Transformující růstový faktor – β: rozmanitost přenosu signálu a funkce

Karel Souček

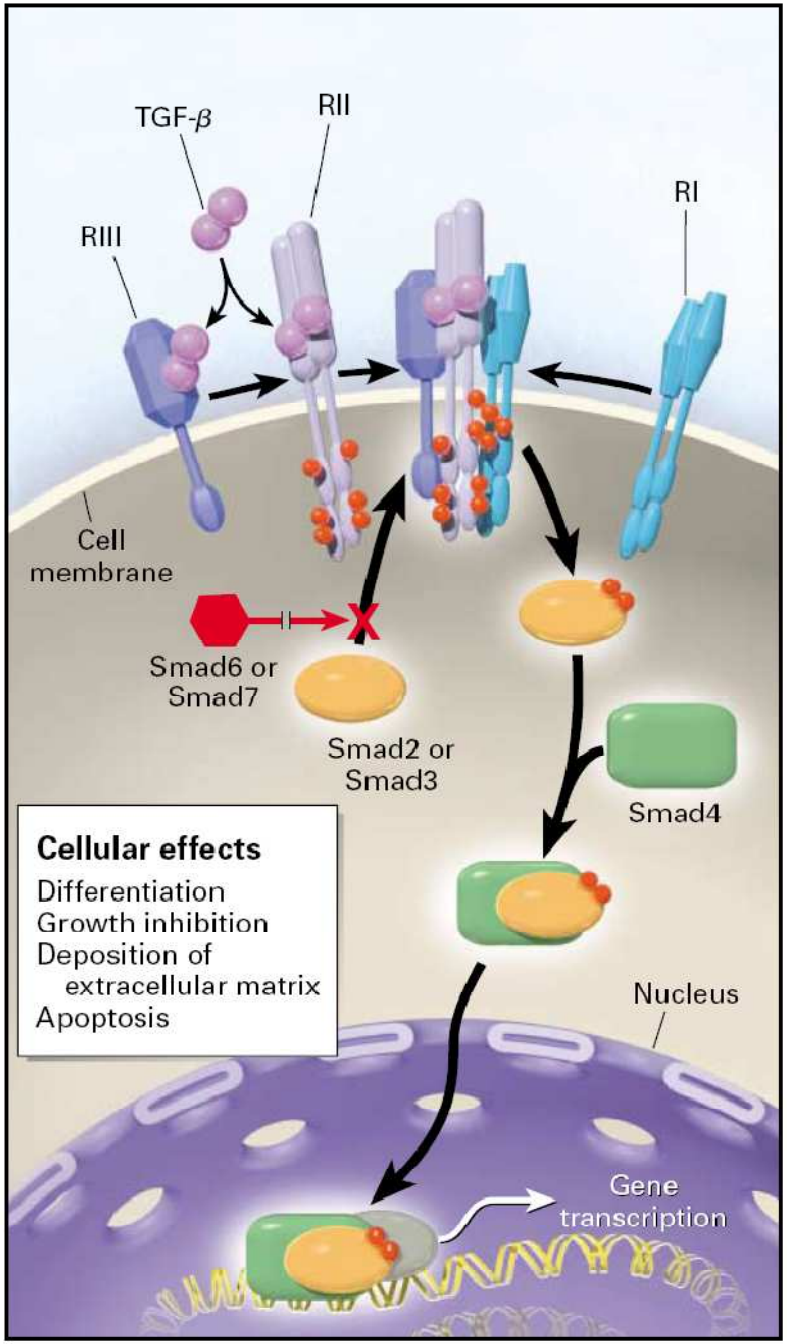
Bi6051 Molekulární fyziologie živočichů

Transforming growth factor -β (TGF-β)

TGF-β rodina ~ TGF-βs, activins, bone morphogenic proteins (BMP)

TGF-β_1

- pleiotropní cytokin
- negativní regulátor



Epstein, F.H., N Engl J Med 2000; 342:1350-1358, 2000

Biologické funkce TGF-β

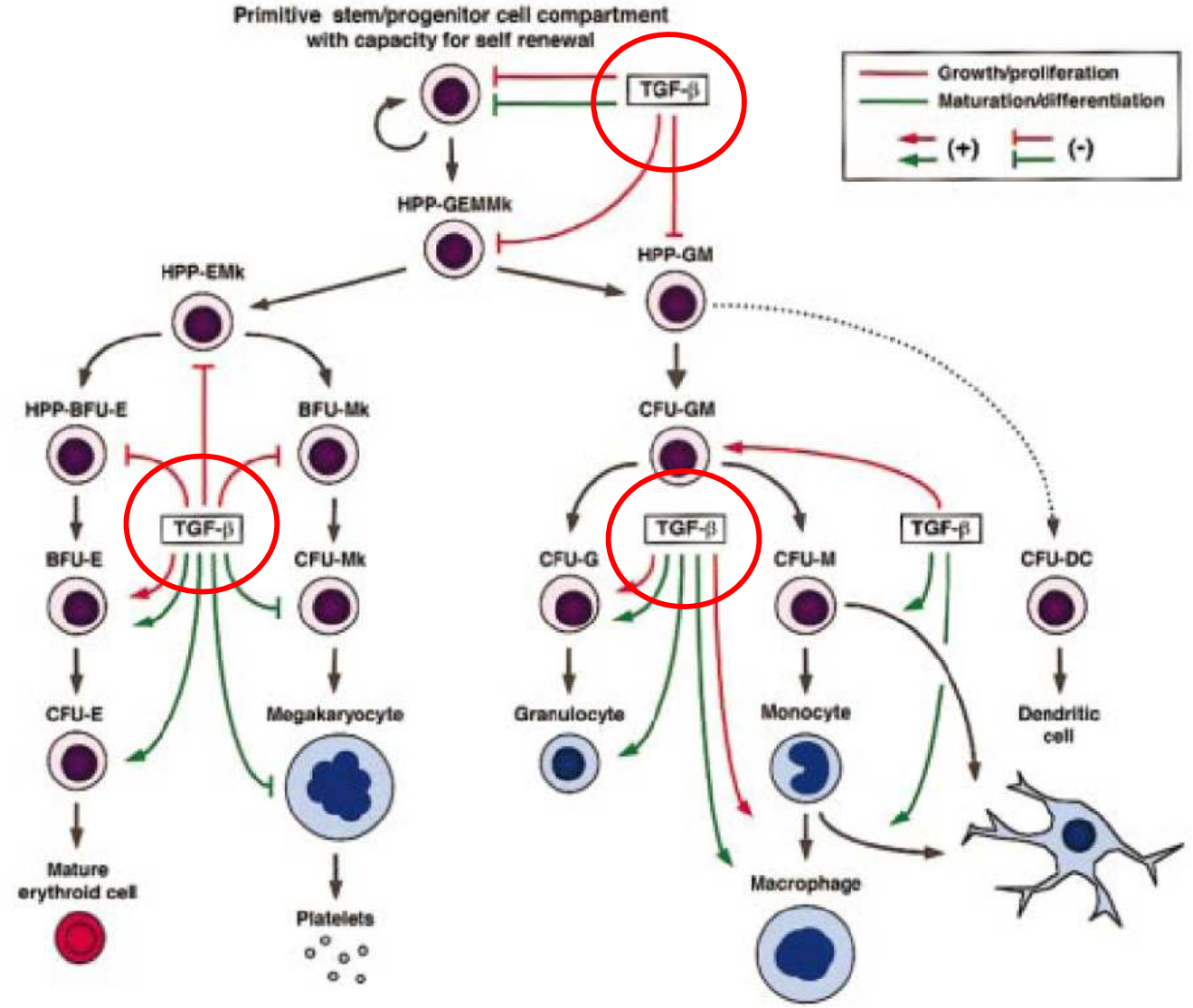
- Reguluje proliferaci, diferenciaci, buněčnou smrt, motilitu, adhezi (v závislosti na buněčném typu) = ovlivňuje homeostázu;
- reguluje expresi extracelulární matrix;
  - indukuje fibrilární kolagen a fibronectin;
  - inhibuje degradaci ECM (prostřednictvím inhibice MMPs a indukce TIMPs).

Biologické funkce TGF-β

- **TGF-β1 knockout**
  - Multifocal inflammatory disease followed by a wasting syndrome
    - Multifocal infiltration of lymphocytes and macrophages into diverse organs. Increased adhesion of mononuclear leukocytes (MLN) to extracellular matrix and to endothelial cells in vitro. Blockage of MLN infiltration by synthetic fibronectin peptides
    - Decreased thymus size
    - Enlargement of lymph nodes
    - Elevated constitutive levels of IL-2 mRNA in the thymus
    - Elevated IL-2r mRNA in lymph nodes
  - Cachexia
    Death roughly 20 days after birth
- **TGF-β2 knockout**
  - Multi-organ defects (lung, heart, limb, craniofacial, spinal column, eye, inner ear, urinary tract, genital tract)
  - **Perinatal mortality**

http://www.bioscience.org/knockout/knochome.ht

Regulace růstu/proliferace a zrání/diferenciace hematopoetických buněk působením TGF-β



N.O. Fortunel, A. Hatzfeld, J.A. Hatzfeld, Transforming growth factor-beta: pleiotropic role in the regulation of hematopoiesis, Blood 96 (2000) 2022-2036.

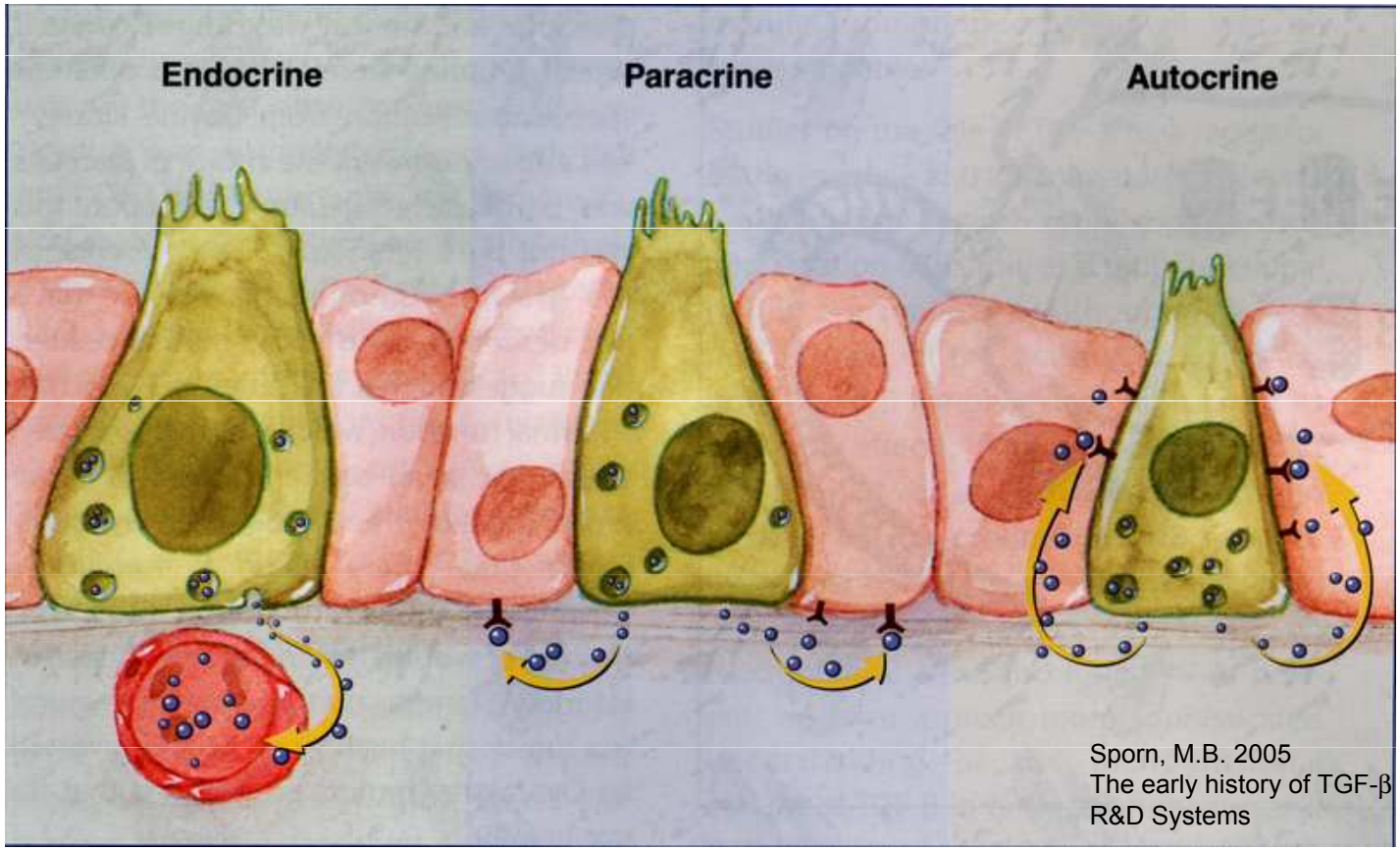
Transforming growth factor-β family

- Historie
- Zástupci rodiny a jejich nejvýznamnější funkce
- Syntéza, produkce a aktivace
- Přenos signálu a jeho regulace
  - receptory
  - sekundární přenašeči
  - „alternativní“ dráhy
  - regulace genové exprese
- Role v rozvoji patologických stavů

Historie TGF-β

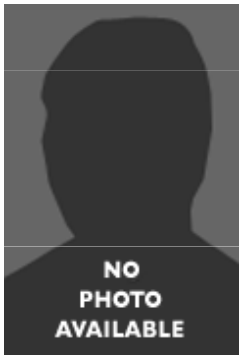
- na konci 70. let byla identifikována celá řada růstových faktorů;
- bylo zřejmé, že nádorové buňky se liší od normálních buněk mmj. ve schopnosti reagovat na některé z nich;
- Robert Holley ( 1968) naznačil, že transformované nebo nádorové buňky unikají z normální růstové kontroly tím, že potřebují méně hormonů či růstových faktorů;
- Michael B. Sporn vyslovil v roce 1980 hypotézu o možném podílu autokrinních faktorů na buněčné transformaci

Endokrinní, autokrinní & parakrinní regulace



Sporn, M.B. 2005
The early history of TGF-β
R&D Systems

Historie TGF-β



- Todaro a De Larco (1978) popsali „faktor“ způsobující transformaci normálních buněk – pojmenovali ho *sarcoma growth factor (SGF)*

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 4001–4005, August 1978
Microbiology

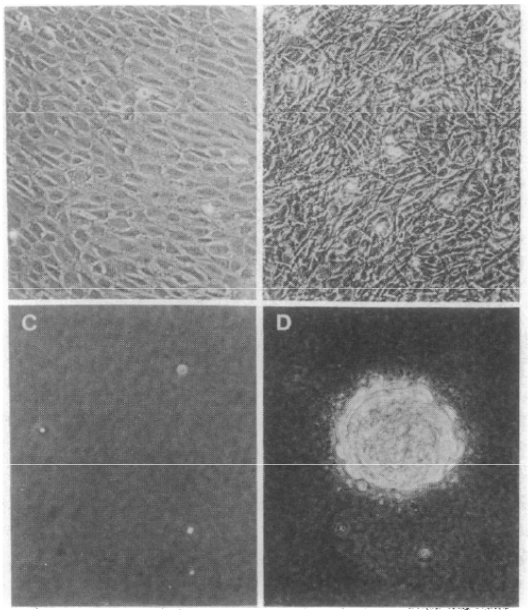
Growth factors from murine sarcoma virus-transformed cells

(epidermal growth factor/polypeptide hormones/cell transformation/radioreceptor assays)

JOSEPH E. DE LARCO AND GEORGE J. TODARO

Laboratory of Viral Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

Communicated by David Baltimore, May 11, 1978



Historie TGF-β

- A.B. Roberts a M.A. Anzano (1982) prokázali, že SGF není jen jeden faktor
  - Frakce indukující málo kolonií a silně kompetitivní s EGF= **TGF-α**
  - Frakce indukující mnoho velkých kolonií a bez kompetice s EGF = **TGF-β**

Cancer Res. 1982 Nov;42(11):4776-8.

Synergistic interaction of two classes of transforming growth factors from murine sarcoma cells.

Anzano MA, Roberts AB, Meyers CA, Komoriya A, Lamb LC, Smith JM, Sporn MB.

Historie TGF-β

- Na začátku 80. let byli vyvinuty metody purifikace TGF-β
- V té tobě již bylo jasné, že produkce TGF-β není nádorově specifická
- purifikace zejména z placenty, krevních destiček a prasečích ledvin

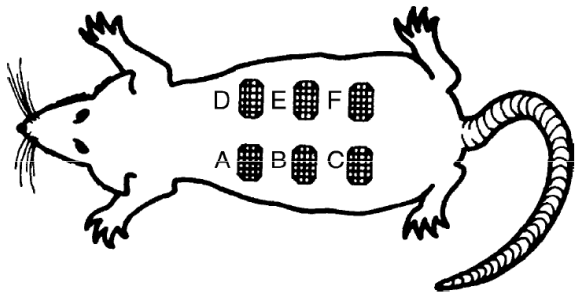
Historie TGF-β

- M.B. Sporn (1983) prokázal *in vivo* schopnost TGF-β podporovat tvorbu kolagenu a vaskularizaci normální tkáně během hojení

Science. 1983 Mar 18;219(4590):1329-31.

Polypeptide transforming growth factors isolated from bovine sources and used for wound healing in vivo.

Sporn MB, Roberts AB, Shull JH, Smith JM, Ward JM, Sodek J.



Historie TGF-β

- Rik Derynck et al. (1985) naklonovali TGF-β

NATURE VOL. 316 22 AUGUST 1985

701

Human transforming growth factor-β complementary DNA sequence and expression in normal and transformed cells

Rik Derynck, Julie A. Jarrett, Ellson Y. Chen, Dennis H. Eaton, John R. Bell*, Richard K. Assoian†, Anita B. Roberts†, Michael B. Sporn† & David V. Goeddel

Departments of Molecular Biology and * Protein Biochemistry, Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, California 94080, USA
† Laboratory of Chemoprevention, National Cancer Institute, Bethesda, Maryland 20205, USA

Historie TGF-β

- Kathleen Flanders et al. (1988) vyvinula protilátky proti specifickým epitopům TGF-β a tím umožnil studium exprese *in vivo*

Transforming Growth Factor-β1: Histochemical Localization with Antibodies to Different Epitopes

Kathleen C. Flanders, Nancy L. Thompson, David S. Cissel, Ellen Van Obberghen-Schilling, Carl C. Baker,* Mary E. Kass,§ Larry R. Ellingsworth,‡ Anita B. Roberts, and Michael B. Sporn

Laboratory of Chemoprevention and *Laboratory of Tumor Virus Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892; ‡Connective Tissue Research Laboratory, Collagen Corporation, Palo Alto, California 94303; and §Department of Pathology, Washington Hospital Center, Washington DC 20005

Historie TGF-β

- Joan Massagué (1985) detailněji charakterizoval receptory pro TGF-β

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 260, No. 5, Issue of March 10, pp. 2636–2645, 1985
Printed in U.S.A.

Cellular Receptors for Type β Transforming Growth Factor

LIGAND BINDING AND AFFINITY LABELING IN HUMAN AND RODENT CELL LINES*

(Received for publication, August 6, 1984)

Joan Massagué and Betsy Like

From the Department of Biochemistry, University of Massachusetts Medical School, Worcester, Massachusetts 01605

Historie TGF-β

- V letech 1992 a 1993 byly naklonovány receptory pro TGF-β

Cell, Vol. 68, 775–785, February 21, 1992, Copyright © 1992 by Cell Press

Expression Cloning of the TGF-β Type II Receptor, a Functional Transmembrane Serine/Threonine Kinase

Herbert Y. Lin,*† Xiao-Fan Wang,*‡ Elinor Ng-Eaton,* Robert A. Weinberg,*† and Harvey F. Lodish*†
*Whitehead Institute for Biomedical Research
Cambridge, Massachusetts 02142
†Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

TGF-β was originally described as a factor that induced normal rat kidney fibroblasts to proliferate in soft agar in the presen
1981). TG
number of
Roberts an
TGF-β can

Cell, Vol. 75, 681–692, November 19, 1993, Copyright © 1993 by Cell Press

Cloning of a TGFβ Type I Receptor That Forms a Heteromeric Complex with the TGFβ Type II Receptor

Petra Franzén, Peter ten Dijke, Hidenori Ichijo,* Hidetoshi Yamashita, Peter Schulz, Carl-Henrik Heldin, and Kohei Miyazono
Ludwig Institute for Cancer Research
Biomedical Center
S-751 24 Uppsala
Sweden

in morphogenesis, e.g., during different stages of development (Akhurst et al., 1991; Lyons et al., 1991).

TGFβs exert their effects through binding to specific cell surface receptors. By affinity labeling and cross-linking to radioiodinated TGFβs, a number of TGFβ receptors (or binding proteins) have been identified, including type I (53 kd), type II (75 kd), and type III receptors (or betaglycan [300 kd]), which are found in most cells (for reviews see

Historie TGF-β

- Objev intracelulárních přenašečů signálu TGF-β - v roce 1995 na *Drosophila melanogaster* a v roce 1996 na *Caenorhabditis elegans.*

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 790–794, January 1996
Developmental Biology

Caenorhabditis elegans genes _sma-2, sma-3, and sma-4_ define a conserved family of transforming growth factor β pathway components

(signal transduction/pattern formation/bone morphogenetic protein/multigene family)

CATHY SAVAGE*, PRADEEP DAS*, ALYCE L. FINELLI*, SCOTT R. TOWNSEND*, CHING-YU SUN†, SCOTT E. BAIRD‡, AND RICHARD W. PADGETT*§

*Waksman Institute and Department of Molecular Biology and Biochemistry, Rutgers University, Piscataway, NJ 08855-0759; †Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15260; and ‡Department of Biological Sciences, Wright State University, Dayton, OH 45435

Communicated by Clyde A. Hutchison III, University of North Carolina, Chapel Hill, NC, September 15, 1995 (received for review August 11, 1995)

Genetic Characterization and Cloning of _Mothers against dpp_, a Gene Required for _decapentaplegic_ Function in _Drosophila melanogaster_

Jeff J. Sekelsky,[1] Stuart J. Newfeld, Laurel A. Raftery,[2] Elena H. Chartoff and William M. Gelbart

The Biological Laboratories, Harvard University
Cambridge, Massachusetts 02138

Manuscript received September 23, 1994
Accepted for publication December 7, 1994

Historie TGF-β

- Jeffrey Wrana, Lilana Attisano a Joan Massagué (1994) – popis aktivace receptoru

Mechanism of activation of the TGF-β receptor

Jeffrey L. Wrana, Liliana Attisano, Rotraud Wieser, Francesc Ventura & Joan Massagué*

Howard Hughes Medical Institute and Cell Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA

NATURE · VOL 370 · 4 AUGUST 1994



Historie TGF-β

- *Mad* (*mothers against decapentaplegic*) + *Sma* = SMAD

Cell, Vol. 87, 173, October 18, 1996, Copyright ©1996 by Cell Press

Nomenclature: Vertebrate Mediators of TGFβ Family Signals

Rik Derynck,[1] William M. Gelbart,[2]
Richard M. Harland,[3] Carl-Henrik Heldin,[4]
Scott E. Kern,[5] Joan Massagué,[6,7] Douglas A. Melton,[2,7]
Marek Mlodzik,[8] Richard W. Padgett,[9]

Anita B. Roberts,[10] Jim Smith,[11] Gerald H. Thomsen,[14]
Bert Vogelstein,[7,12] and Xiao-Fan Wang,[13]

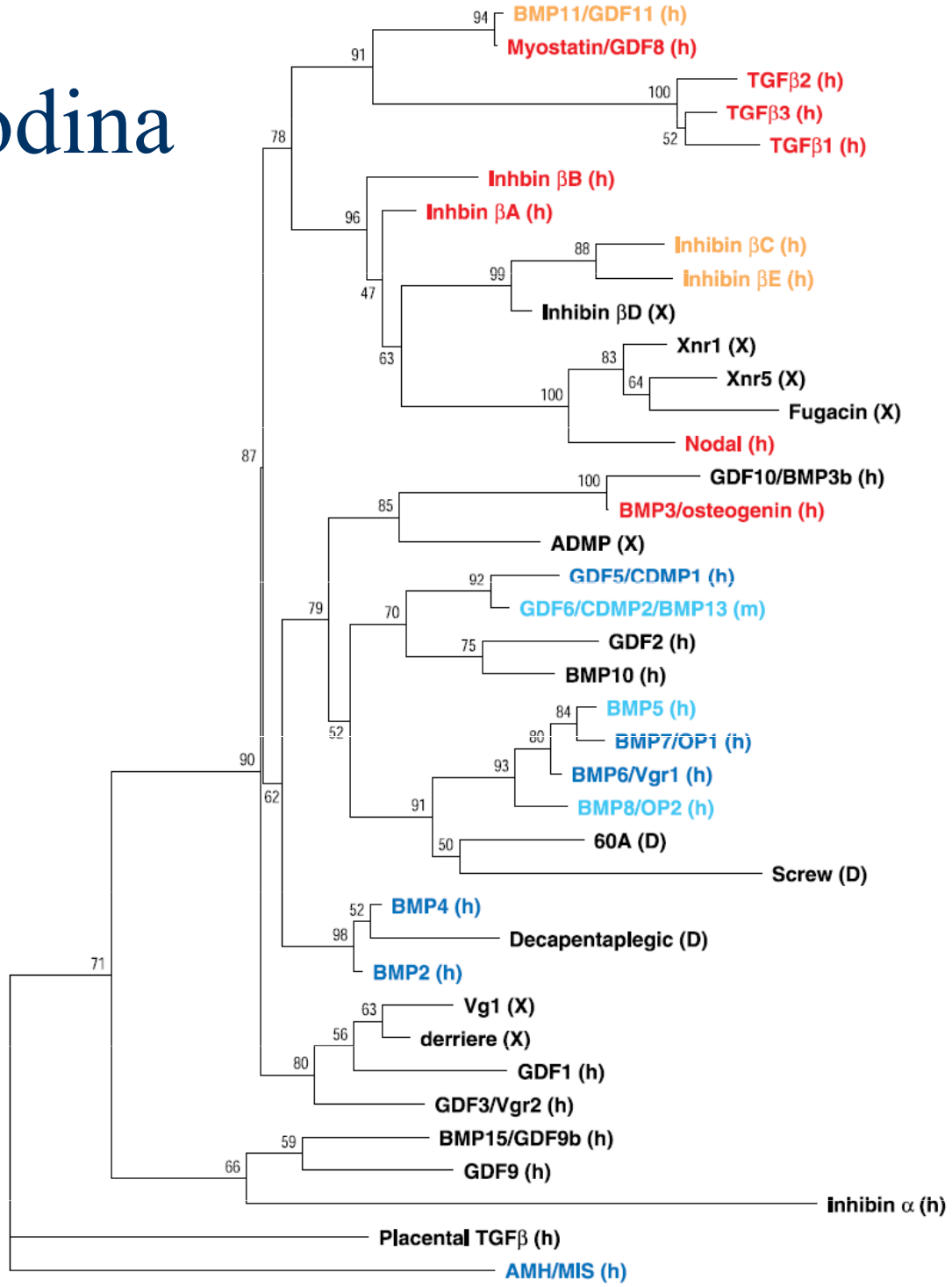
Transforming growth factor-β

- Zástupci rodiny a jejich nejvýznamnější funkce

TGF-β rodina

- více než 60 proteinů
  - Transformující růstové faktory – β (TGF-β)
  - Activin(y)
  - Bone Morphogenetic Proteins (BMP); Growth/Differentiation Factors (GDF)

TGF-β rodina



Genes to Cells (2002) 7, 1191-12

TGF-β rodina

- Bone Morphogenetic Proteins (BMP)
  - klíčové faktory pro vývoj kostí a chrupavek, ale i další funkce.

BMP	Funkce	Genový lokus
BMP1	Nenáleží do TGF-β rodiny. Metaloproteinása.	8p21
BMP2	Indukuje vývoj kostí a chrupavek; klíčový regulátor diferenciace osteoblastů.	20p12
BMP3	Indukuje tvorbu kostí.	14p22
BMP4	Reguluje tvorbu zubů, končetin a kostí z mesodermu; ovlivňuje hojení zlomenin.	14q22-q23
BMP5	Úloha při tvorbě chrupavek.	6p12.1
BMP6	Důležitý pro funkci kloubů.	6p12.1
BMP7	Klíčový faktor diferenciace osteoblastů a vývoje ledvin.	20q13
BMP8a	Reguluje vývoj kostí a chrupavek.	1p35-p32
BMP8b	Exprimován v hipokampu.	1p35-p32
BMP10	? Vývoj srdce.	2p14
BMP15	?Vývoj oocytů a folykulů.	Xp11.2

Chen, Di, Zhao, Ming, and Mundy, Gregory R. (2004). "Bone Morphogenetic Proteins". *Growth Factors* **22** (4): 233–241

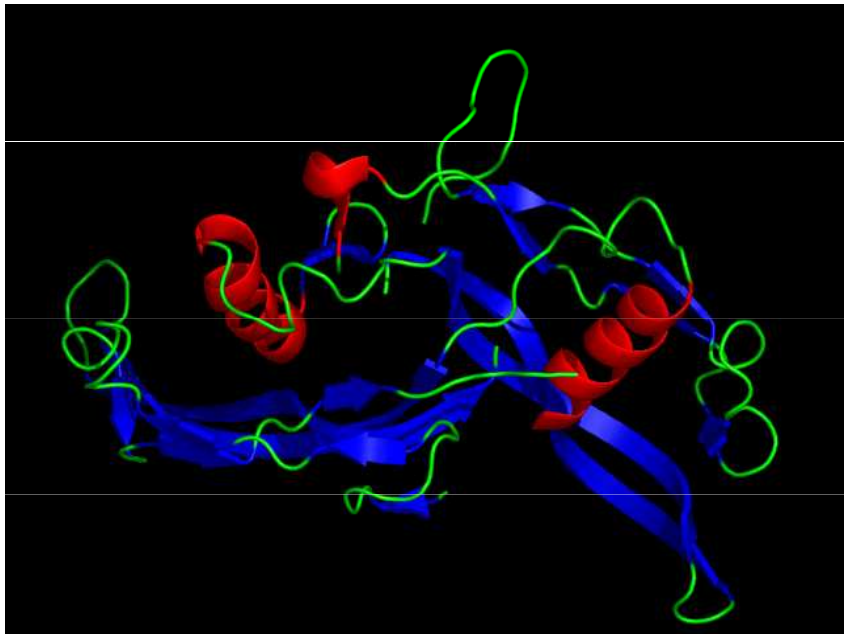
TGF-β rodina

- Growth/Differentiation Factors (GDF)
  – faktory podobné BMP

GDF	Funkce	Genový lokus
GDF1	Regulátor vývoje levo-pravé asymetrie během embryogeneze.	19p12
GDF2	Indukuje cholinergní fenotyp.	Chr.10
GDF3	?	12p13.1
GDF5	Důležitý pro vývoj kostí a kloubů.	20q11.2
GDF6	Důležitý pro vývoj kostí a kloubů.	Chr. 8
GDF7	Důležitý pro vývoj kostí a kloubů.	Chr. 2
GDF8	Myostatin; regulátor funkce kosterního svalstva. Negativní regulátor svalového růstu.	2q32.2
GDF9	Exprese v oocytech během folikulogeneze.	Chr. 5
GDF10	BMP3b; kontroluje endochondrální osifikaci	Chr. 28
GDF11	Důležitý při vývoji pátěře.	12q13.13
GDF15	Vysoká exprese v placentě; indukovaný NSAIDs; inhibitor karcinogeneze; induktor apoptózy ?	19p13.2-p13.1

TGF-β rodina

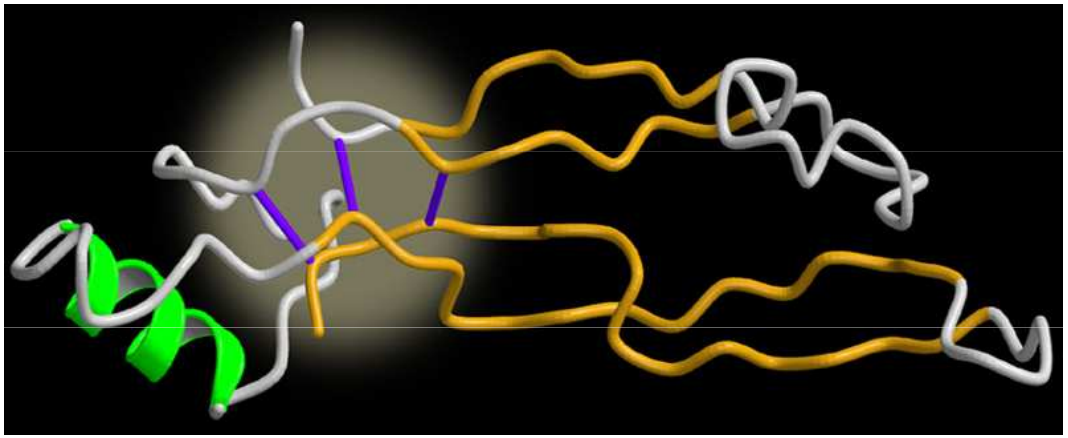
- Activin(y)
  - dimerické proteiny regulující syntézu a sekreci FSH a regulující menstruační cyklus, ale také imunitní a nervový systém; důležité faktory při tvorbě kůže a hojení ran;
  - dimer obsahuje dvě identické β podjednotky a dvě β podjednotky inhibin(u) (A nebo B);
  - Activin A (βAβA);
  - Activin B (βBβB);
  - Activin AB (βAβB).
- Inhibin(y)
  - Inhibuje produkci FSH;
  - dimer α a β podjednotky (A nebo B)



Sulyok, S., Wankell, M., Alzheimer, C., and Werner, S. Activin: an important regulator of wound repair, fibrosis, and neuroprotection. Mol. Cell. Endocrinol., *225:* 127-132, 2004.

TGF-β rodina

- Transformující růstové faktory – β
  - důležité faktory řídící embryogenezi, diferenciaci, tkáňovou regeneraci, ale i rozvoj řady onemocnění
  - TGF-β1 (Chr. 19)
  - TGF-β2 (Chr. 1)
  - TGF-β3 (Chr. 14)
  - 76-80% homologie



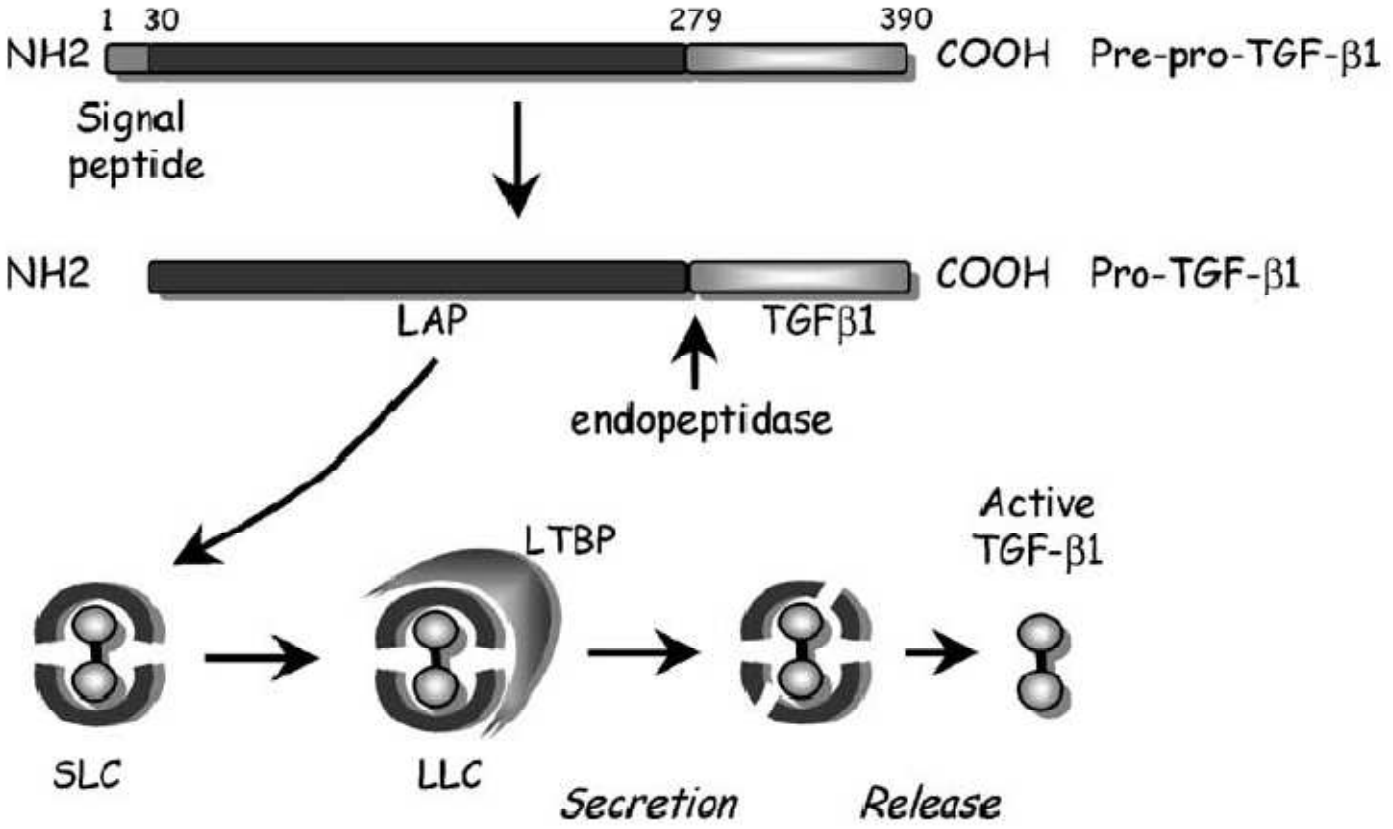
Transforming growth factor-β

- Syntéza, produkce a aktivace

Syntéza a sekrece TGF-β

- Syntetizován a sekretován v podobě latentního komplexu
- asociovaný s Latency Associated Peptide (LAP) = small latent complex;
- LAP dimer spolu s TGF-β dimerem je kovalentně vázán na Latent TGF-β Binding Protein (LTBP) = large latent complex

Syntéza a sekrece TGF-β



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The International Journal of Biochemistry & Cell Biology 36 (2004) 1161–1165
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Molecules in focus

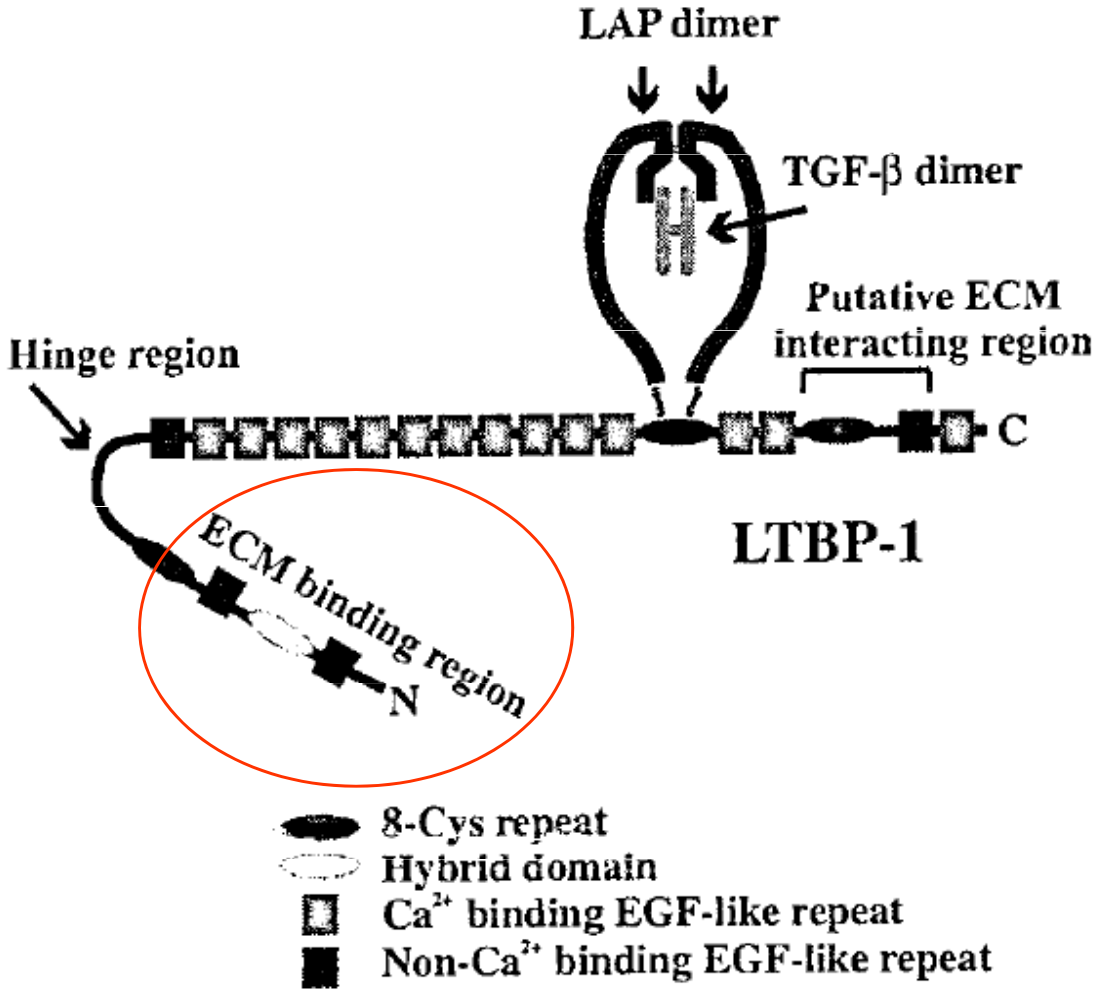
Mammalian transforming growth factor-βs: Smad signaling and physio-pathological roles

Delphine Javelaud, Alain Mauviel*

INSERM U532, Institut de Recherche sur la Peau, Université Paris VII, Hôpital Saint-Louis, Pavillon Bazin, 1, Avenue Claude Vellefaux, 75010 Paris, France

Received 15 May 2003; received in revised form 13 June 2003; accepted 13 June 2003

Syntéza a sekrece TGF-β

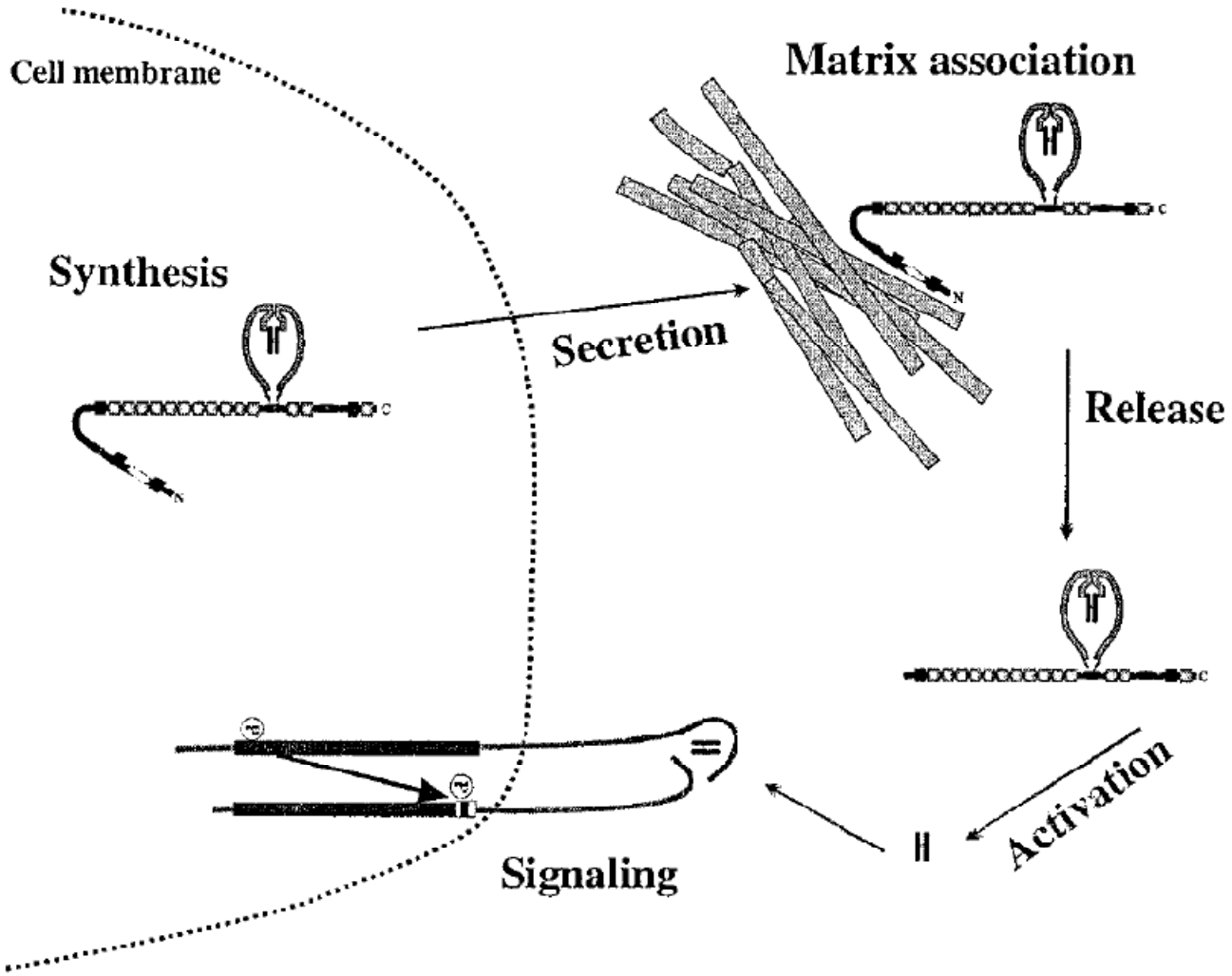


MICROSCOPY RESEARCH AND TECHNIQUE 52:354–362 (2001)

Latency, Activation, and Binding Proteins of TGF-β

KATRI KOLI,* JUHA SAHARINEN, MARKO HYYTIÄINEN, CARITA PENTTINEN, AND JORMA KESKI-OJA
Departments of Virology and Pathology, Haartman Institute, University of Helsinki, FIN-00014 Helsinki, Finland

Syntéza a sekrece a aktivace TGF-β



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KATRI KOLI,* JUHA SAHARINEN, MARKO HYYTIÄINEN, CARITA PENTTINEN, AND JORMA KESKI-OJA
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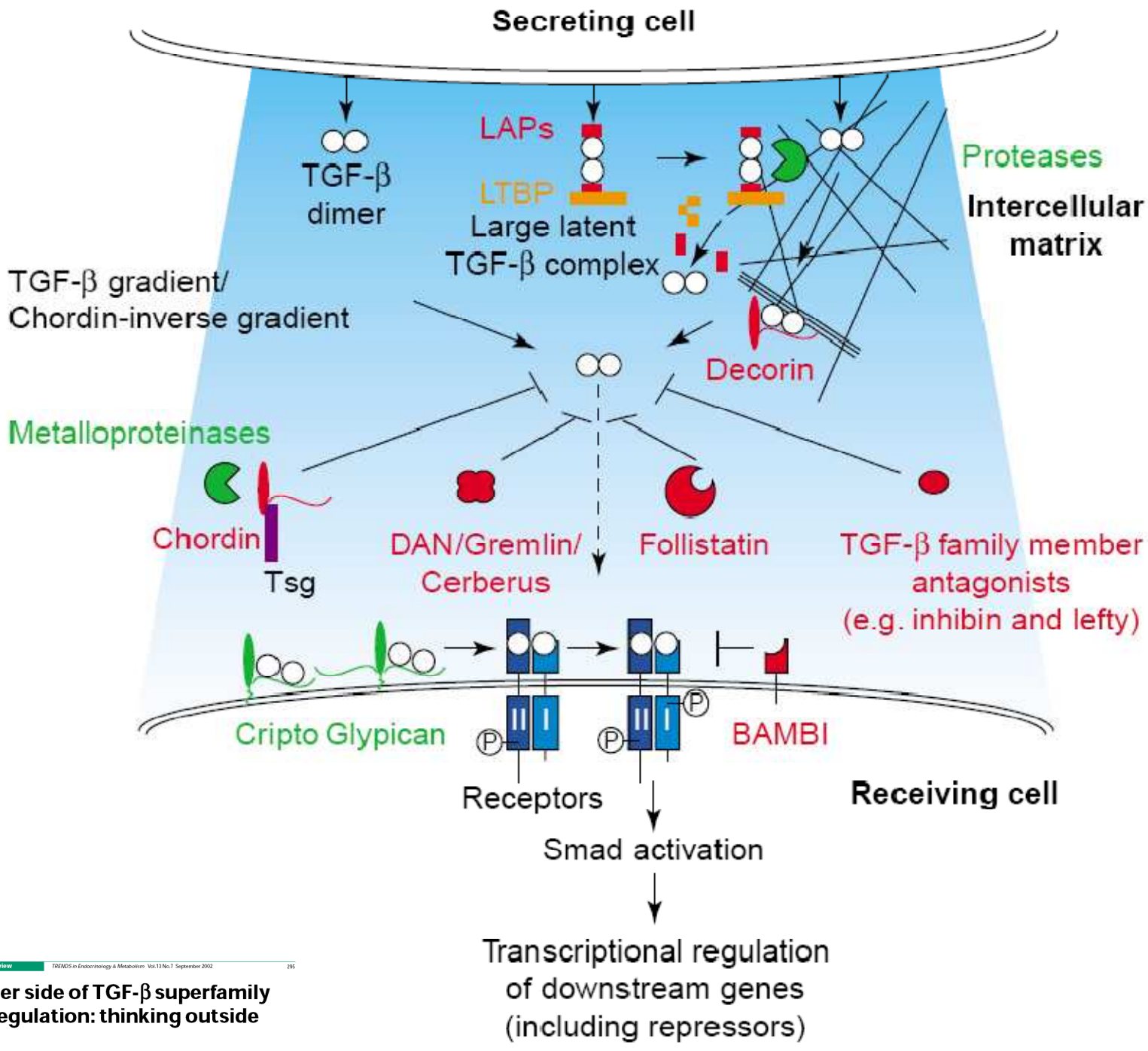


Review TRENDS in Endocrinology & Metabolism Vol.13 No.7 September 2002 295

The other side of TGF-β superfamily signal regulation: thinking outside the cell

Tina L. Gumienny and Richard W. Padgett

TRENDS in Endocrinology & Metabolism

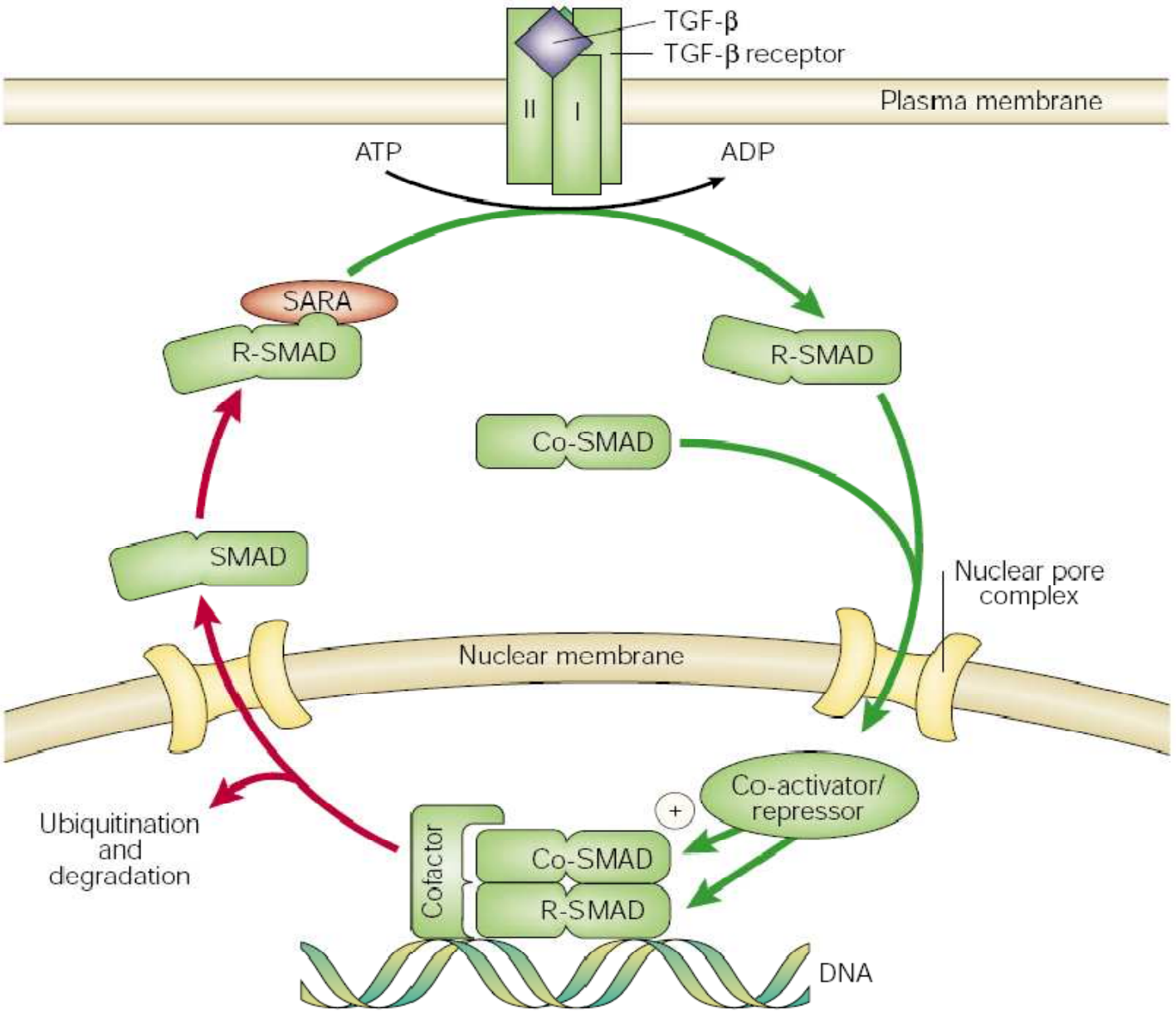
Aktivace TGF-β

- Fyzikálně-chemicky
  - v kyselém mikroprostředí buněk
  - extrémními změnami pH
  - γ zářením
  - reaktivními skupinami kyslíku
  - zvýšenou teplotou
- Enzymaticky a prostřednictvím nespecifických proteinových interakcí
  - Proteázy
    - Plasmin, Catepsin G
    - Calpain
  - MMP-9 a MMP-2
  - Glykosidázy
  - Interakce s trombospondinem
  - Interakce s integrinem $\alpha_v\beta_6$

Transforming growth factor-β

- Přenos signálu a jeho regulace
  - receptory
  - sekundární přenašeči
  - „alternativní“ dráhy
  - regulace genové exprese

Přenos signálu TGF-β



Massague J. Nat. Rev. Mol. Biol. 200

Transforming growth factor-β

- Přenos signálu a jeho regulace
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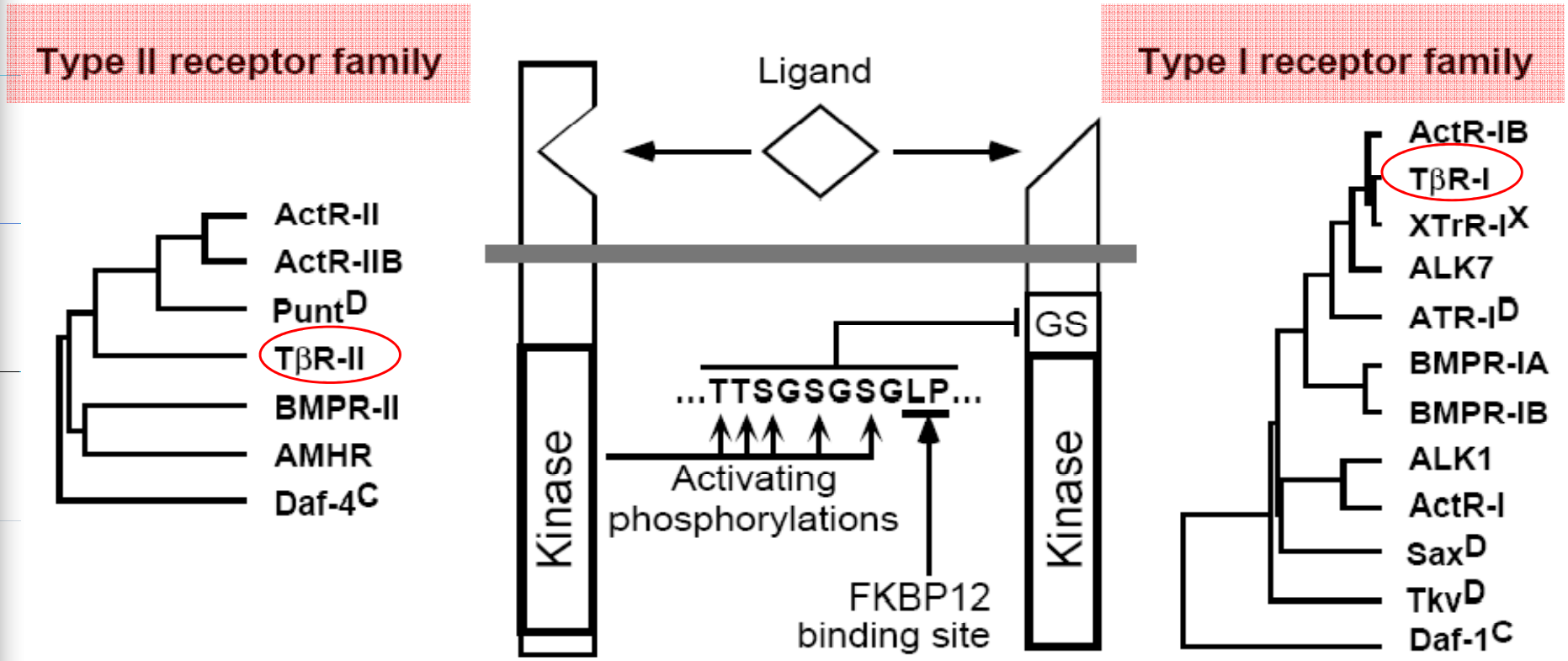
  - „alternativní“ dráhy
  - regulace genové exprese

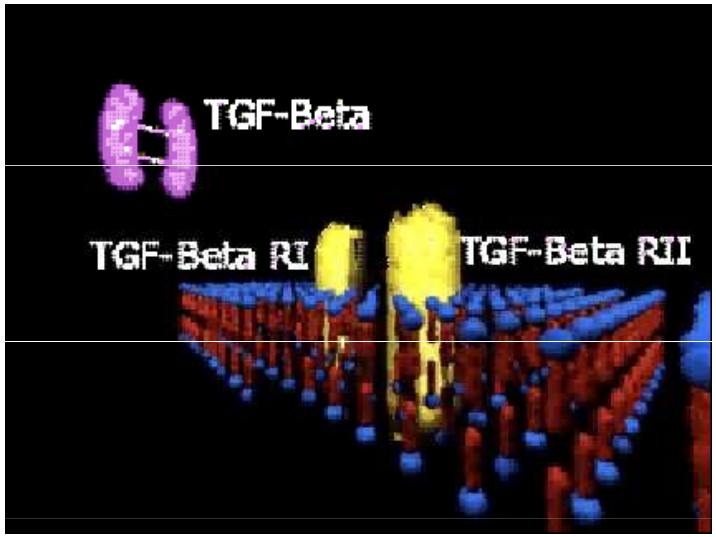
Receptory TGF-β rodiny



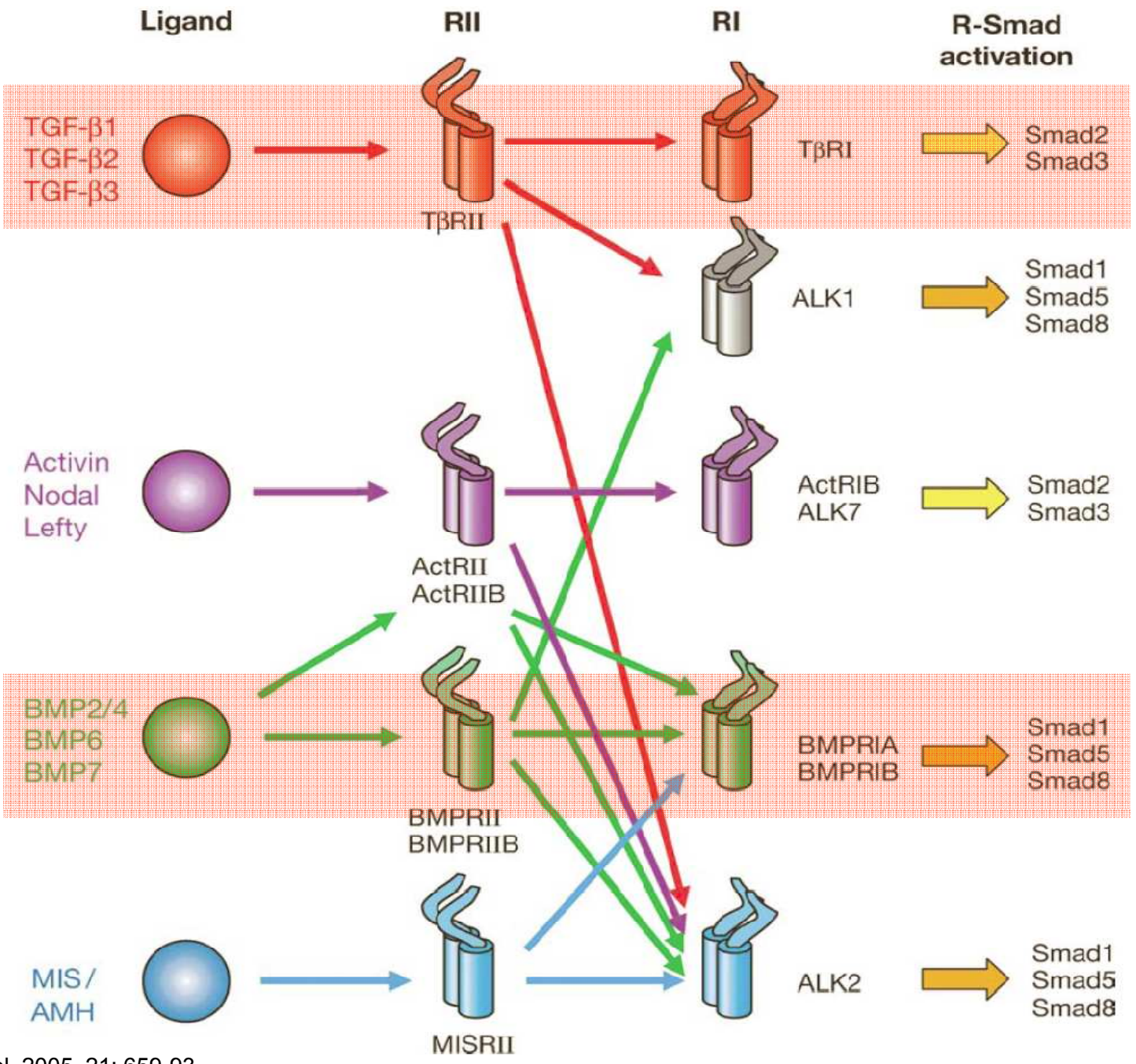
Accesory Receptors – Type III: betaglycan, endoglin

Massague J. Annu. Rev. Biochem. 1998. 67: 753

Receptory TGF-β rodiny

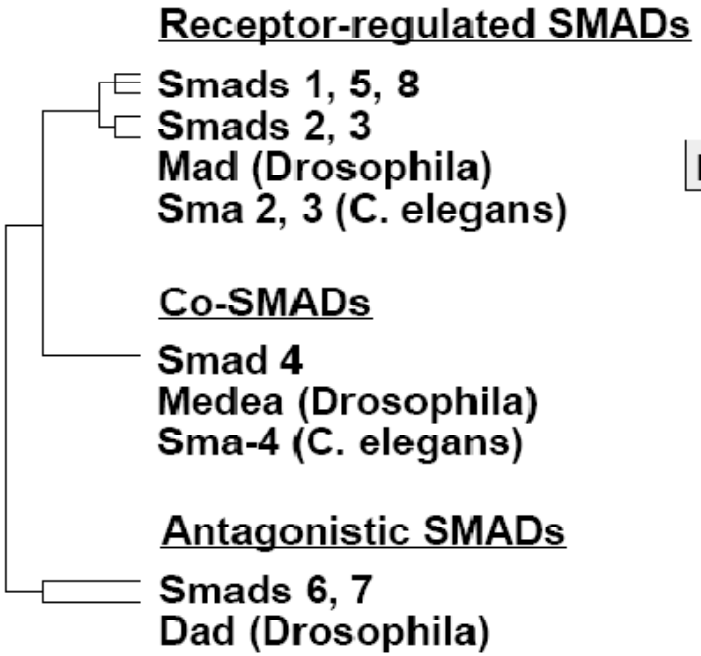


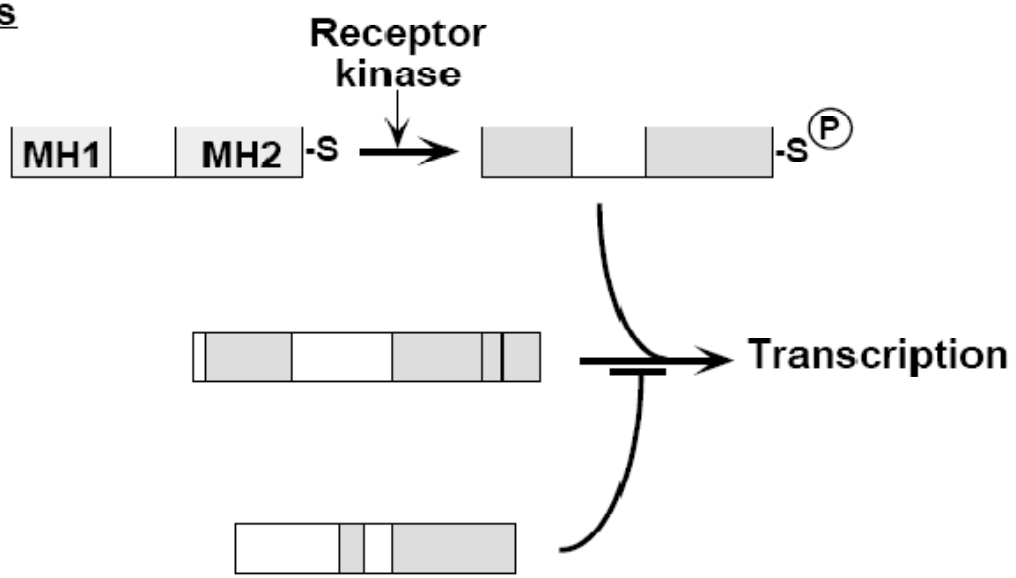
R-SMAD



Annu. Rev. Cell. Dev. Biol. 2005. 21: 659-93

SMAD



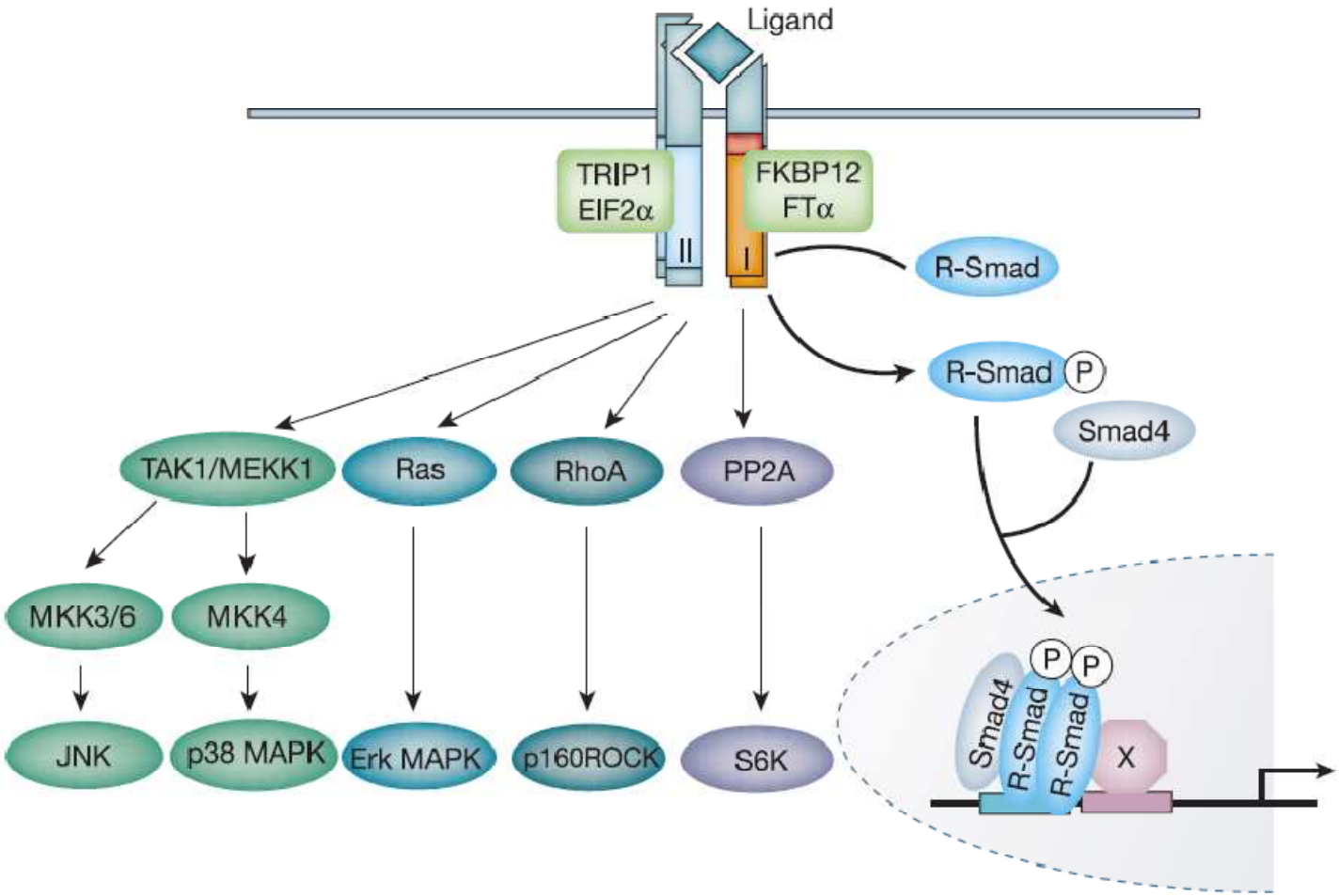


Massague J. Annu. Rev. Biochem. 1998. 67: 753

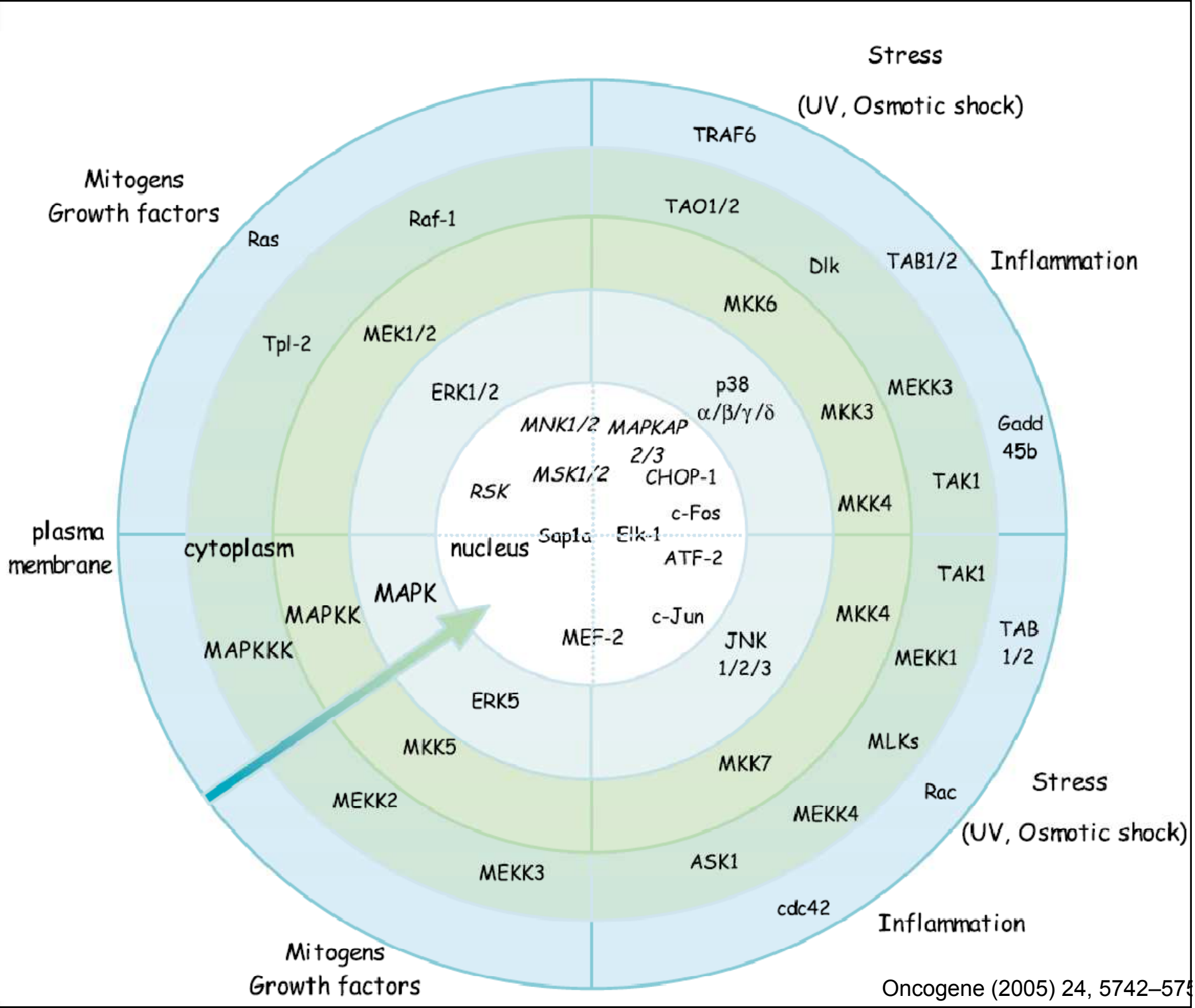
Transforming growth factor-β

- Přenos signálu a jeho regulace
  - receptory
  - sekundární přenašeči
  - „alternativní“ dráhy
  - regulace genové exprese

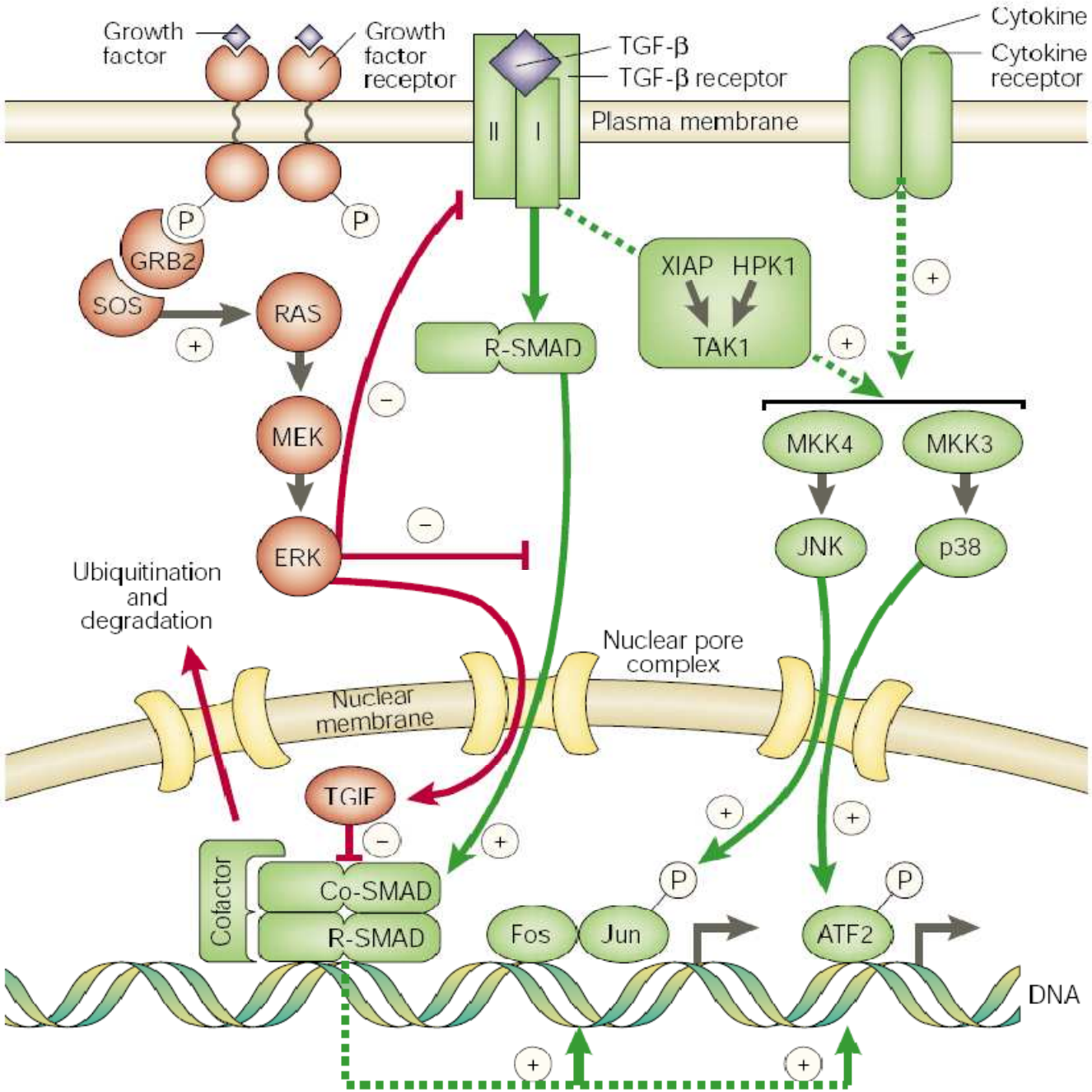
Přenos signálu nezávislý na SMAD



Nature 425 (2003) 577-584

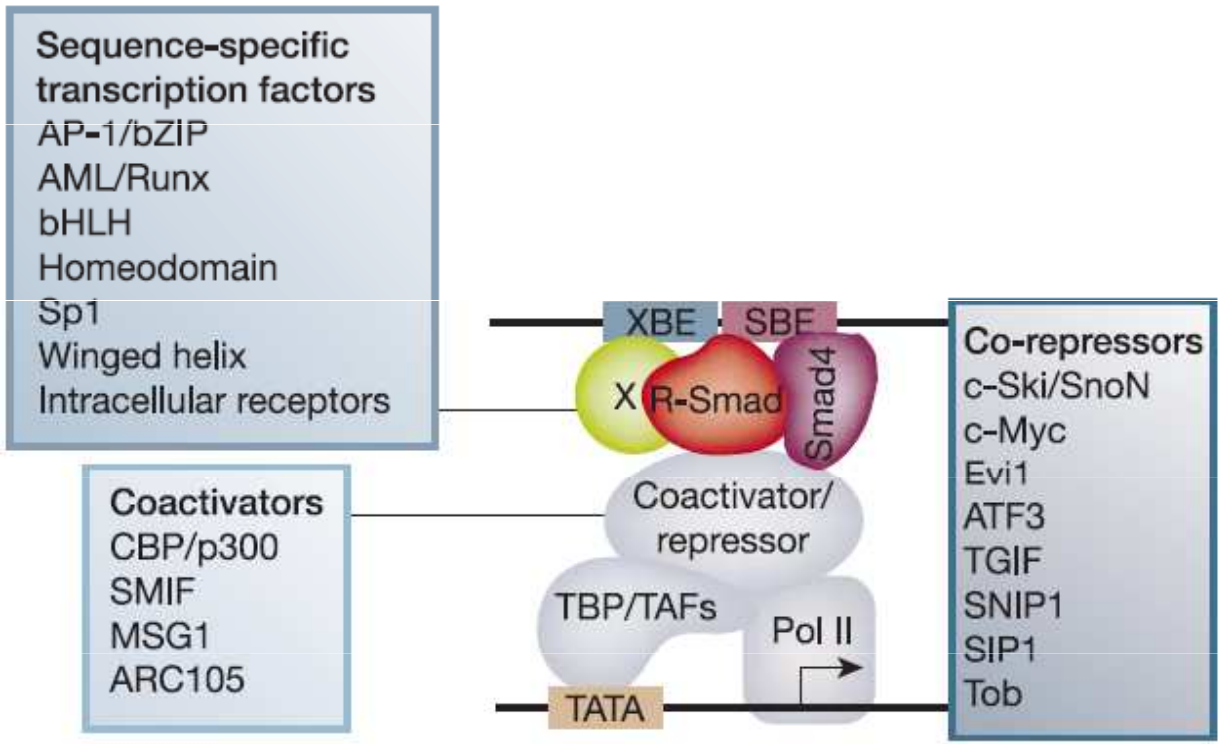


Oncogene (2005) 24, 5742–575



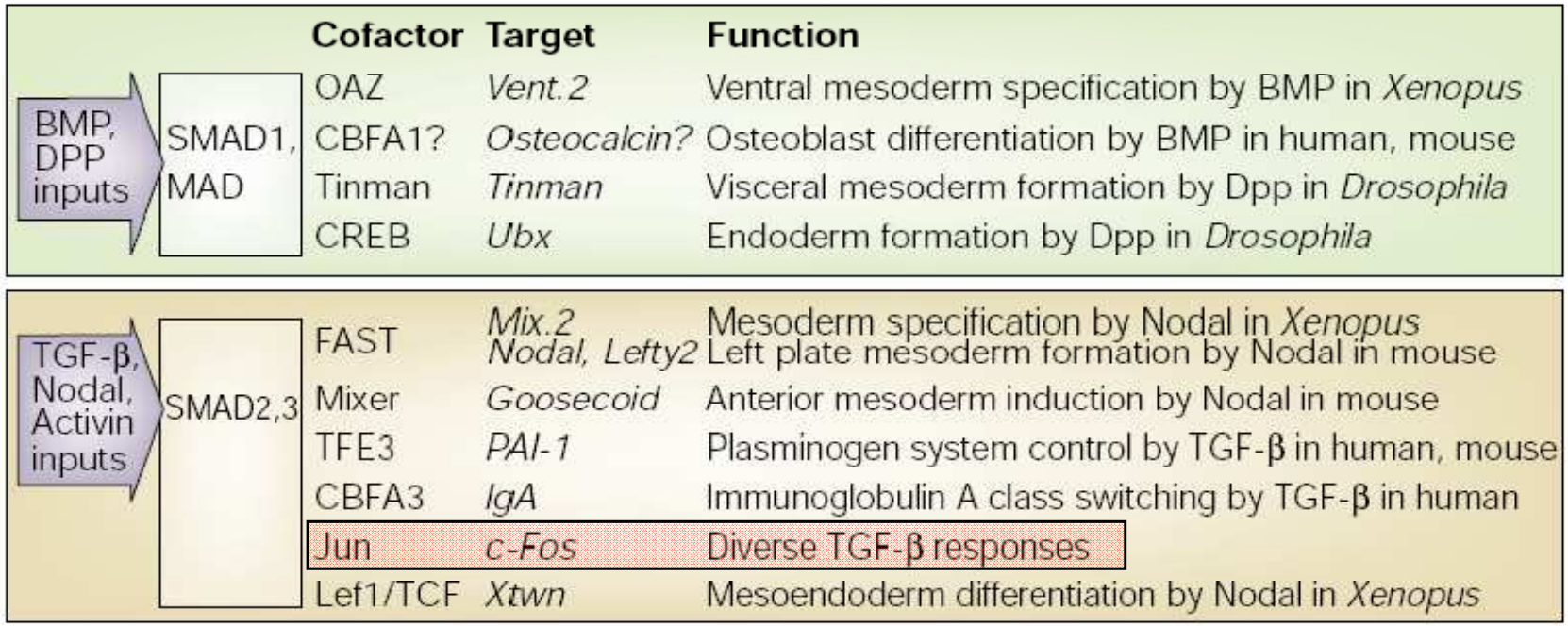
Massague J. Nat. Rev. Mol. Biol. 200

Regulace transkripce



Nature 425 (2003) 577-584

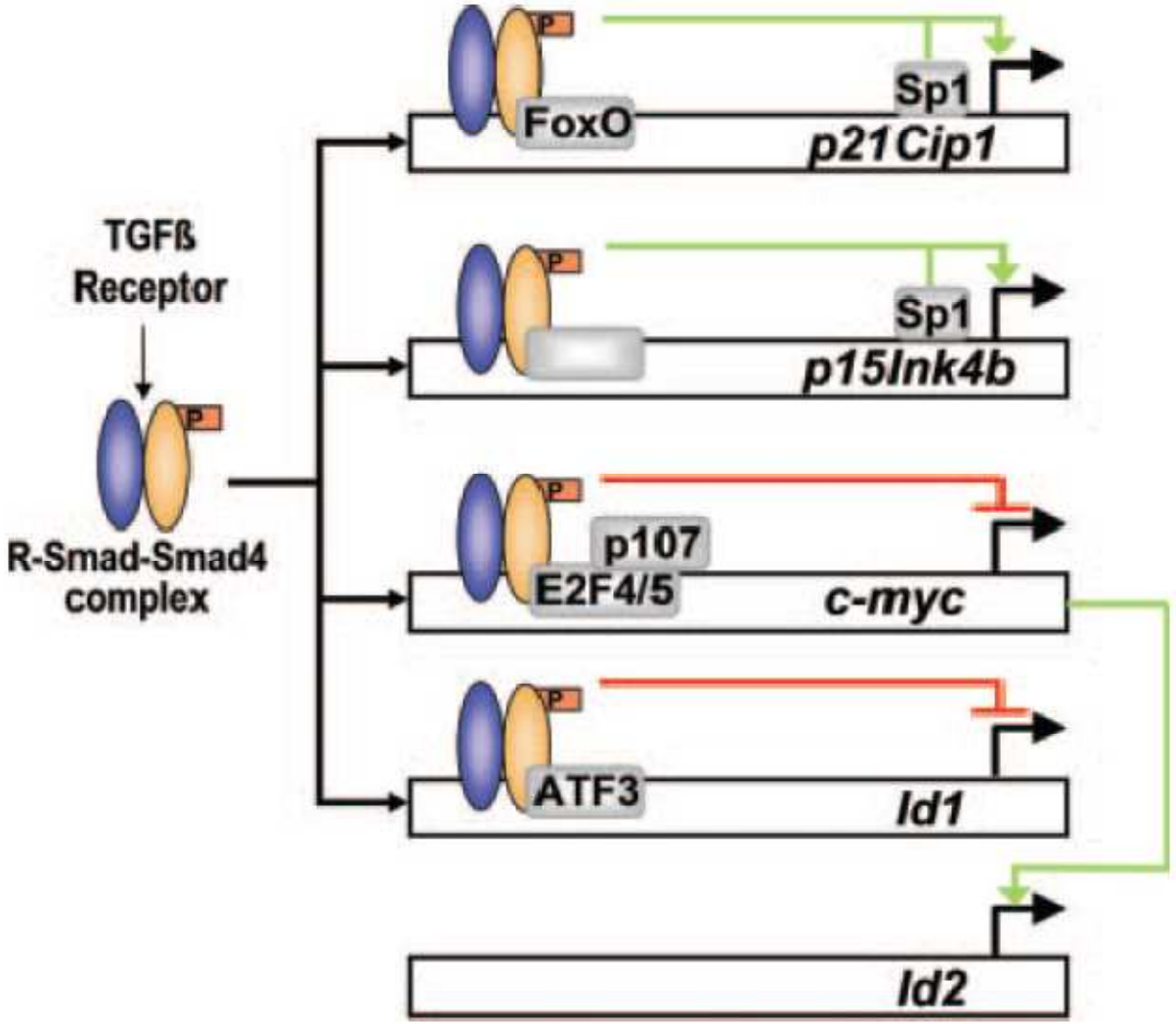
Kofaktory



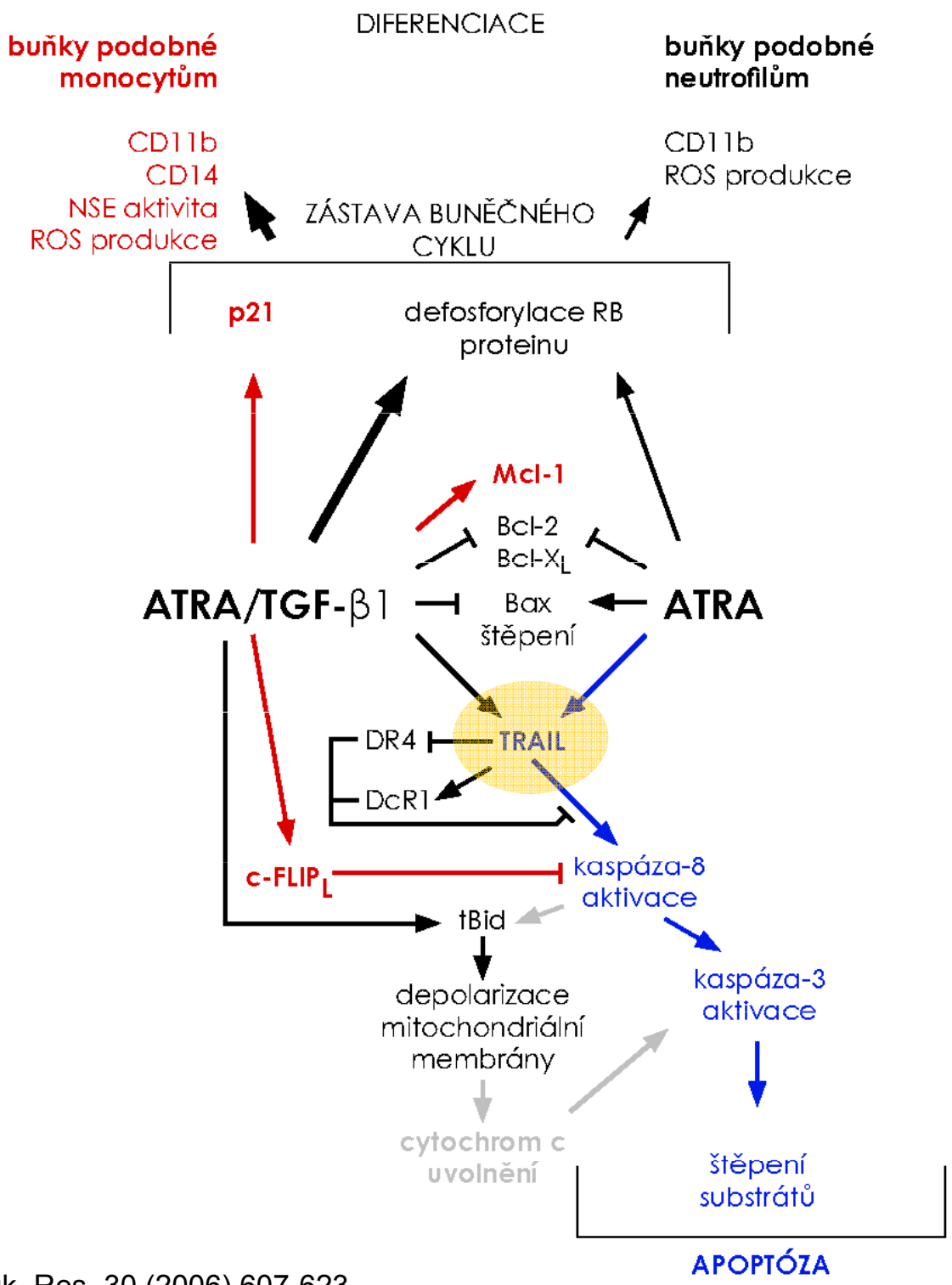
Cofactor	Target	Function
OAZ	*Vent.2*	Ventral mesoderm specification by BMP in *Xenopus*
CBFA1?	*Osteocalcin?*	Osteoblast differentiation by BMP in human, mouse
Tinman	*Tinman*	Visceral mesoderm formation by Dpp in *Drosophila*
CREB	*Ubx*	Endoderm formation by Dpp in *Drosophila*
FAST	*Mix.2*	Mesoderm specification by Nodal in *Xenopus*
	Nodal, Lefty2	Left plate mesoderm formation by Nodal in mouse
Mixer	*Goosecoid*	Anterior mesoderm induction by Nodal in mouse
TFE3	*PAI-1*	Plasminogen system control by TGF-β in human, mouse
CBFA3	*IgA*	Immunoglobulin A class switching by TGF-β in human
Jun	*c-Fos*	Diverse TGF-β responses
Lef1/TCF	*Xtwn*	Mesoendoderm differentiation by Nodal in *Xenopus*

Massague J. Nat. Rev. Mol. Biol. 200

Inhibice proliferace u epiteliálních buněk



Carcinogenesis vol.27 no.11 pp.2148–2156, 2006



Souček, et al. Leuk. Res. 30 (2006) 607-623

Growth factors in cancer cell signaling

Karel Souček
ksoucek@ibp.cz
Eva Lincová
Andrea Staršíchová
Zuzana Pernicová

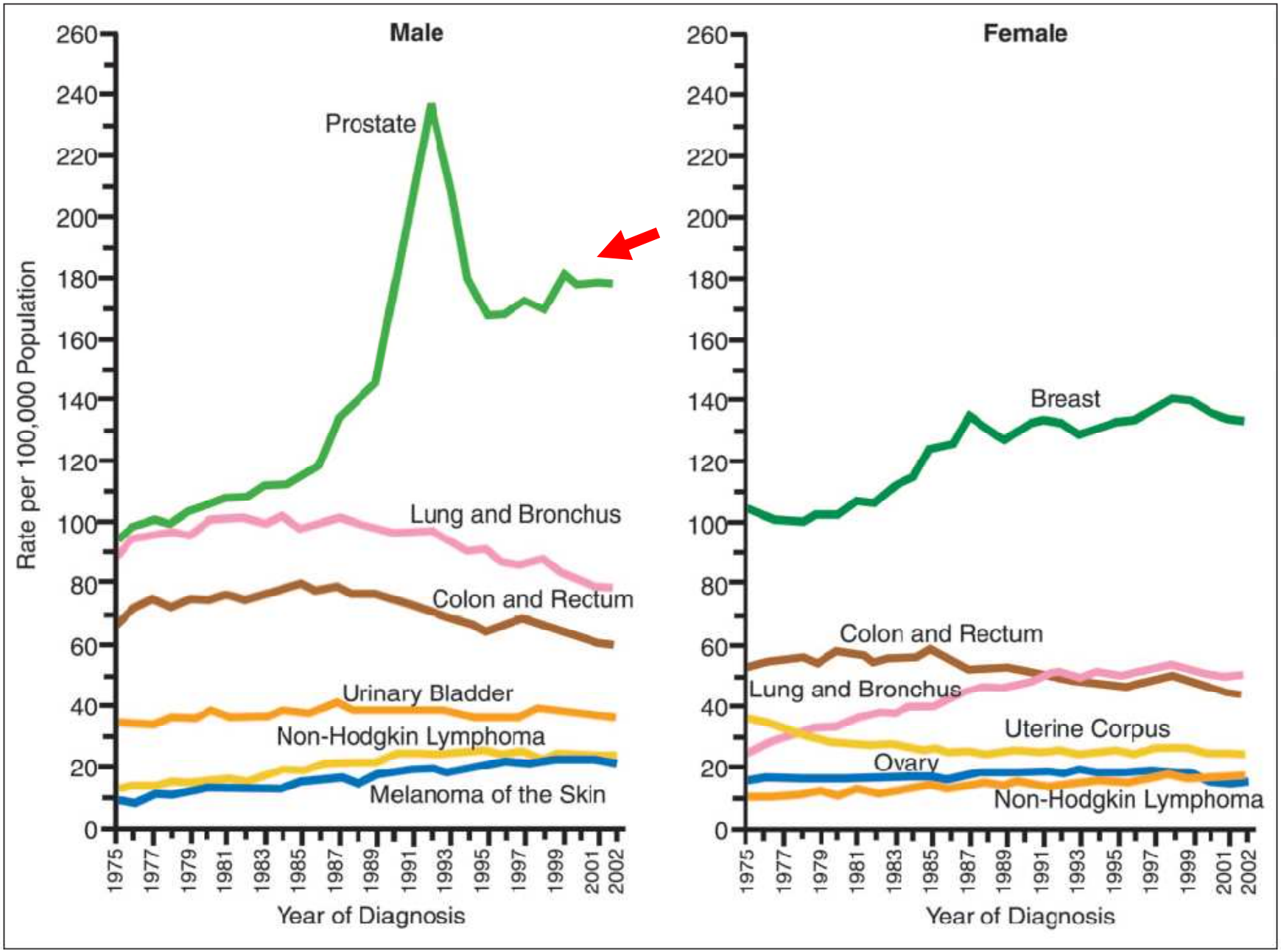
Department of Cytokinetics
Institute of Biophysics AS CR, v.v.i., Brno, Czech Republic

Growth factors in cancer cell signaling

- cancer **is not** single cell disease;
- **tissue microenvironment** plays an important role in tumor initiation and progression;
- **growth factors - cytokines** - play crucial role in cancer development and some of them belong to the **significant autocrine/paracrine factors** produced by various cell types in tumor microenvironment;
- modulation of their signal transduction represent potential target for therapy.

Growth factors in cancer cell signaling

- What is a role of TGF-β family cytokines in chemopreventive action of inhibitors of arachidonic acid metabolim?
- How we can effectively modify neuroendocrine differentiation of the cancer cells?



Cancer Statistics, 2006

CA
A Cancer Journal for Clinicians

What is a role of TGF-β family cytokines in chemopreventive action of inhibitors of arachidonic acid metabolim?

Eva Lincová

Growth Differentiation factor – 15 (GDF-15)

NAG-1 (Non Steroidal Anti-Inflammatory Drugs (NSAIDs)-Activated Gene)
placental transforming growth factor beta (PTGF-β)
macrophage inhibitory cytokine-1 (MIC-1)
placental bone morphogenetic protein
Prostate-derived factor (PDF)

- TGF-β family member
- Cancer progression inhibitor
  - Inductor of apoptosis
  - Inhibitor of proliferation?

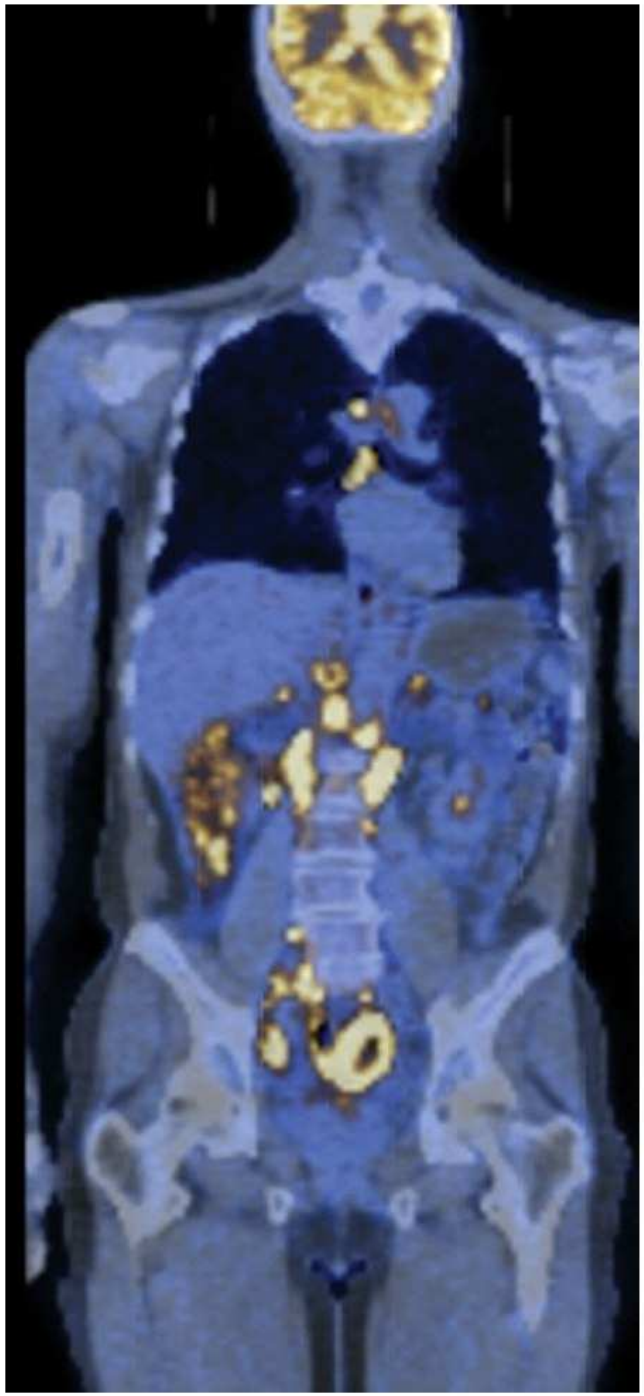


Figure 14.1 *The Biology of Cancer* (© Garland Science 2007)

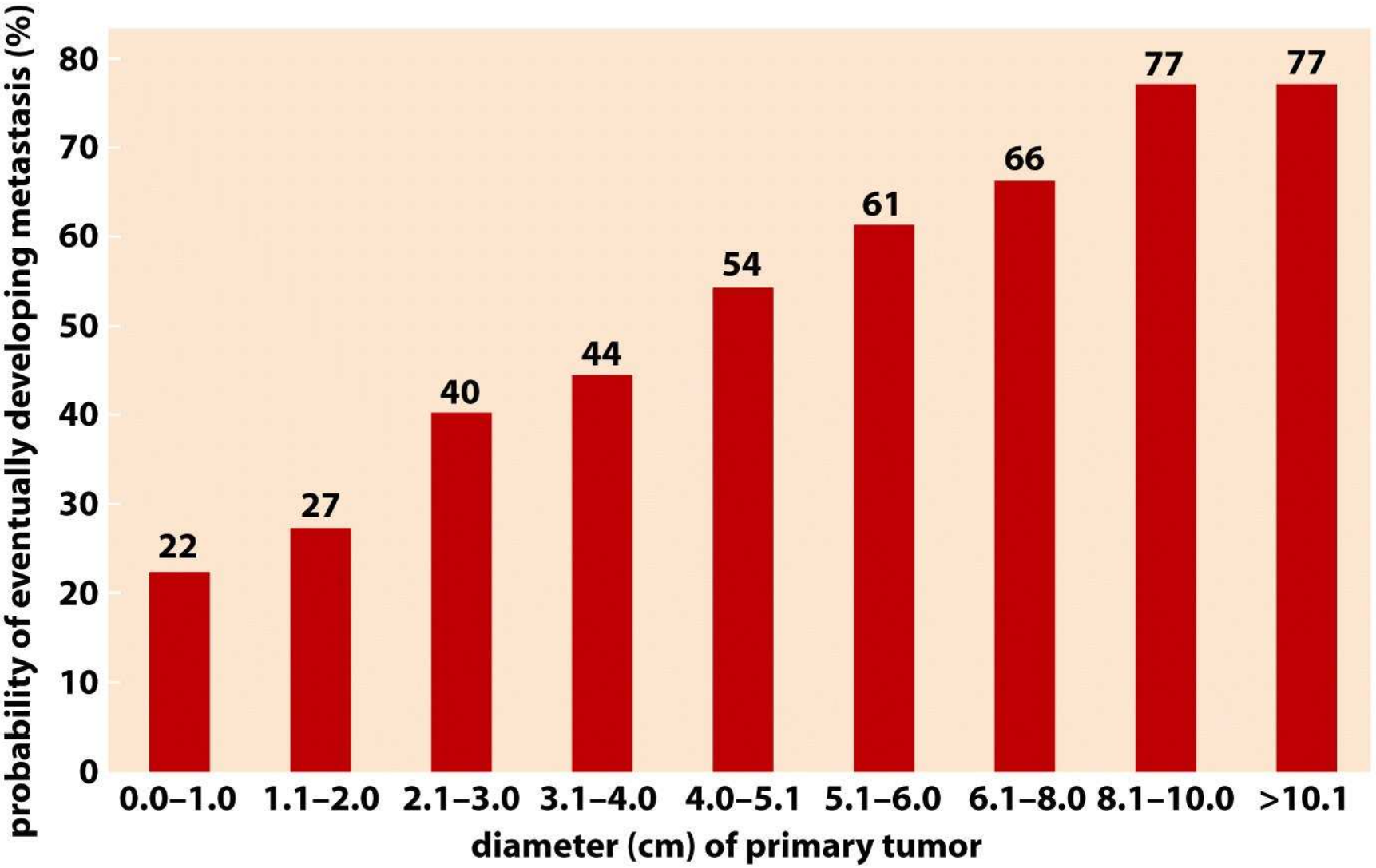


Figure 14.3 *The Biology of Cancer* (© Garland Science 2007)

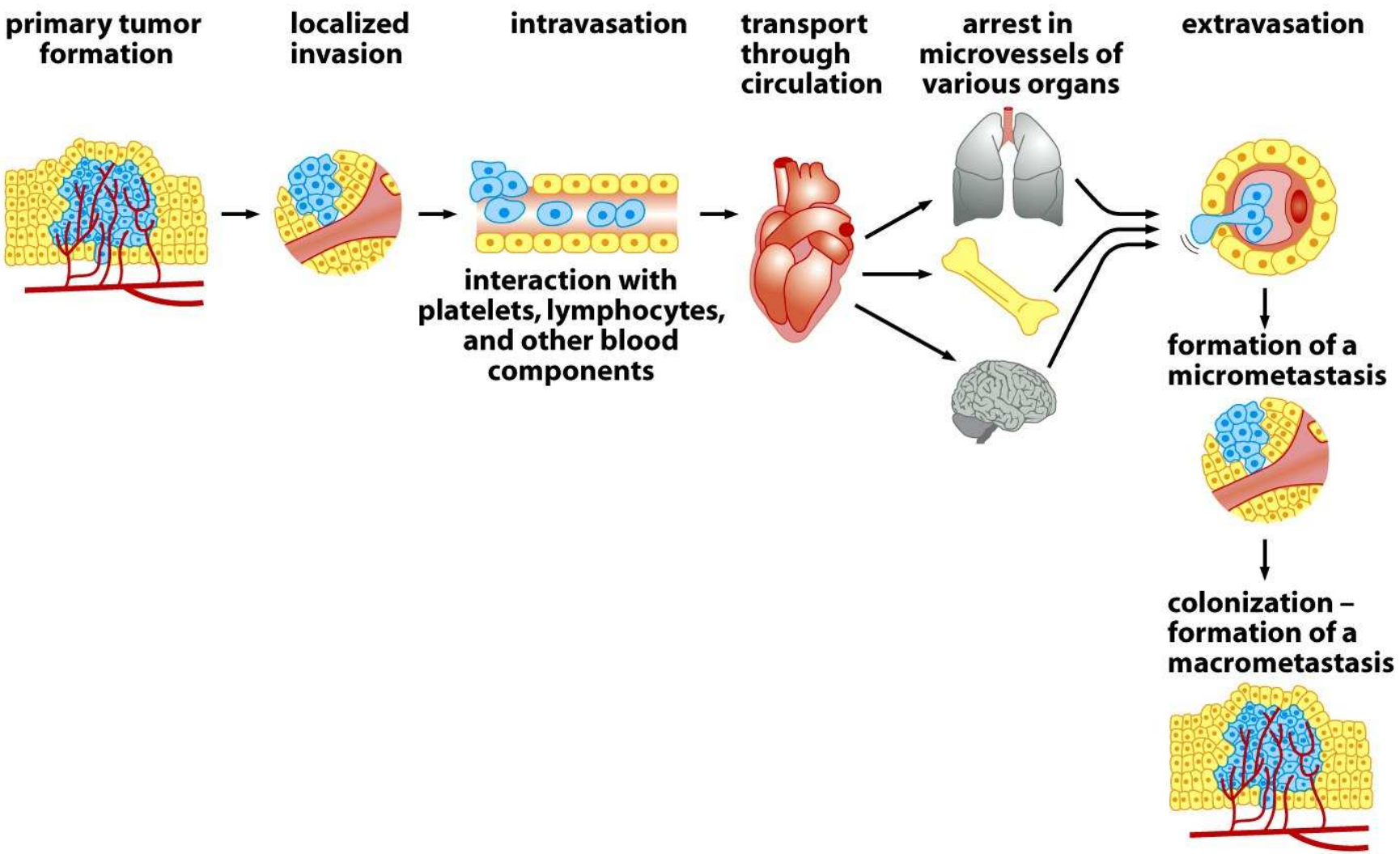
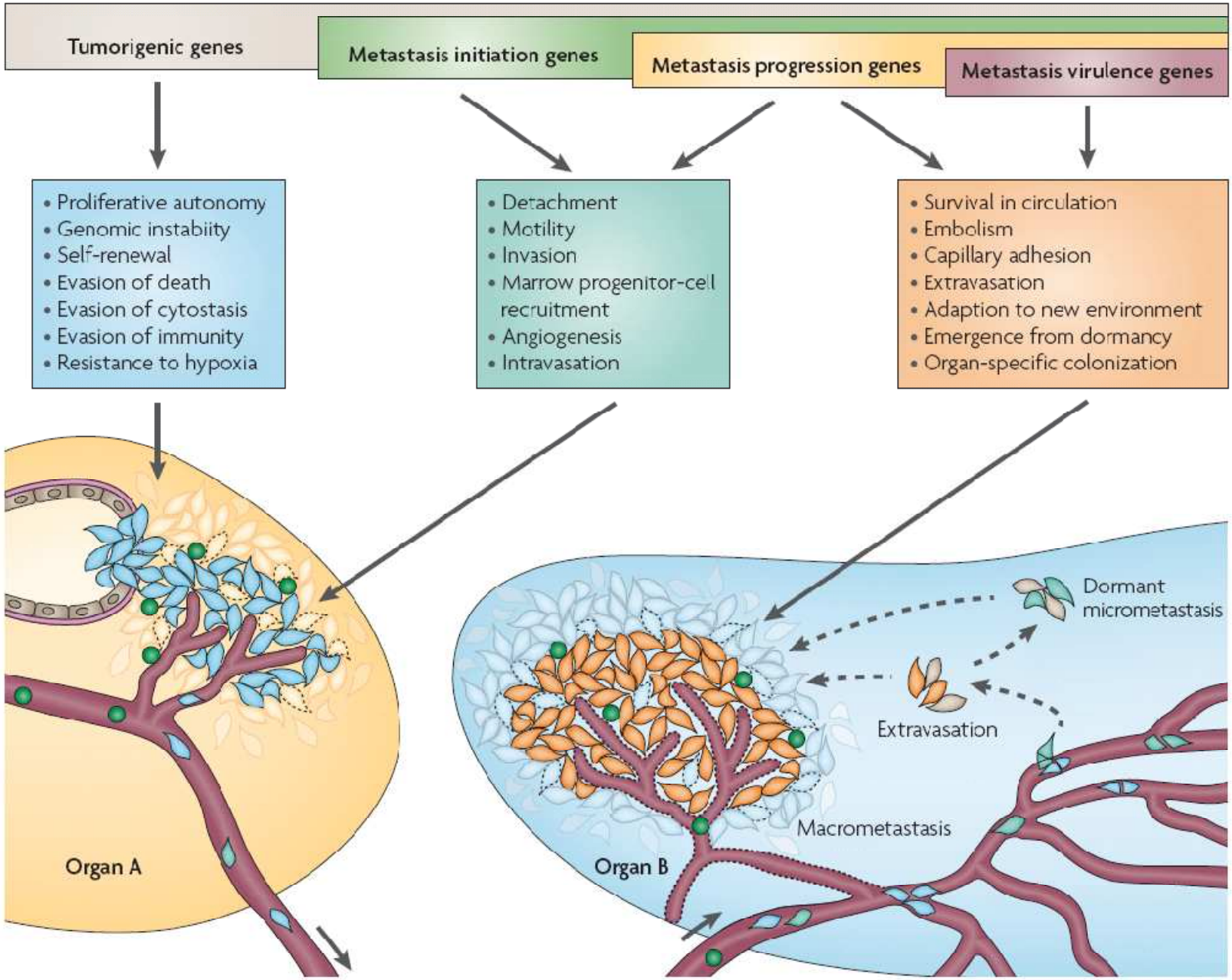


Figure 14.4 *The Biology of Cancer* (© Garland Science 2007)

Genetic determinants of cancer metastasis

Don X. Nguyen and Joan Massagué



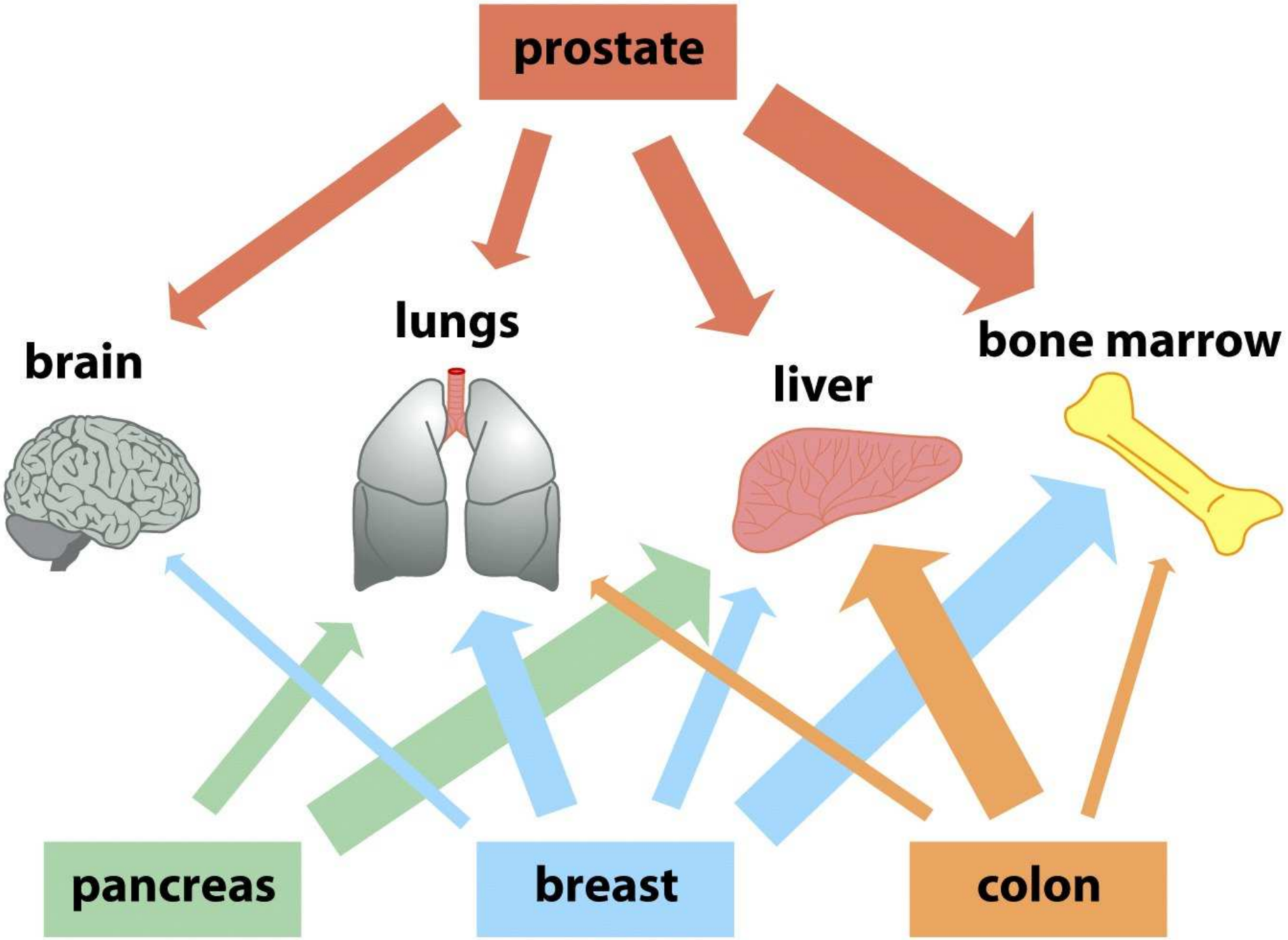
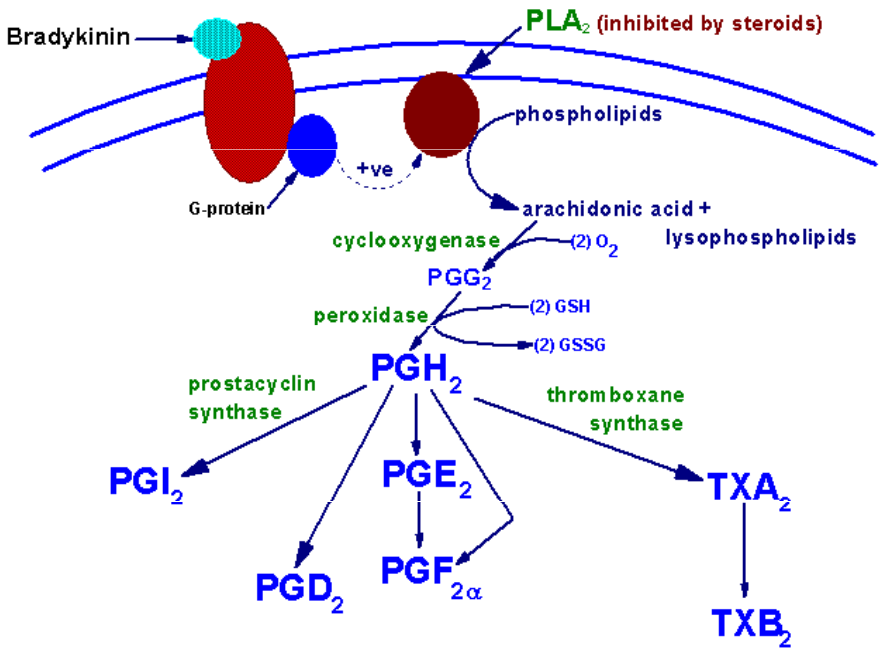
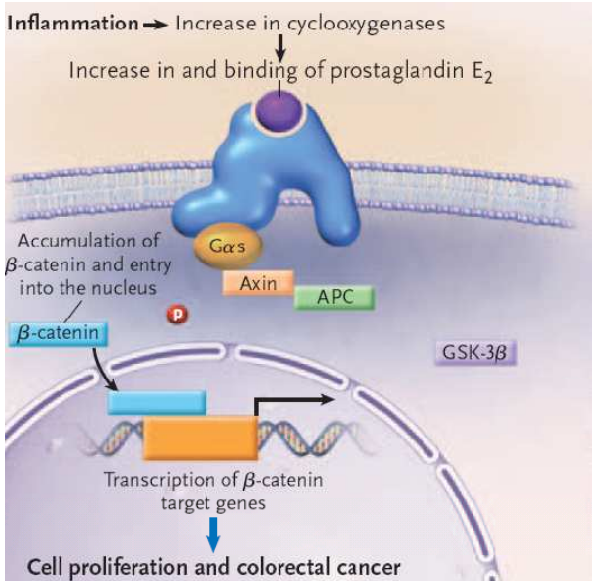


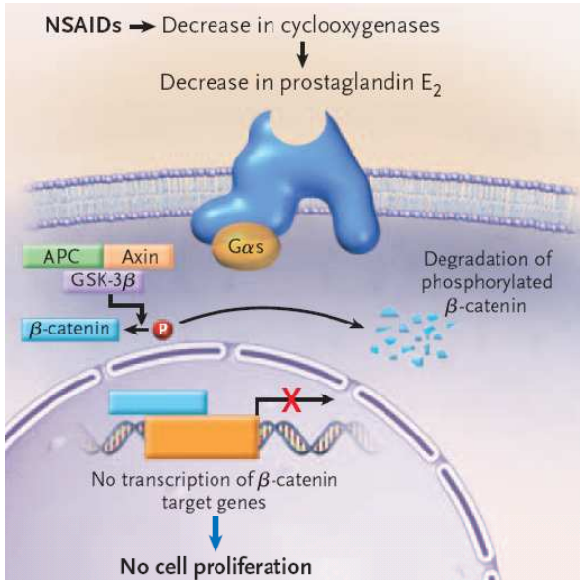
Figure 14.42 *The Biology of Cancer* (© Garland Science 2007)

Cyclooxygenases (COX-1, -1b, -2)

- key enzymes of arachidonic acid metabolism







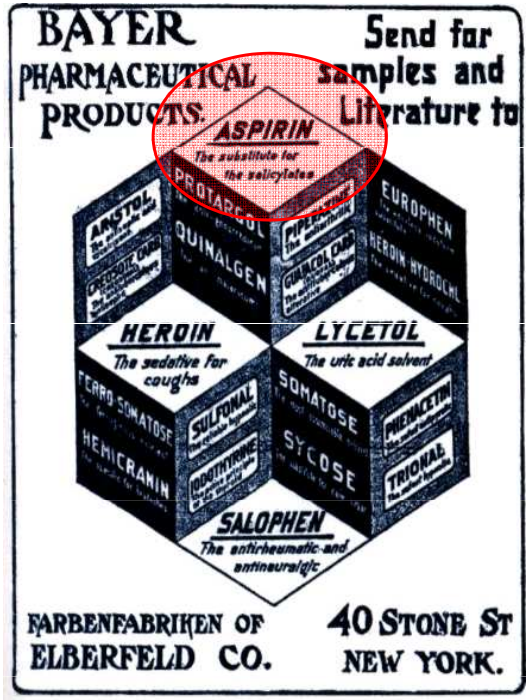
... and its inhibitors

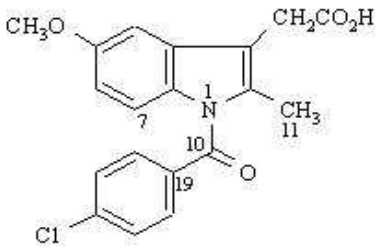
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- COX-2 specific inhibitors

H. Clevers, "Colon cancer--understanding how NSAIDs work," *N Engl J Med*, vol. 354, no. 7, pp. 761-763

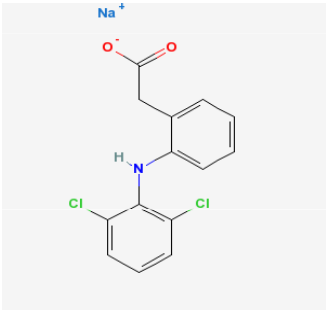
Nonsteroidal anti-inflammatory drugs (NSAIDs)

- variety of mechanisms
- cancer chemoprevention

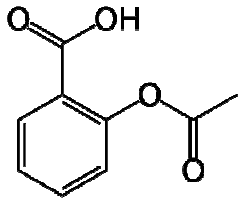




http://www.home.duq.edu/~harrold/Chem3D/NSAID_binding_page1.html



http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=27194



http://en.wikipedia.org/wiki/Aspirin

Some effects of NSAIDs are independent on inhibition of prostaglandin synthesis

Table I. A list of the 10 genes most highly induced by 5 mM aspirin treatment, together with their GeneBank accession numbers and the mean fold induction

GenBank acc. no.	Gene name	Mean fold induction
AF019770	Prostate differentiation factor	3.8
M29870	Small GTP binding protein Rac1	2.6
M80563	S100 calcium-binding protein A4 (metastasin)	2.5
S40706	DNA-damage-inducible transcript 3	2.5
X54941	CDC28 protein kinase 1	2.1
M60854	Ribosomal protein S16	2.1
J04111	v-jun avian sarcoma virus 17 oncogene homologue	2.1
X16277	Ornithine decarboxylase 1	2.0
K02770	Interleukin 1, beta	1.8
M27364	Eukaryotic translation elongation factor 1 alpha 1	1.7

Table II. A list of the 10 genes most highly repressed by 5 mM aspirin treatment, together with their GeneBank accession numbers and the mean fold repression

GenBank acc. no.	Gene name	Mean fold repression
X53587	HLA-G histocompatibility antigen, class I, G	1.69
X92106	Cyclin D3	1.56
M92287	Serine proteinase inhibitor	1.49
S85655	Glutathione transferase omega	1.45
M35543	Cell division cycle 42 (GTP-binding protein, 25 kDa)	1.39
U65410	Heat shock protein 70 kDa	1.33
X51521	Mitotic feedback control protein MADP2 homologue	1.30
U58048	Neurotrophic tyrosine kinase receptor type 1	1.30
X56681	NF-κB (p105)	1.28
M93056	Mitogen-activated protein kinase kinase 1	1.28

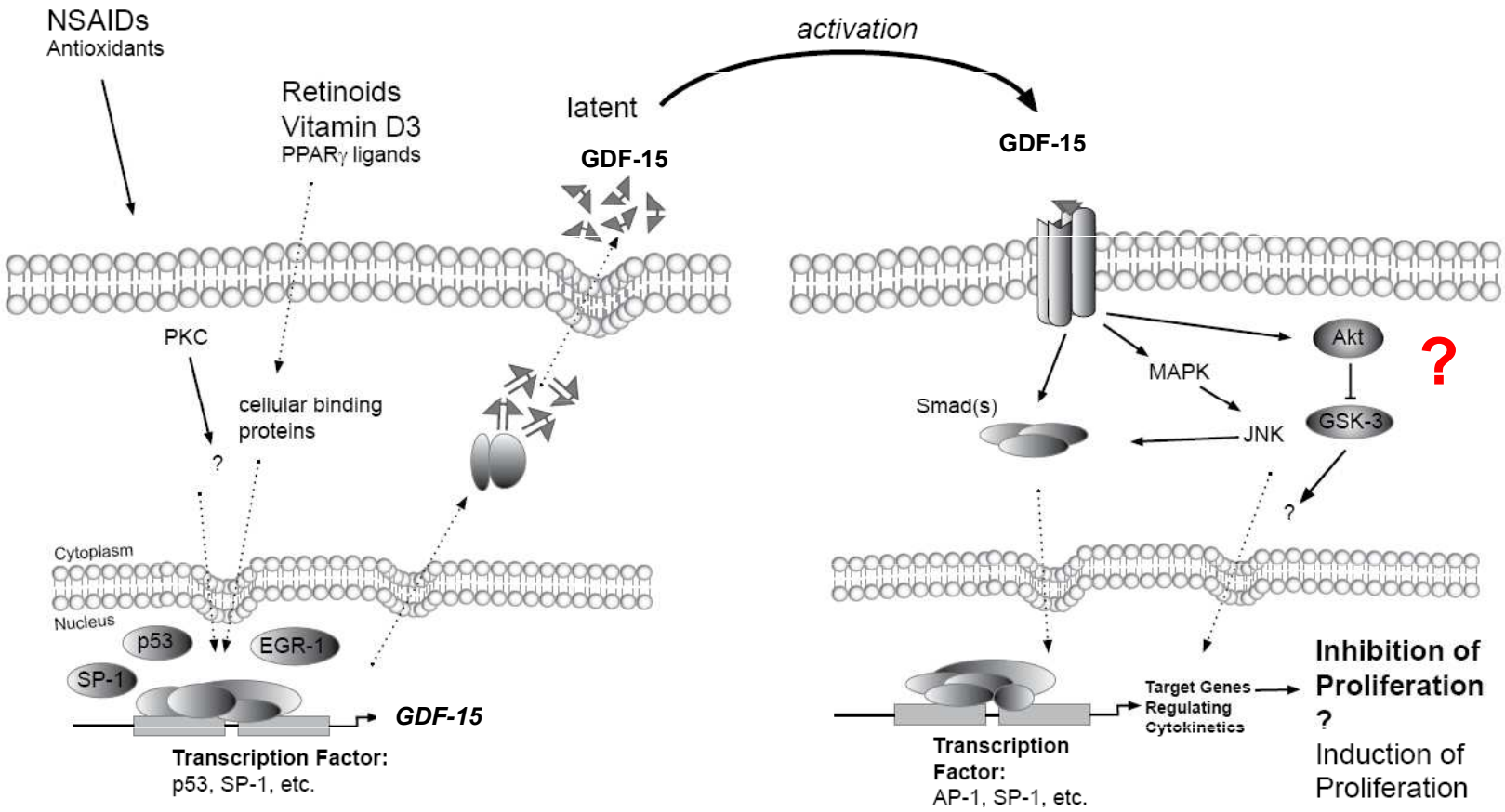
Carcinogenesis vol.25 no.7 pp.1293–1298, 2004
DOI: 10.1093/carcin/bgh118

DNA array analysis of the effects of aspirin on colon cancer cells: involvement of Rac1

James C.H.Hardwick[1], Marije van Santen, Gijs R.van den Brink, Sander J.H.van Deventer and Maikel P.Peppelenbosch

Growth Differentiation Factor - 15 (GDF-15)

NSAID-Activated Gene (NAG-1)
macrophage inhibitory cytokine-1 (MIC-1)
placental transforming growth factor beta (PTGF-β)
placental bone morphogenetic protein
Prostate-derived factor (PDF)



Transforming growth factor-β

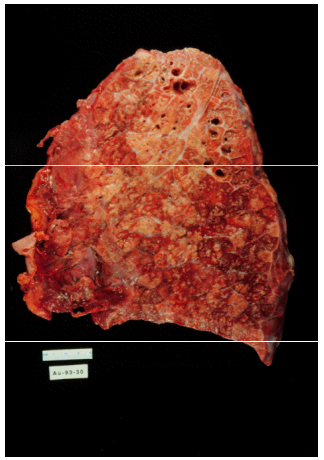
- Role v rozvoji patologických stavů

Biologické funkce TGF-β

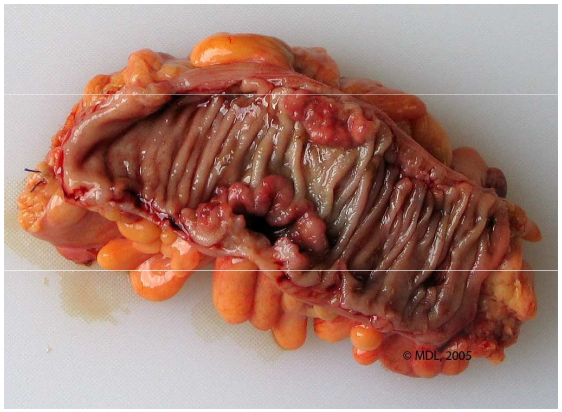
- Hraje klíčovou úlohu během embryogeneze;
- reguluje proliferaci, diferenciaci, buněčnou smrt, motilitu, adhezi (v závislosti na buněčném typu) = ovlivňuje homeostázu;
- reguluje expresi extracelulární matrix;
  - indukuje fibrilární kolagen a fibronectin;
  - inhibuje degradaci ECM (inhibicí MMPs a indukci TIMPs).

Role TGF-β v rozvoji patologických stavů

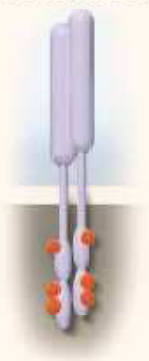
- Fibróza
  - deregulace exprese ECM prostřednictvím indukce proliferace fibroblastů a jejich myofibroblastového fenotypu.



- Nádorová onemocnění
  - ztráta citlivosti epiteliálních buněk k inhibičnímu působeni TGF-β;
  - indukce angiogeneze.

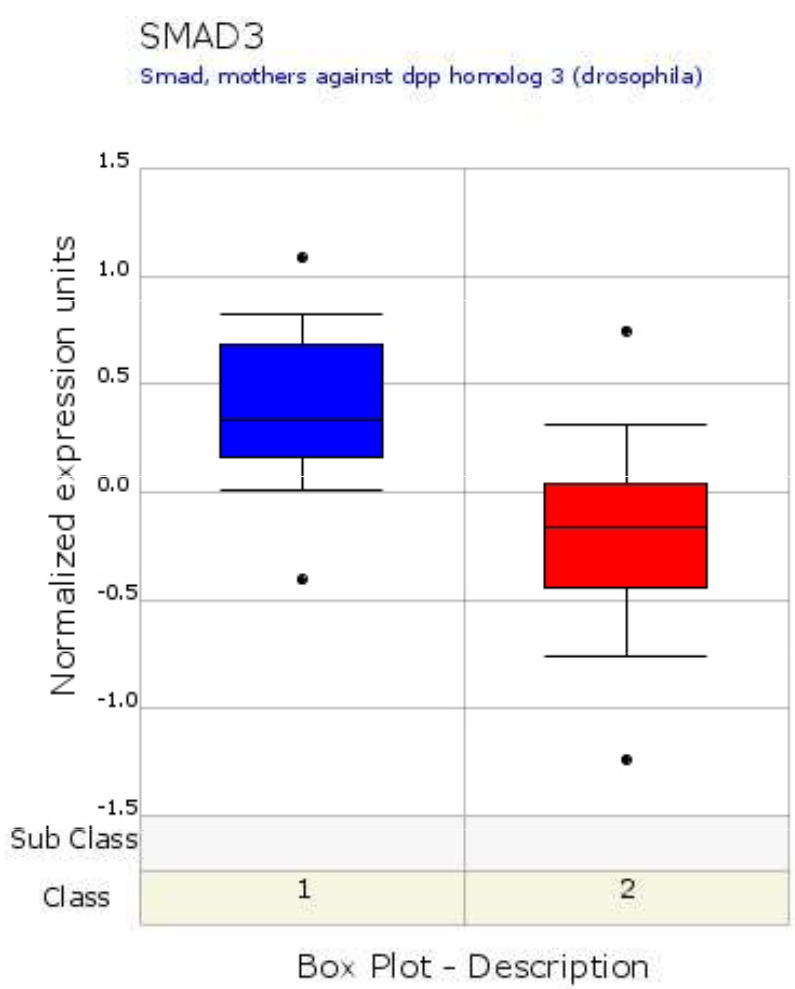


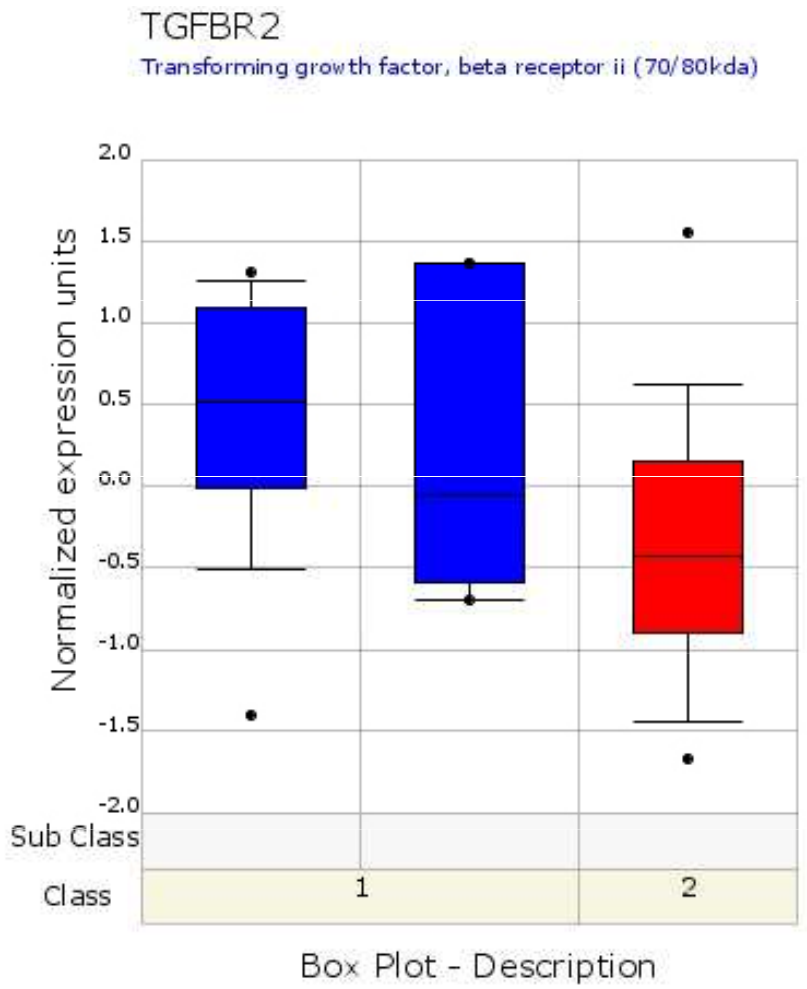
Role TGF-β v carcinogenezi

TGF-β signaling component	TGF-β	Endoglin	Type II receptors	Type I receptors	Smad2	Smad4
						
Cancers (somatic mutations)	Increased expression leads to enhanced invasion and metastasis		Colorectal (30%) Gastric (15%) Endometrial Prostate Breast Lung Hepatic Pancreatic Cervical Glioma Head and neck	Breast (16%) Pancreatic Biliary Cervical Chronic lymphocytic leukemia	Colorectal (11%) Lung (7%) Hepatocellular	Pancreatic (50%) Colorectal (30%) Lung (10%) Breast Prostate Ovarian Head and neck Esophageal Gastric Bladder Hepatocellular Renal cell
Other diseases (germ-line mutations or polymorphisms)	Fibrosis Hypertension Osteoporosis Atherosclerosis	Hereditary hemorrhagic telangiectasia	Atherosclerosis			Familial juvenile polyposis

NEJM 342, **18** (2000) 1350-135

Role TGF-β v carcinogenezi

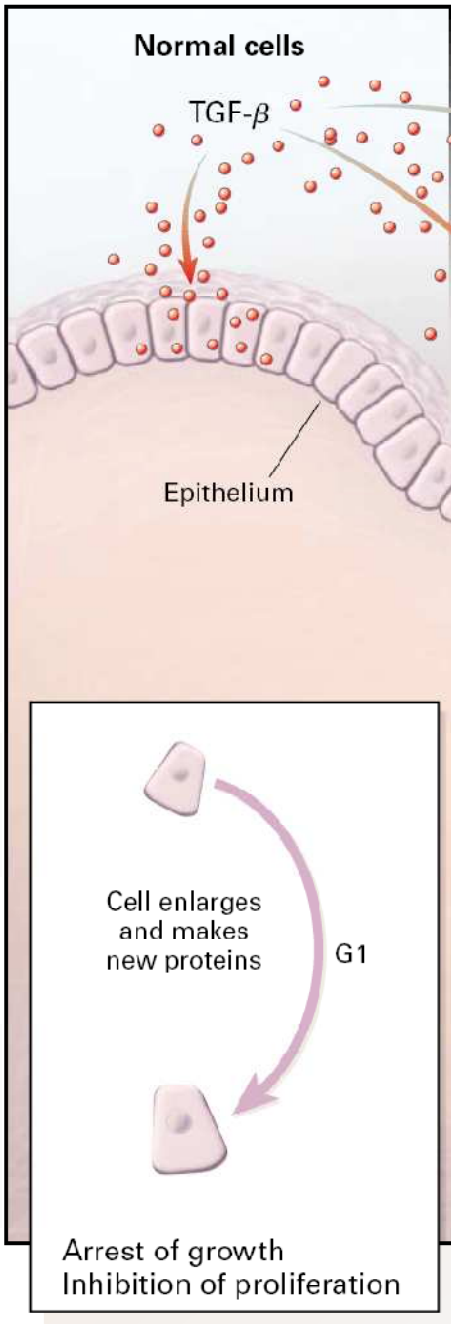




Prostate – normal vs. cancer

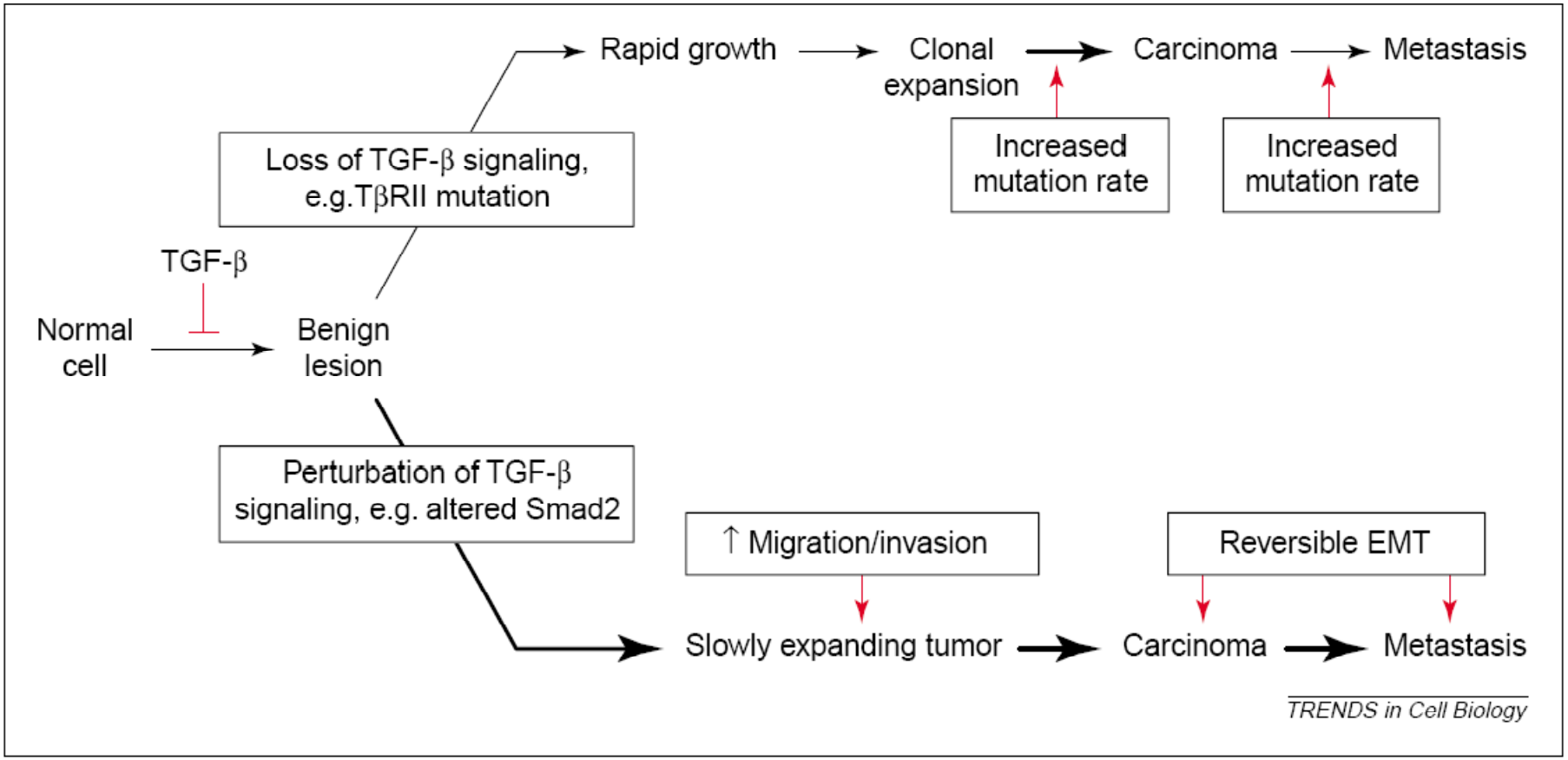
normal, hyperplasia vs. cancer

Role TGF-β v carcinogenezi



NEJM 342, **18** (2000) 1350-135

Role TGF-β v carcinogenezi

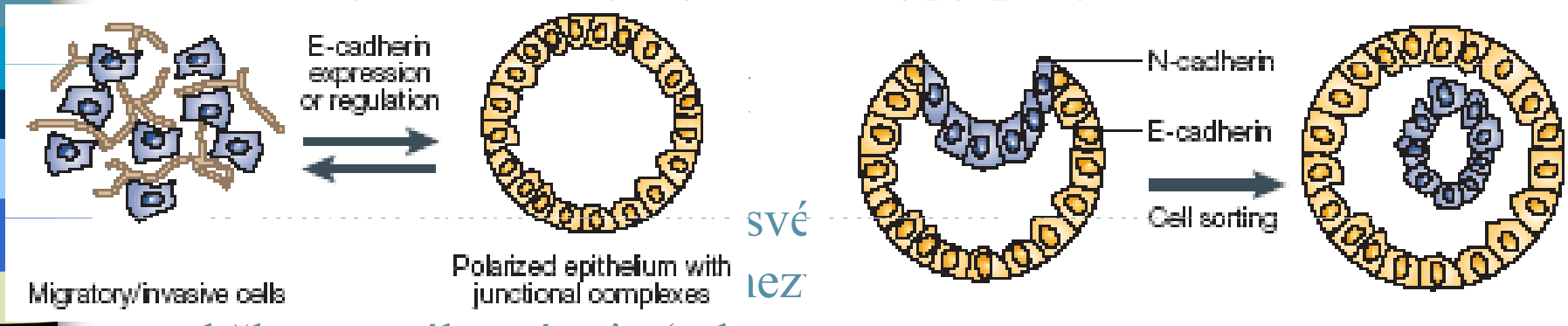


Epithelial-Mesenchymal Transition (EMT)

- Změna buněčného fenotypu spojená se ztrátou adheze a zvýšením motility

BUNĚČNÝ POHYB A **EMT**

- **během embryonálního vývoje - zákl. typy pohybu:**



své

ıez

během raného vývoje (ryby, obojživelníci)

2) INDIVIDUÁLNÍ BUN. MIGRACE - EMT

- ztráta bun. kontaktů
- migrace jednotlivých b. či malých skupin b. skrz EXTRACELULÁRNÍ MATRIX
- během formování - mezodermu Amniot (plazi, ptáci, savci)
  - neurální lišty (neural crest) obratlovců

EMT & Cancer

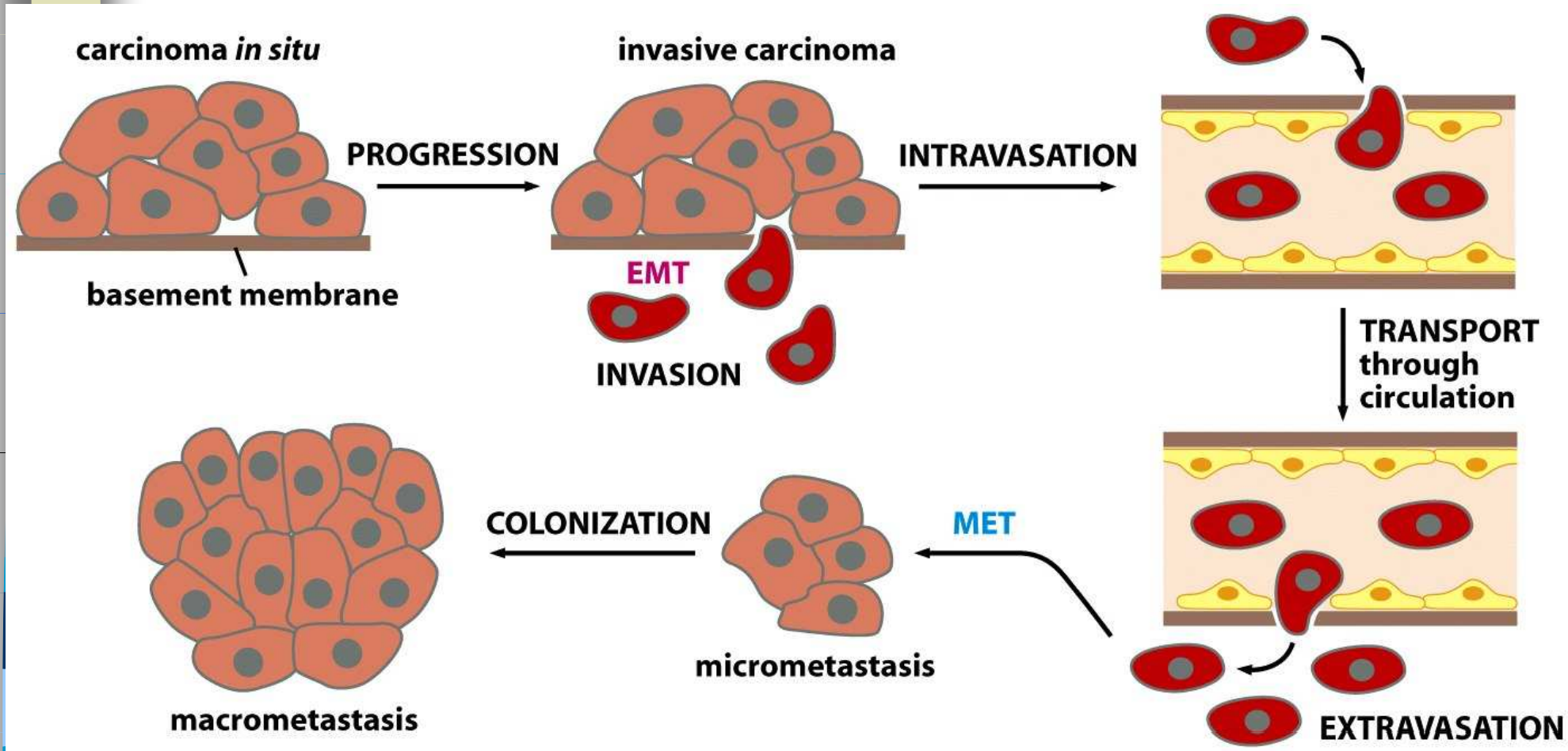
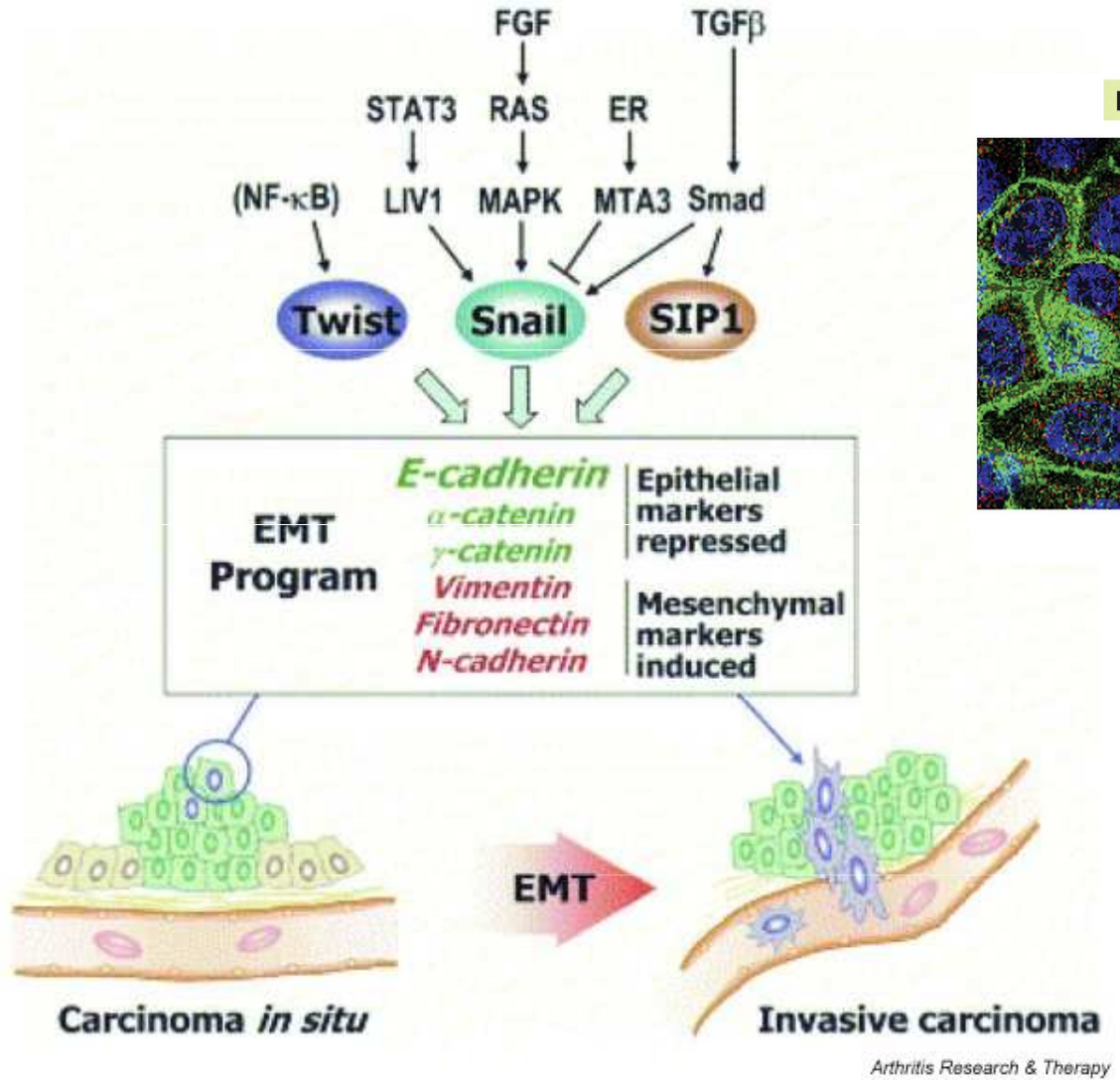
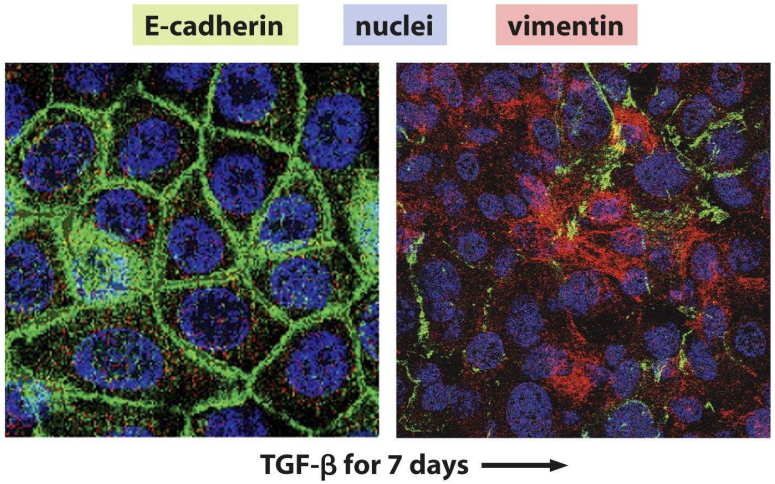


Figure 14.17b *The Biology of Cancer* (© Garland Science 2007)

EMT


FGF
TGFβ
STAT3
RAS
ER
(NF-κB)
LIV1
MAPK
MTA3
Smad
Twist
Snail
SIP1
EMT Program
E-cadherin
α-catenin
γ-catenin
Vimentin
Fibronectin
N-cadherin
Epithelial markers repressed
Mesenchymal markers induced
EMT
Carcinoma in situ
Invasive carcinoma
Arthritis Research & Therapy


E-cadherin
nuclei
vimentin
TGF-β for 7 days

Dvojí úloha TGF-β v carcinogenezi

- Deregulace inhibice proliferace epiteliálních buněk;
- Epithelia-mesenchymal transition
- podpora migrace, metastázování a angiogeneze.

Role TGF-β v diagnóze, prognóze a léčbě

- Vysoká sérová hladina TGF-β1 je spojena s nádory tlustého střeva, prostaty a rozvojem fibrózy;
- polymorfismus genu pro TGF-β1 vedoucí k jeho zvýšené produkci určuje predispozici k fibróze, hypertenzi a osteoporéze;
- blokování produkce a aktivity TGF-β má velký potenciál pro léčbu fibrózy;
- protektivní účinek retinoidů a vitamínu D3 může být způsoben prostřednictvím TGF-β.

Shrnutí přednášky

- TGF-β rodina zahrnuje řadu multifunkčních proteinů.
- Přenos signálu je intracelulárně přenášen SMAD proteiny, ale interaguje s řadou dalších signálních drah.
- Působení TGF-β je závislé na buněčném typu a také přítomnosti dalších faktorů.
- TGF-β hraje významnou roli v rozvoji karcinogeneze a dalších patologických stavů.

Na konci dnešní přednášky by jste měli:

1. znát základní zástupce a funkce proteinů TGF-β rodiny;
2. umět popsat přenos signálu který závisí na SMAD;
3. být schopni vysvětlit úlohu TGF-β v karcinogenezi.