
INTRACELLULAR SIGNALLING

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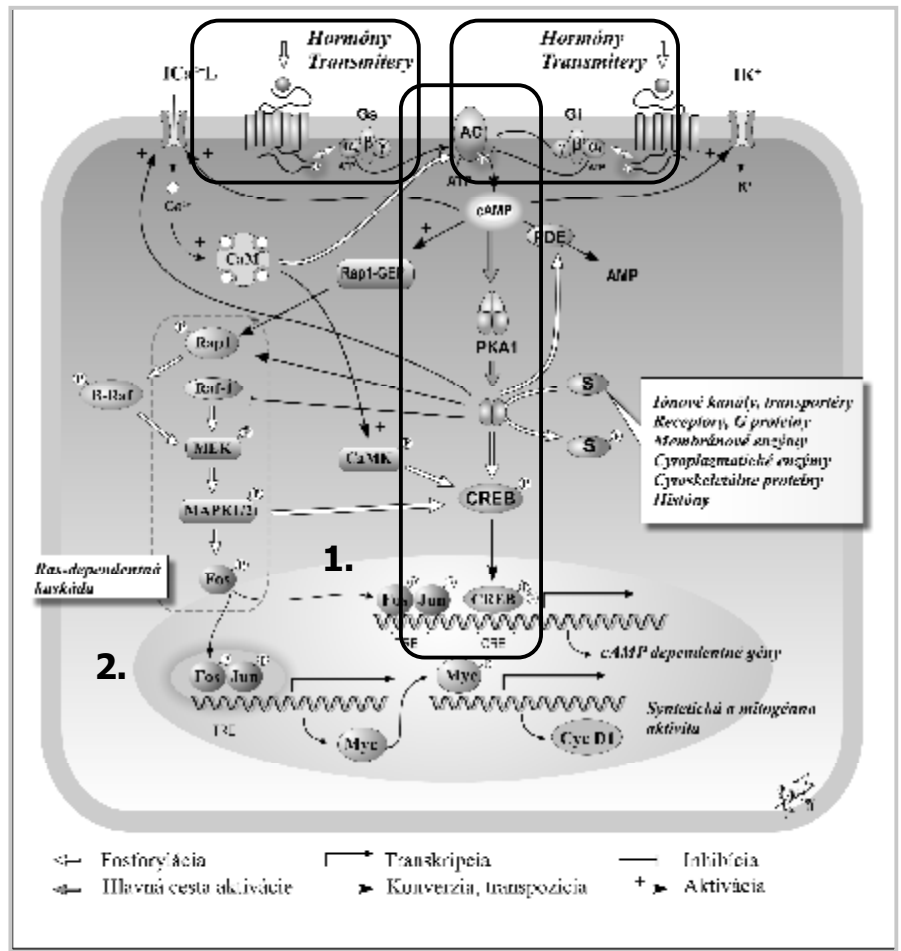
1. Long distance chemosignalling

A. Receptors without enzymatic activity

- n c-AMP signalling
- n IP3- dependent signalling
- n c-GMP/NO – signalling
- n PLA2 –dependent signalling
- n Ca²⁺- dependent signalling

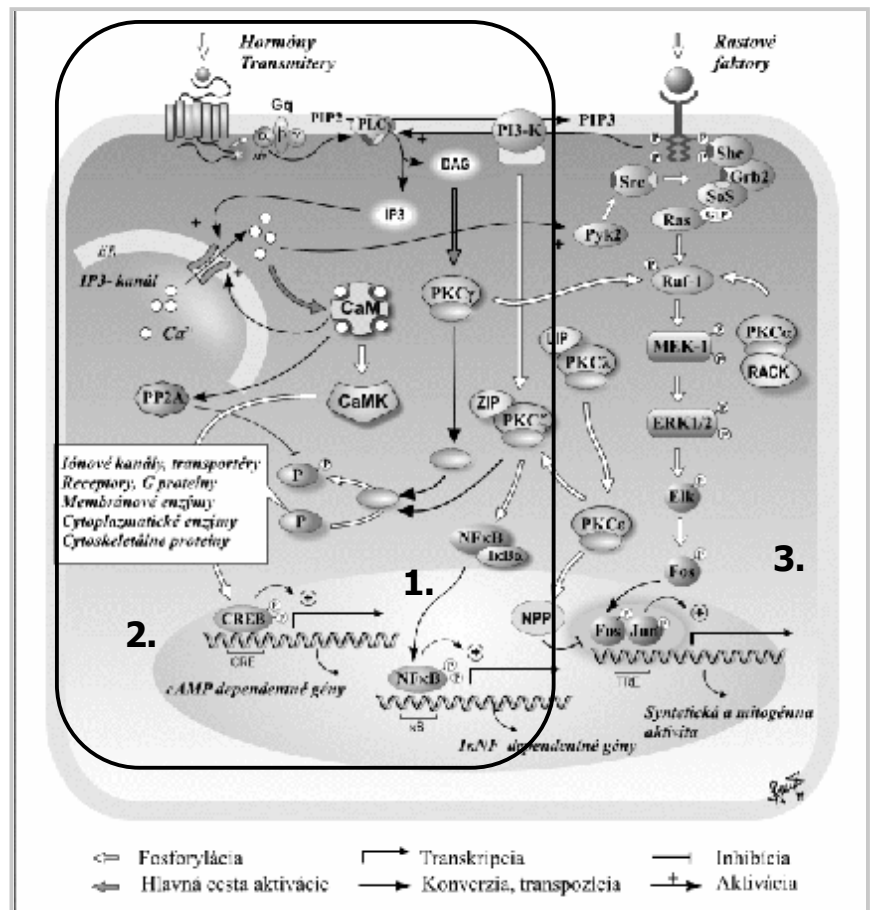
c-AMP-dependent signalling

- n Trigger: many hormones, transmitters, cytokines
- n Membrane G.protein coupled receptors
- n Stimulatory & inhibitory transfer (Gs or Gi)
- n Effectors: Adenyl cyclase – cAMP - PKA
- n Effects: widespread
 - Immediate: phosphorylation of proteins
 - Late: gene expression



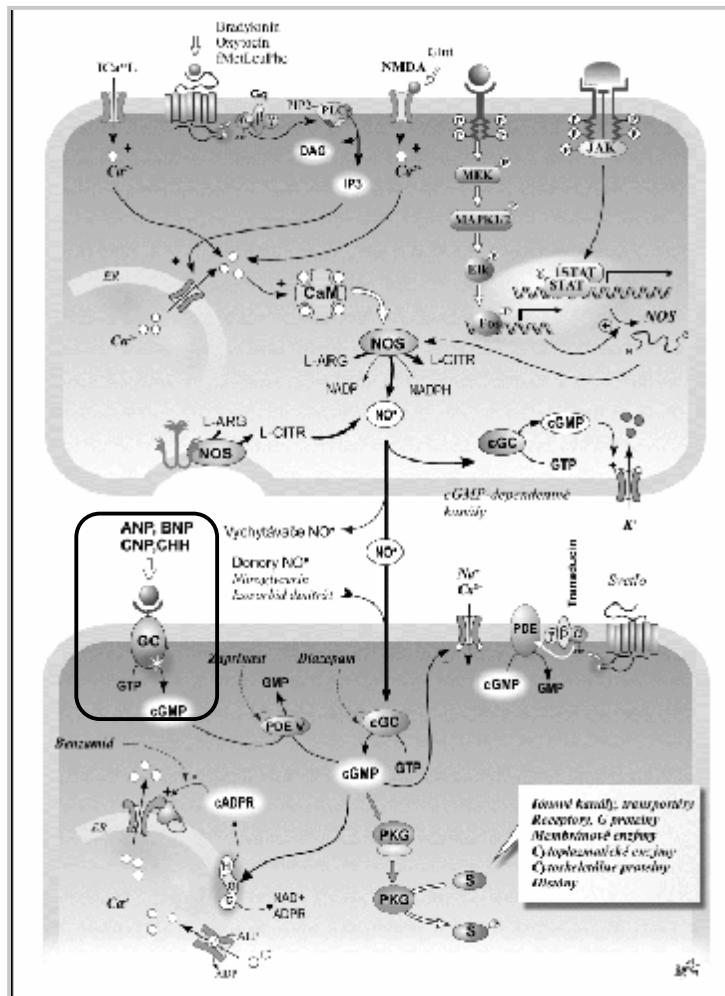
IP3 / DAG – signalling

- n Trigger: many hormones, transmitters, cytokines
- n Membrane G.protein coupled receptors (Go)
- n Both stimulatory & inhibitory influence
- n Effectors: Phospholipase C (PLC) – DAG, IP3 - PKC
- n Effects: widespread
 - Immediate: phosphorylation of proteins
 - Late: gene expression



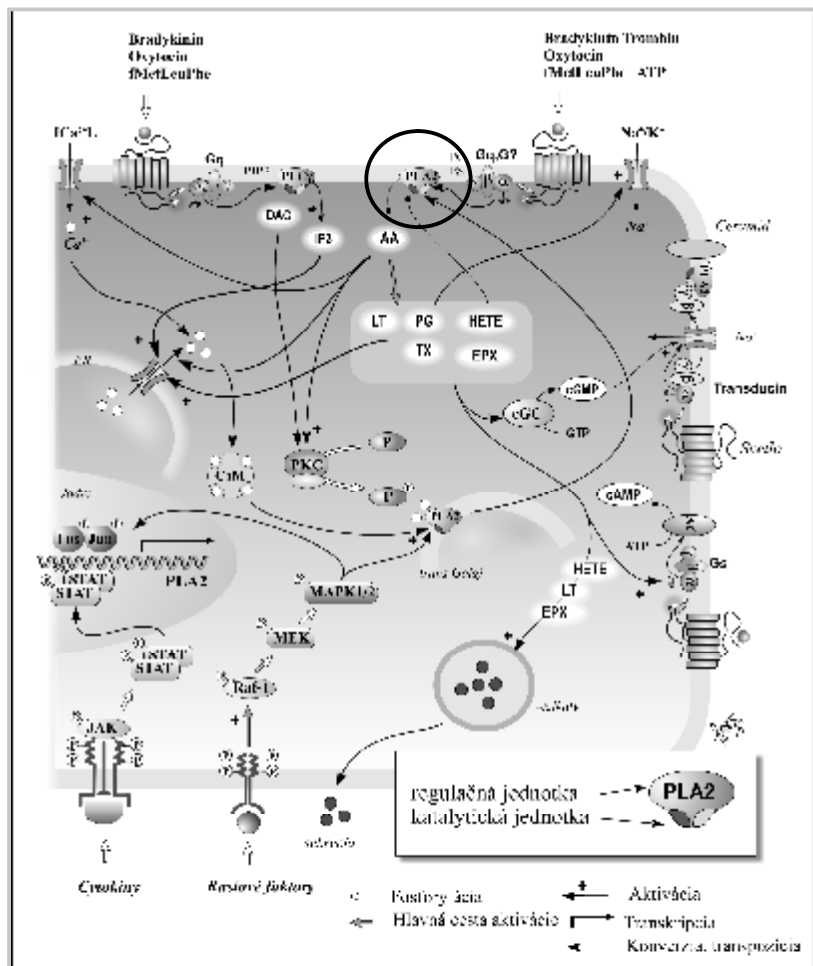
cGMP/NO – signalling

- n Triggers:
 - A. Ca²⁺ - signalling
 - B. ANP, BNP
 - C. NO - donors
- n Membrane G-protein coupled receptors + Membrane receptors with GC activity
- n Effectors: NO, cGMP - PKG
- n Effects: phosphorylation of proteins
- n Use: - vascular smooth muscle dilation
 - vision, etc.



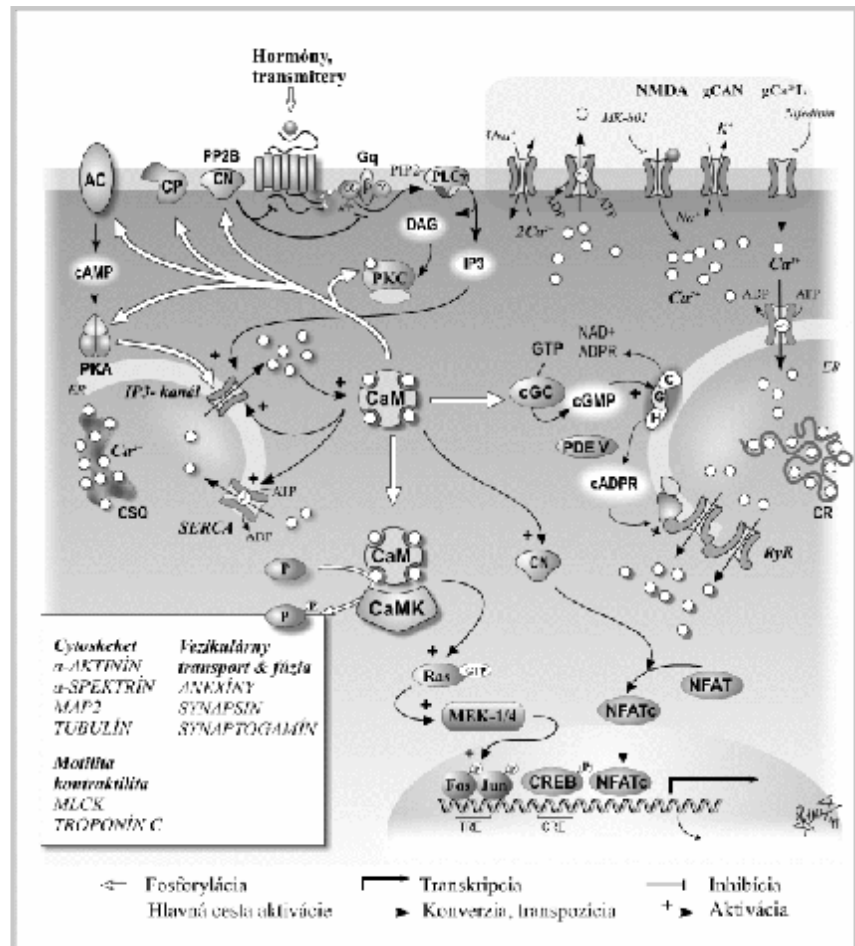
PLA2 – dependent signalling

- n G-protein coupled receptors
- n Use: supplementar to IP3-dependent signalling
- n Phospholipase A2 (PLA2)
- n Arachidonic acid (AA)
- n 2nd messeng.: AA derivatives
 - Leucotriens (LT)
 - Prostaglandins (PG)
 - Tromboxans (TX)
 - Epoxides (EPX)
 - HETE
- n Interactions with other signalling: cAMP, cGMP, JAK/STAT, MEK



Ca²⁺-dependent signalling

- n Ubiquitous, of particular importance in skeletal & smooth muscles, nervous sy.
- n Trigger: any rise of cytosolic [Ca²⁺]_i
- n Effectors: calmodulin (CaM)
 - Ser/Thr kinase
- n Effects:
 - Immediate: phosphorylation/ dephosphorylation
 - Late: gene transcription
- n Use: trasmission of excitatory processes



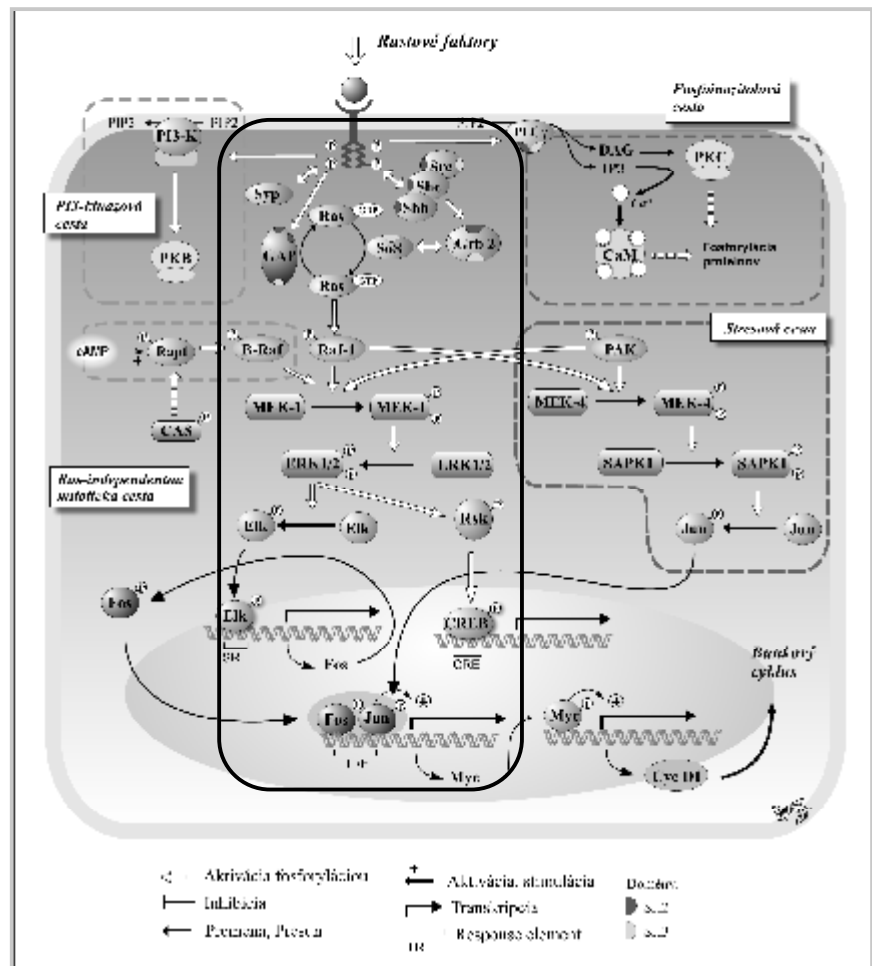
1. Long distance chemosignalling

B. Receptors with enzymatic activity

- n c-AMP signalling
- n IP3- dependent signalling
- n c-GMP/NO – signalling
- n PLA2 –dependent signalling
- n Ca²⁺- dependent signalling

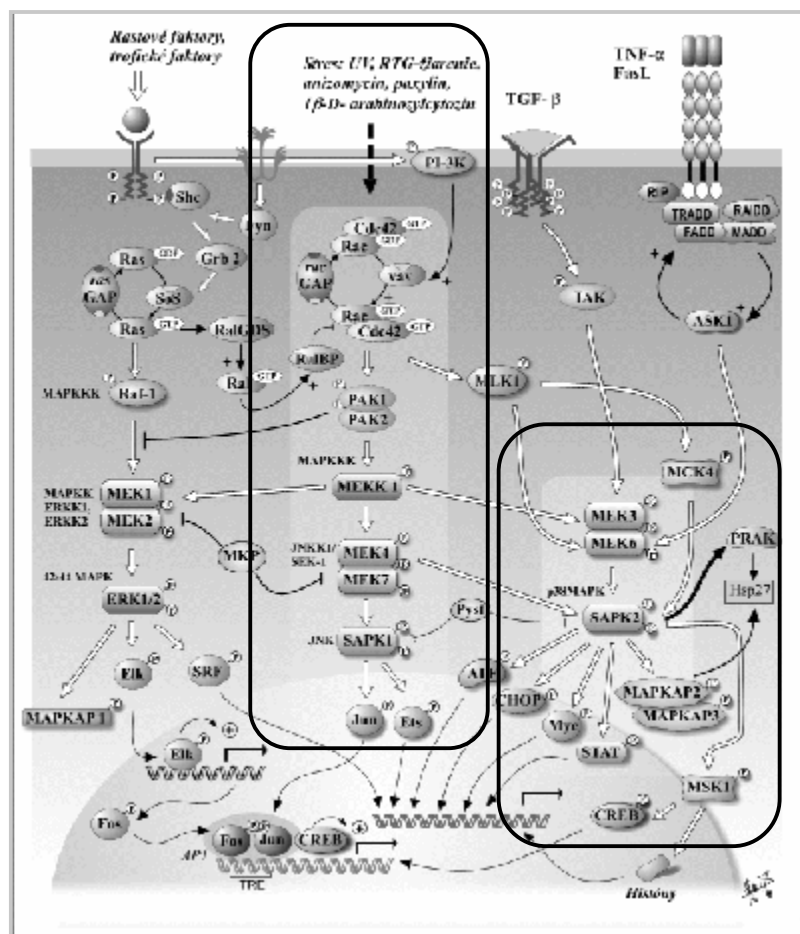
Classical growth signalling

- n **Trigger:** growth factor families
- n **Receptors** with enzymatic activity
- n **Effectors:**
 - Ras – switch
 - MAPK cascade
- n **Effect:**
 - Gene transcription
- n **Use:**
 - proliferative & growth process
 - mitosis



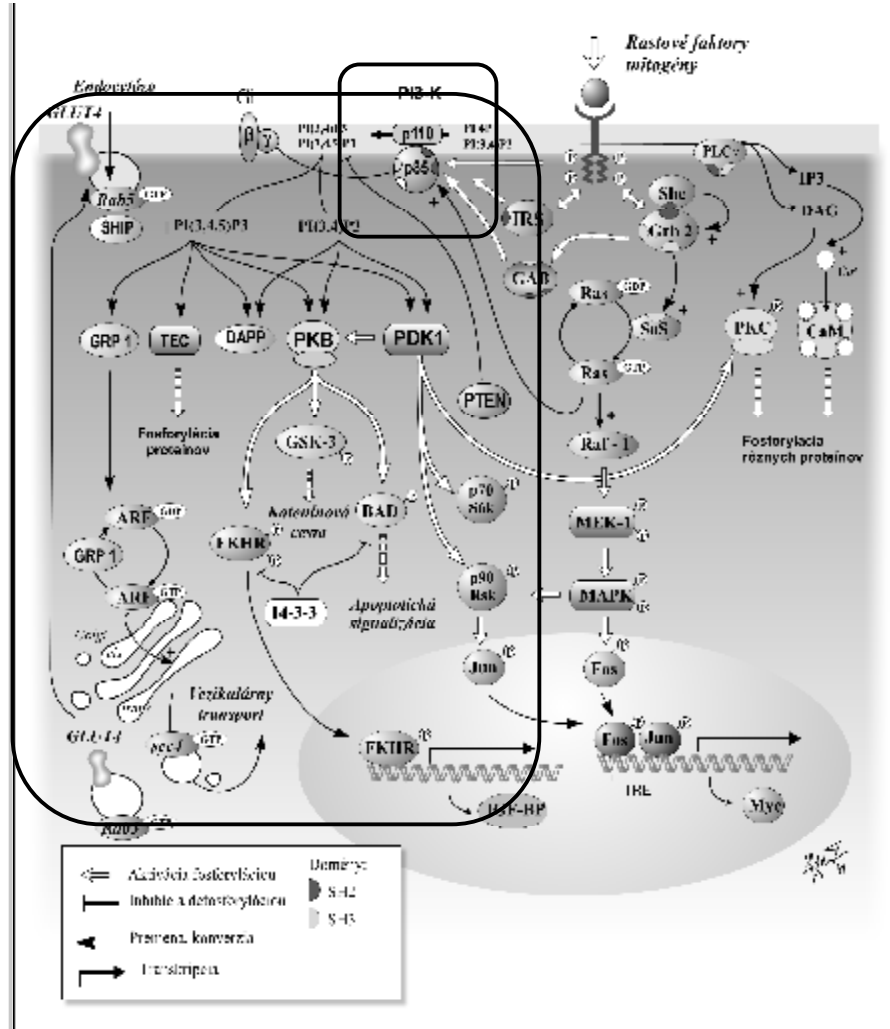
Stress signalling

- n **Trigger:**
 - growth factor families
 - physical : UV, X-rays, temp.
 - chemicals
- n **Receptors with enzymatic activity**
- n **Effectors:**
 - Ras – switch
 - MAPK cascade
- n **Effect:**
 - Gene transcription
- n **Usage:**
 - proliferative & growth process (mitosis)
 - adaptations



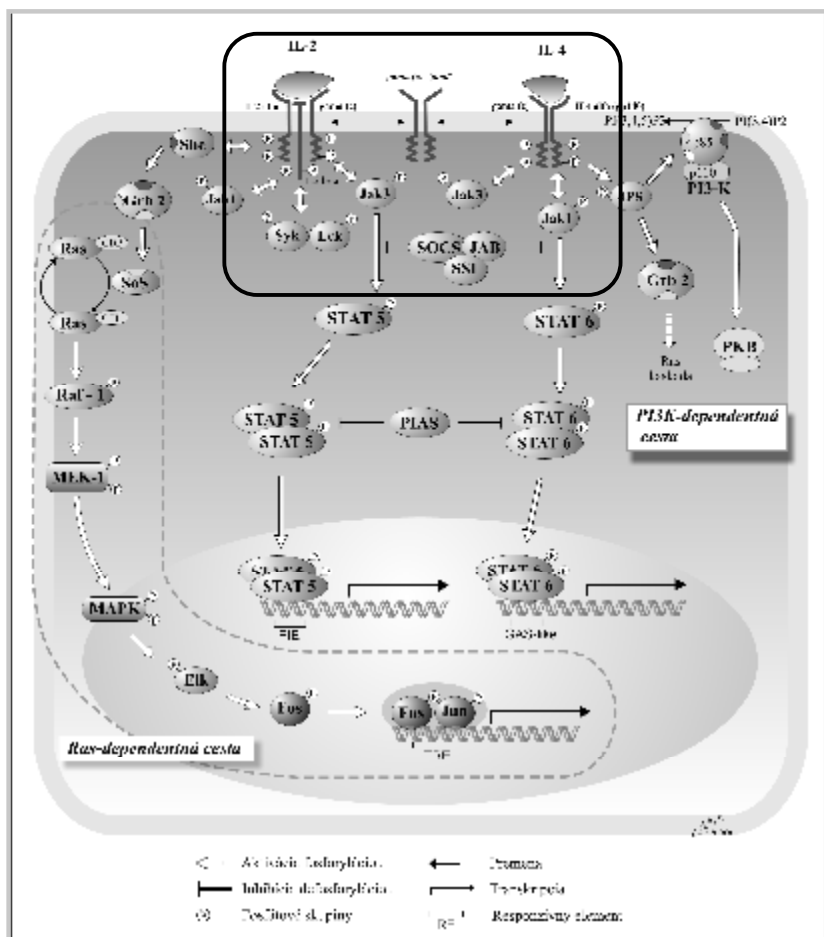
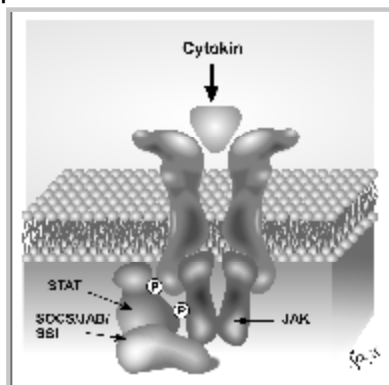
Signalling via PI-3K

- n **Trigger:** growth factor families
- n **Receptors** with enzymatic activity
- n **Effectors:**
 - **PI3K –PKB, PDK**
- n **Effect:**
 - Gene transcription
 - Vesicular transportation
 - Apoptotic machinery
 - Fosforylacia of proteins
- n **Use:** proliferative & growth process control



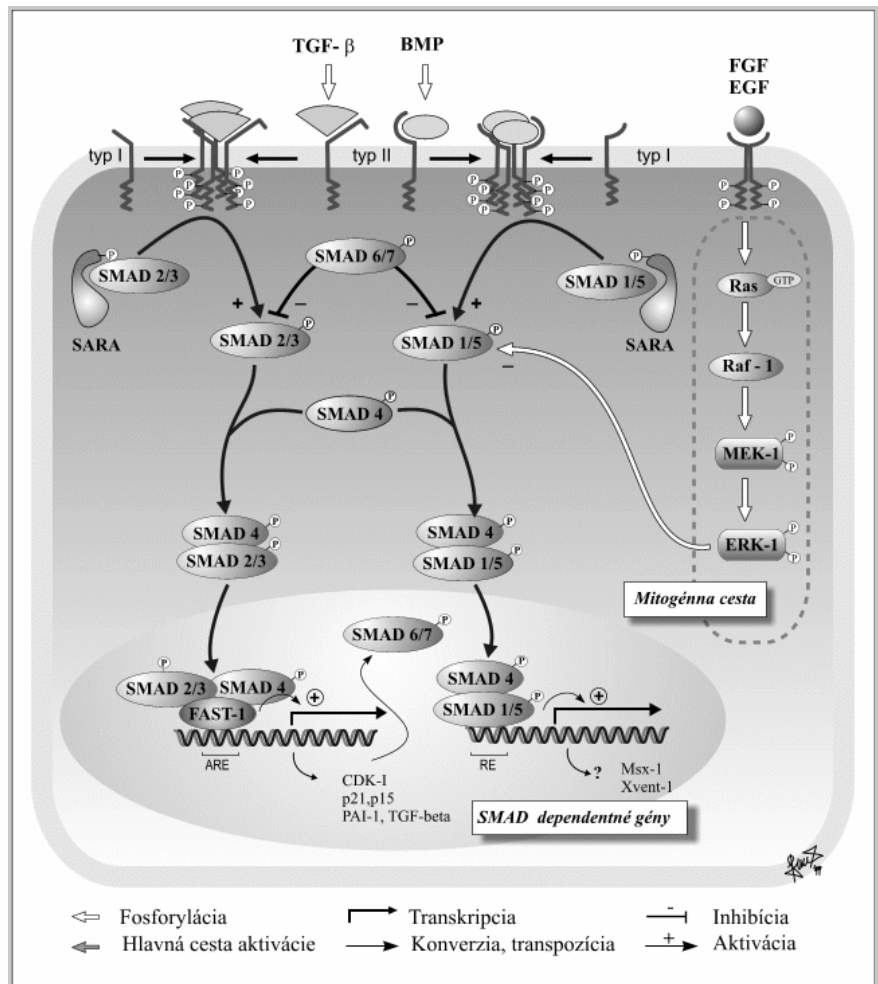
Signalling through JAK/STAT

- n Membrane receptors with associated enzymatic activity
- n Trigger: IL-2, IL.4, IL-6 family, GH, PRL EPO
- n Effectors: SMAD family
- n Effect: early responses gene expression
- n Use: growth & differentiation processes



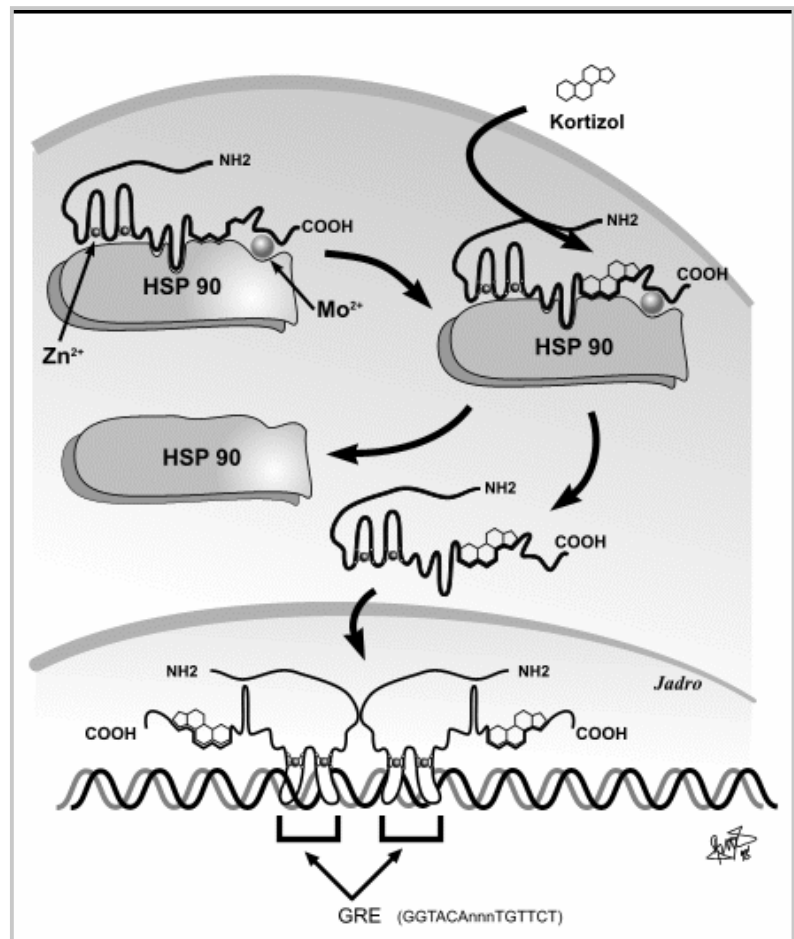
Signalling via SMAD

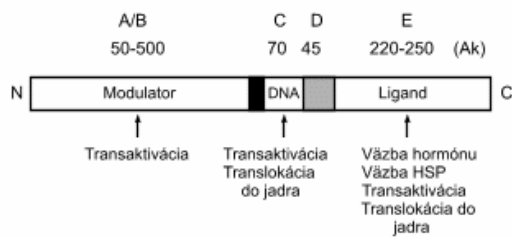
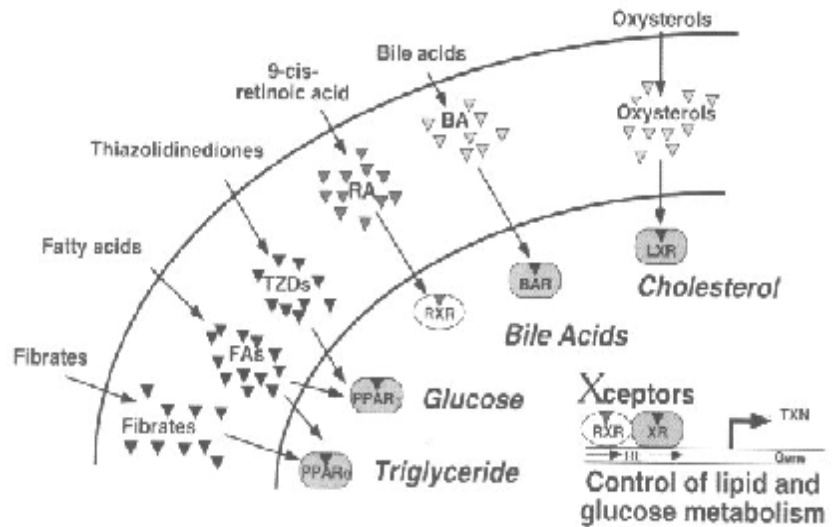
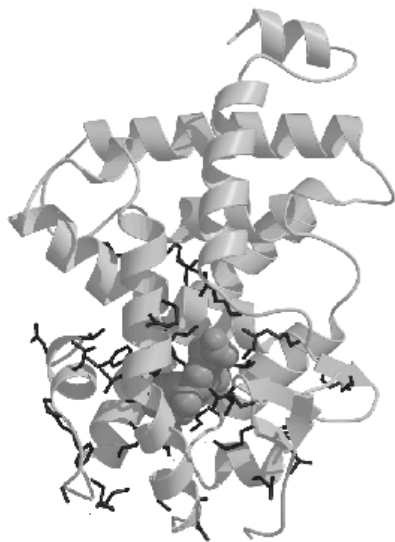
- n Mutiunit membrane receptors with enzymatic activity
- n Trigger: TGF & BMP factors
- n Effectors: SMAD family
- n Effect: delayed - gene expression
- n Use: growth & differentiation processes



Signalling via nuclear receptors

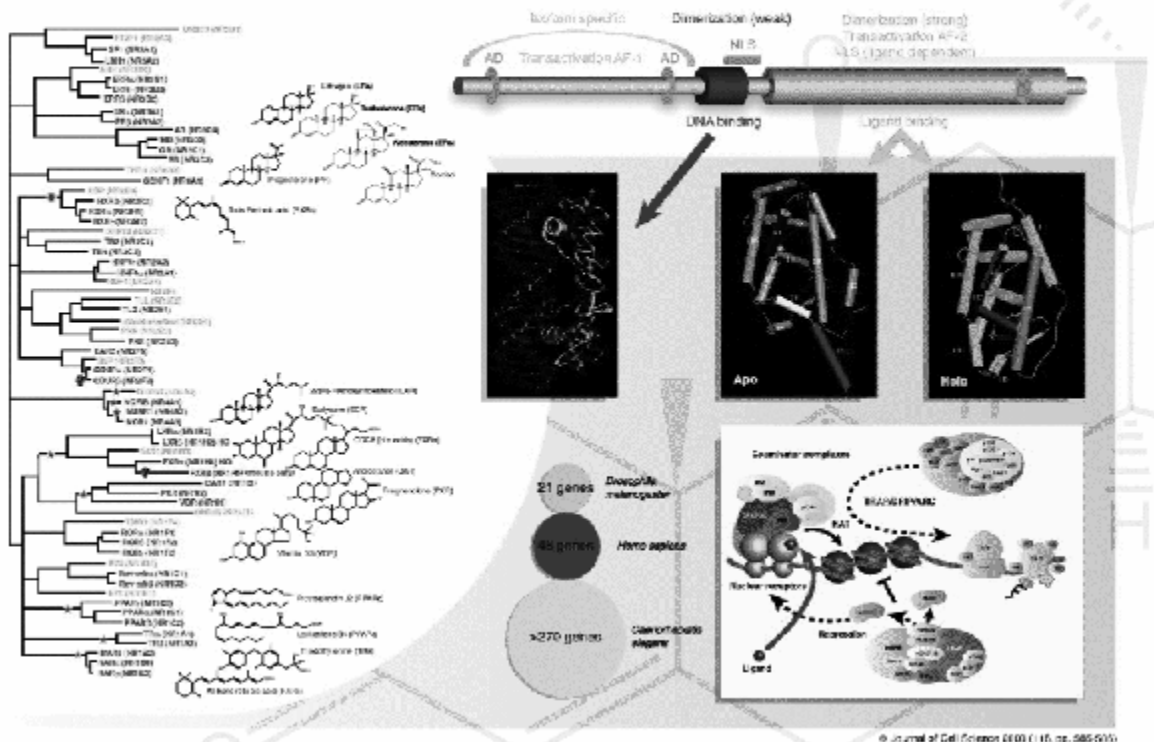
- n **Trigger:** gonadosteroids, retinoids, adrenocorticosteroids, T4/T3, vitD3, deoxycholesterol, PGJ2, LTB4, fatty acids?, bile acids
- n **Effect:** gene transcription





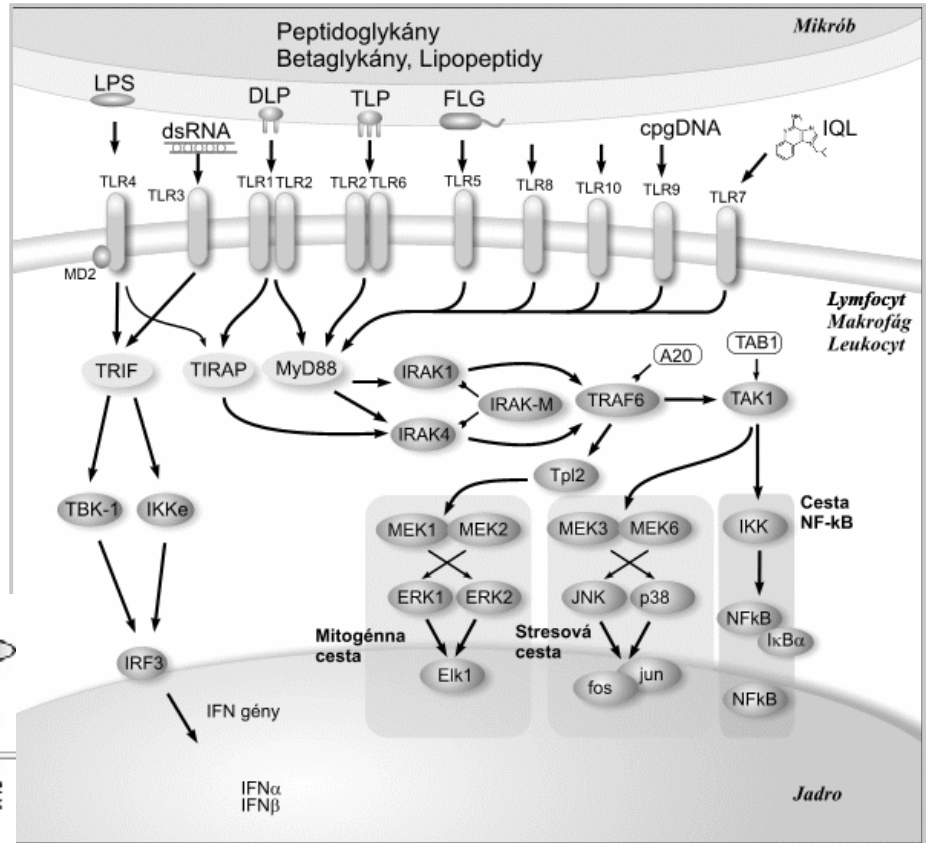
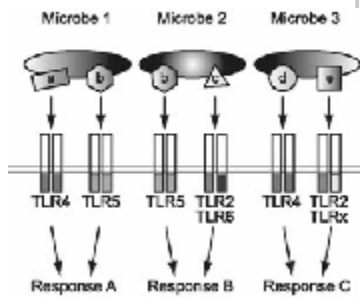
The Nuclear Receptor Superfamily

Marc Robinson-Rechavi, Hector Escriva Garcia and Vincent Laudet



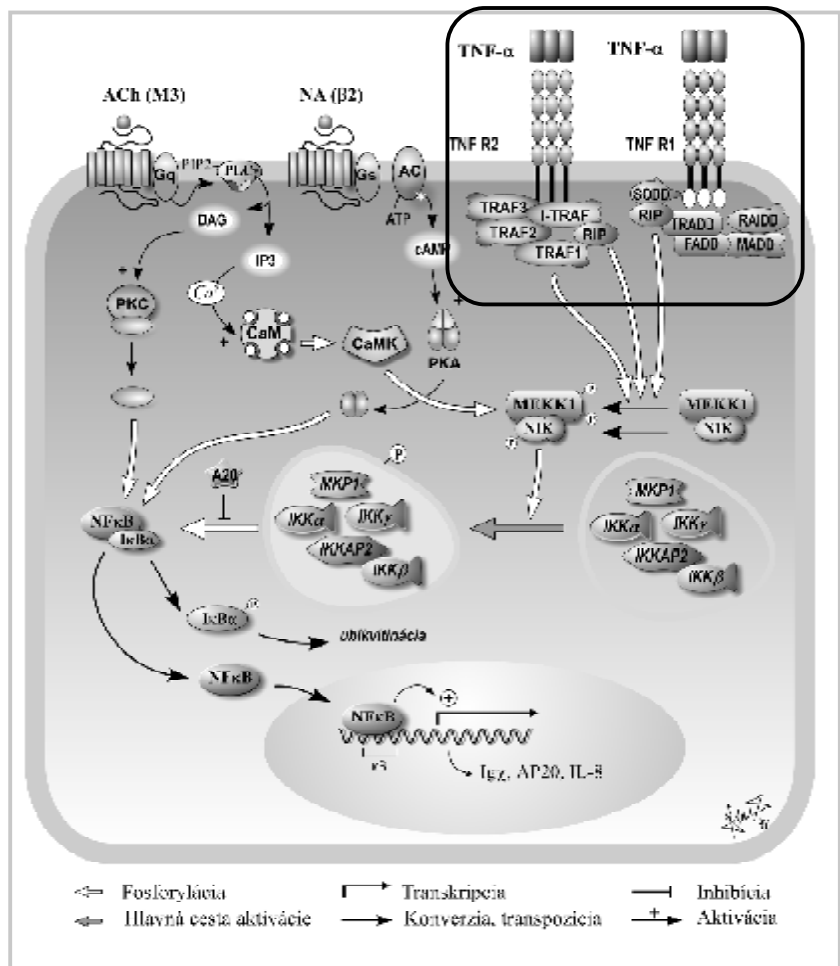
Signalling via Toll receptors

- n **Trigger:** components of bacterial body, chemicals
- n **Effectors:** IRAK, TRIF, TIRAP
- n **Effect:** modifying other signalling pathways
- n **Use:** Component of innate immune response
- n Inflammation – „specific” response to antigen



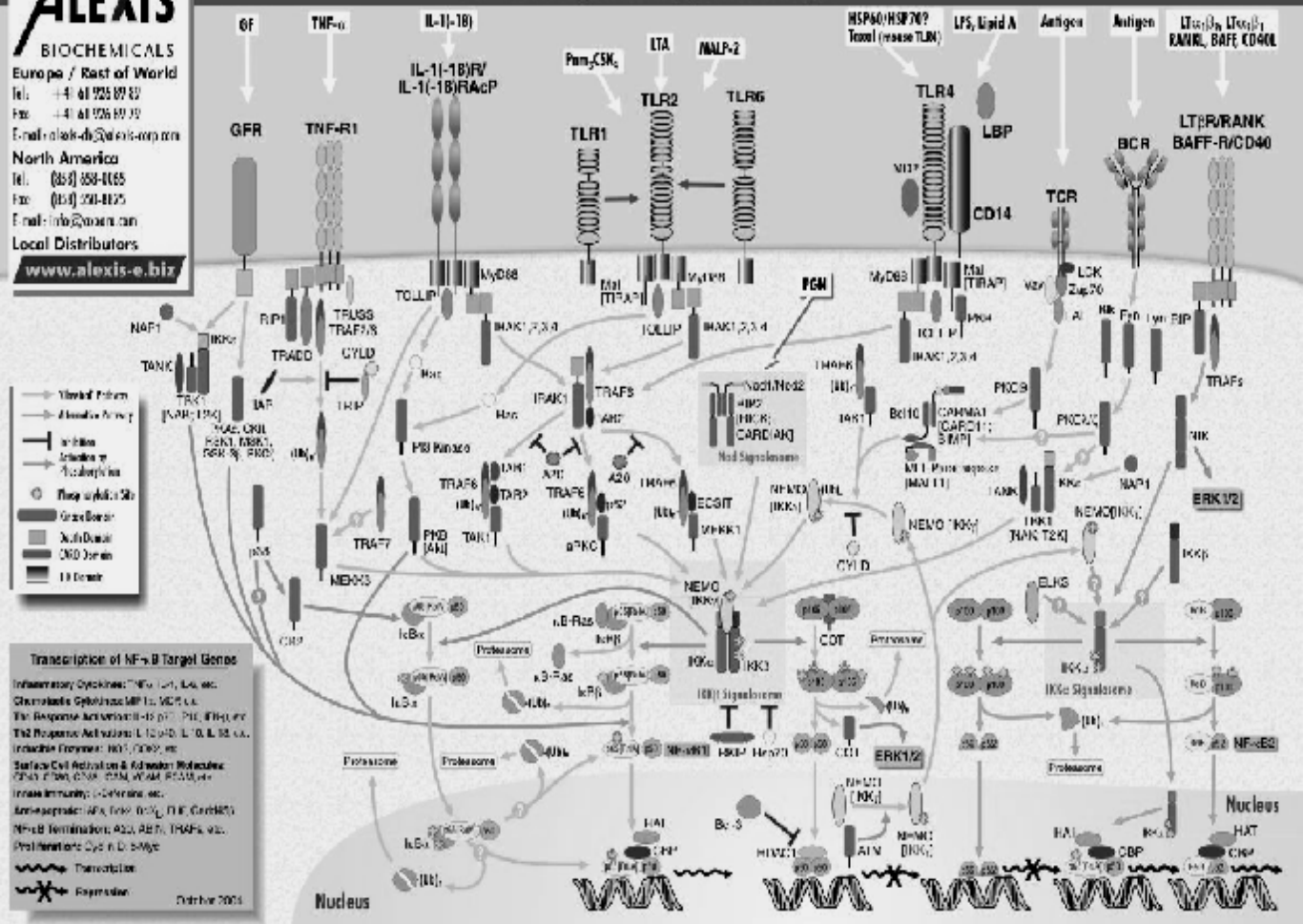
Signalling via NFκB

- n **Trigger:** TNF.alpha family
- n **Effectors:** TRAF, TRADD, RIP
- n **Effects:** Gene expression
- n **Use:** wide spread immune reactions



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NF-κB Signalling Pathways

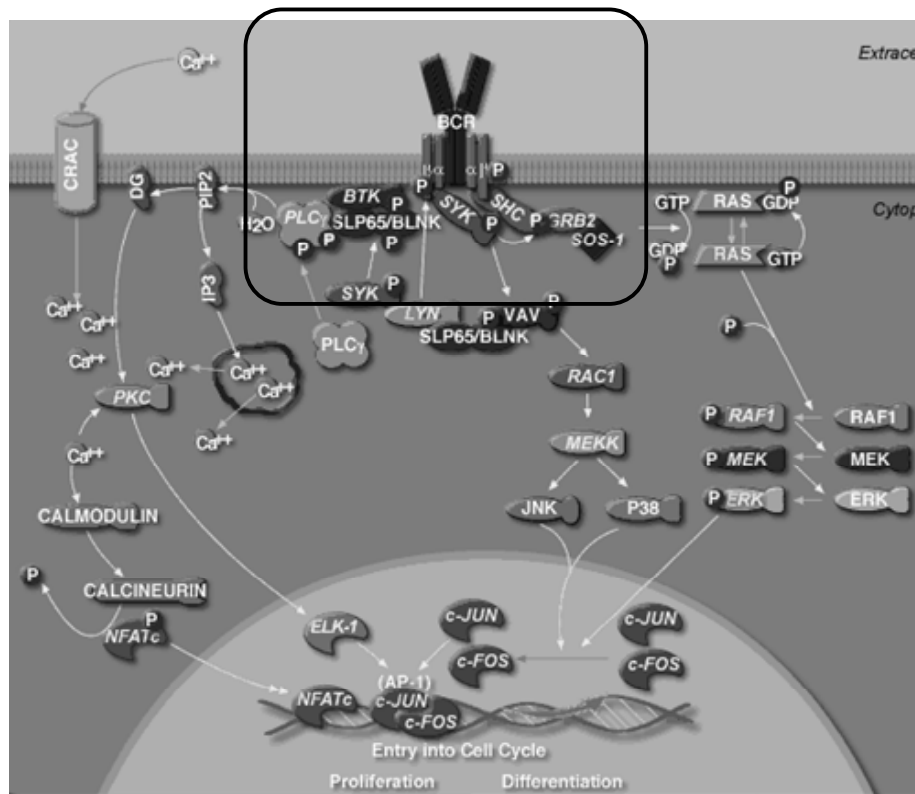


2. Close contact chemosignalling

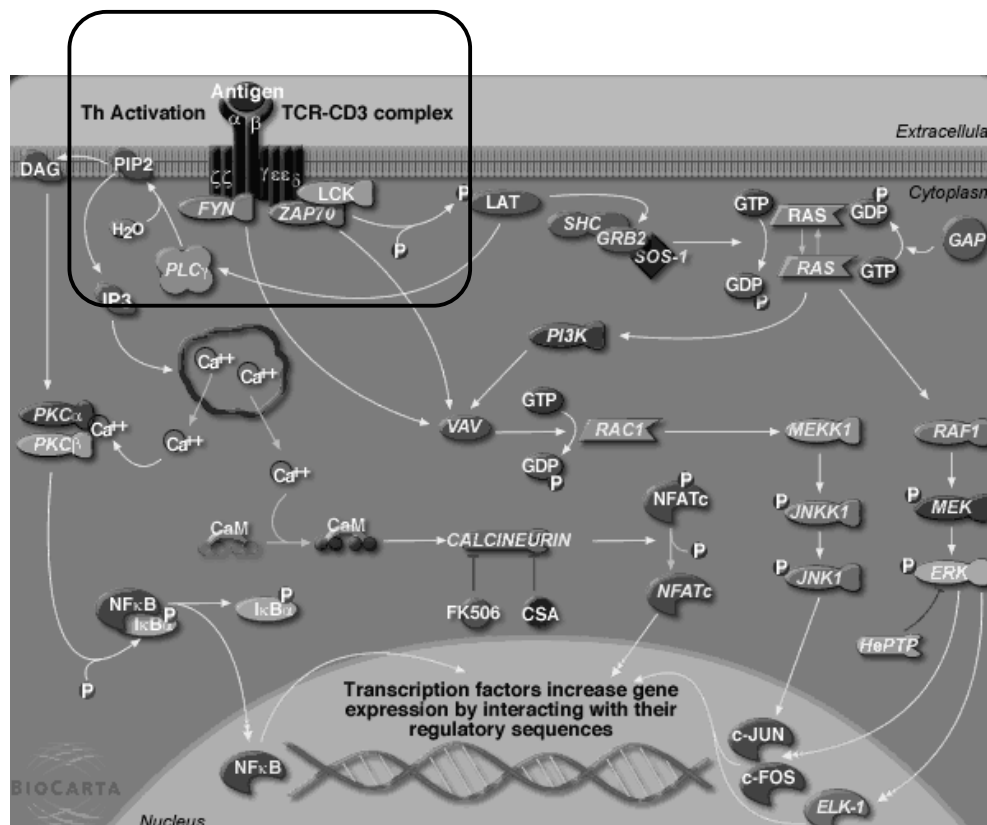
- n BCR signalling
- n TCR signalling
- n Wnt + β-catenin
- n DSL-Notch
- n Hedgehog signalling

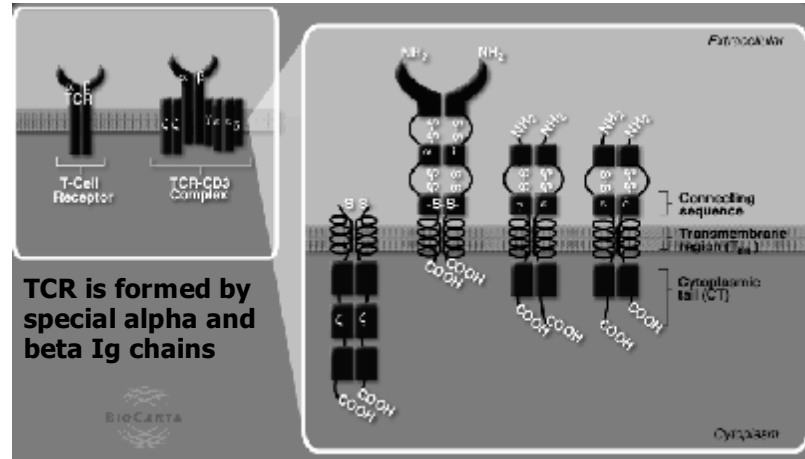
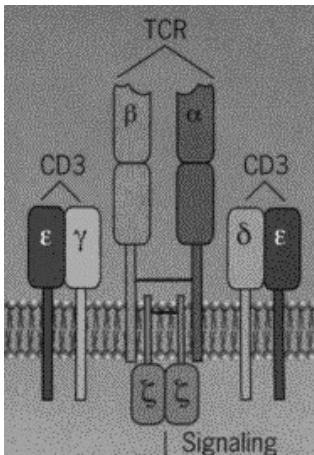
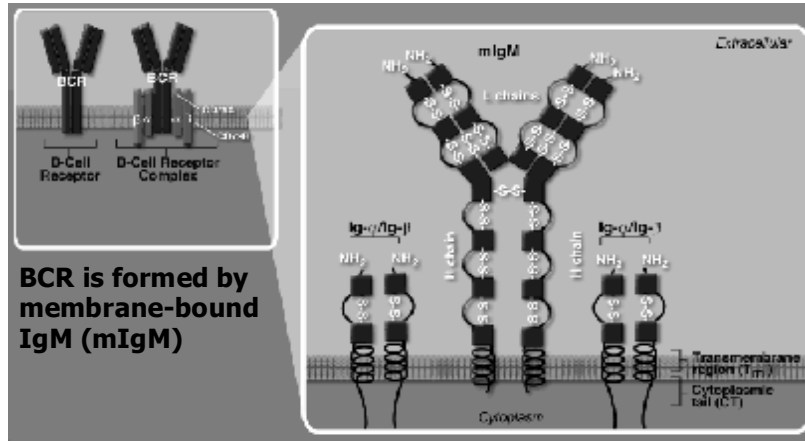
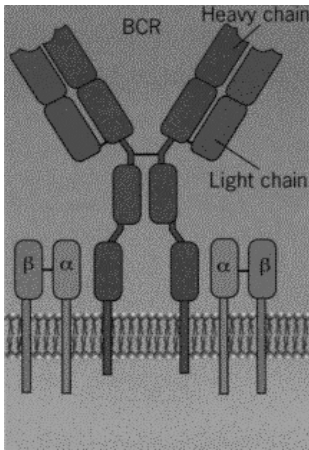
BCR signalling

- n **Trigger:** antigen
- n **Receptors** – multicomponent Ig-family
- n **Effectors:**
 - Growth pathway (Ras-Raf-MEK-ERK)
 - Stress pathway (Rac-MEKK-Jnk,P38)
 - Ca²⁺-CaM pathway
- n **Effect:**
 - Gene transcription
- n **Use:**
 - proliferation (mitosis)
 - synthesis of new proteins

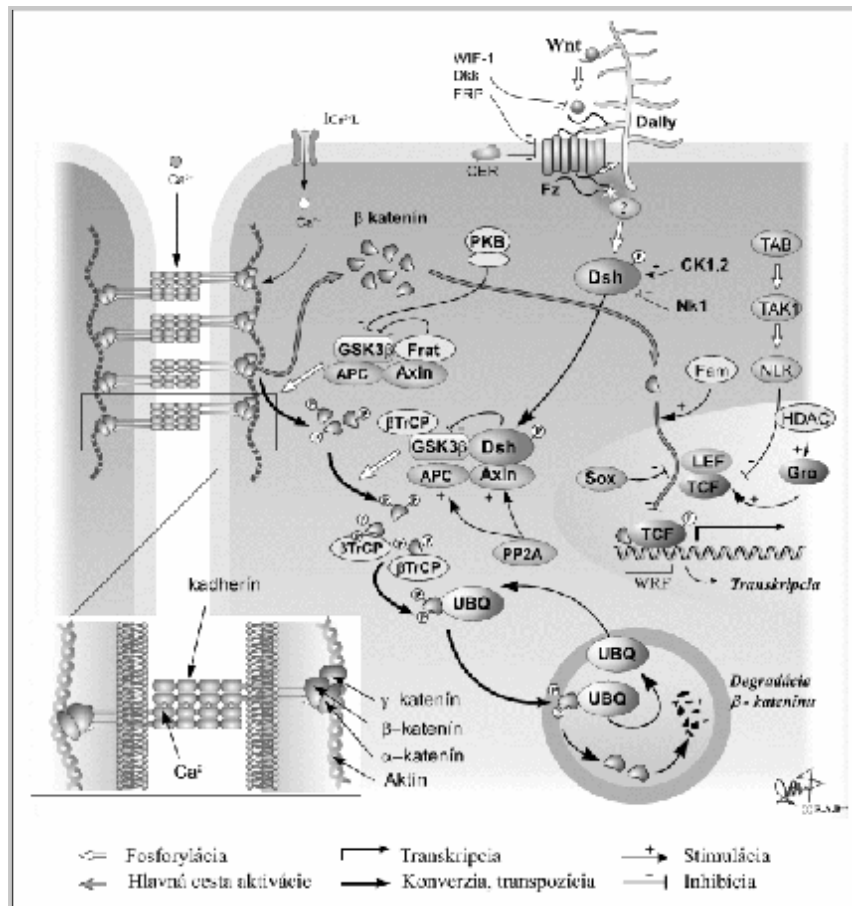


TCR signalling

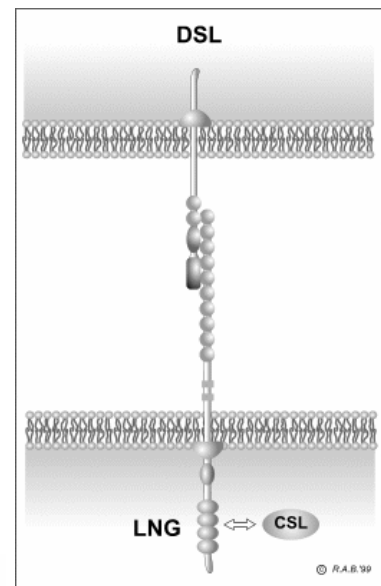
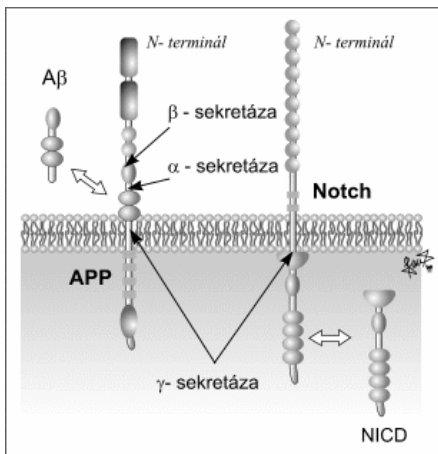
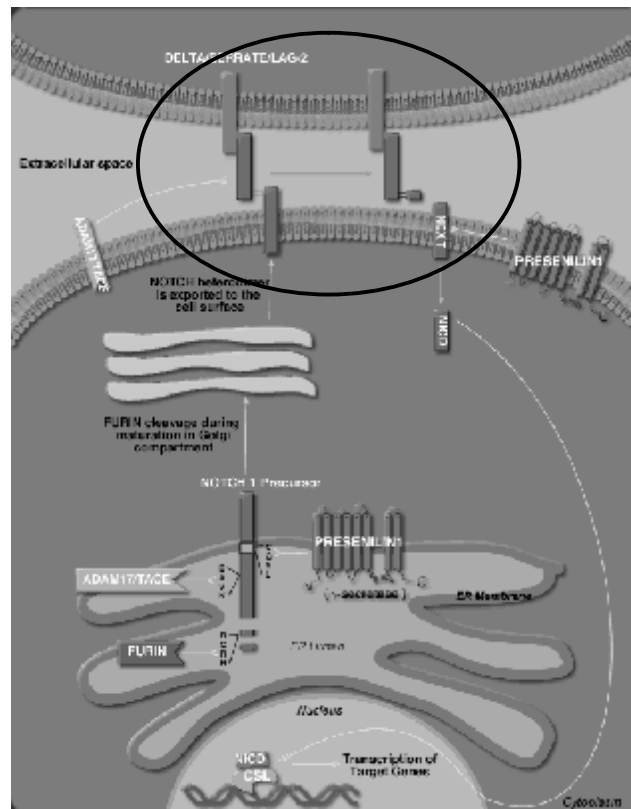
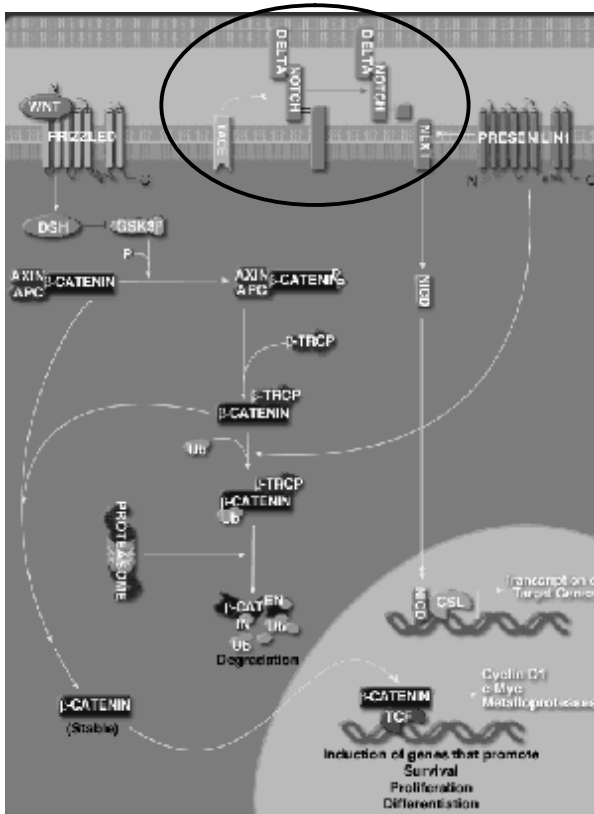




Wnt + b - catenin

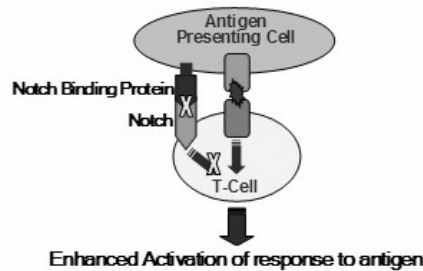
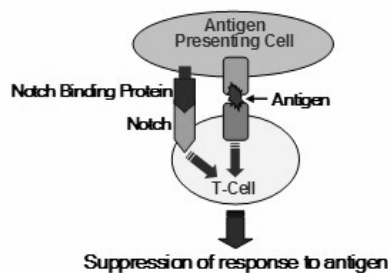


DSL-Notch signalling



T-Cell Response: Suppression

Notch Blockade: Enhanced Activation



Hedgehog signalling

n **Trigger:** Hh family

n **Receptors:**

- Ptc – patched
- Smo –smoothed

n **Effect:**

- Gene expression
- Other signalling

n **Use:**

- Control over proliferation & differentiation

