Growth factors in cancer cell signaling

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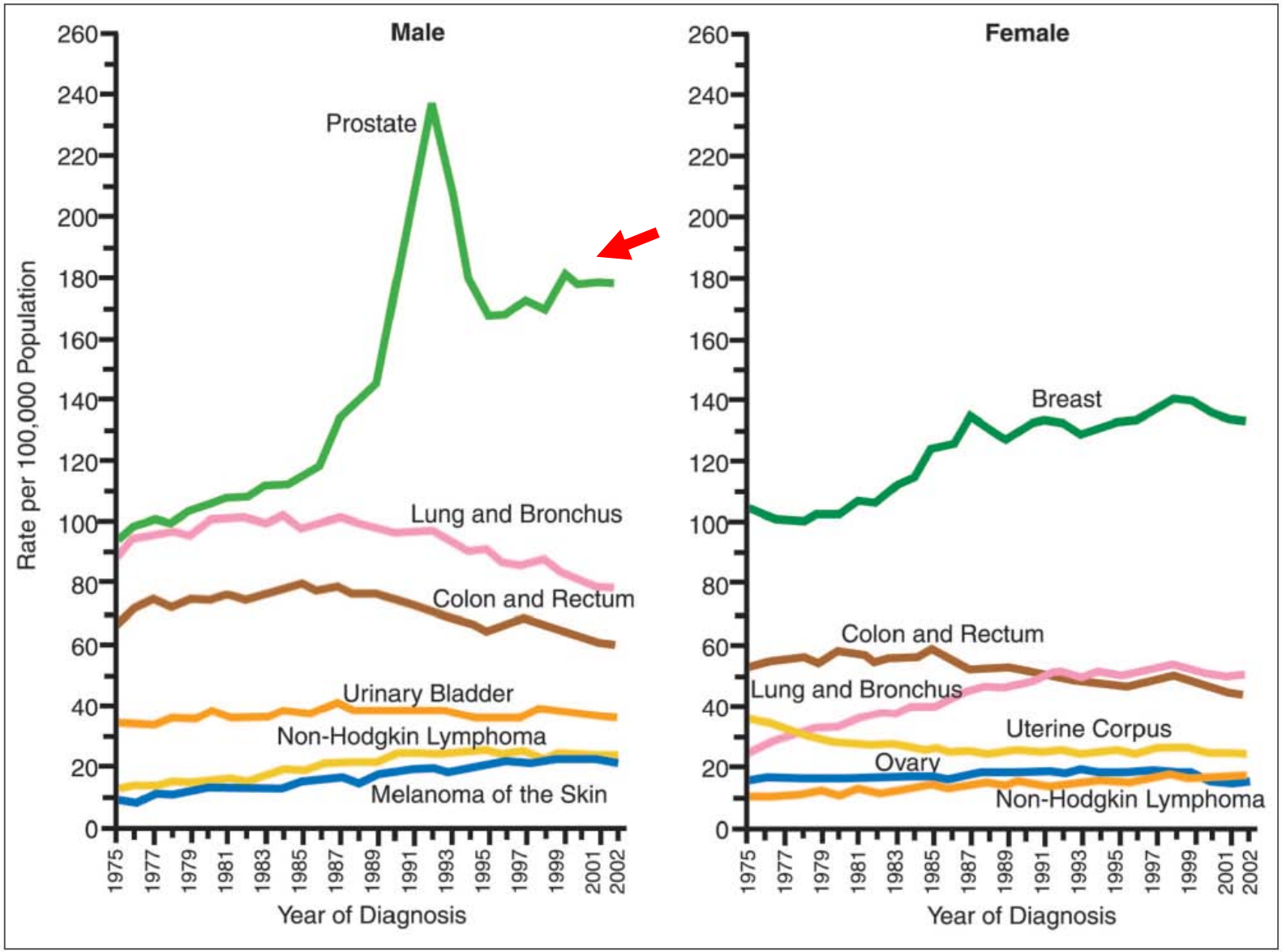
Growth factors in cancer cell signaling

- 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?

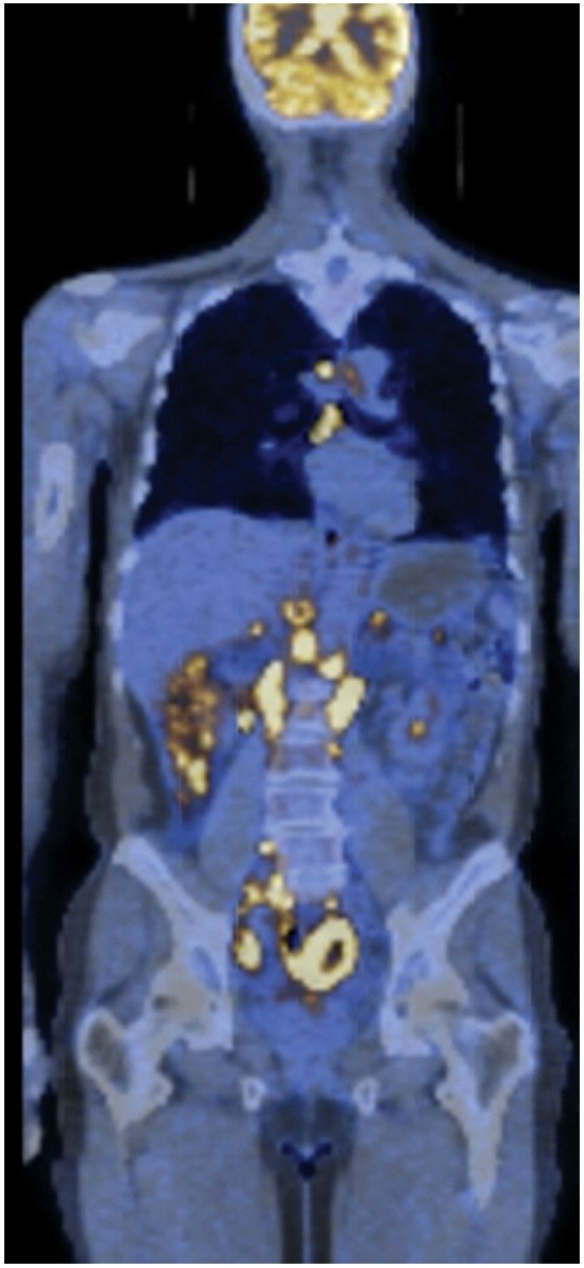


Figure 14.1 *The Biology of Cancer* (© Garland Science 2007)

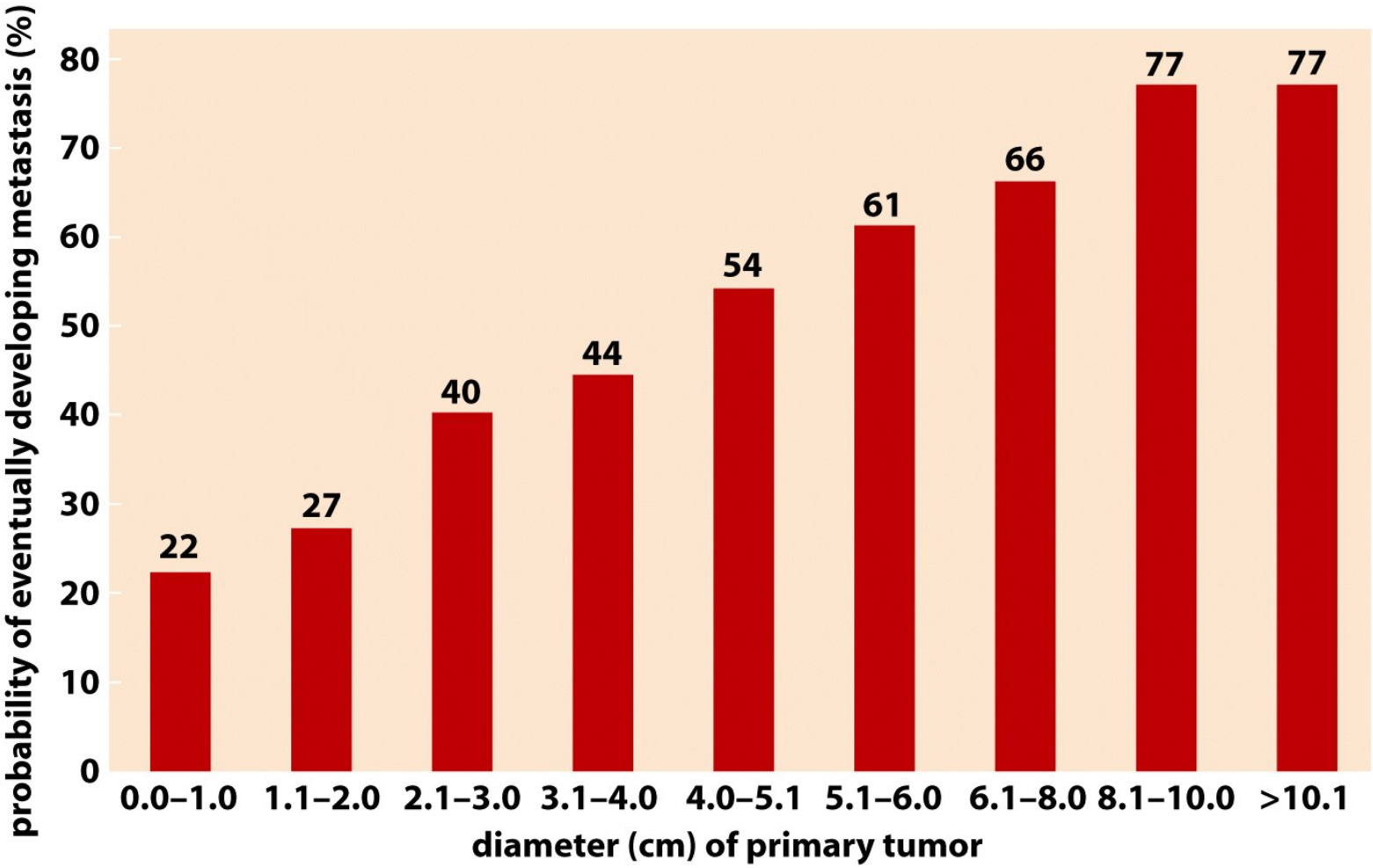


Figure 14.3 *The Biology of Cancer* (© Garland Science 2007)

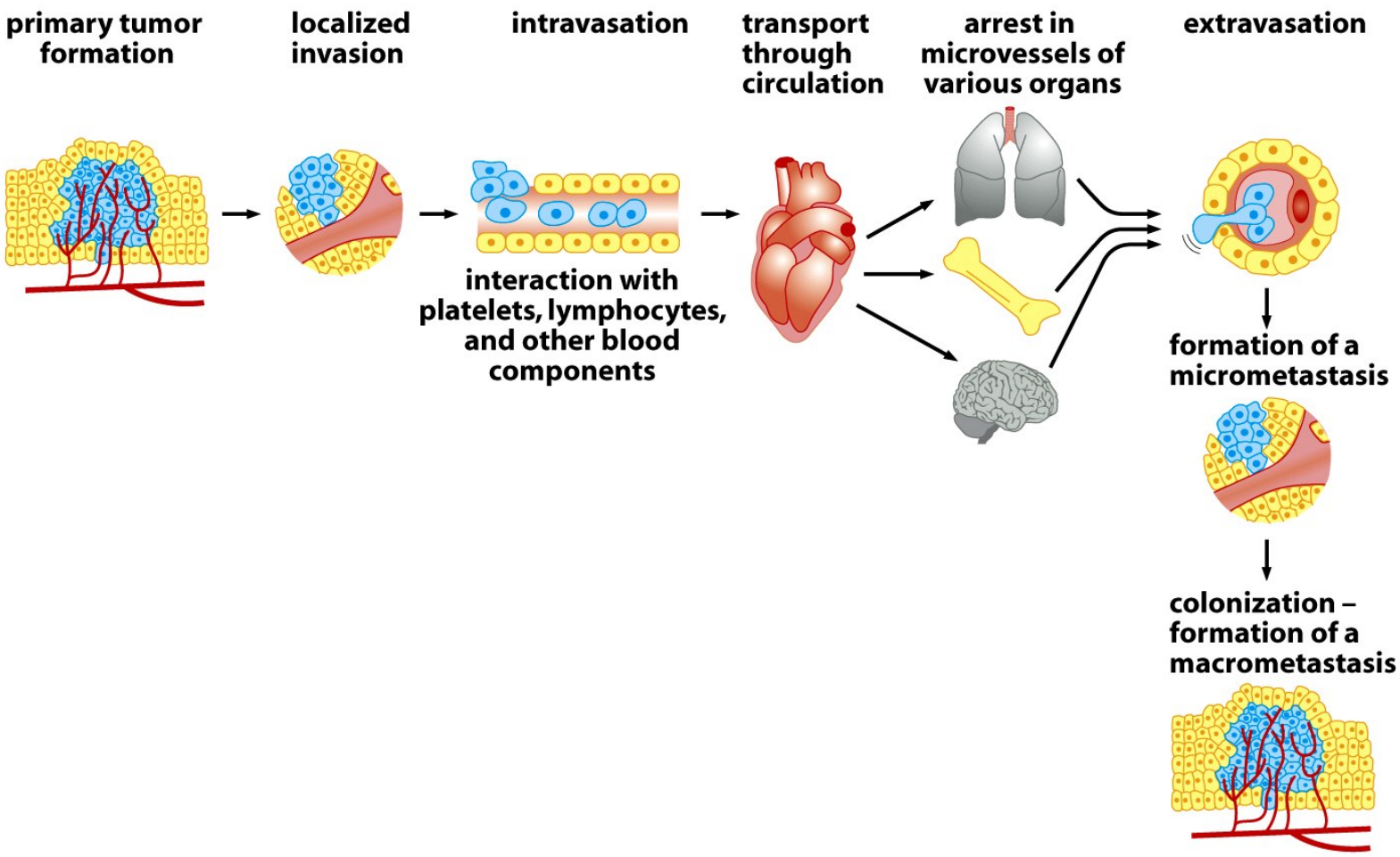
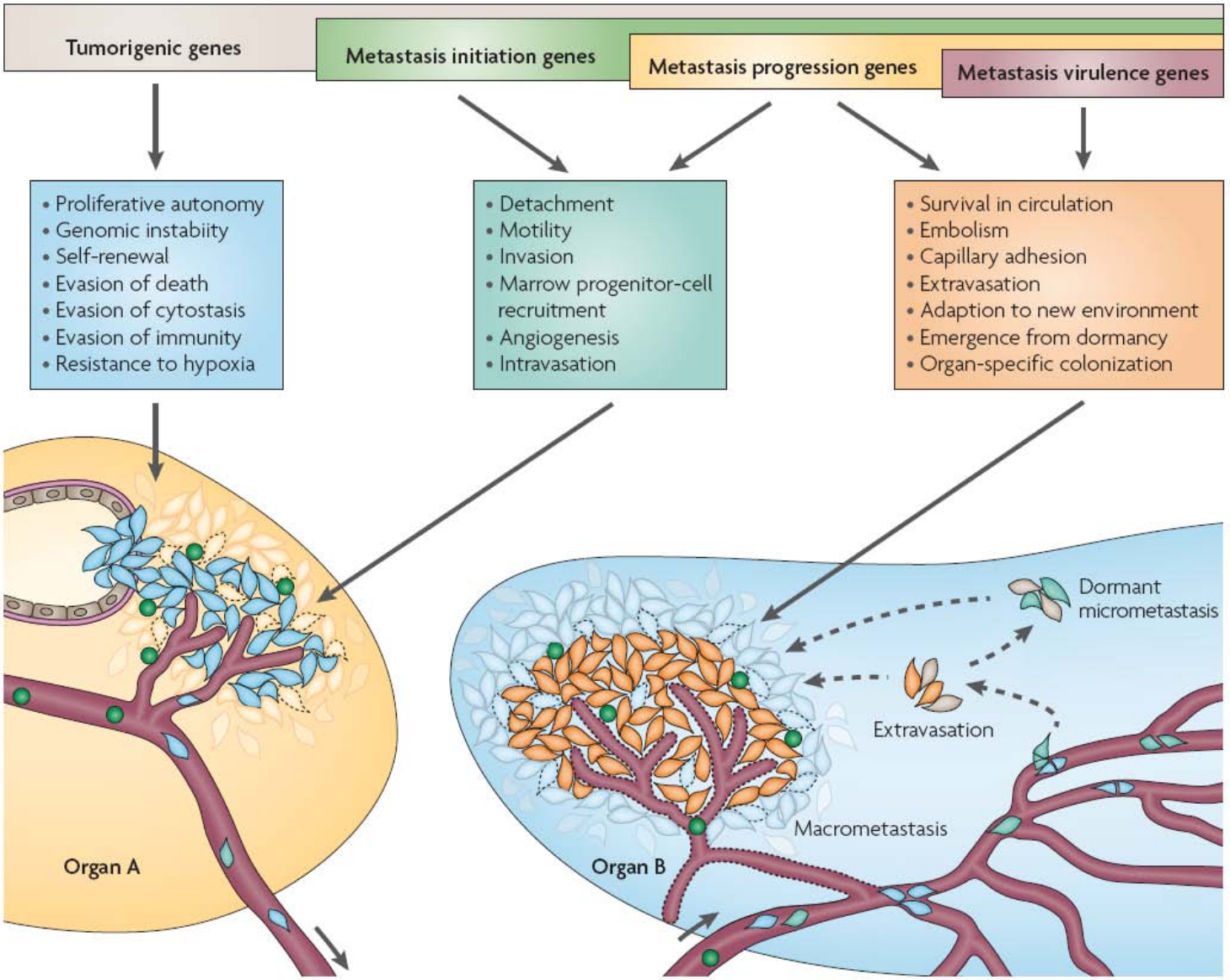


Figure 14.4 *The Biology of Cancer* (© Garland Science 2007)

Genetic determinants of cancer metastasis

Don X. Nguyen and Joan Massagué



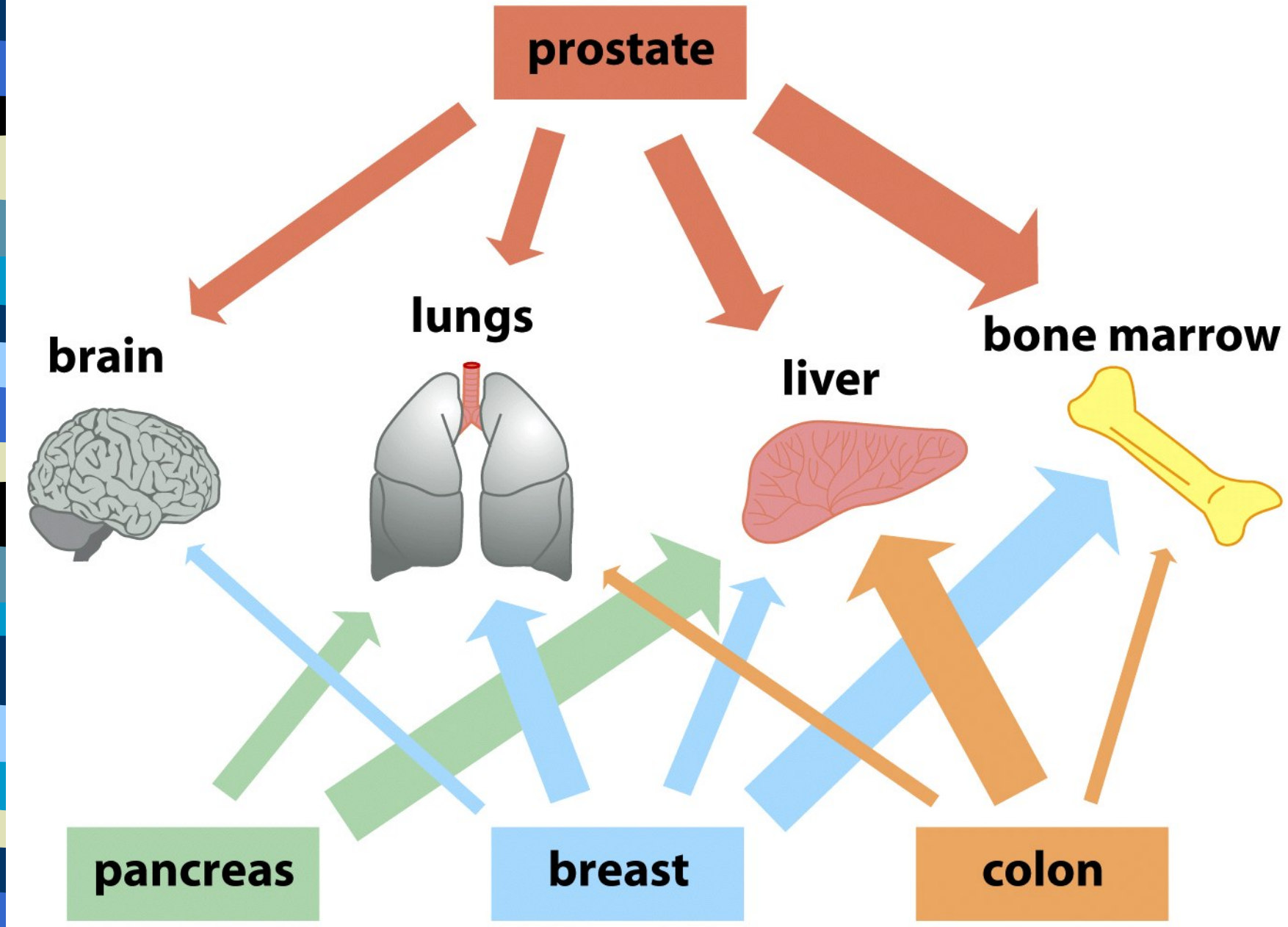
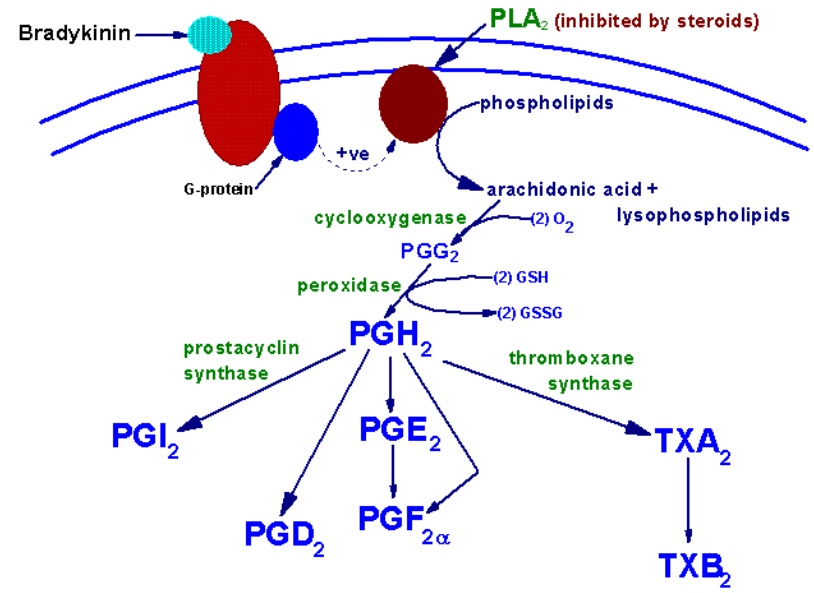
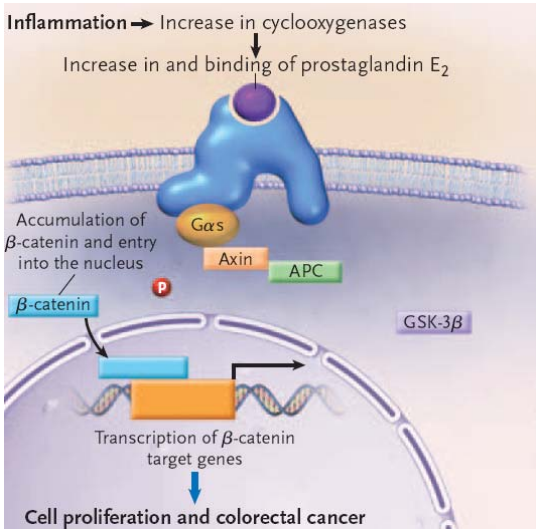


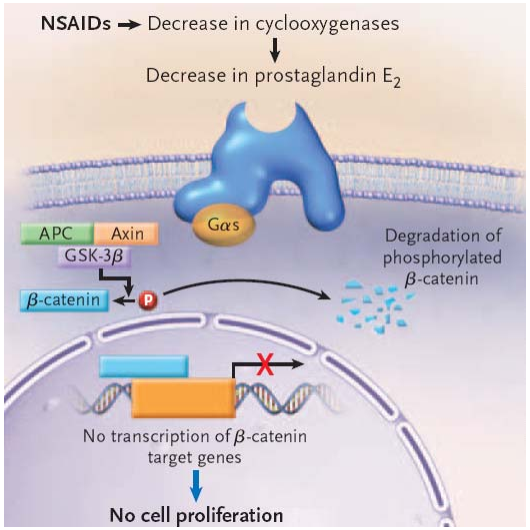
Figure 14.42 *The Biology of Cancer* (© Garland Science 2007)

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

- key enzymes of arachidonic acid metabolism







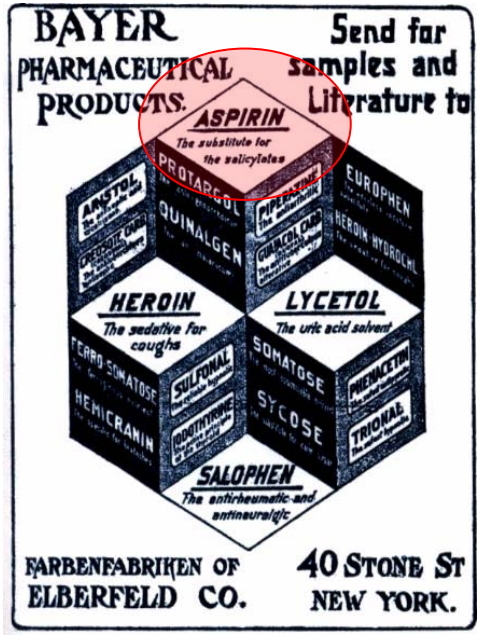
... and its inhibitors

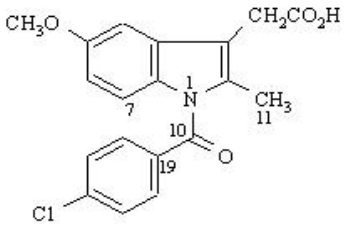
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- COX-2 specific inhibitors

H. Clevers, "Colon cancer--understanding how NSAIDs work," *N Engl J Med*, vol. 354, no. 7, pp. 761-763, 2006.

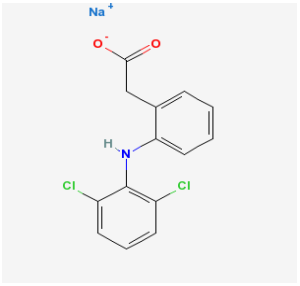
Nonsteroidal anti-inflammatory drugs (NSAIDs)

- variety of mechanisms
- cancer chemoprevention

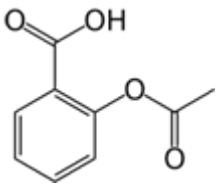




http://www.home.duq.edu/~harrold/Chem3D/NSAID_binding_page1.html



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)
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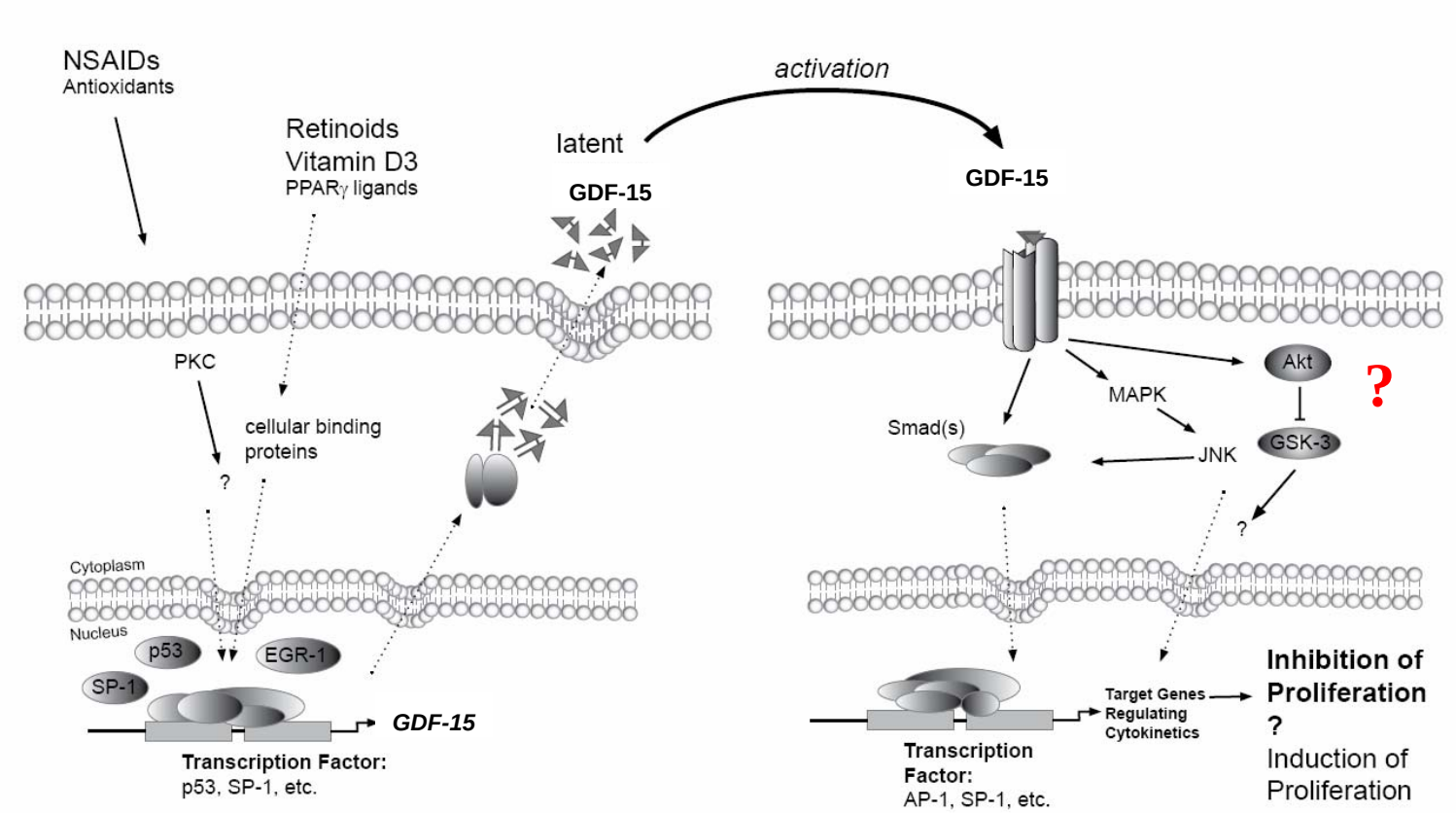
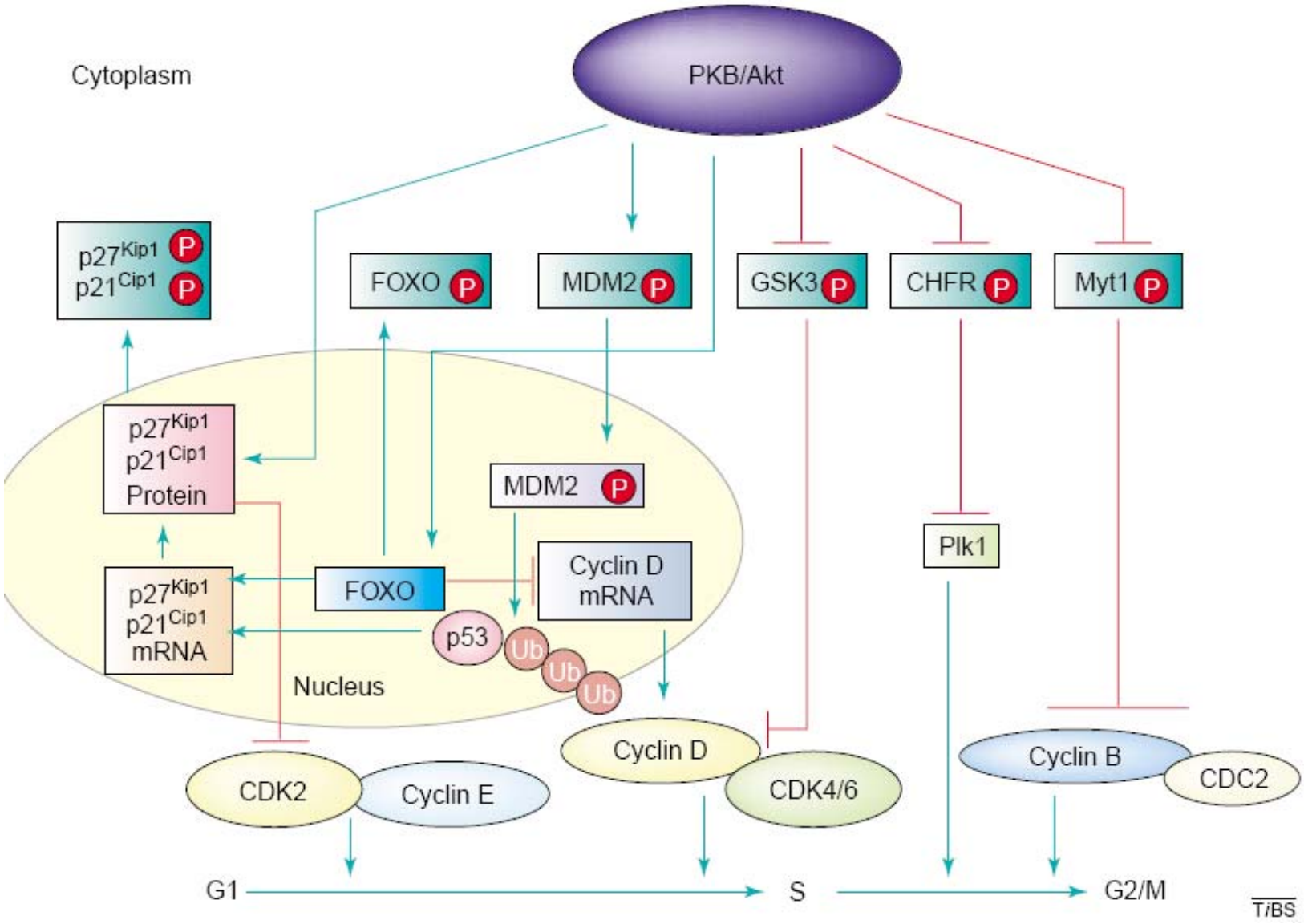
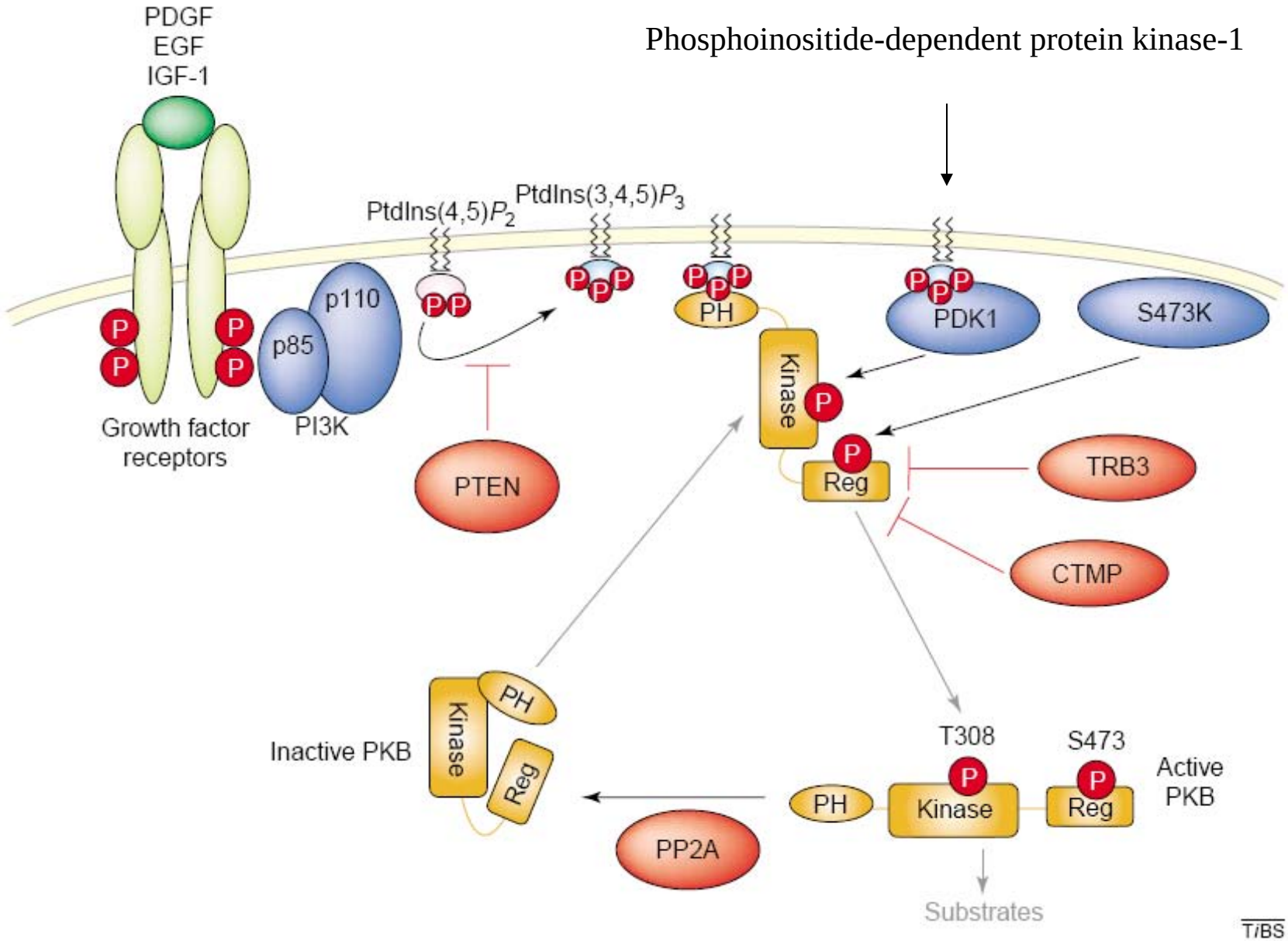




TRENDS in Biochemical Sciences Vol.29 No.5 May 2004

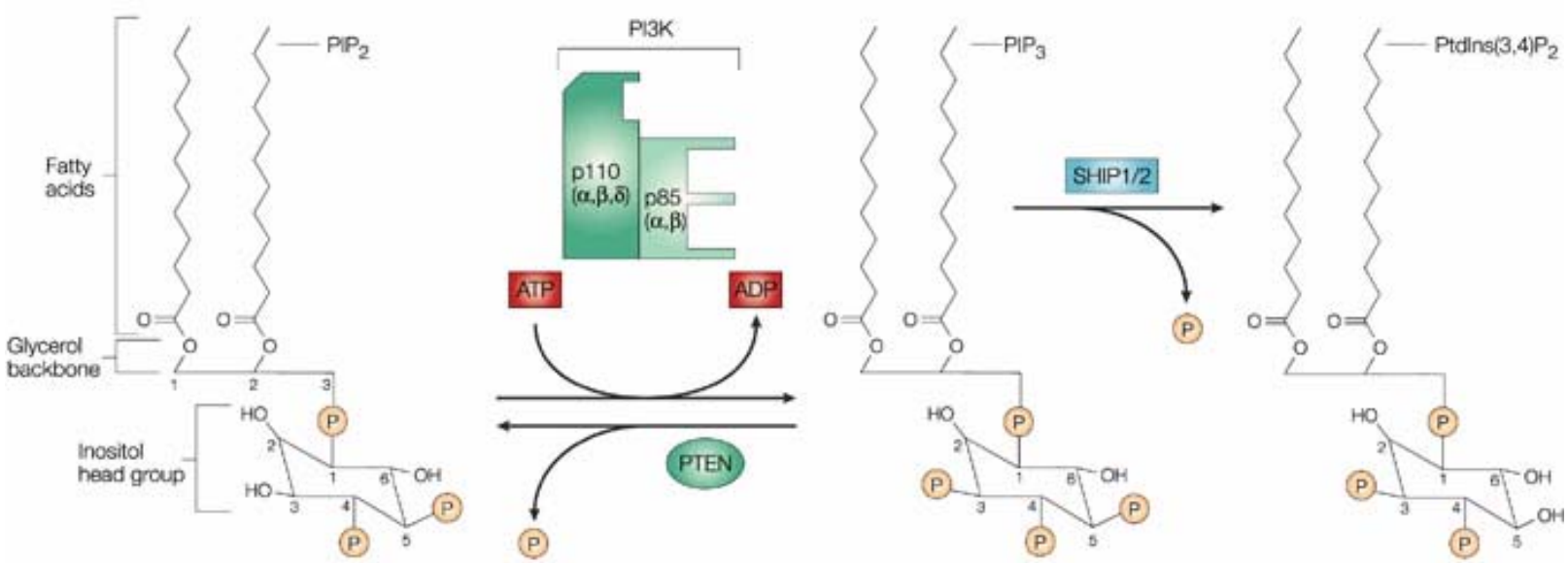
Phosphoinositide-dependent protein kinase-1



TRENDS in Biochemical Sciences Vol.29 No.5 May 2004

Negative regulators of PI3K

- PTEN - phosphatase and tensin homolog
  - Tumor suppressor;
  - dual-specificity protein phosphatase;
  - lipid phosphatase, removing the phosphate in the D3 position of the inositol ring from PI3P
- SHIP1/2- inositol polyphosphate 5-phosphatases
  - Regulators of proliferation
  - key role in insulin metabolism and obesity



Presumptions

- NSAIDs induce expression of GDF-15.
- GDF-15 is an autocrine mediator of proapoptotic effects of NSAIDs.

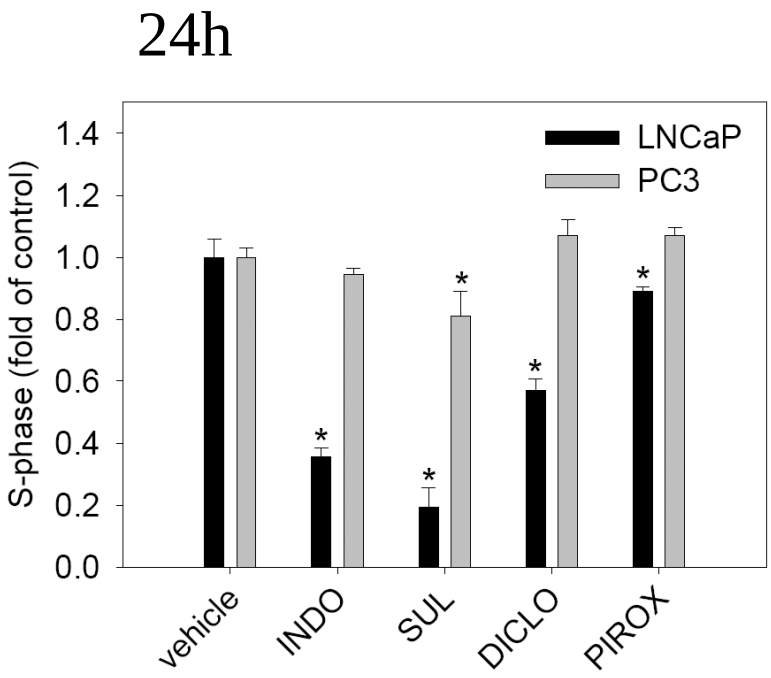
Hypotheses

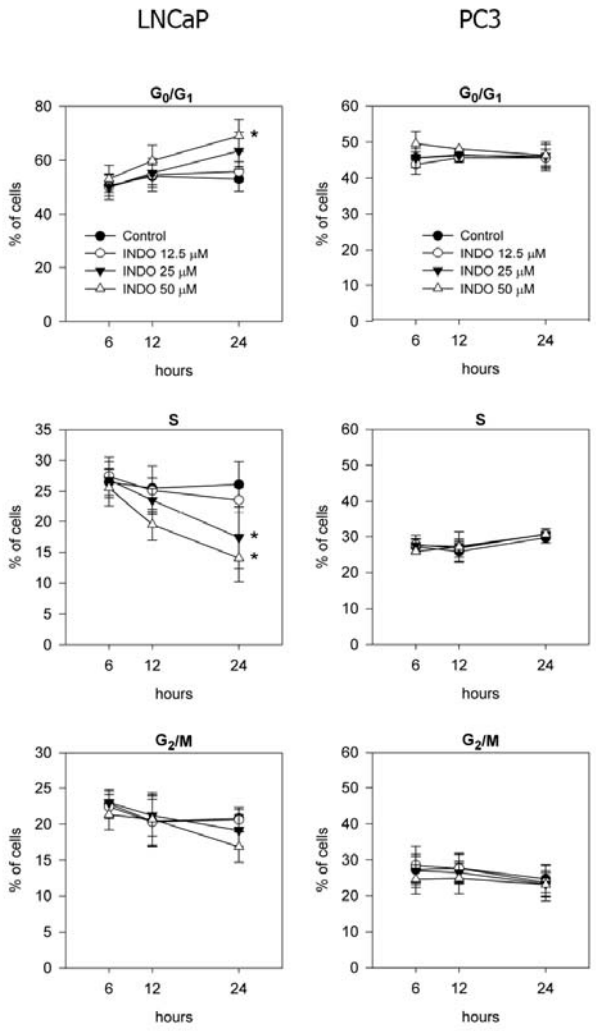
- GDF-15 is a mediator of antiproliferative effects of NSAIDs;
- GDF-15 induction is one of the key determinant of different sensitivity of cancer cells to the antiproliferative effects of NSAIDs;
- PKB/Akt activation is part of the mechanism of NSAIDs effects.

Experimental models

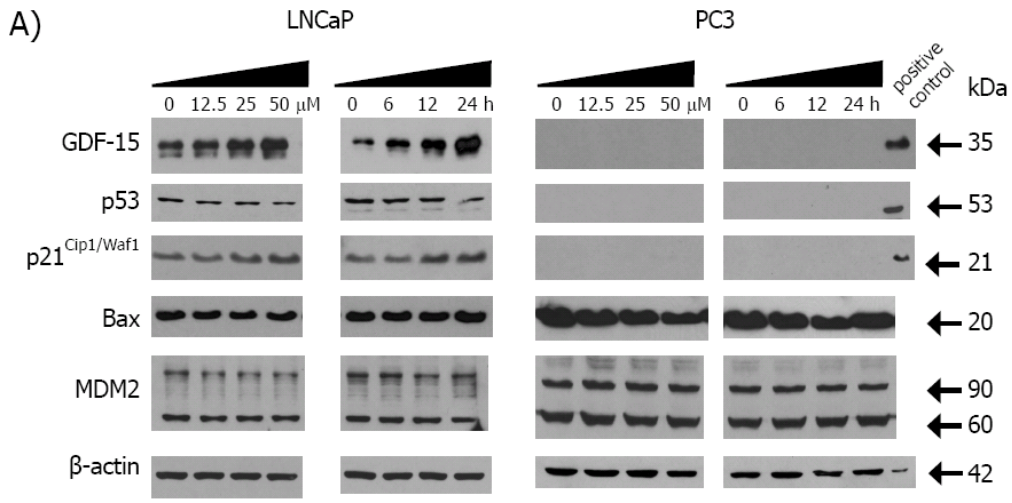
- Prostate cancer cells
  - **LNCaP** – androgen sensitive, p53 wt, PTEN -/-, SHIP2 -/-
  - **PC3** – AR -/-, p53 -/-, PTEN -/-
- Colon cancer cells
  - **HCT-116** Neo
  - **HCT-116** PTEN -/-

LNCaP cells are more sensitive to the anti-proliferative effects of NSAIDs

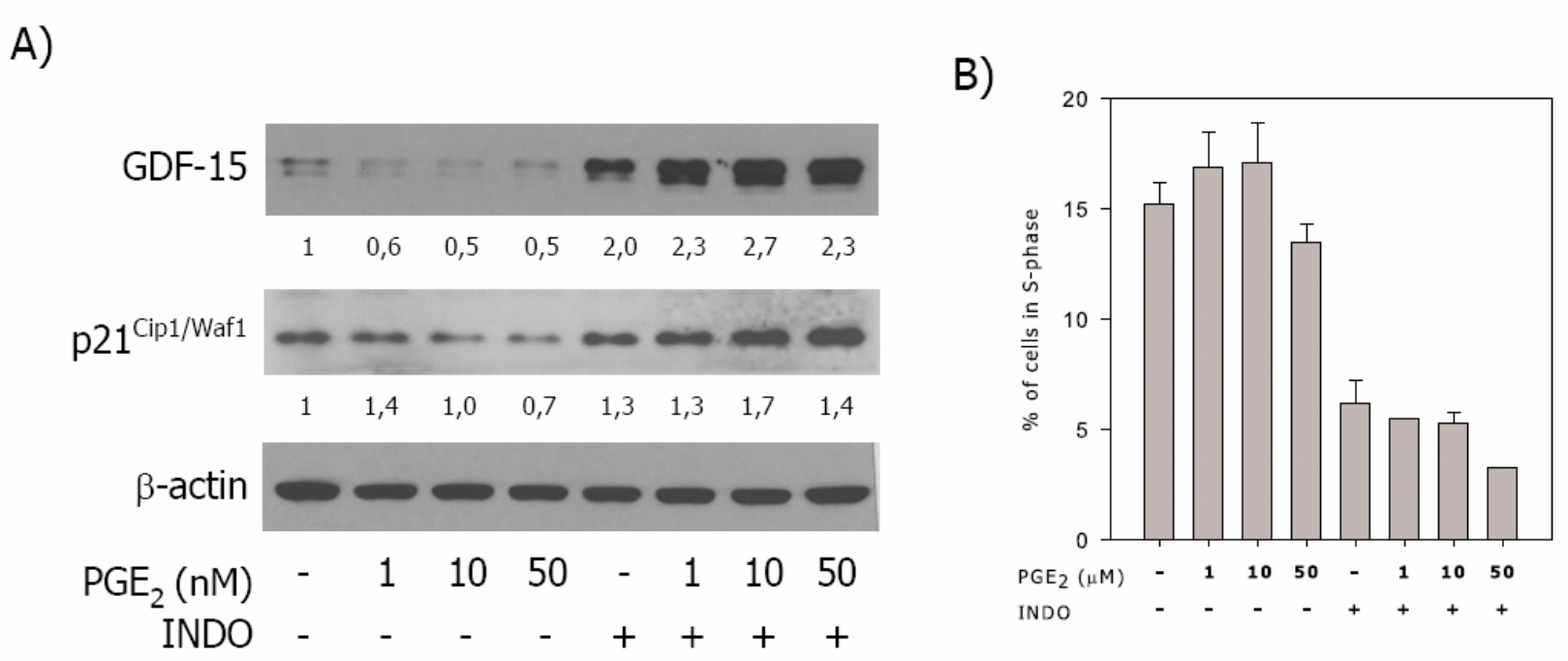




Expression of p21 and GDF-15 proteins is induced by INDO in LNCaP cells

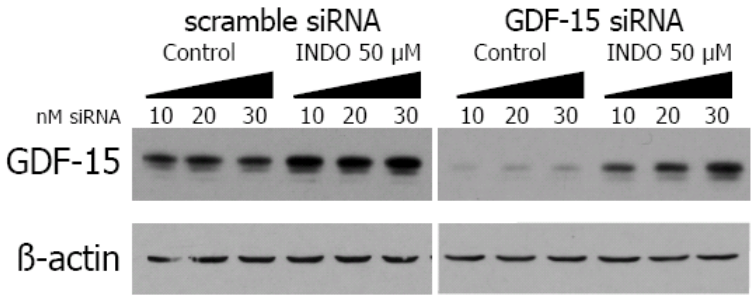


INDO effects on LNCaP cells are independent on COX inhibition

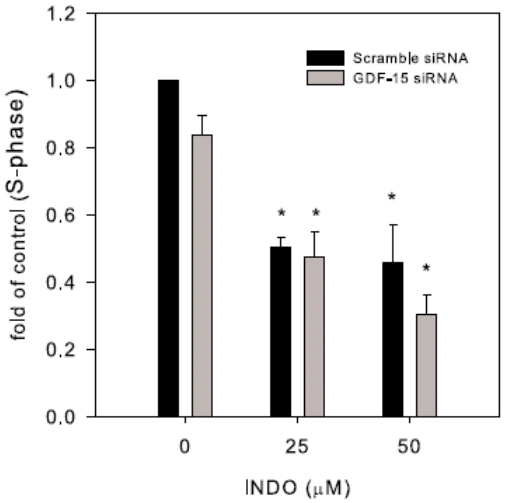


GDF-15 siRNA does not affect INDO-induced cell cycle arrest in LNCaP cells

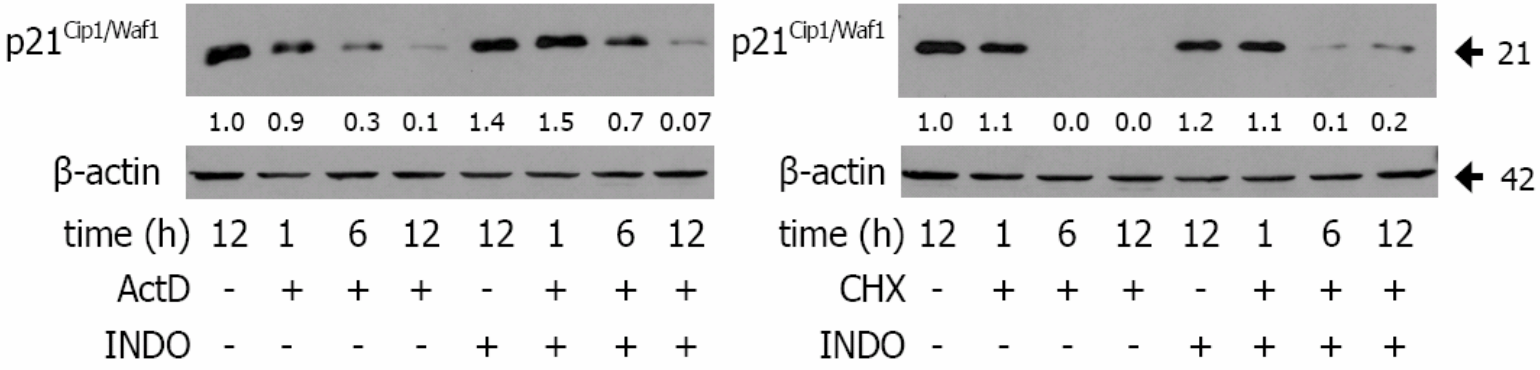
A)



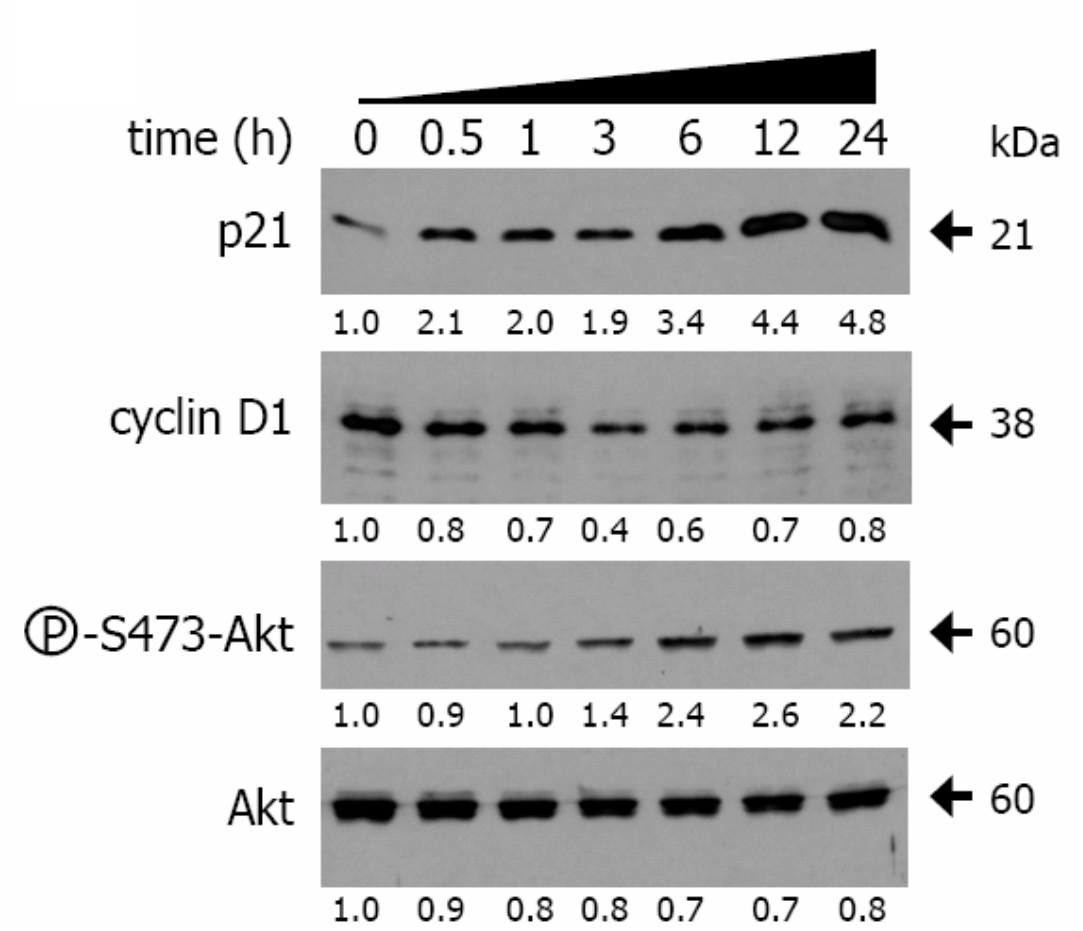
B)



INDO delays a decrease of $p21^{WAP1/CIP1}$ level induced by ActD and/or CHX



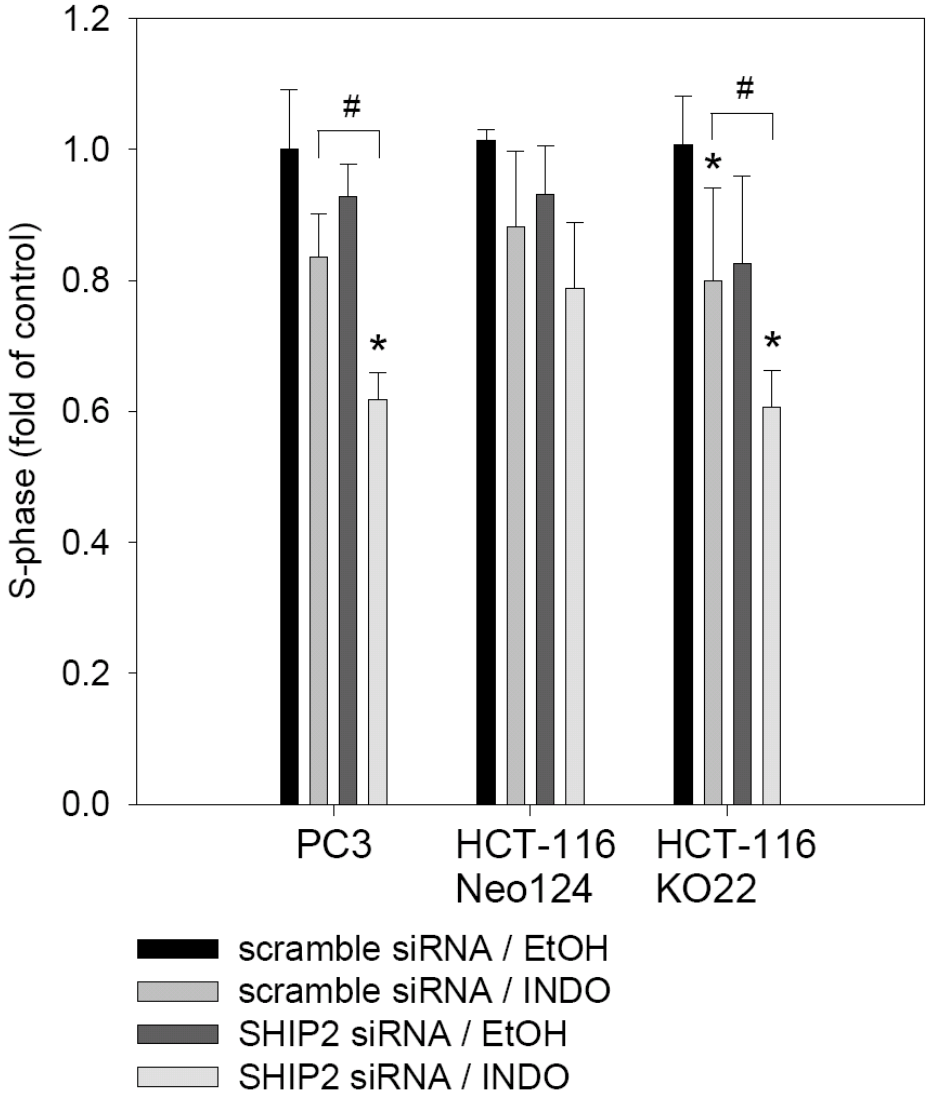
PKB/Akt phosphorylation is induced by INDO in LNCaP cells



Is SHIP2 expression responsible for resistance to NSAIDs in PTEN -/- cells?

- Prostate cancer cells
  - **LNCaP** – PTEN -/-, SHIP2 -/-
  - **PC3** – PTEN -/-
- Colon cancer cells
  - **HCT-116** Neo
  - **HCT-116** PTEN -/-

SHIP2 siRNA sensitizes PC3 and HCT116 PTEN -/- cells to the antiproliferative effects of INDO



Summary I

- GDF-15 is not mediator of early induction of G_0/G_1 arrest induced by NSAIDs;
- Posttranslational stabilization of $p21^{WAF1/CIP1}$ through PKB/AKT activation is a novel mechanism of NSAIDs effects;
- Multiple defects in negative regulation of PI3K/Akt activity sensitize cancer cells to the effects of NSAIDs.

How we can effectively modify neuroendocrine differentiation of the cancer cells?

Andrea Staršíchová
Zuzana Pernicová

Neuroendocrine cells

- „hybrid“ epithelial/nerve/endocrine cells
- Secretion of various factors

Produced factors

- Chromogranins
- **Serotonin**
- **Gastrin releasing peptide (bombesin)**
- Calcitonin gene family
- Somatostatin
- Parathyroid hormone-related protein
- Neuropeptide Y
- **Vascular endothelial growth factor (VEGF)**
- Cholecystokinin
- Proadrenomedullin N-terminal peptide
- TSH-like peptide
- Histamine

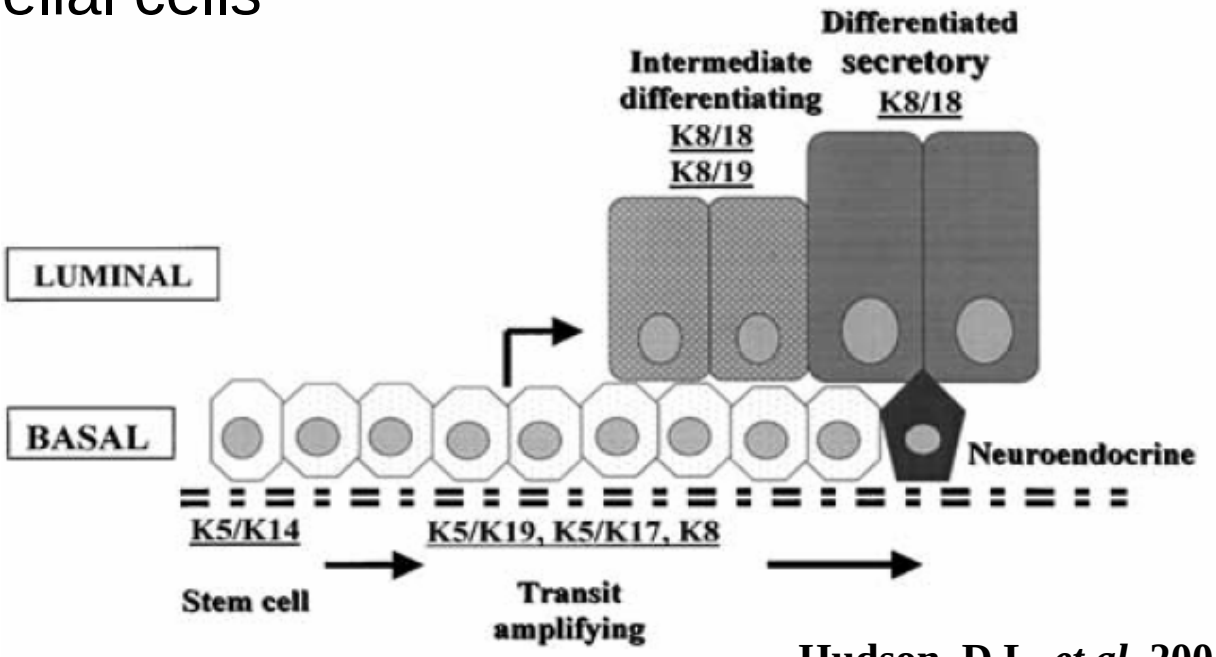
Neuroendocrine prostate cancer

- develops as an aggressive disease that does not respond to androgen ablation therapy;
- paracrine action of NE cells promote the progression of androgen dependent adenocarcinoma to an androgen independent state;
- significant role for NE cells during failure of androgen ablation therapy.

„normal“ prostate epithelium

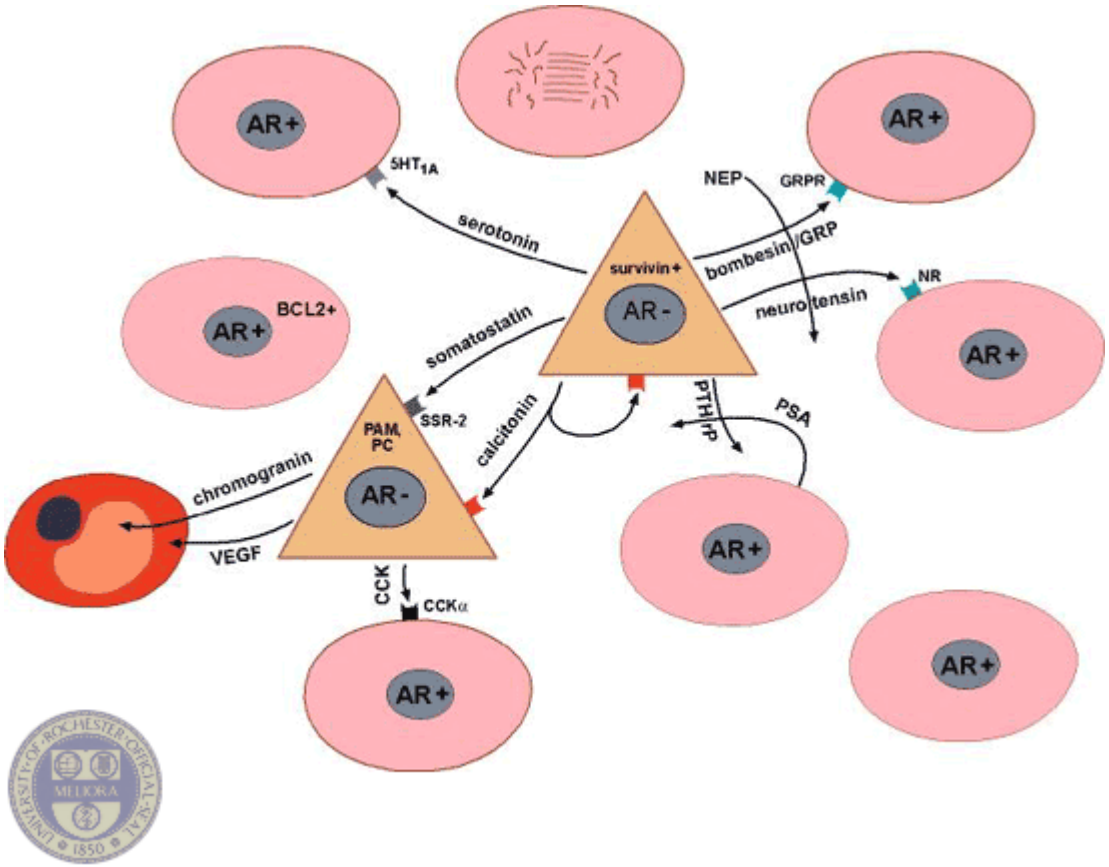
- stem cells
- basal epithelial cells
- transitamplifying cells
- neuroendocrine cells
- secretory luminalepithelial cells

Lam, J.S. *et al.*, 2006



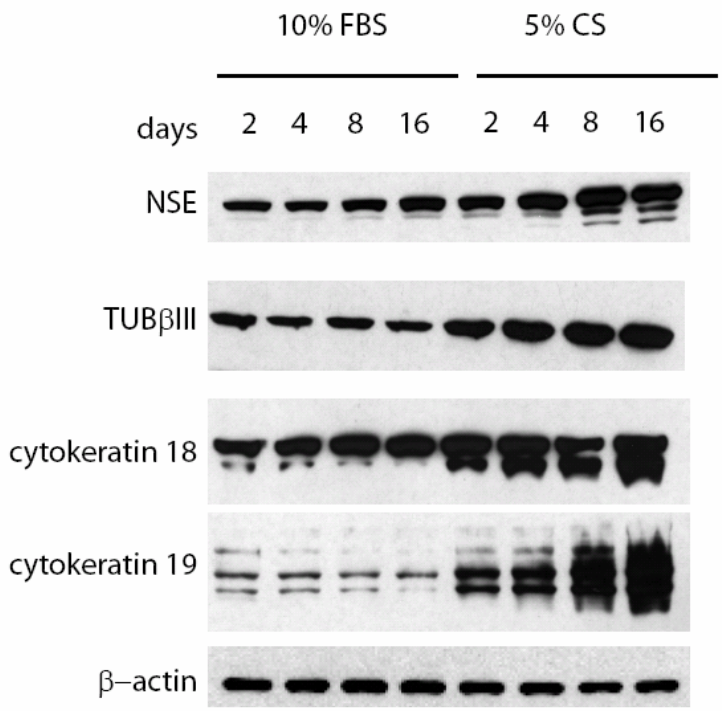
Hudson, D.L. *et al,* 2004

Neuroendocrine cells



Androgen depletion-induced neuroendocrine differentiation of prostate cancer cells

Differentiation markers



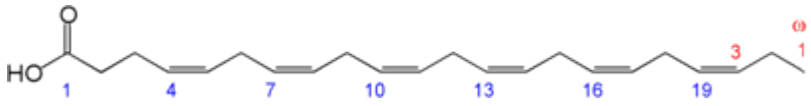
Inflammation & Cancer

- Chronic inflammation plays important role in development of several type of cancer.
- Pro inflammatory cytokines such as IL-6 induce neuroendocrine differentiation.

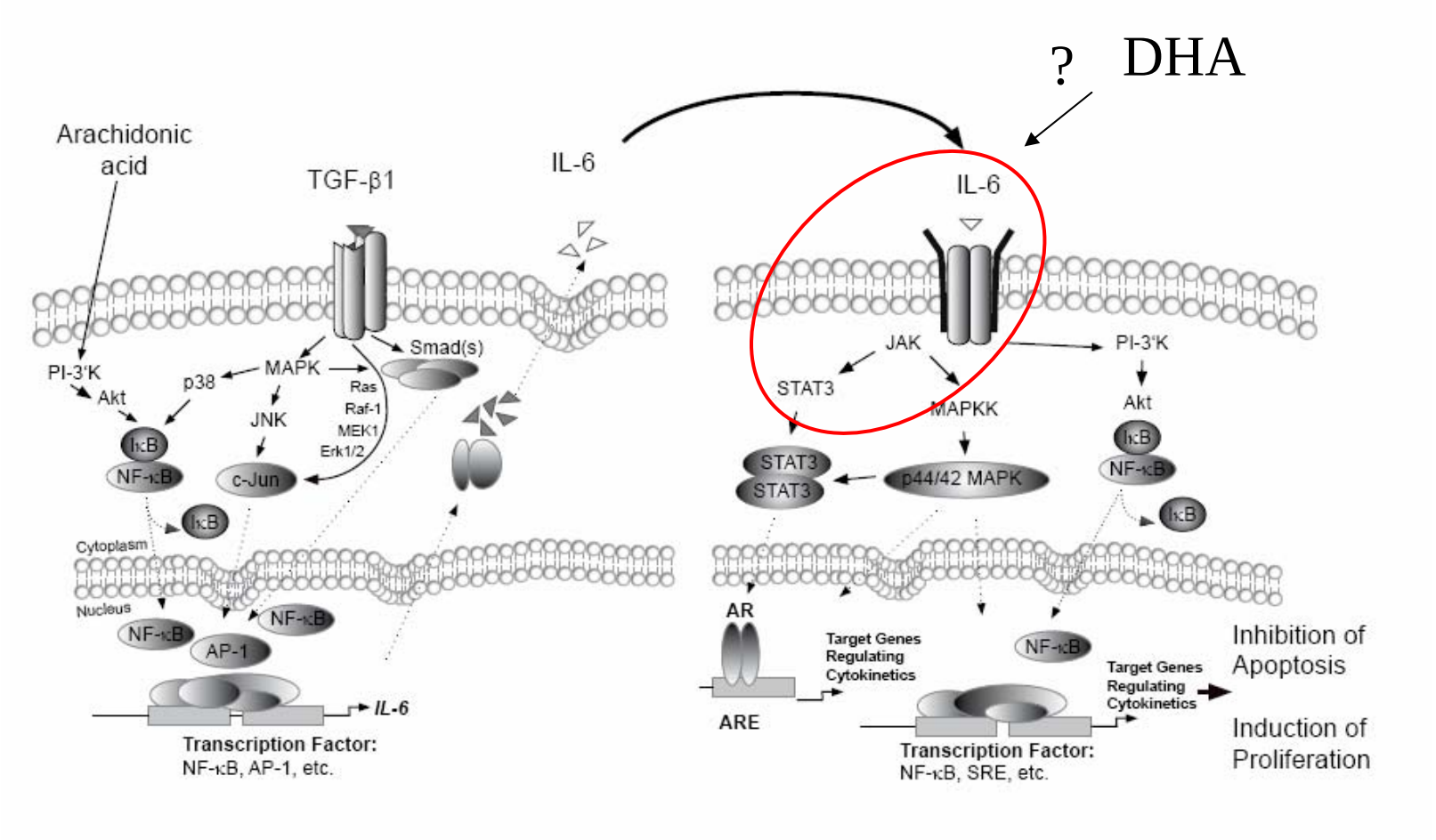
Polyunsaturated fatty acids (PUFAs)

- Modulators of carcinogenesis
- n-6 – pro-inflammatory
- n-3 – anti-inflammatory

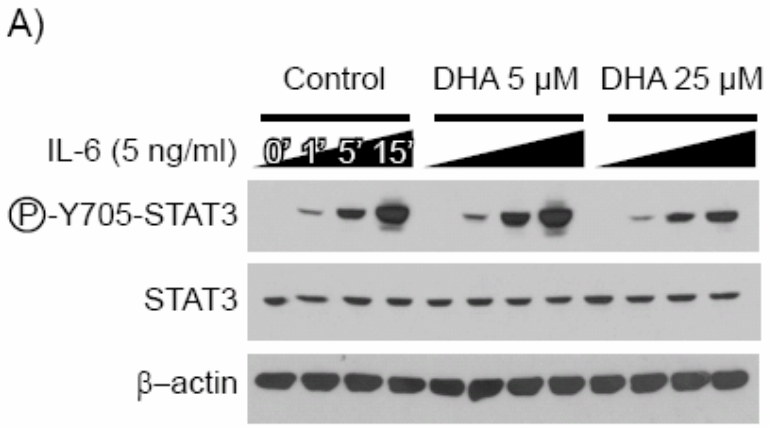
- Docosahexaenoic acid (DHA (n-3)) – modulates signal transduction of various cytokines through lipid rafts.



Modulation of IL-6 signaling pathway



Modulation of IL-6 signaling pathway by DHA



Summary II

- We have characterized model of NED of LNCaP cells;
- DHA has potential to modulate signal pathway of IL-6.

Acknowledgement

- Alois Kozubík
  Head of Department of Cytokinetics
  Institute of Biophysics, Brno

- Pavel Krčmář, Miroslav Machala, Veterinary Research Institute, Brno
- Todd Waldman, Georgetown University, Washington DC