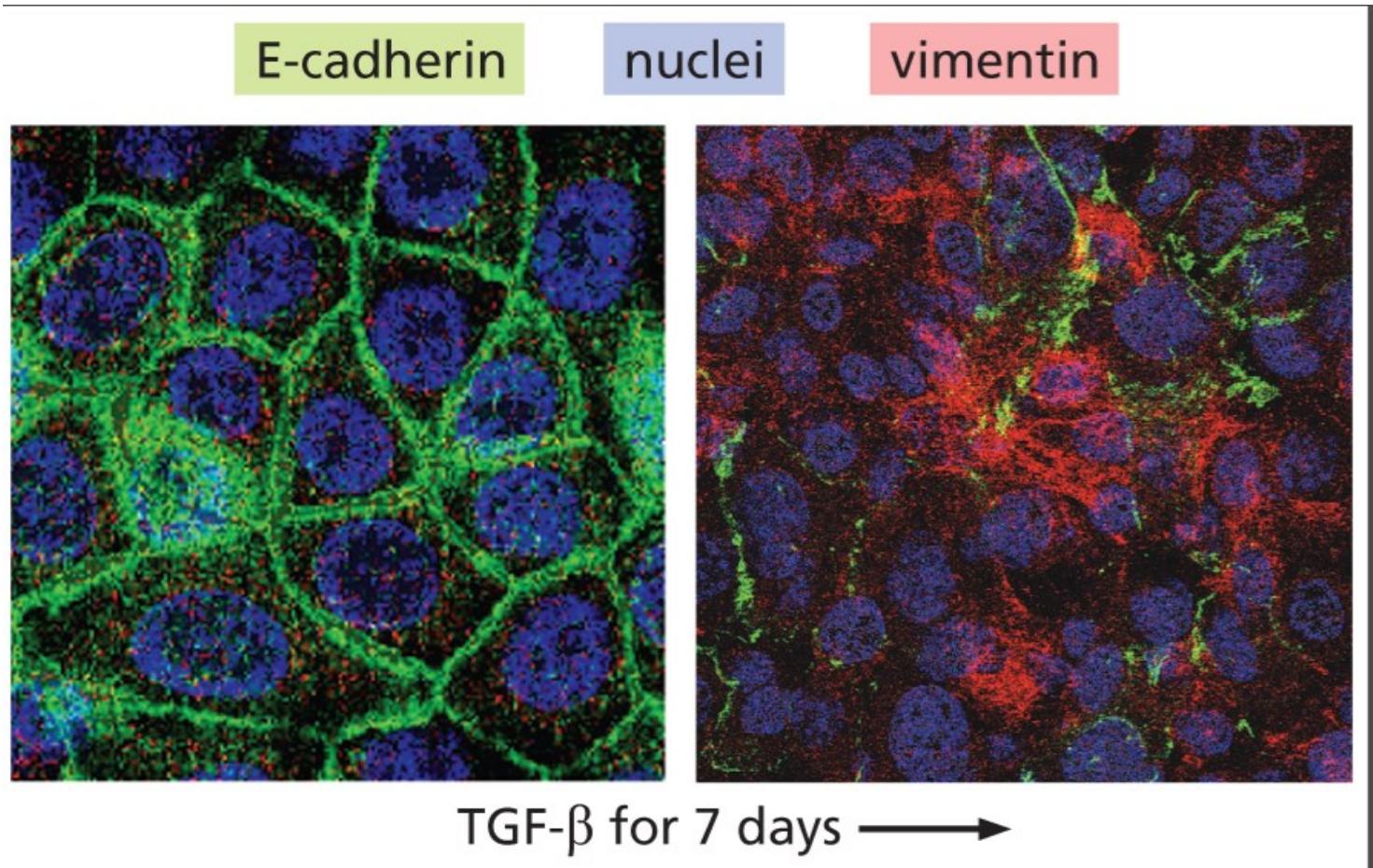
Změny doprovázející EMT

Table 14.2 Cellular changes associated with an epithelial–mesenchymal transition

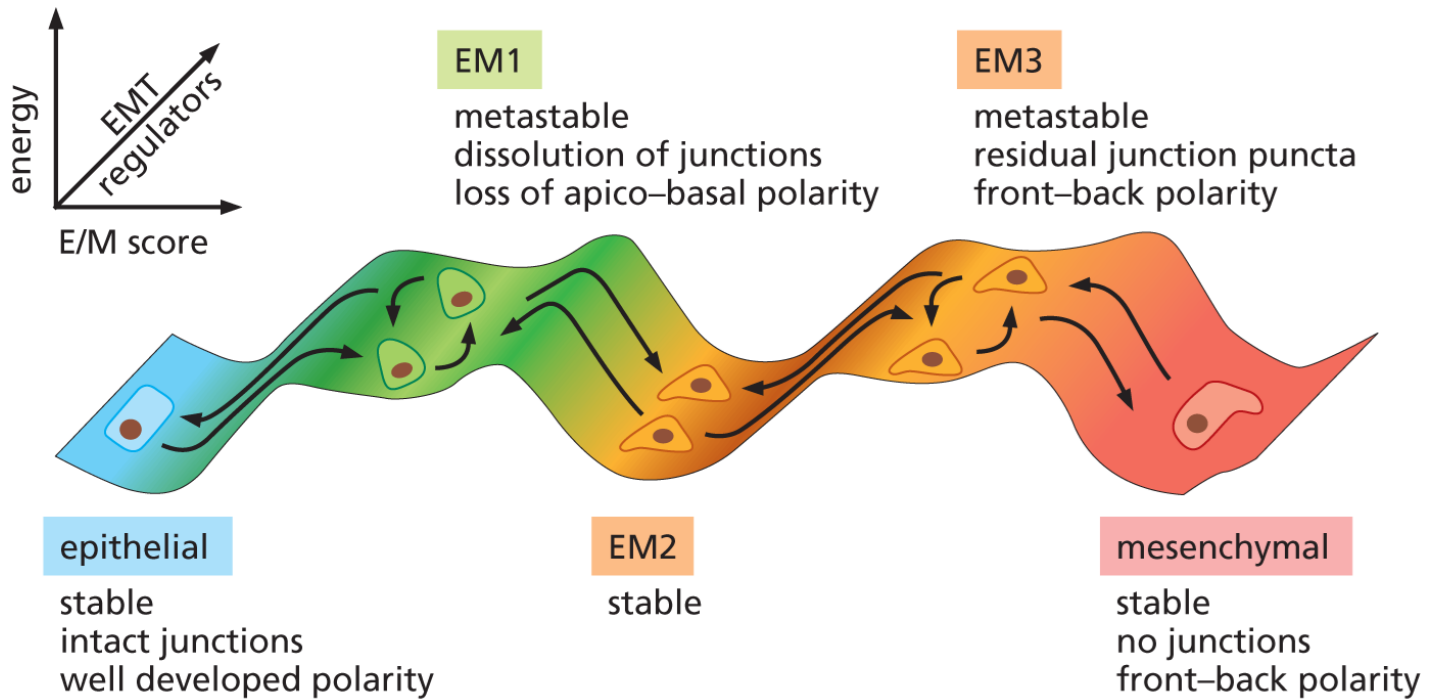
Loss of
cytokeratin (intermediate filament) expression
tight junctions and epithelial adherens junctions involving E-cadherin
epithelial cell polarity
epithelial gene expression program
Acquisition of
fibroblast-like shape
motility
invasiveness
increased resistance to apoptosis
increased resistance to radiotherapy
mesenchymal gene expression program including EMT-inducing transcription factors
mesenchymal adherens junction protein (N-cadherin)
protease secretion (MMP-2, MMP-9)
vimentin (intermediate filament) expression
fibronectin secretion
PDGF receptor expression
$\alpha_v\beta_6$ integrin expression
stem cell-like traits



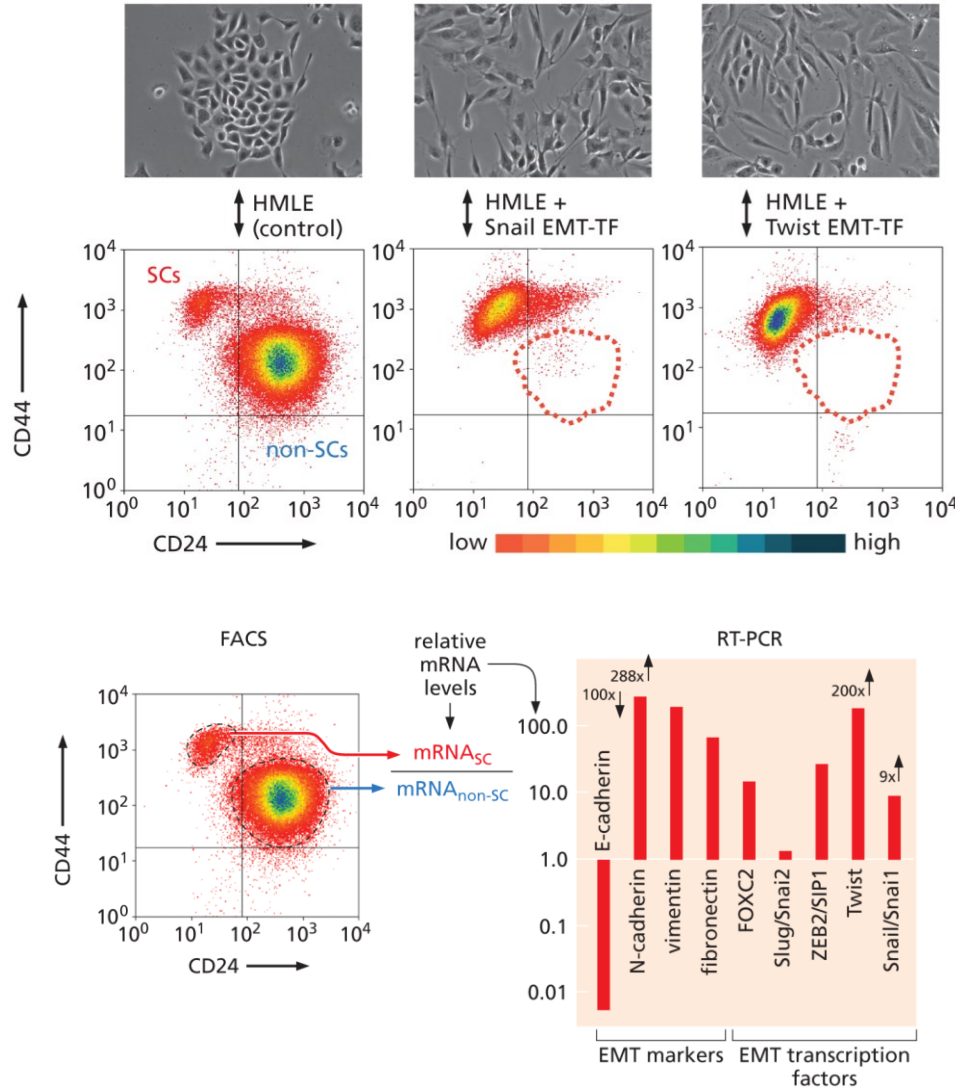
TGF β řídí EMT



Více přechodných stavů mezi epiteliálním a mezenchymálním fenotypem



Transkripční faktory indukující EMT propůjčují epiteliálním buňkám vlastnosti kmenových buněk



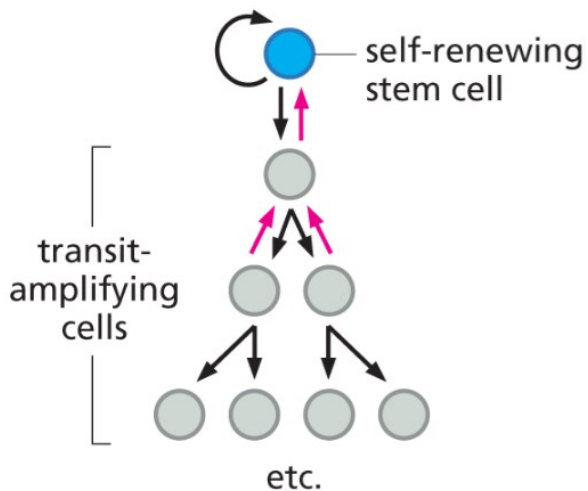
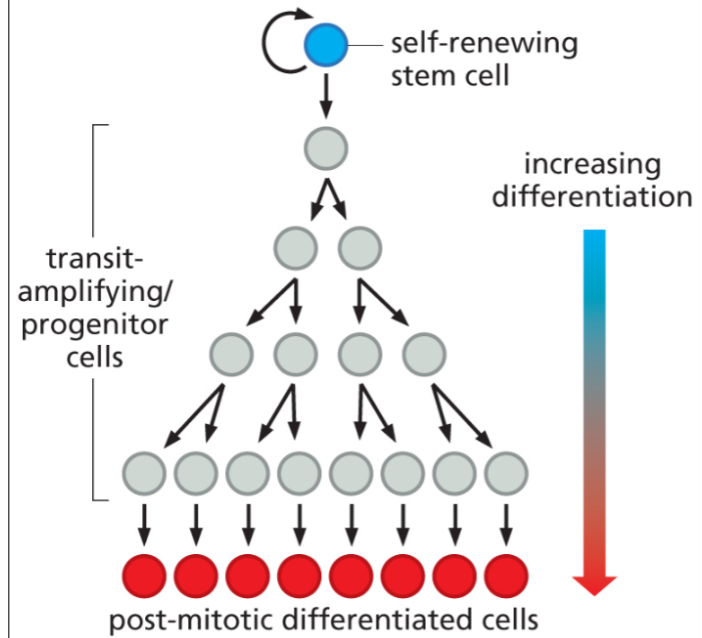
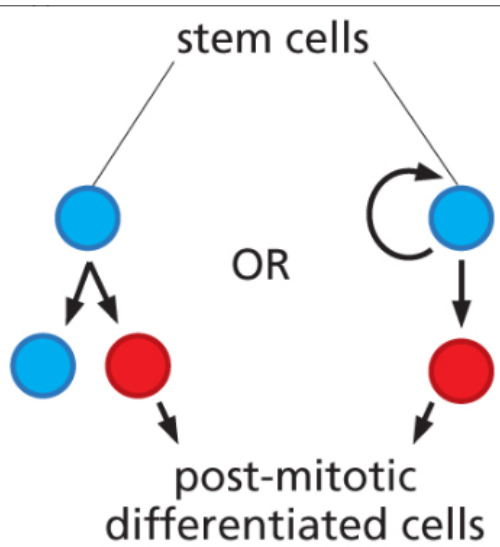
Cell

The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells

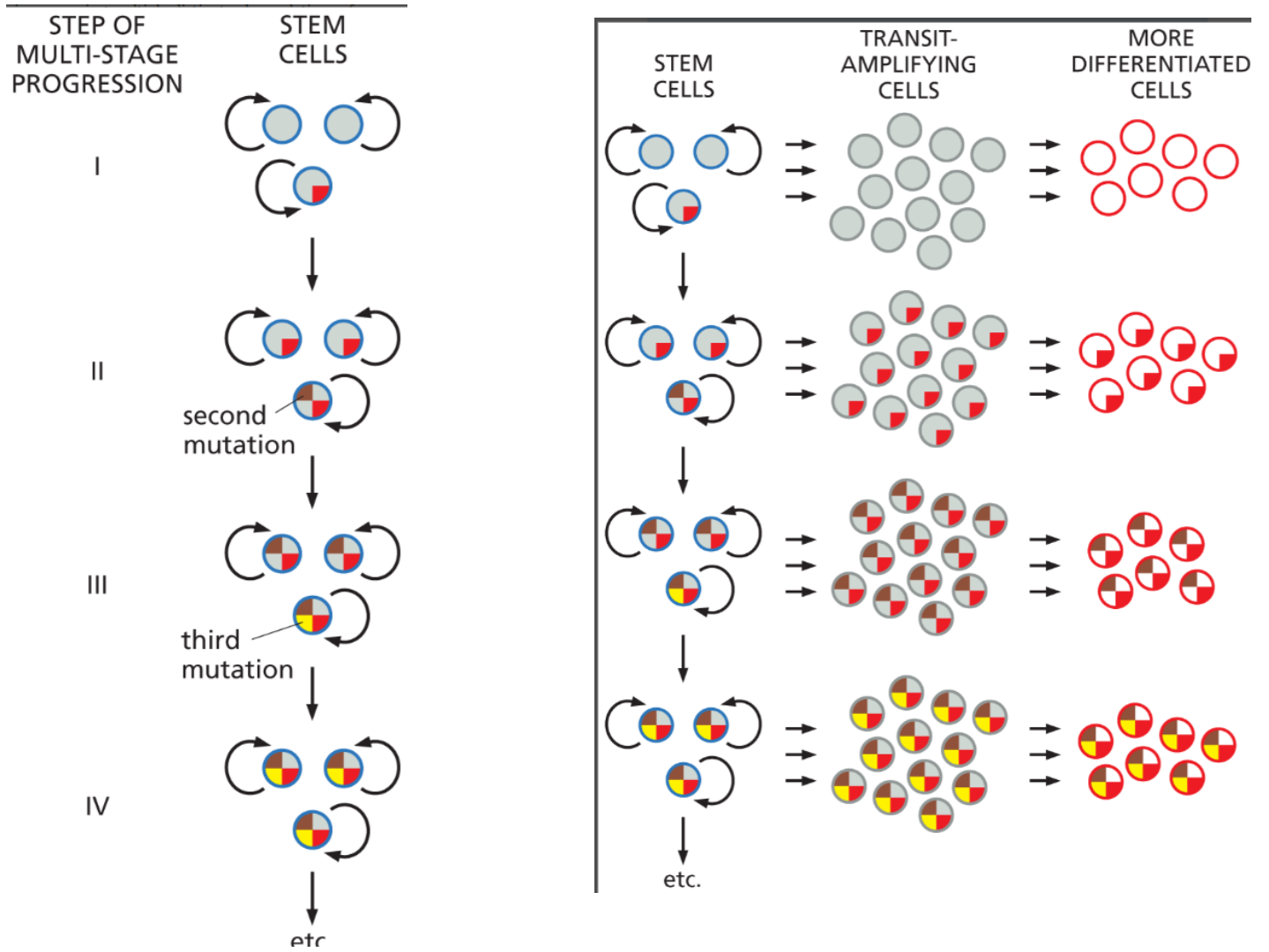
Sensibar A, Ma X,^{1,2,10} Wengun Guo,^{1,10} Mai-Jing Liao,^{1,10} Elinor Ng, Eaton,¹ Ayyakkannu Ayyanar,⁴ Alicia Y. Zhou,^{1,2} Mary Brooks,¹ Francis Bonnard,¹ Cheng Cheng Zhang,¹ Michael Shih,^{1,11} Lauren L. Campbell,¹² Konomi Poljak,^{1,6,7} Cathrin Braken,⁷ Jing Yang,¹ and Robert A. Weinberg^{1,8,9}

¹Whitehead Institute for Biomedical Research, 7 Cambridge Center, Cambridge, MA 02142, USA
²Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
³Department of Molecular Pathology, University of Texas M.D. Anderson Cancer Center, 7450 Favin Street, Houston, TX 77054, USA
⁴École polytechnique fédérale de Lausanne (EPFL), SBRC - Swiss Institute for Experimental Cancer Research, 1015 Molecular Oncology, CH-1066 Epalinges, Switzerland
⁵Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA
⁶Department of Medicine
⁷Program in Biological and Biomedical Sciences
⁸Harvard Medical School, Boston, MA 02115, USA
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¹⁰Ludwig Center for Molecular Oncology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
¹¹These authors contributed equally to this work.
¹²Correspondence: weinberg@mit.edu (R.A.W.), smari@mdanderson.org (S.A.M.)
 DOI 10.1016/j.cell.2008.03.027

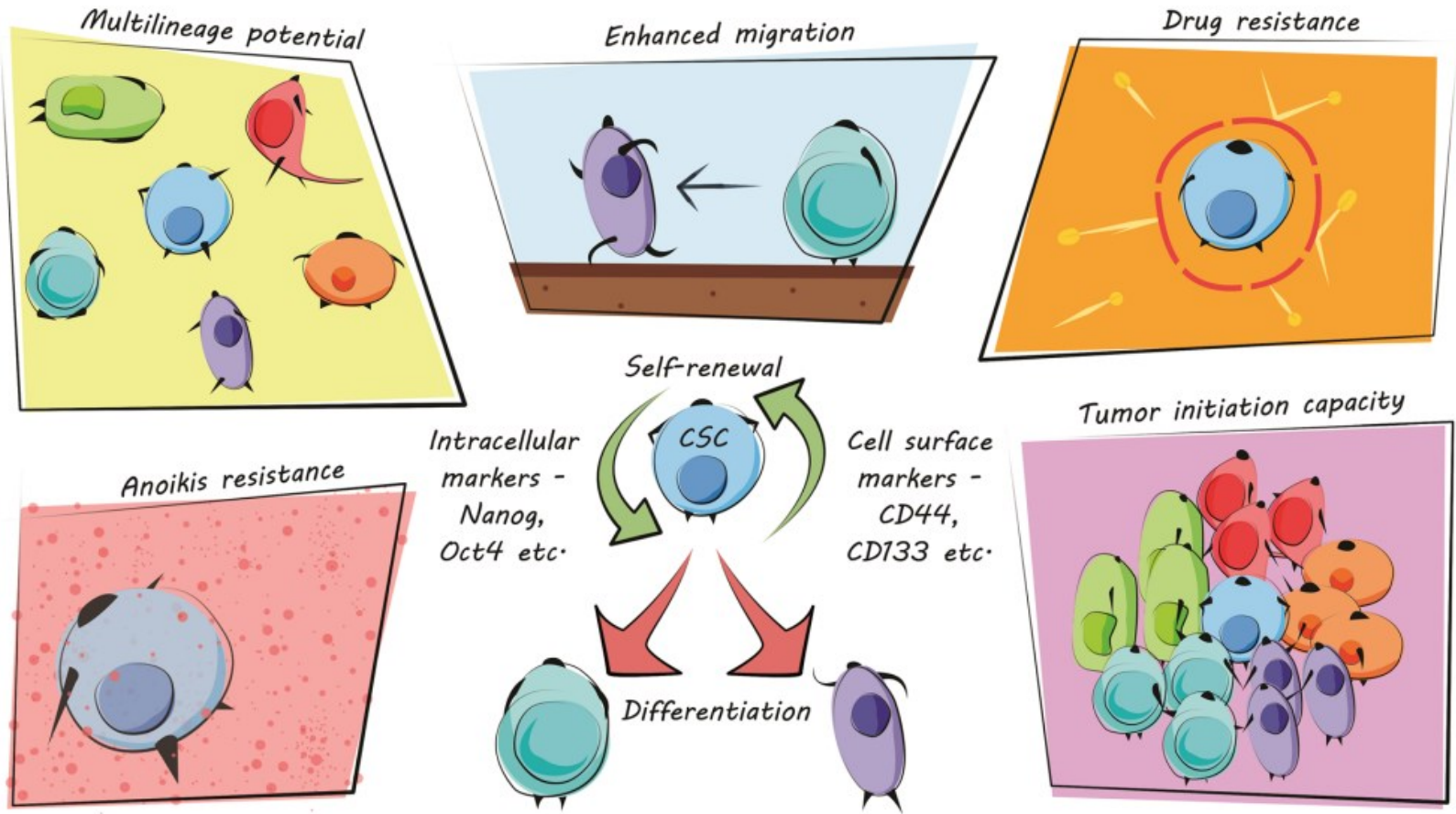
Kmenové buňky



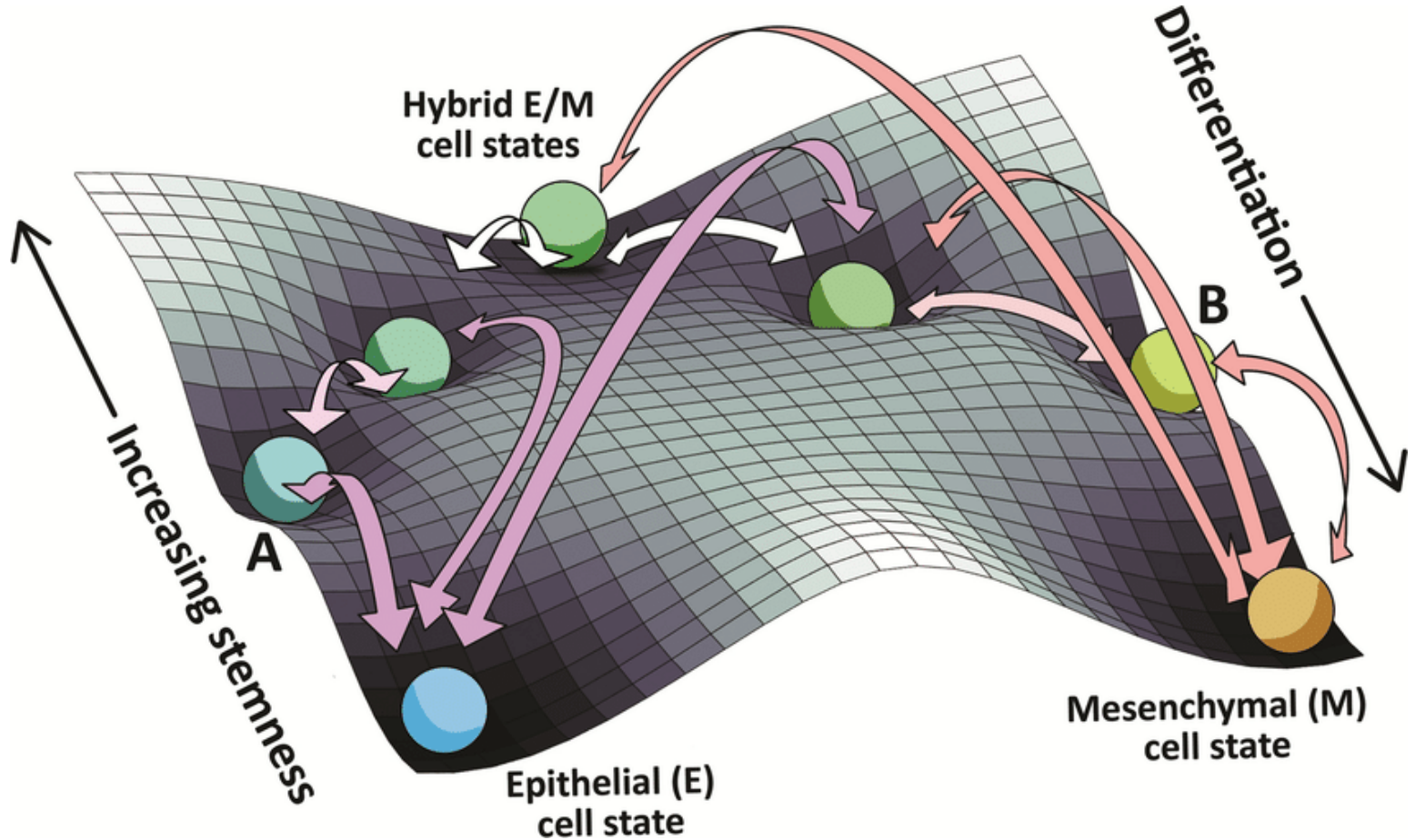
Nádorové kmenové buňky



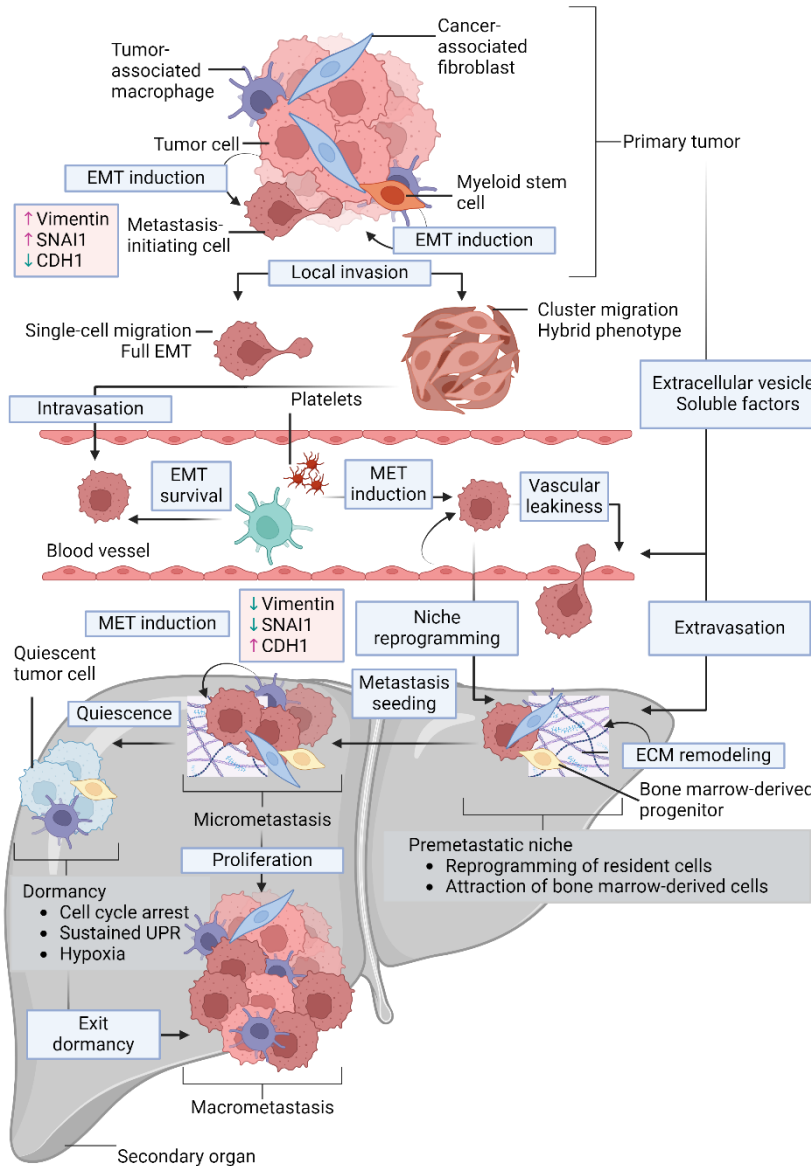
Nádorové kmenové buňky



Kmenovost buněk a EMT

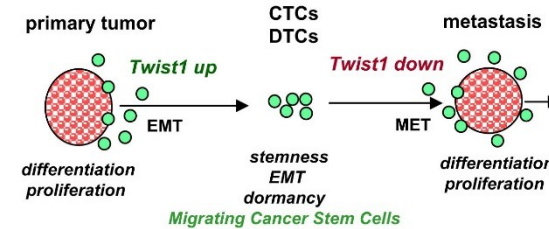


Buněčná plasticita a metastázování

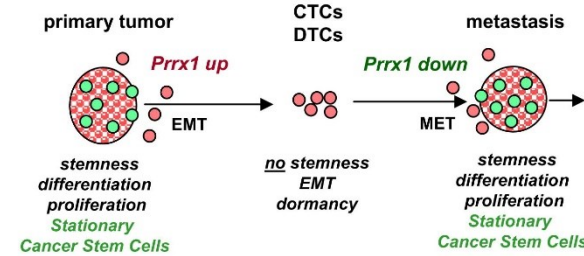


Cancer Cell
Article

A Twist1 - type



B Prrx1 - type



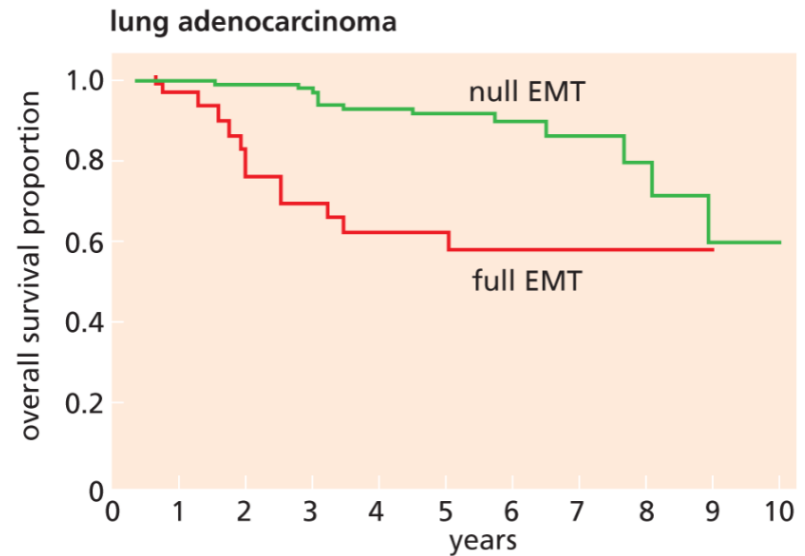
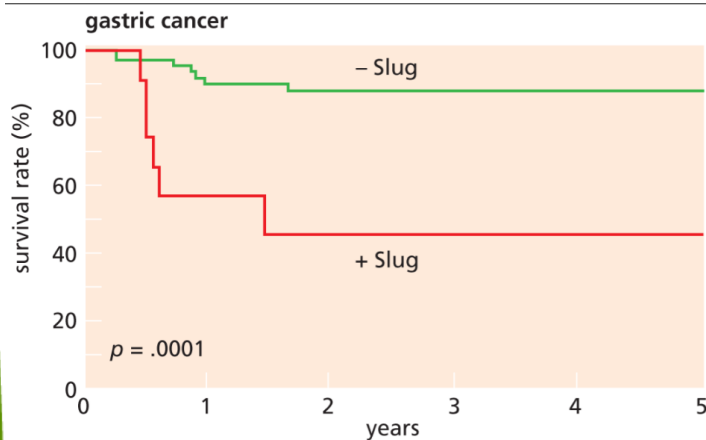
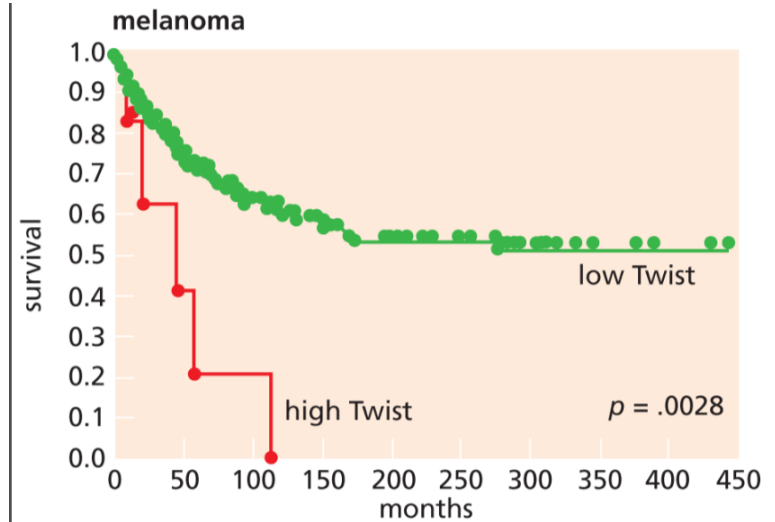
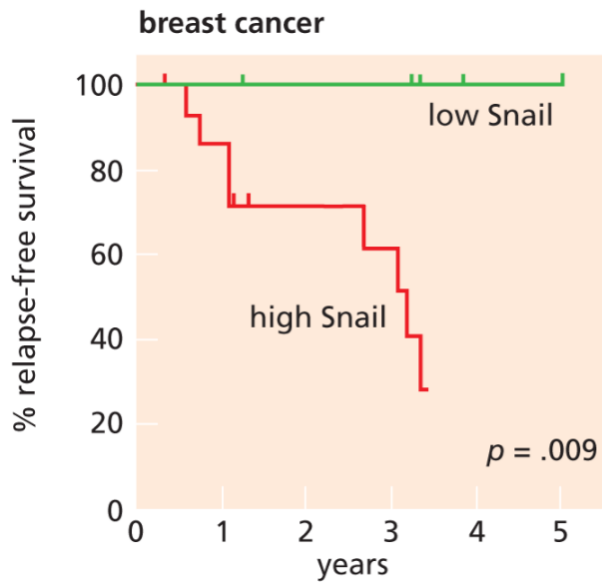
Metastatic Colonization Requires the Repression of the Epithelial-Mesenchymal Transition Inducer Prrx1

Oscar H. Ocaña,¹ Rebeca Córcoles,^{1,5} Ángels Fabra,^{2,5} Gema Moreno-Bueno,^{3,4} Hervé Aclouque,^{1,6} Sonia Vega,¹ Alejandro Barrallo-Gimeno,^{1,7} Amparo Cano,³ and M. Angela Nieto^{1,*}
¹Instituto de Neurociencias CSIC-UMH, Avda. Ramón y Cajal s/n, 03550 San Juan de Alicante, Spain
²IDIBELL (Bellvitge Biomedical Research Institute), Centre d' Oncologia Molecular, Gran Via de L'Hospitalet, 199 Barcelona, Spain
³Departamento de Bioquímica, UAM. Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM, IdiPAZ, Arturo Duperier, 4, 28029 Madrid, Spain
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<http://dx.doi.org/10.1016/j.ccr.2012.10.012>

SUMMARY

The epithelial-mesenchymal transition (EMT) is required in the embryo for the formation of tissues for which cells originate far from their final destination. Carcinoma cells hijack this program for tumor dissemination. The relevance of the EMT in cancer is still debated because it is unclear how these migratory cells colonize distant tissues to form macrometastases. We show that the homeobox factor Prrx1 is an EMT inducer conferring migratory and invasive properties. The loss of Prrx1 is required for cancer cells to metastasize in vivo, which revert to the epithelial phenotype concomitant with the acquisition of stem cell properties. Thus, unlike the classical EMT transcription factors, Prrx1 uncouples EMT and stemness, and is a biomarker associated with patient survival and lack of metastasis.

Náznaky úlohy transkripčních faktorů indukujících EMT v progresi lidských nádorů



EMT jako cíl terapie

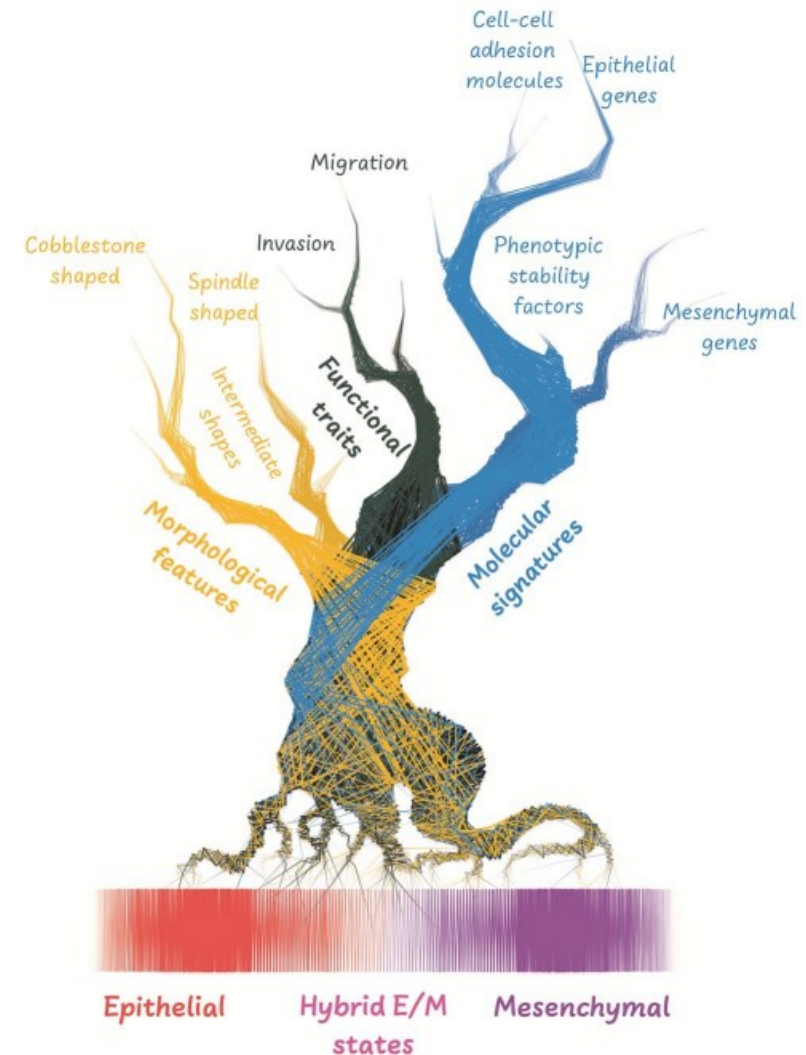
Table 1. A list of drugs targeting EMT regulatory components in TNBC clinical trials.

Drug	Mechanisms	Clinical Trial ID	Monotherapy/Combination
Buparlisib	PI3K inhibitor	NCT02000882	Capecitabine
PF-03084014	Notch inhibitor	NCT02299635	Monotherapy
RO4929097		NCT01071564	Vismodegib
Fresolimumab	TGF- β blocking antibody	NCT01401062	Radiation therapy
Galunisertib	TGF β R1 kinase inhibitor	NCT02672475	Paclitaxel
Reparixin	IL-8 receptor CXCR1/2 inhibitor	NCT02370238	Paclitaxel
Entinostat	class I HDAC inhibitor of NF- κ B, IL-6 and IL-8	NCT02708680	Atezolizumab
Everolimus	mTORC1 inhibitor reducing HIF-1 α expression	NCT01931163	Cisplatin
Bicalutamide	androgen antagonist preventing AR-induced hypoxia	NCT03090165	Ribociclib
Cetuximab	EGFR inhibitor inhibiting synthesis of HIF-1 α	NCT01097642	Ixabepilone
Lucitanib	angiogenesis inhibitor reducing MMPs and collagen	NCT02202746	Monotherapy
Vismodegib	Smoothed receptor antagonist, inhibiting Hedgehog signalling	NCT02694224	Paclitaxel Epirubicin Cyclophosphamide
Sonidegib		NCT01576666	Buparlisib
ARRY-382	CSF1R inhibitor	NCT02027376	Docetaxel
Pexidartinib		NCT02880371	Pembrolizumab
MEDI4736	anti-PD-L1 antibody	NCT01596751	Eribulin
Vantictumab		NCT02484404	Cediranib
	Wnt pathway inhibitor	NCT02403271	Durvalumab
		NCT01973309	Paclitaxel

EMT - souhrn

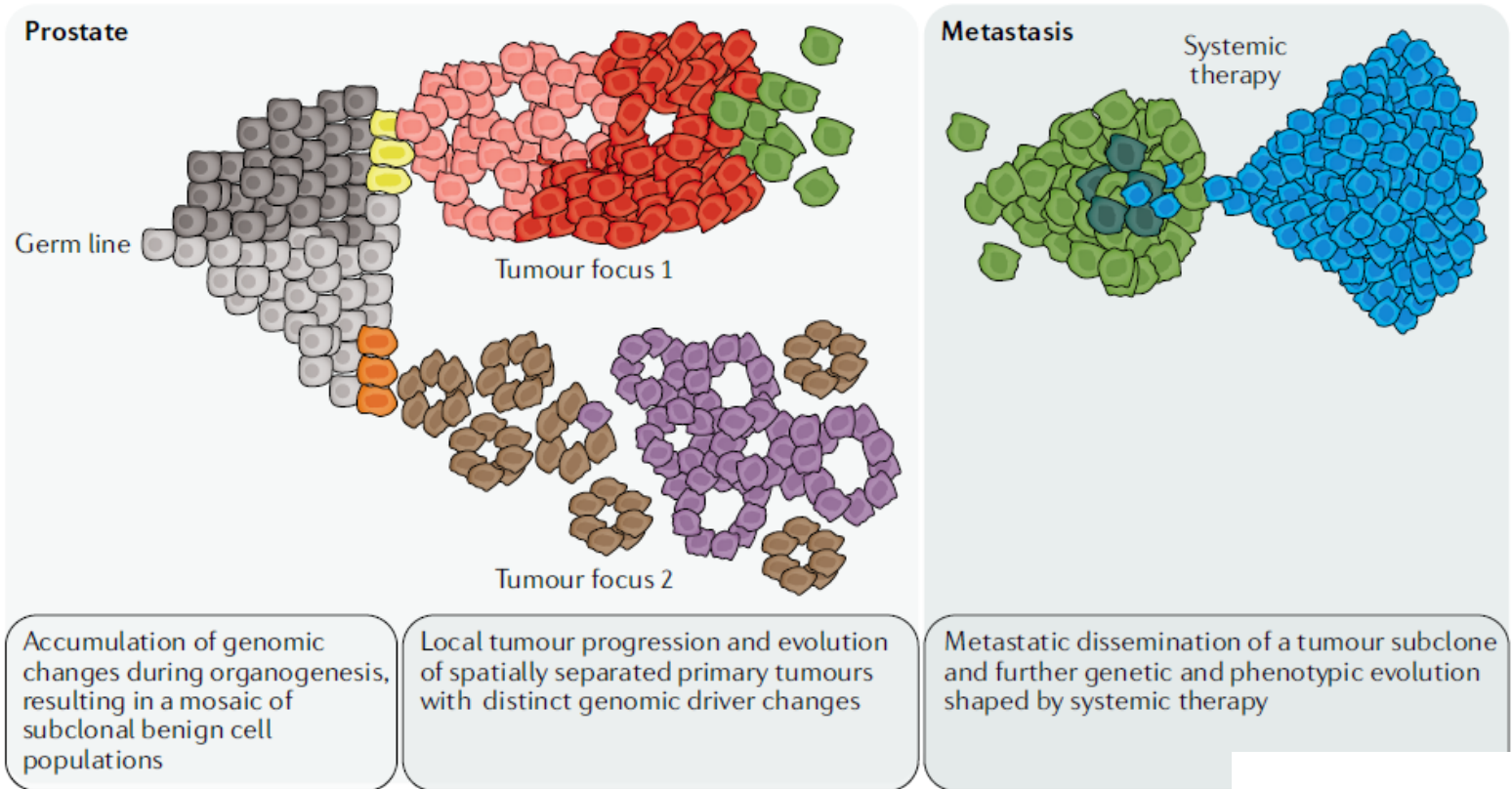
- ▶ EMT může být řízena pleiotropně působícími transkripčními faktory, které se běžně podílejí na organizaci různých kroků časně embryogeneze.
- ▶ EMT zahrnuje ztrátu programu genové exprese epiteliálních buněk a získání mezenchymální genové exprese. Ta umožňuje buňkám získat invazivitu, pohyblivost a zvýšenou odolnost vůči apoptóze.
- ▶ Díky EMT se nádorové buňky dostávají do stavu podobnému nádorovým kmenovým buňkám

Clinical & Experimental Metastasis (2022) 39:279–290



Nádorové onemocnění prostaty

- Primární karcinomy prostaty jsou často multifokální s prostorově a morfologicky odlišnými nádorovými ložisky.
- Jednotlivá nádorová ložiska mohou vykazovat nepřekrývající se kmenové genomové změny, což naznačuje, že u daného pacienta může vzniknout více klonálně odlišných nádorů.
- Vnitronádorová a mezinádorová heterogenita přítomná v prostatě představuje diagnostickou výzvu.
- Navzdory multiklonalitě primárního karcinomu se zdá, že klonální selekce vynucená metastatickým procesem a dále terapeutickými zásahy selektují jediný dominantní klon smrtelného metastatického karcinomu prostaty.

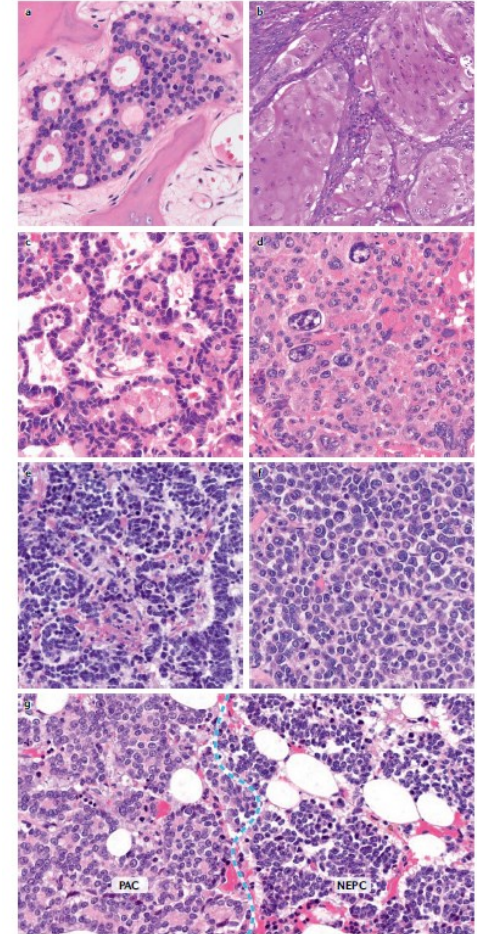
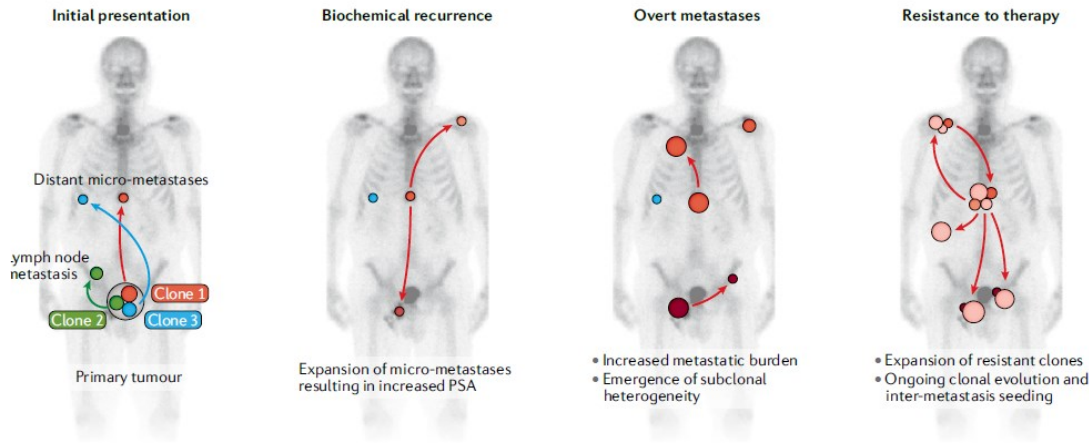
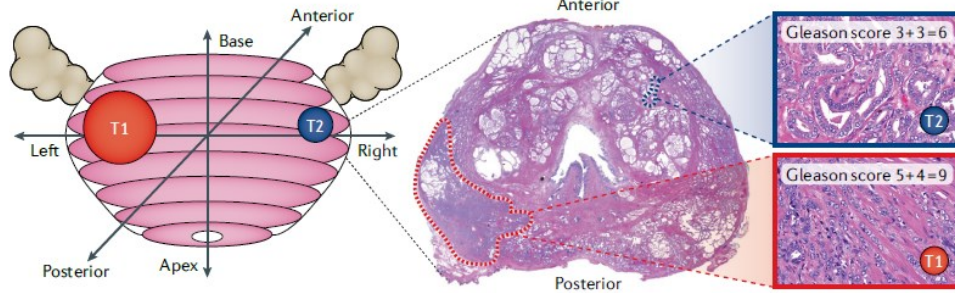


REVIEWS

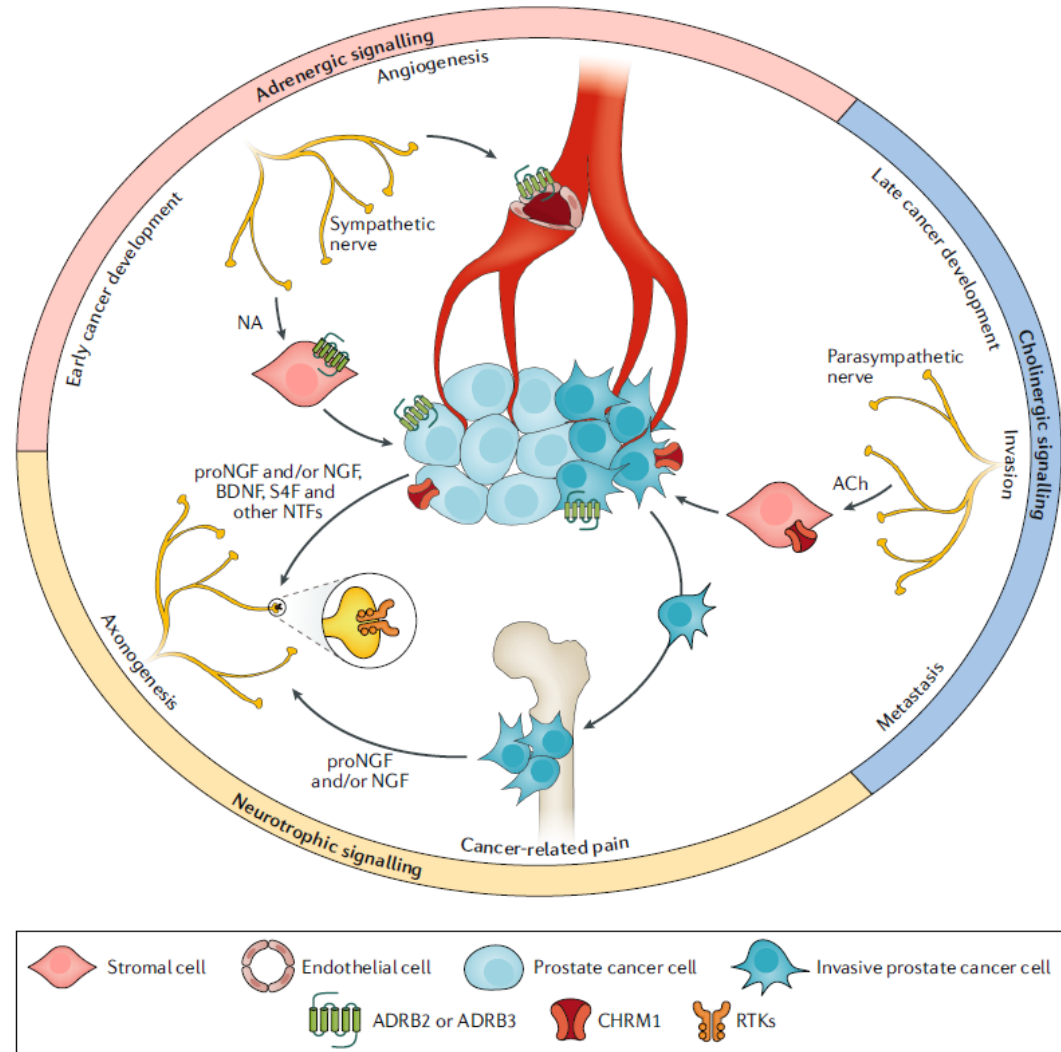
Genomic and phenotypic heterogeneity in prostate cancer

Michael C. Hoffner^{1,2,3}, Wilbert Zwart⁴, Martine P. Roudier⁵, Lawrence D. True⁶, William G. Nelson^{6,7}, Jonathan I. Epstein^{8,9}, Angelo M. De Marzo^{6,10}, Peter S. Nelson¹¹ and Srinivasan Vigneshbramanian⁶

Multifokální nádory prostaty, jejich heterogenita a klonální evoluce



Inervace a neurosignalizace u karcinomu prostaty



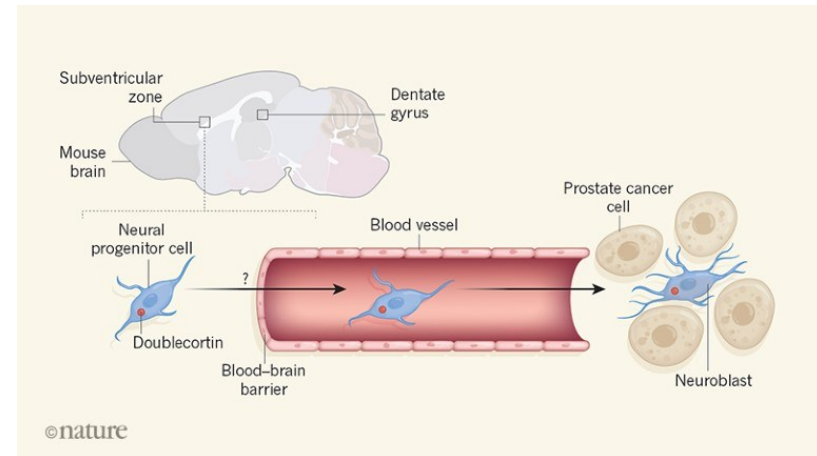
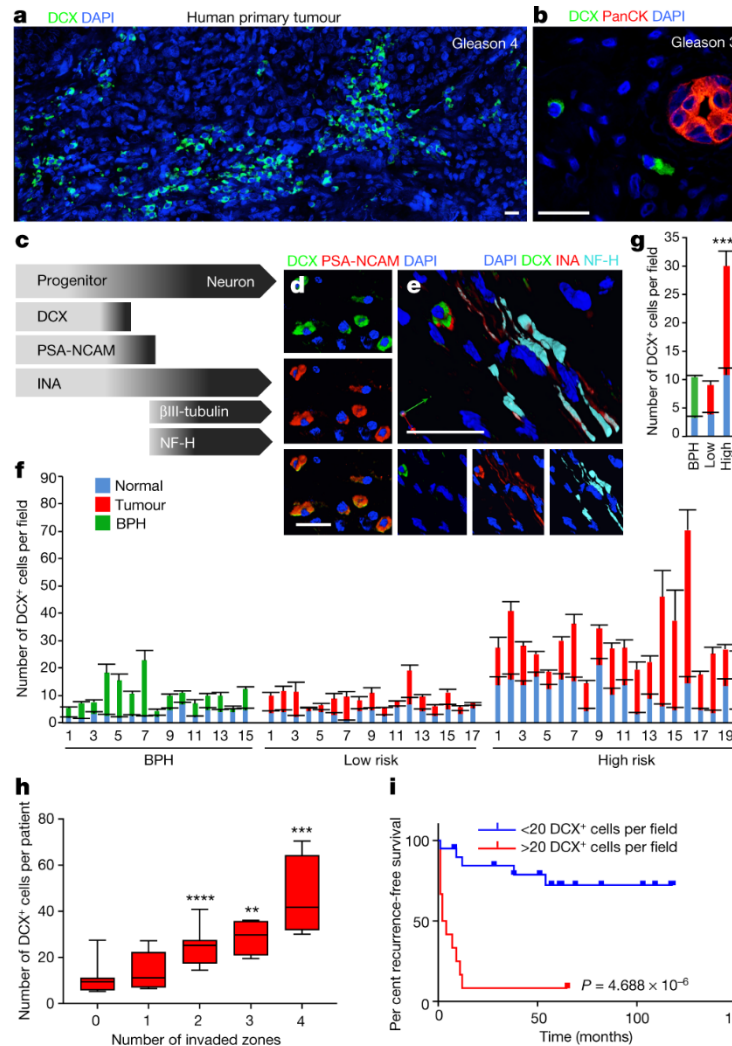
Inervace nádoru a neurosignalizace u karcinomu prostaty

- Hustota nervů je zvýšená u preneoplastických lézí a karcinomu prostaty
- Axonogenezi usnadňují neurotrofiny a molekuly navádějící axony pocházející z nádoru
- Adrenergní signalizace stimuluje progresi nádoru od intraepiteliální neoplazie prostaty k adenokarcinomu
- Adrenergní signalizace aktivuje angio-metabolický přepínač
- Cholinergní signalizace stimuluje nádorovou proliferaci, invazi a metastazování
- Chemická nebo chirurgická denervace prostaty inhibuje účinky neurosignalizace
- Chemická denervace vyvolaná botulotoxinem vede ke zvýšené apoptóze nádorových buněk
- Adrenergní neurosignalizace reaktivuje spící diseminované nádorové buňky prostaty v kostní dřeni
- Hustota nervů pozitivně koreluje se špatnými klinickými výsledky
- Pacienti s poraněním míchy mají nižší výskyt rakoviny prostaty
- Antagonisté adrenergních β -receptorů snižují mortalitu specifickou pro karcinom prostaty

Progenitors from the central nervous system drive neurogenesis in cancer

Philippe Mauffrey¹, Nicolas Tchitchek^{2,7}, Vilma Barroca^{1,7}, Alexis-Pierre Bemelmans¹, Virginie Firlej¹, Yves Allory¹, Paul-Henri Roméo⁸ & Claire Magnon^{1*}

doublecortin (DCX) ~ klasický marker neurálních progenitorů

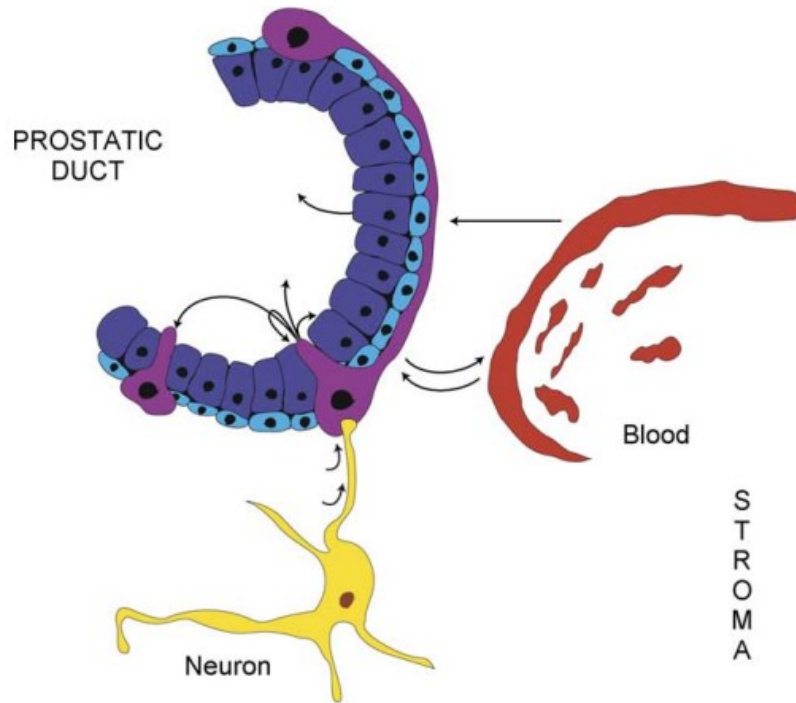


CANCER

Brain cells invade prostate tumours

Prostate cancer contains nerve cells that are linked to disease progression, but their source was unknown. A mouse study reveals that cells from the brain invade prostate tumours and give rise to this nerve-cell population. [SEE ARTICLE P.672](#)

Neuroendokríní buňky prostaty



N. Vashchenko, P.-A. Abrahamsson/European Urology 47 (2005) 147–155

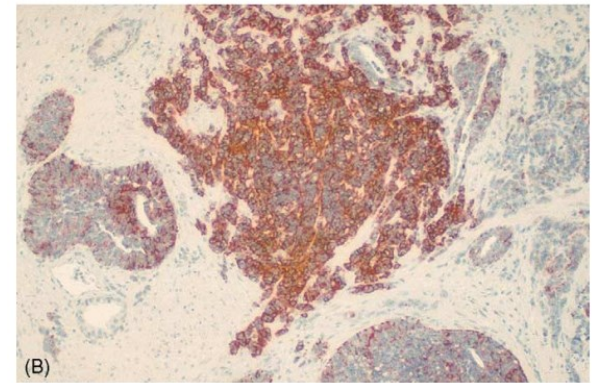
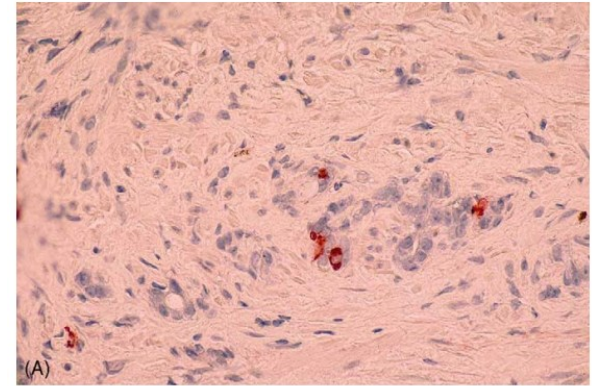


Fig. 2. (A) Neuroendocrine tumour cells (stained brown) in moderately differentiated prostatic carcinoma as visualized by immunoreactivity to chromogranin A, $\times 150$. (B) In contrast, a large number of malignant cells in poorly differentiated adenocarcinoma of the prostate display immunoreactivity to chromogranin A (stained brown), $\times 130$.

Neuroendokríní buňky prostaty

Table 1

General characteristics, functional roles, products and receptors of the neuroendocrine cell

General characteristics

- Androgen-receptor negative
- Non-proliferating
- PSA-negative
- Bcl-2-negative
- Express intermediate & luminal cytokeratins

Functional roles

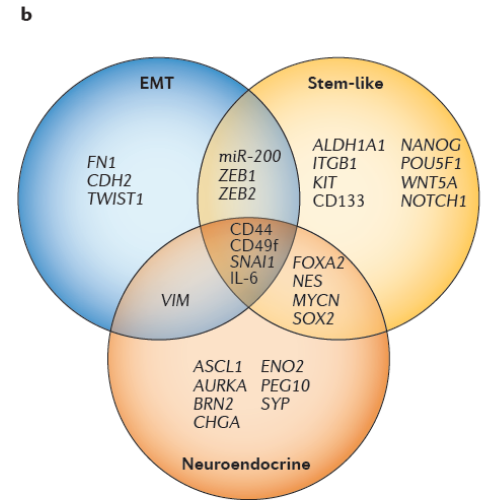
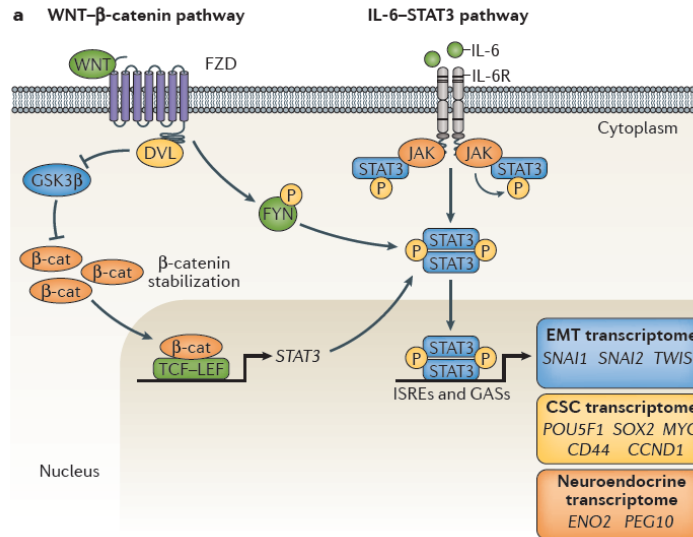
- Regulation of cell growth and differentiation
- Regulation of homeostasis
- Regulation of prostatic secretion

Products

- Calcitonin gene family
- Chromogranin A
- Chromogranin B
- Cholecystokinin (CCK)
- Gastrin-releasing peptide
- Histamine
- Neuron-specific enolase
- Neuropeptide Y
- Parathyroid hormone-related protein
- Proadrenomedullin N-terminal peptide
- Serotonin
- Somatostatin
- TSH-like peptide
- Vascular endothelial growth factor

Receptors

- Gastrin releasing peptide (GRPR)
- Serotonin (5HT_{1A}, B)
- Somatostatin (SSTR 1-5)
- Calcitonin (hCTR-2)
- Cholecystokinin
- Neuropeptide Y
- Vasoactive intestinal peptide
- PTHrP receptor (highly expressed in bone metastases from prostate)



REVIEWS

Cellular plasticity and the neuroendocrine phenotype in prostate cancer

Alastair H. Davies^{1,2}, Himisha Beltran³ and Amina Zoubeid^{1,2}

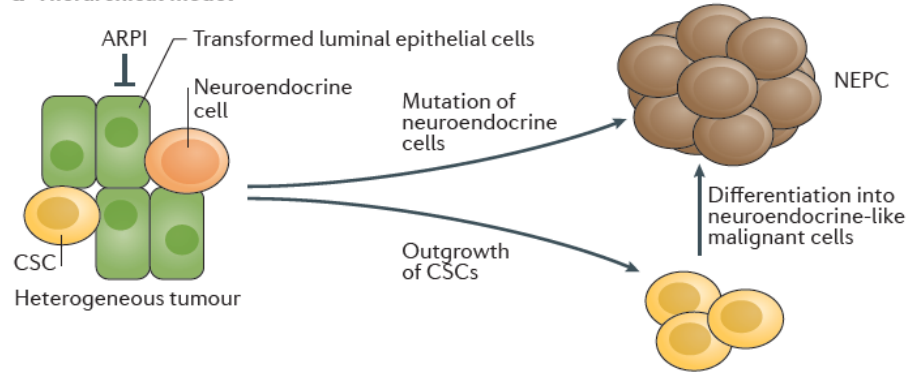
N. Vashchenko, P.-A. Abrahamsson / *European Urology* 47 (2005) 147–155

Neuroendokrinní nádory prostaty (NEPC)

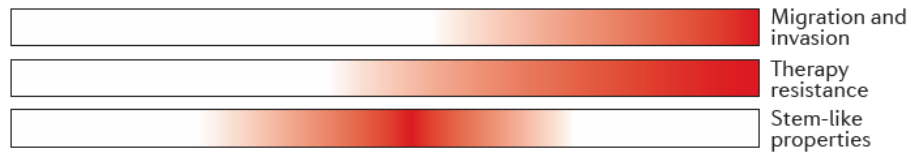
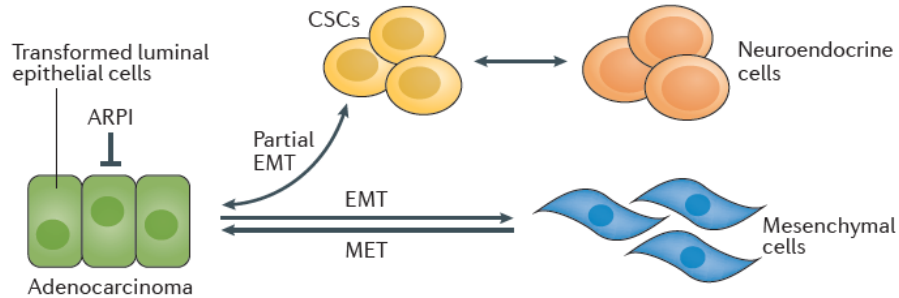
- ▶ NEPC představují <2% nově diagnostikovaných karcinomů prostaty.
- ▶ podskupina karcinomů prostaty rezistentních vůči kastraci (CRPC), které ztrácejí závislost na dráze AR a získávají histologické rysy neuroendokrinní diferenciace.
- ▶ V klinice je NEPC u pacientů s rostoucí zátěží onemocnění, včetně těch s častými viscerálními a/nebo lytickými kostními metastázami, přestože jsou hladiny PSA nízké nebo středně vzrůstající.
- ▶ Tyto nádory jsou obvykle pozitivní na mnoho z markerů nalezených u jiných pokročilých neuroendokrinních karcinomů, včetně chromograninu A (CHGA), neuron-specifické enolázy (NSE), synaptofyzinu (SYP) a CD56.
- ▶ Navíc jsou typicky negativní na luminalní markery diferenciace prostaty, jako je PSA a prostatická kyselá fosfatáza.
- ▶ Bez ohledu na mechanismus původu jsou pacientům s NEPC často předepisovány léčby chemoterapií na bázi cisplatiny současně s standardními režimy používanými pro malobuněčný karcinom kvůli vysoké agresivitě a metastatické povaze těchto nádorů.
- ▶ Navzdory léčbě touto chemoterapií tyto nádory obvykle vedou k úmrtí do 2 let od diagnózy.
- ▶ V současné době nejsou k dispozici cílené terapie pro NEPC.

Mechanismus vzniku NEPC

a Hierarchical model



b Dynamic transdifferentiation model



Mechanismus vzniku NEPC

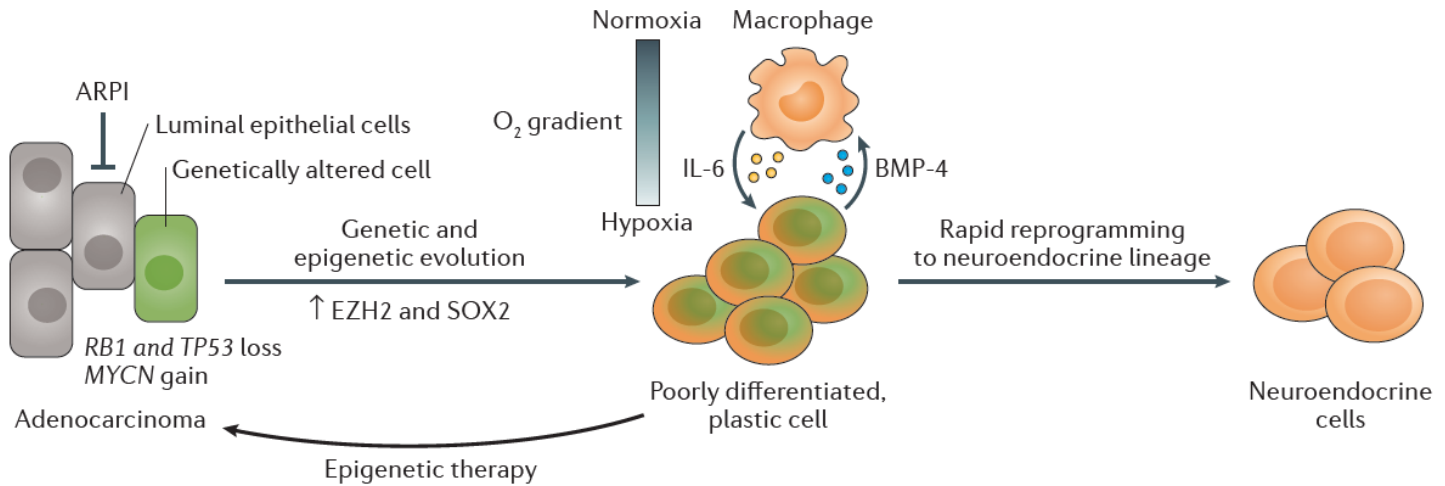


Table 1 | Plasticity in NEPC models

Name or characteristic	Origin of cells	Histology	Evidence of plasticity	Refs
<i>Cell line</i>				
NCI-H660	Lymph node metastasis from a patient with small-cell prostate cancer	NA	Dependency on EZH2	43
<i>GEMMs</i>				
<i>Rb1</i> deletion and <i>Pten</i> loss	Mouse prostate epithelium	Mixed adenocarcinoma and NEPC (SYP ⁺) cells	EZH2 inhibition reverses antiandrogen (enzalutamide) resistance	28
<i>Tp53</i> deletion and <i>Pten</i> loss	Mouse prostate epithelium (luminal cells)	Divergent differentiation, including squamous, sarcomatoid, and small-cell NE-like (SYP ⁺ CHGA ⁺) cells	Lineage tracing demonstrates that luminal adenocarcinoma cells give rise to NE tumours in response to antiandrogen (abiraterone) treatment	27
<i>Mycn</i> induction and <i>Pten</i> loss	Mouse prostate epithelium	Foci of poorly differentiated carcinoma with divergent differentiation, including sarcomatoid and small-cell NE (CHGA ⁺) cells	Upregulation of AR-regulated genes following EZH2 inhibition	79
<i>Xenografts</i>				
<i>MYCN</i> induction and <i>AKT</i> activation	Human prostate epithelium	Divergent differentiation, including small-cell NE and mixed NE-acinar adenocarcinoma (SYP ⁺ CHGA ⁺ NCAM1 ⁺) cells	Upregulation of epigenetic regulators (EZH2 and DNMT1); CSC features	110
<i>PDX</i>				
LTL331R	PDX adenocarcinoma (LTL331)	NEPC (SYP ⁺ CHGA ⁺ CD56 ⁺) cells	Rapid emergence of NE tumour following castration	118

AR, androgen receptor; CHGA, chromogranin A; CSC, cancer stem-like cell; DNMT1, DNA (cytosine-5)-methyltransferase 1; EZH2, enhancer of zeste homologue 2; GEMM, genetically engineered mouse model; NA, not applicable; NCAM1, neural cell adhesion molecule 1; NE, neuroendocrine; NEPC, neuroendocrine prostate cancer; PDX, patient-derived xenograft; SYP, synaptophysin.

Single-cell analysis supports a luminal-neuroendocrine transdifferentiation in human prostate cancer

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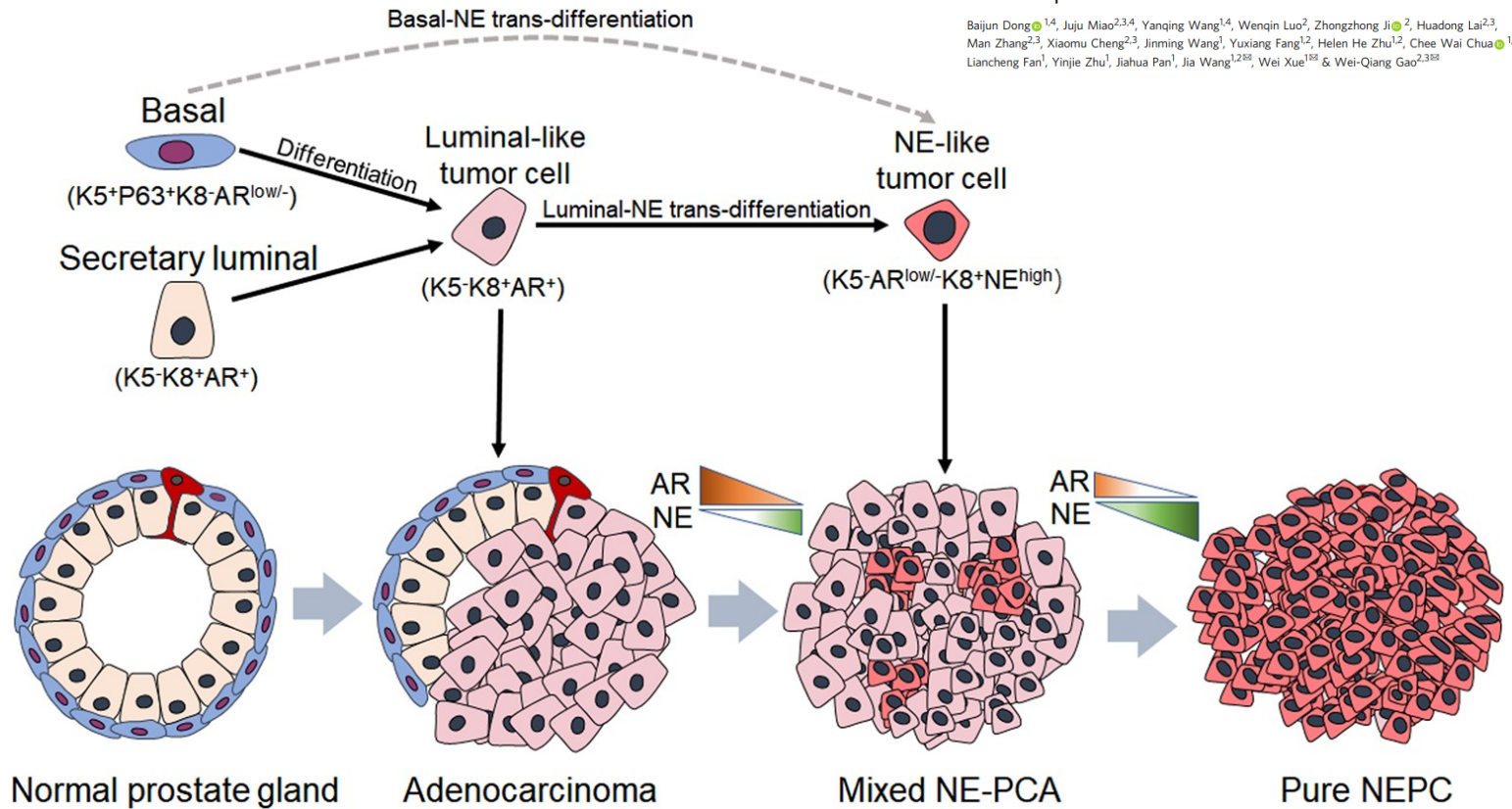


Table 2 | Therapies directed against drivers of cellular plasticity and/or neuroendocrine differentiation

Inhibitor	Mechanism	Clinical status	Clinical outcome	Refs
<i>IL-6–STAT3 inhibitors</i>				
Siltuximab (CNTO 328)	Chimeric monoclonal antibody that binds to and neutralizes IL-6 bioactivity and inhibits STAT3 activity	Phase I trial in combination with docetaxel completed	Efficacy in CRPC	150,151
Lycopene	Inhibits IL-6 signalling and decreases STAT3 expression and phosphorylation	Phase I trial in combination with docetaxel in CRPC completed	Well tolerated with docetaxel; correlative analysis ongoing	152,153
Galiellalactone	Directly inhibits STAT3 transcriptional activity and induces apoptosis in ALDH ^{high} prostate CSCs	Preclinical	NA	203,204
<i>CSC inhibitors</i>				
Disulfiram	Inhibitor of ALDH activity, which is highly expressed in prostate CSCs	Phase Ib trial in mCRPC and NEPC ongoing	NA	159,161
Rovalpituzumab tesirine (Rova-T)	Antibody–drug conjugate targeting the NOTCH ligand DLL3, which is expressed on CSCs and neuroendocrine cells	Phase I trial in DLL3-expressing solid tumours, including a dedicated NEPC arm ongoing	NA	173,174
<i>MYCN and AURKA inhibitors</i>				
Alisertib (MLN8237)	Inhibits AURKA and disrupts the AURKA–MYCN complex to inhibit MYCN-dependent transcription	Phase II trial in confirmed or suspected NEPC completed	Moderate clinical response (18 of 60 patients); clinical progression-free survival of 2.3 months in NEPC arm	11,110,167
ZEN003694	Inhibits BET proteins and induces apoptosis in NEPC cell lines	Phase I trial as a single agent and in combination with enzalutamide in mCRPC ongoing	NA	205,206
GS-5829	Inhibits BET proteins	Phase I and II trials as a single agent and in combination with enzalutamide in mCRPC ongoing	NA	207,208
<i>EZH2 inhibitors</i>				
GSK2816126	Inhibits EZH2 activity and reduces global H3K27me3 and decreases proliferation	Phase I trial in lymphomas and solid tumours, including CRPC, terminated	Well tolerated; stable disease reported in 7 of 30 patients	209,210
Tazemetostat (EPZ-6438)	SAM that competitively inhibits EZH2 and forces terminal differentiation and/or apoptosis	Phase II trial in lymphomas and solid tumours ongoing	Antitumour activity in DLBCL (29% ORR) and FL (92% ORR) with activating EZH2 mutations	179,211
CPI-1205	Inhibits EZH2 activity and reduces global H3K27me3	Phase Ib/II trial in combination with enzalutamide or abiraterone plus prednisone in mCRPC ongoing	NA	212,213

ALDH, aldehyde dehydrogenase; AURKA, Aurora kinase A; BET, bromodomain and extra-terminal domain family; CRPC, castration-resistant prostate cancer; CSC, cancer stem-like cell; DLBCL, diffuse large B cell lymphoma; DLL3, Delta-like protein 3; EZH2, enhancer of zeste homologue 2; FL, follicular lymphoma; H3K27me3, histone H3 lysine 27 tri-methylation; mCRPC, metastatic castration-resistant prostate cancer; MYCN, NMYC proto-oncogene protein; NA, not available; NEPC, neuroendocrine prostate cancer; NOTCH, neurogenic locus Notch homologue protein; ORR, objective response rate; SAM, S-adenosyl-L-methionine; STAT3, signal transducer and activator of transcription 3.

NEPC - souhrn

- ▶ NEPC může vzniknout z ne-neuroendokrinních buněk, jako jsou epitelové buňky, což naznačuje plasticitu buněk.
- ▶ Tento proces se vyskytuje jak experimentálně, tak klinicky, přičemž někteří pacienti léčení ARPIs relabují s nádory NEPC projevujícími extrémní buněčnou plasticitu a vlastnosti podobné kmenovým buňkám.
- ▶ Plasticita buněk je řízena složitými mechanismy zahrnujícími epigenetické a genetické poruchy, stejně jako interakci s mikroprostředím nádoru.