Signal Transductions in Cardiac Hypertrophy

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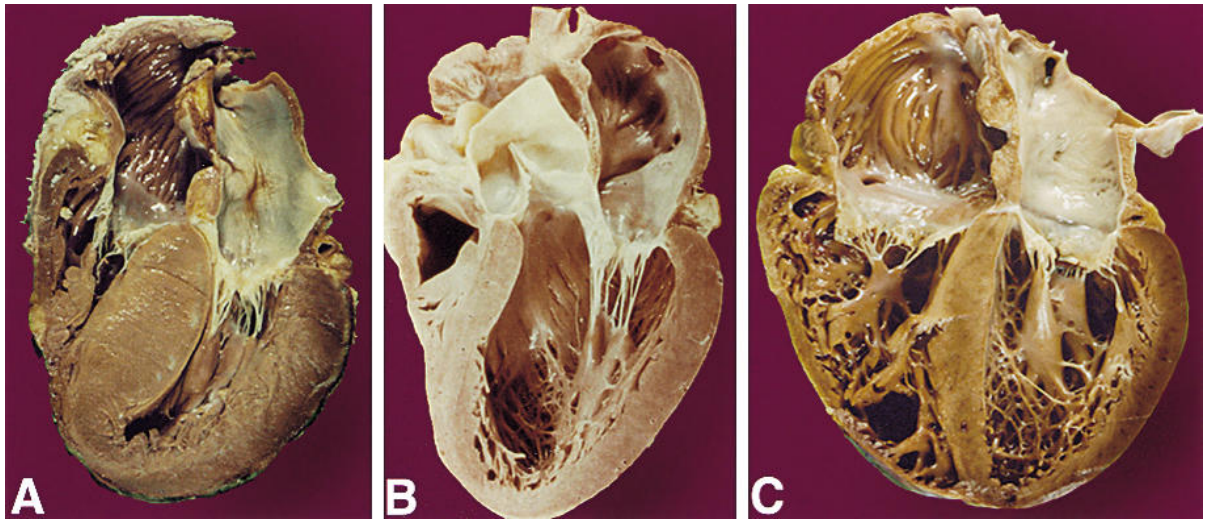
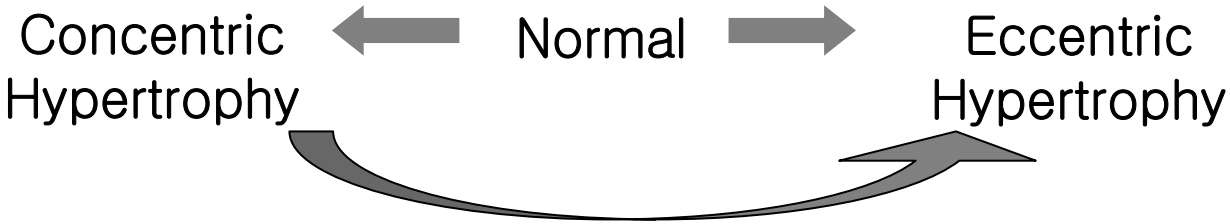
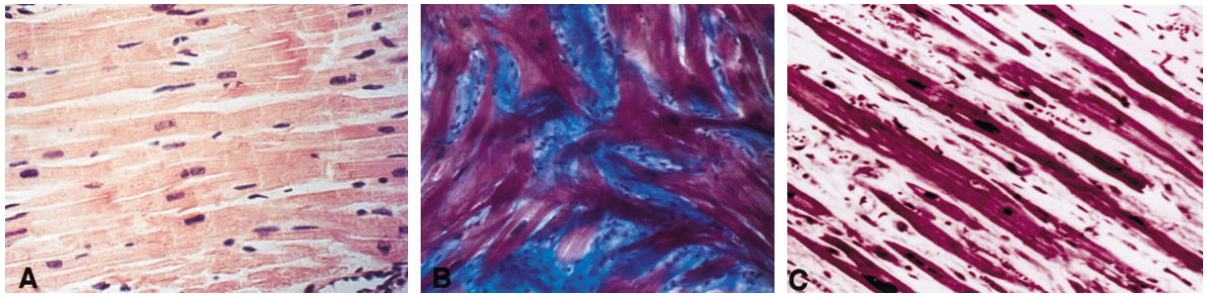
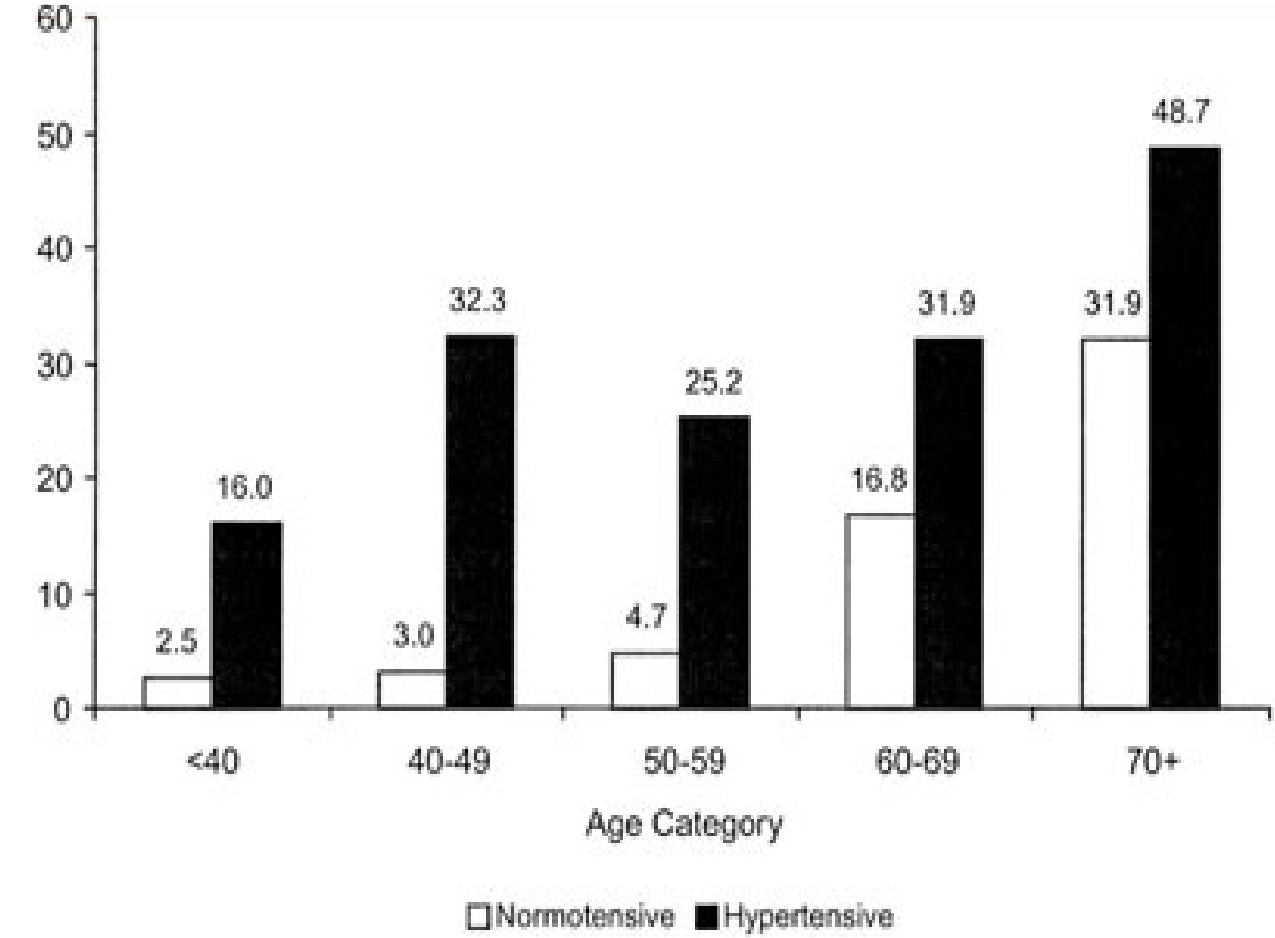
Cardiac hypertrophy

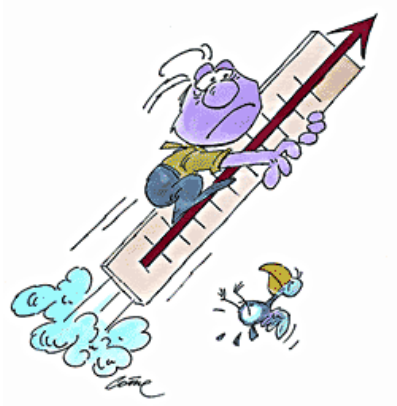






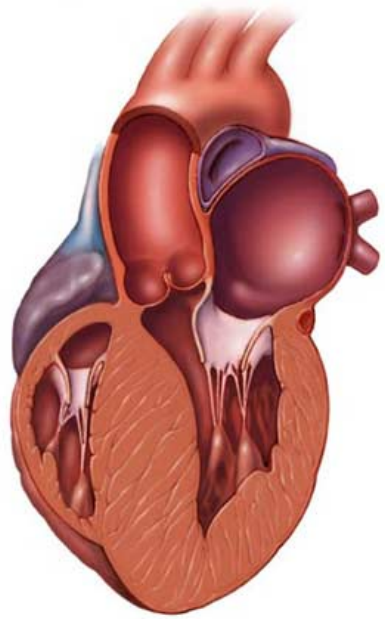
Prevalence of LVH per 1000 population

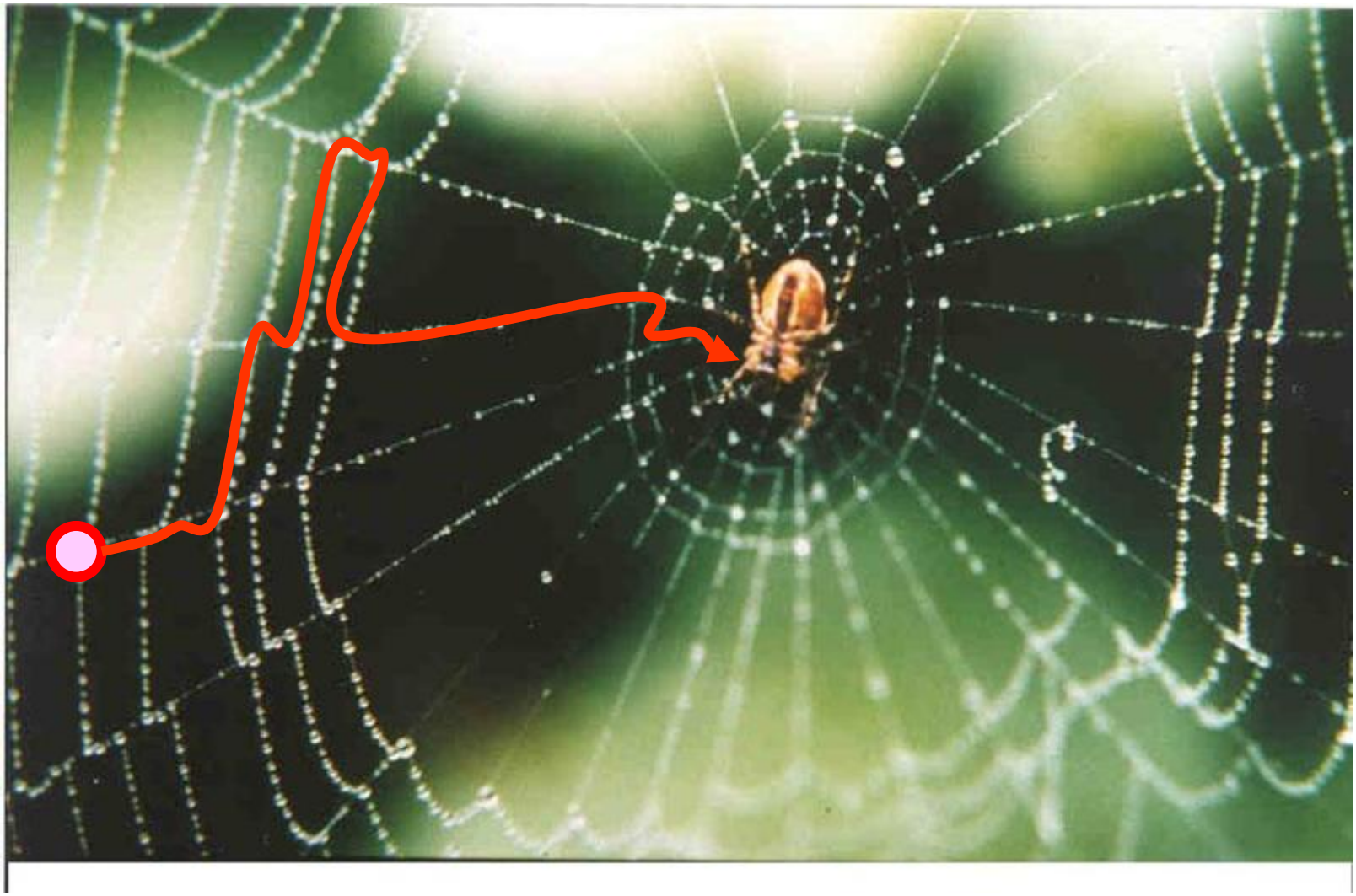


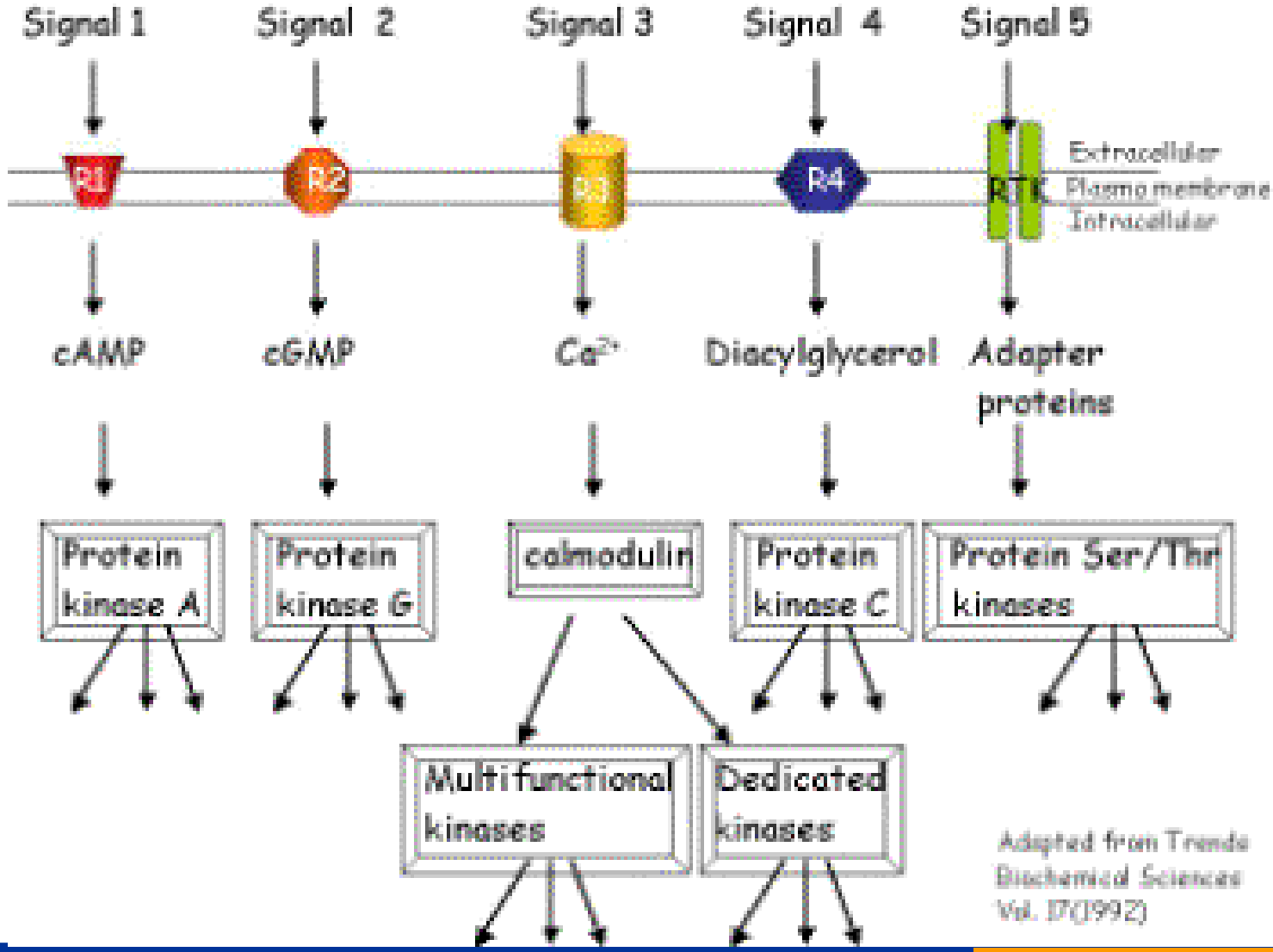


Hypertrophic stimuli in hypertension

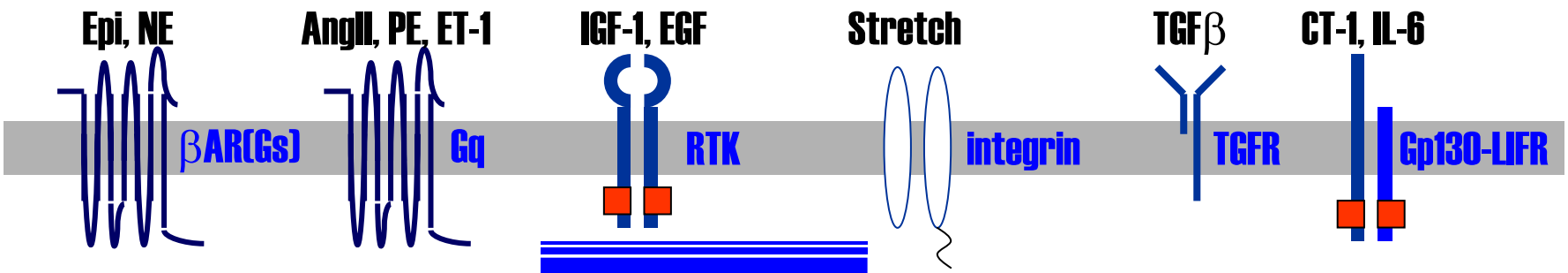
1. **Mechanical stretch: direct**
2. **Mechanical stretch:**
   - **Stimulate the release of local secretary factors**
3. **Neurohumoral pathway:**
   - **Activated by hemodynamic stress**
   - **Release of paracrine and autocrine factors**






Signal 1
Signal 2
Signal 3
Signal 4
Signal 5
R1
R2
R3
R4
RTK
Extracellular
Plasma membrane
Intracellular
cAMP
cGMP
Ca2+
Diacylglycerol
Adapter proteins
Protein kinase A
Protein kinase G
calmodulin
Protein kinase C
Protein Ser/Thr kinases
Multifunctional kinases
Dedicated kinases
Adapted from Trends Biochemical Sciences Vol. 17(1992)

Signals in cardiac hypertrophy



Second messengers

(cAMP, cGMP, Ca^{2+}, DAG, Adaptor protein)

Effectors

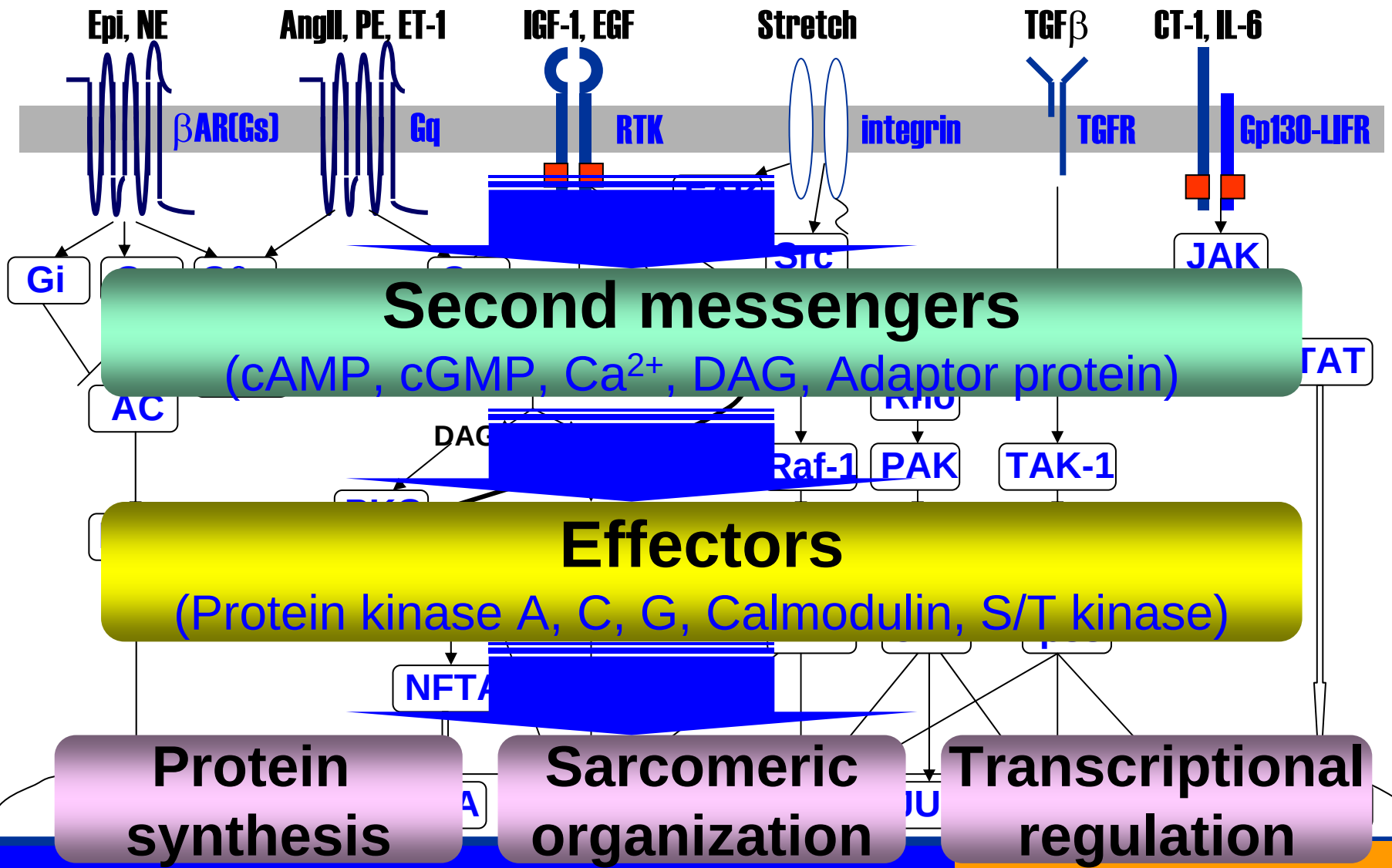
(Protein kinase A, C, G, Calmodulin, S/T kinase)

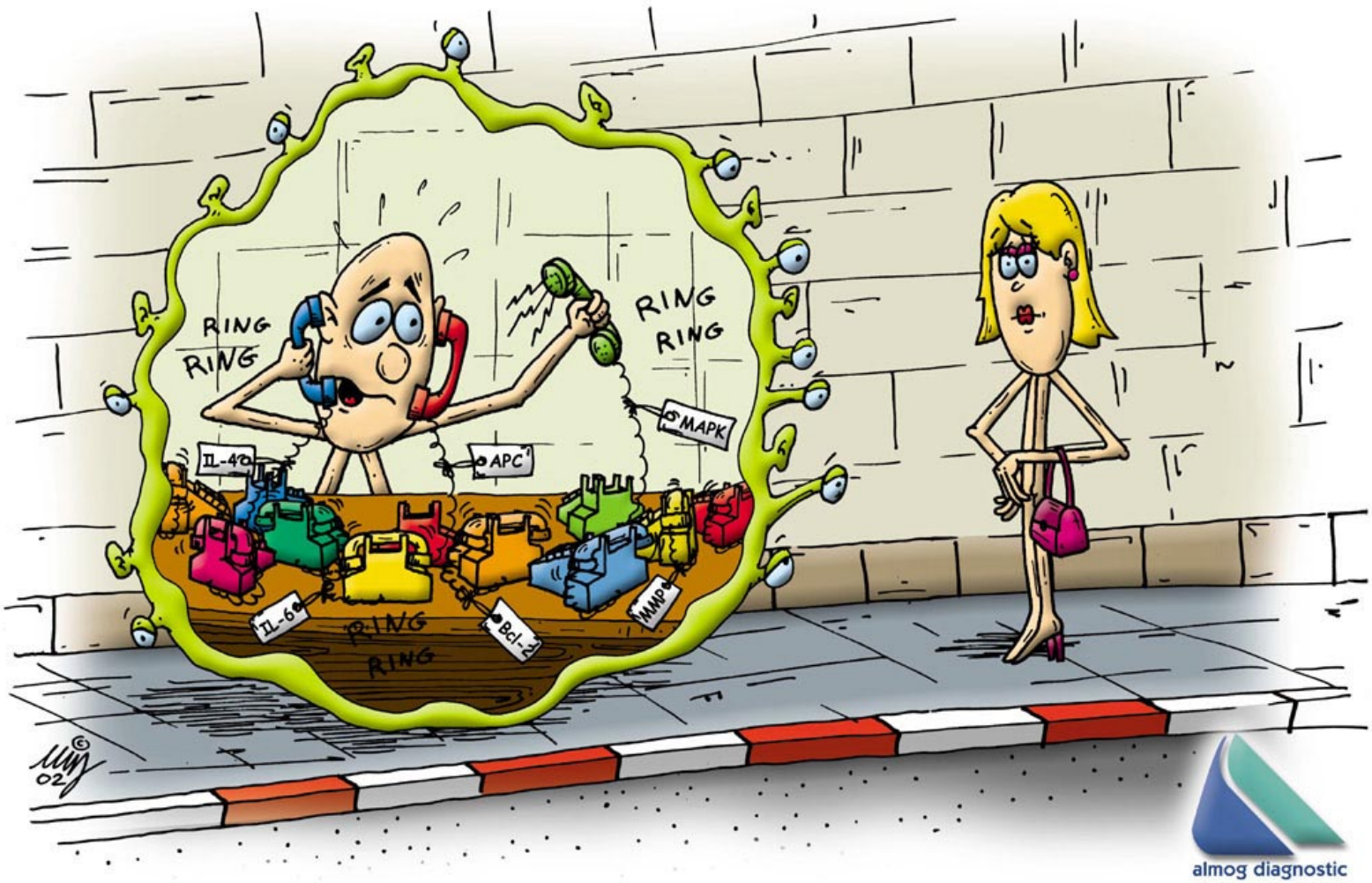
Protein synthesis

Sarcomeric organization

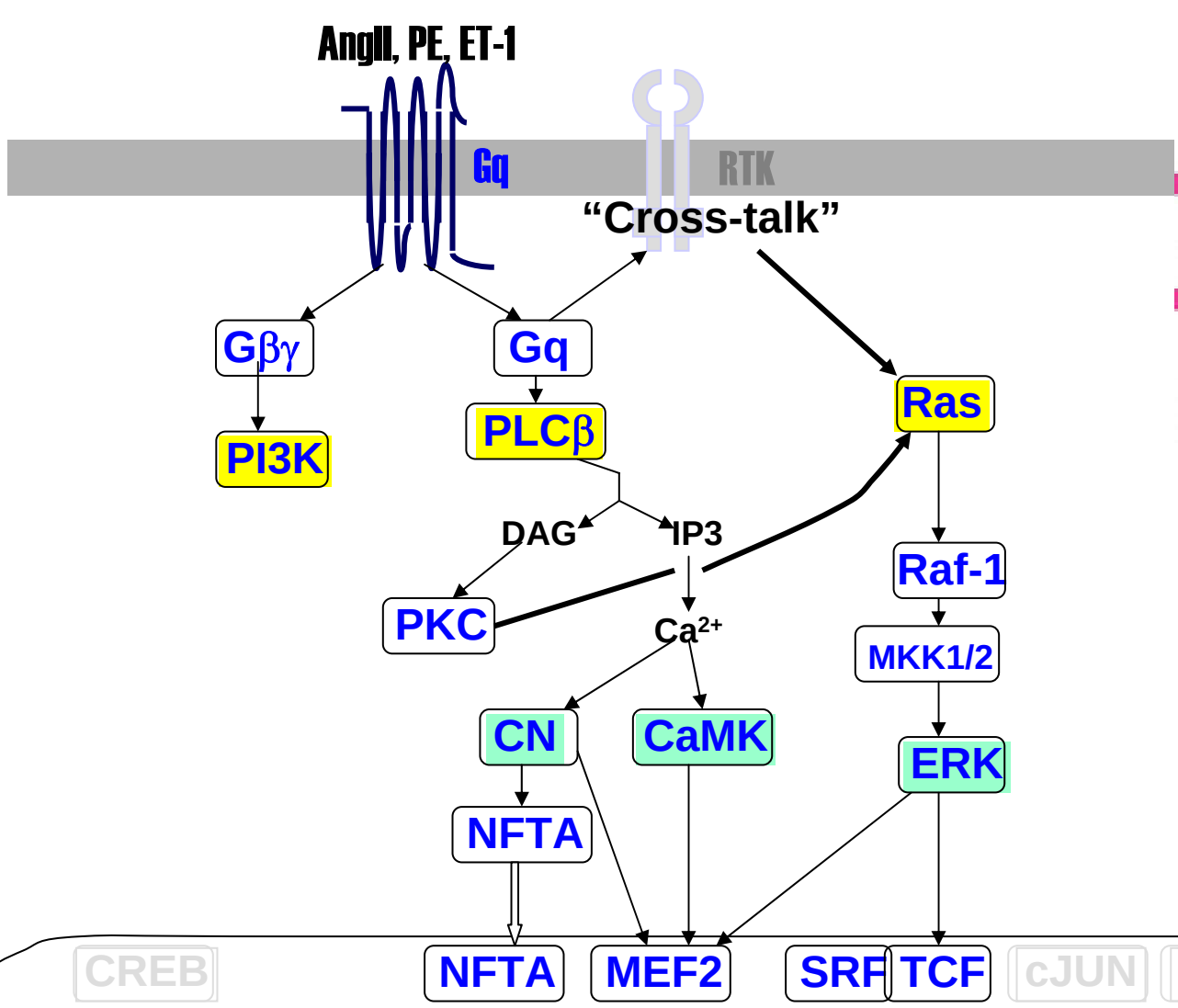
Transcriptional regulation

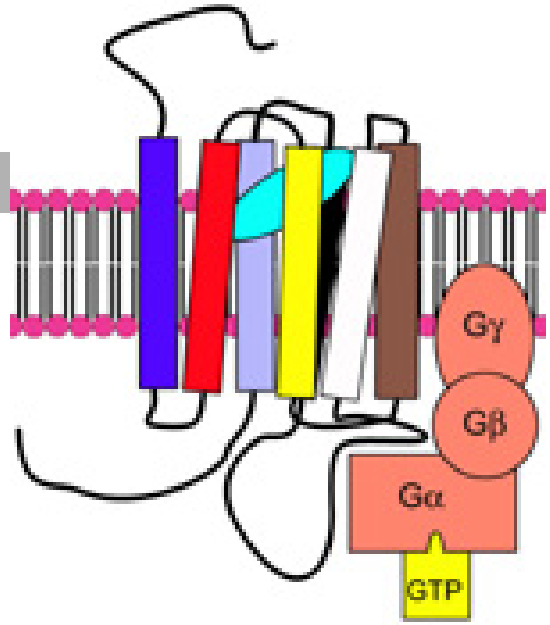
Signals in cardiac hypertrophy




RING
RING
RING
RING
RING
RING
IL-4
APC
MAPK
IL-6
Bcl-2
MAMP
almog diagnostic

Heterotrimeric G proteins





Phospholipase C

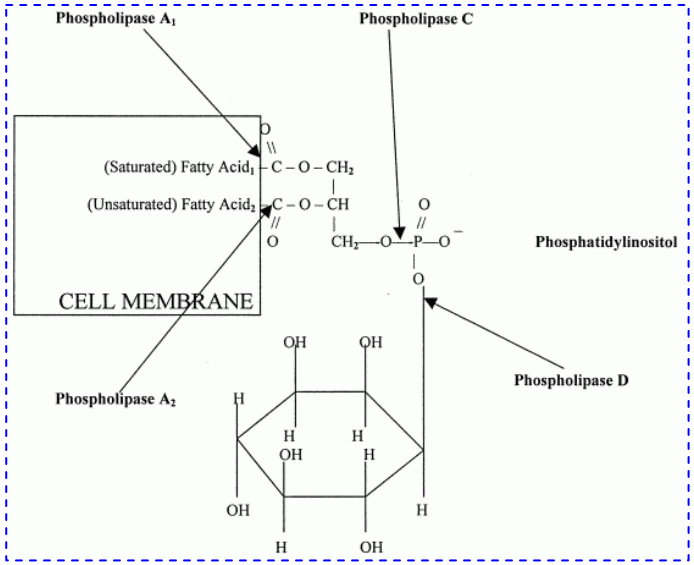
- **Hydrolysis PIP_2 to IP_3+DAG →bind to IP_3 R in SR →Ca^{2+} release →activate CaMK and calcineurin**

PLC-β:

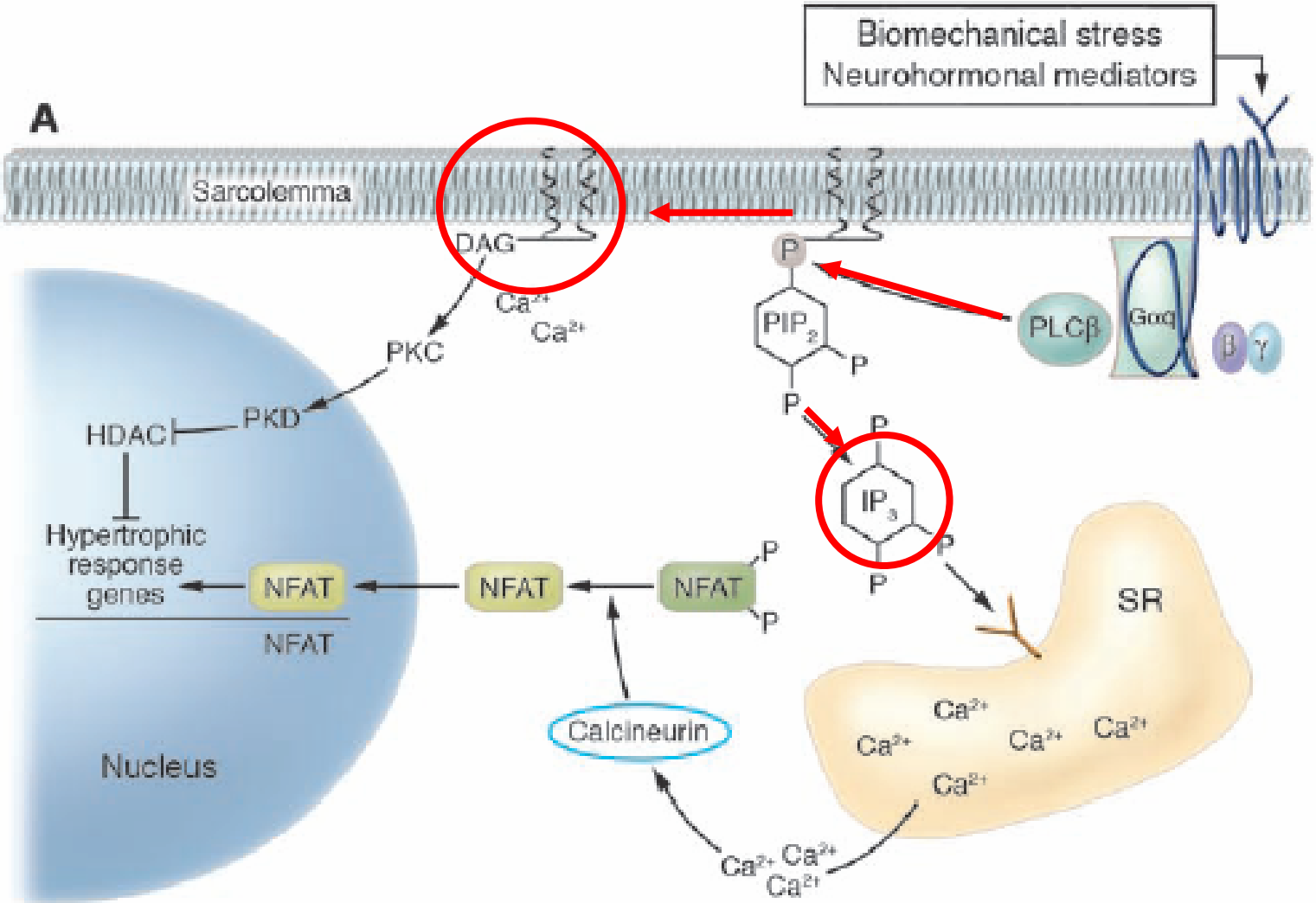
- **Downstream of Gq**
- **Gαq and Gβγ: bind to and activate PLC-β**
- **Related to decompensation**

PLC-γ:

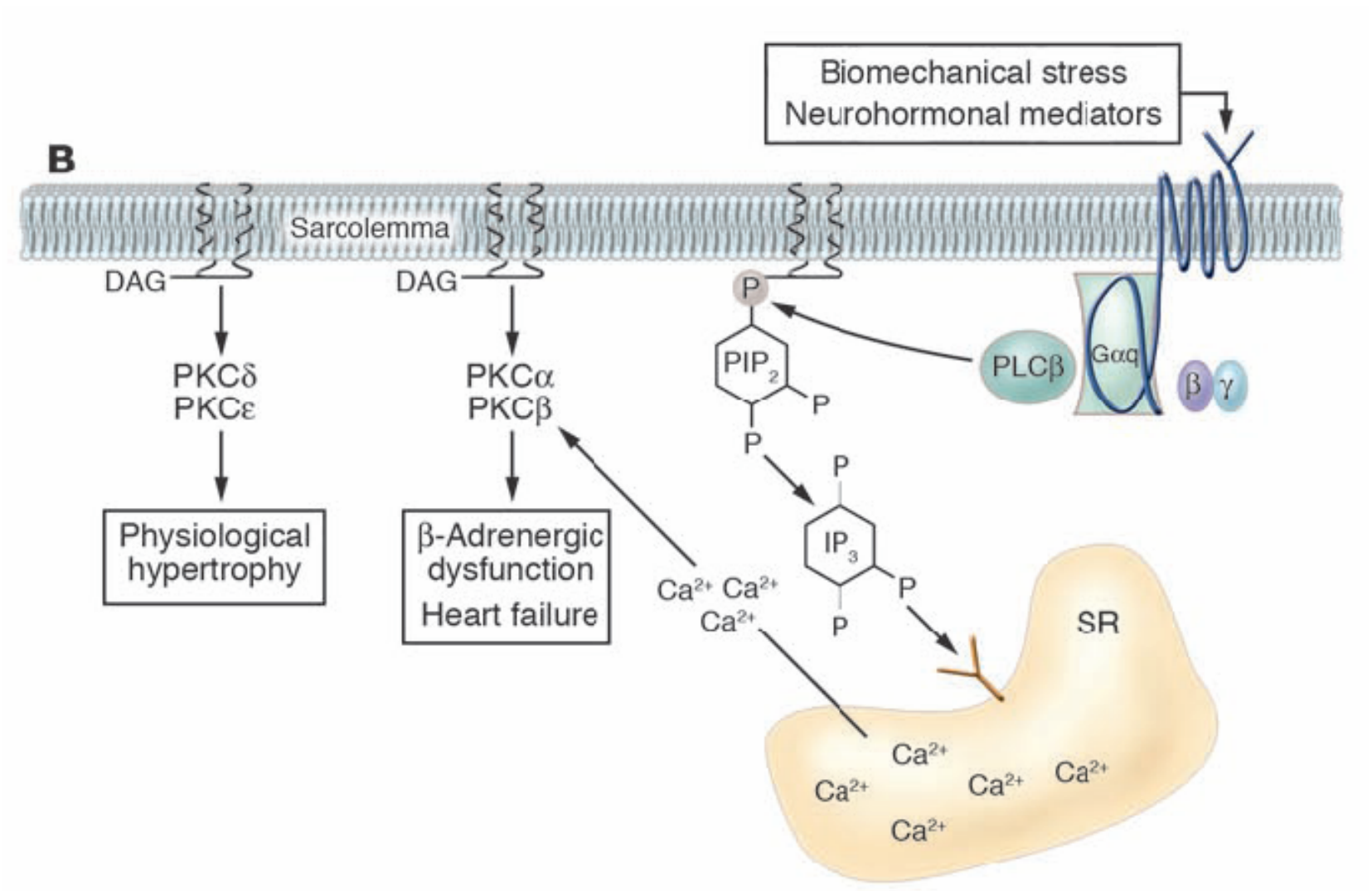
- **Activated by RTK and PI3K**
- **Unknown role**



Phospholipase C

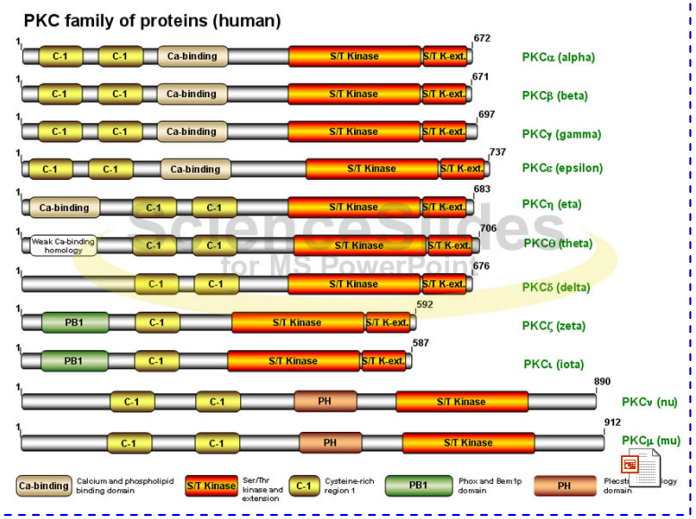


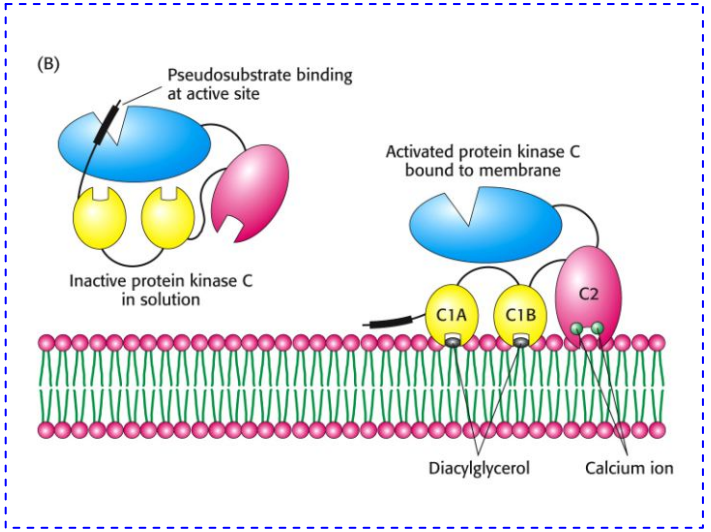
Phospholipase C



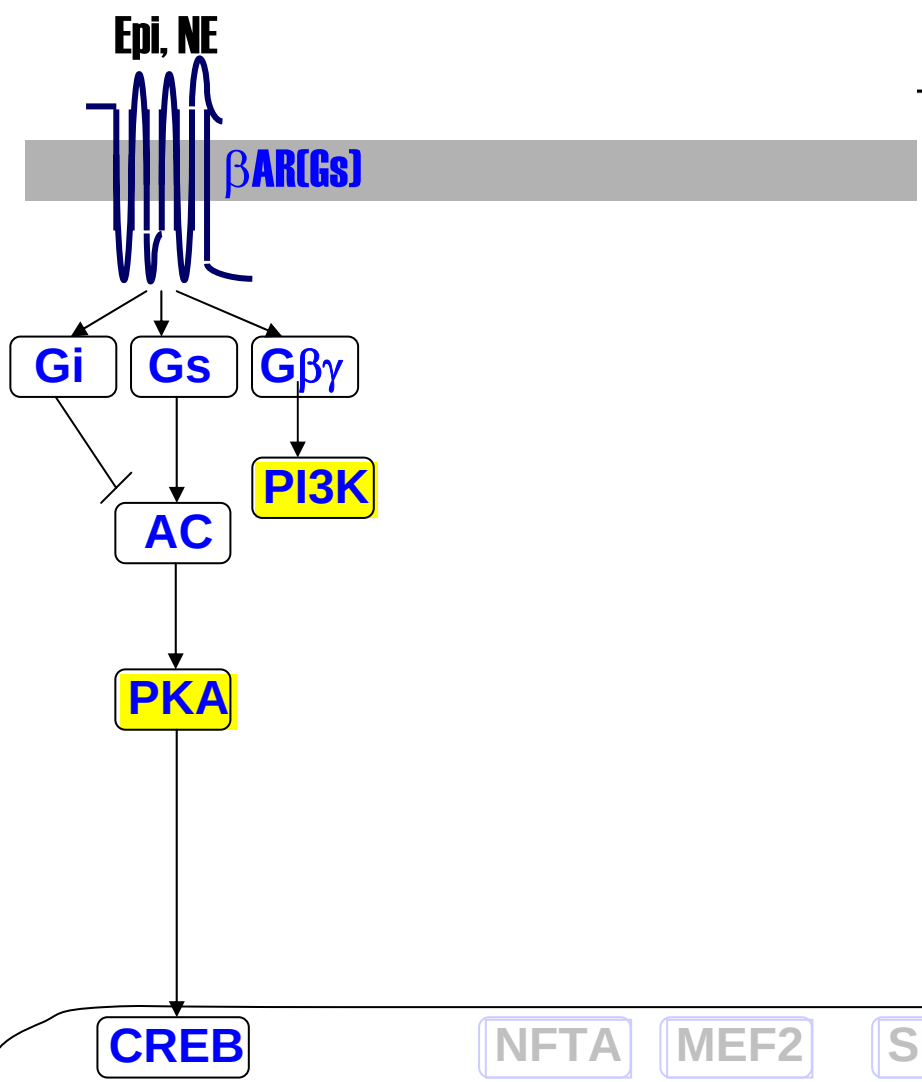
Protein kinase C

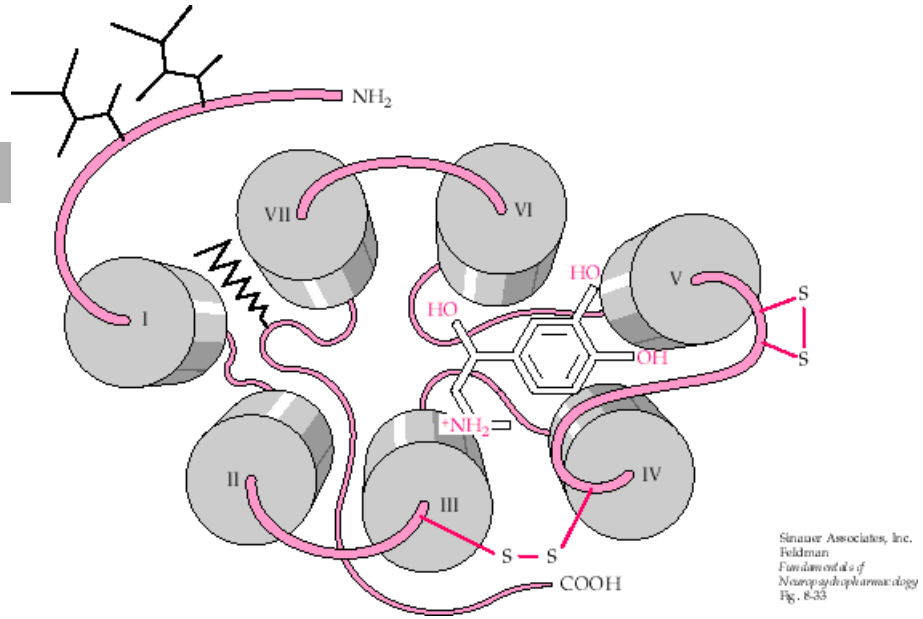
- **Classic isoforms: PKC α, β1, β2, γ**
  - Response to DAG and Ca^{2+}
  - **PKC-β2: deleterious for cardiac function**
- **Novel isoforms: PKC δ, ε, η, θ**
  - Response to DAG
  - **PKC-ε: cardiac protective**
- **Atypical isoforms: PKC μ, λ, ζ**
  - Not response to DAG or Ca^{2+}





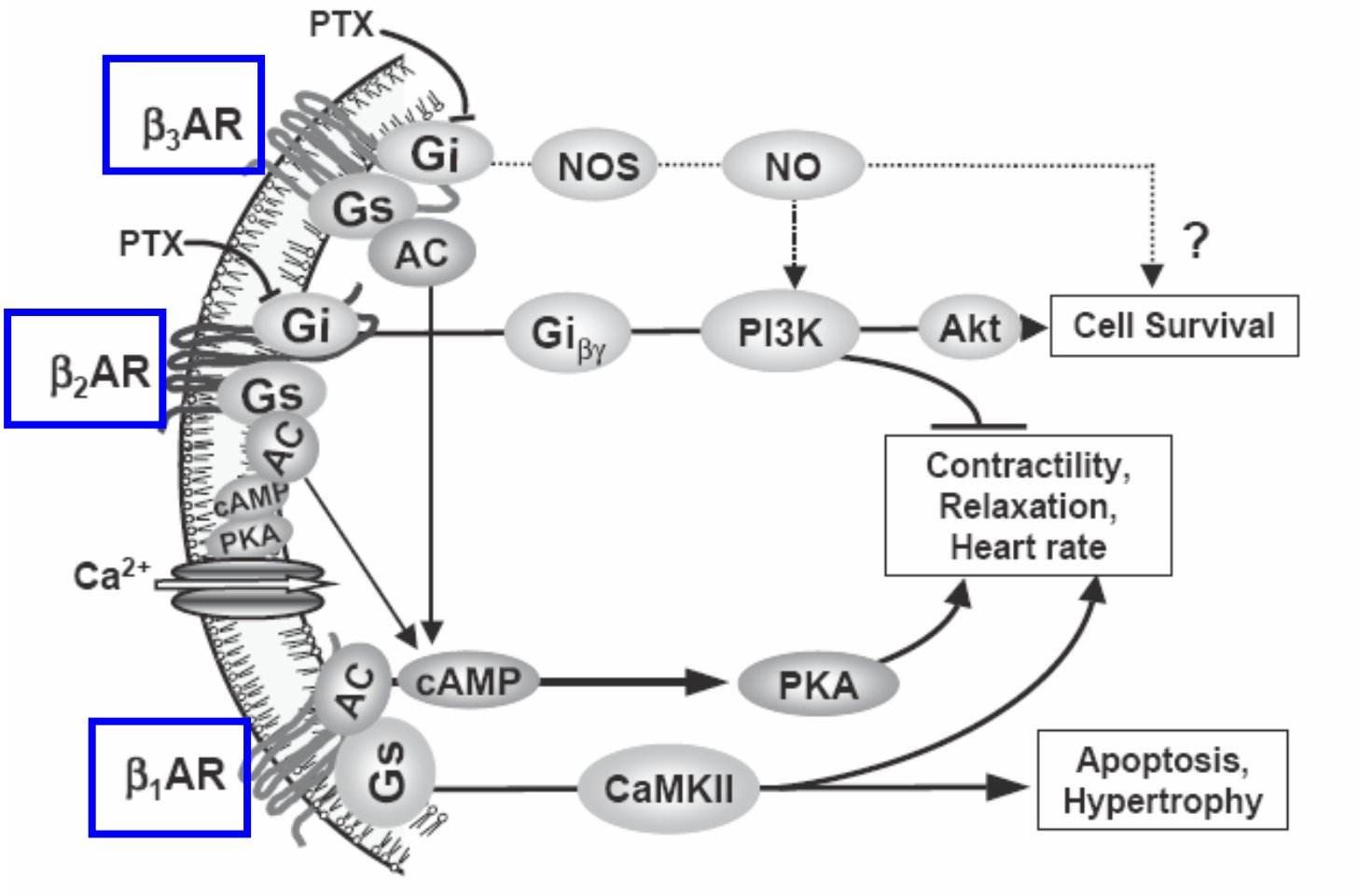
Heterotrimeric G proteins



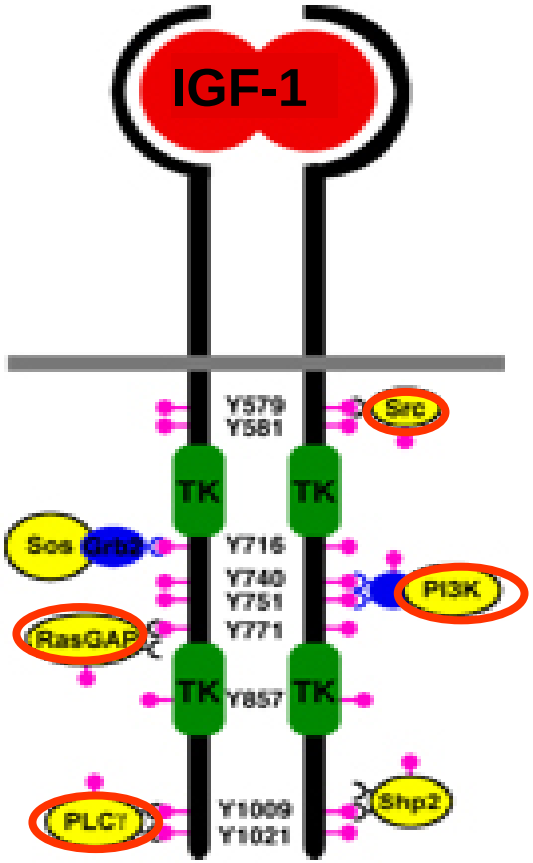


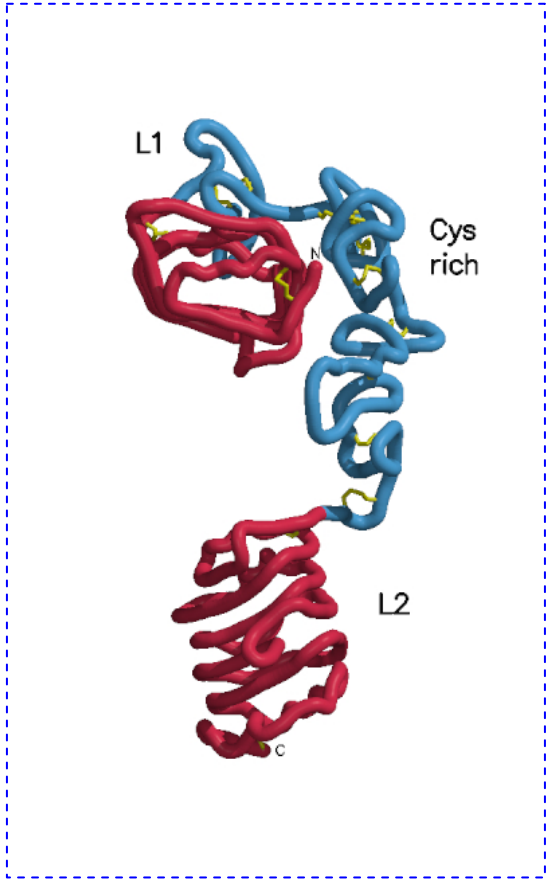
NFTA MEF2 SRF TCF cJUN ATF2 MEF2 STAT

Heterotrimeric G proteins



Growth factor receptor (RTK)





Growth factor receptor (RTK)

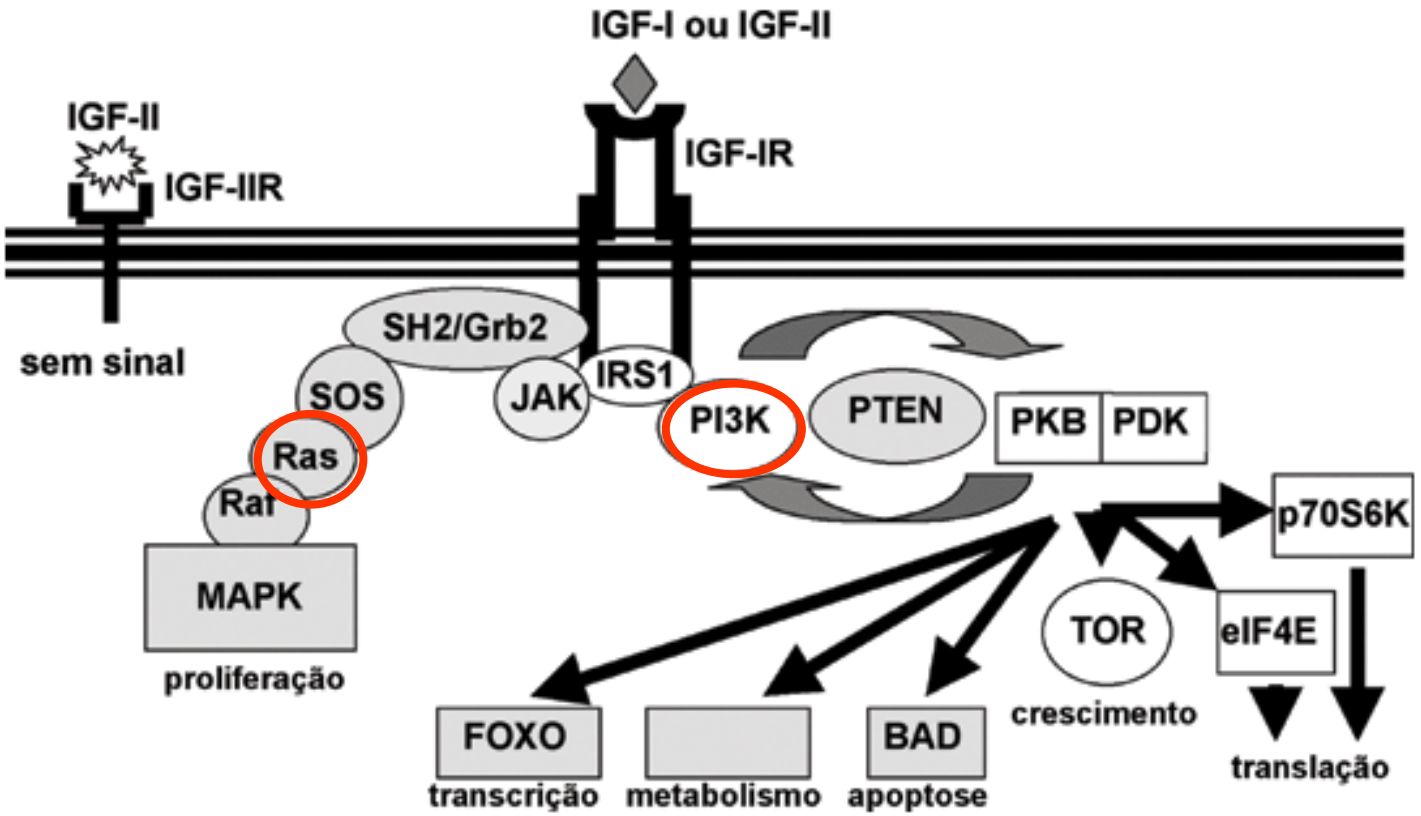
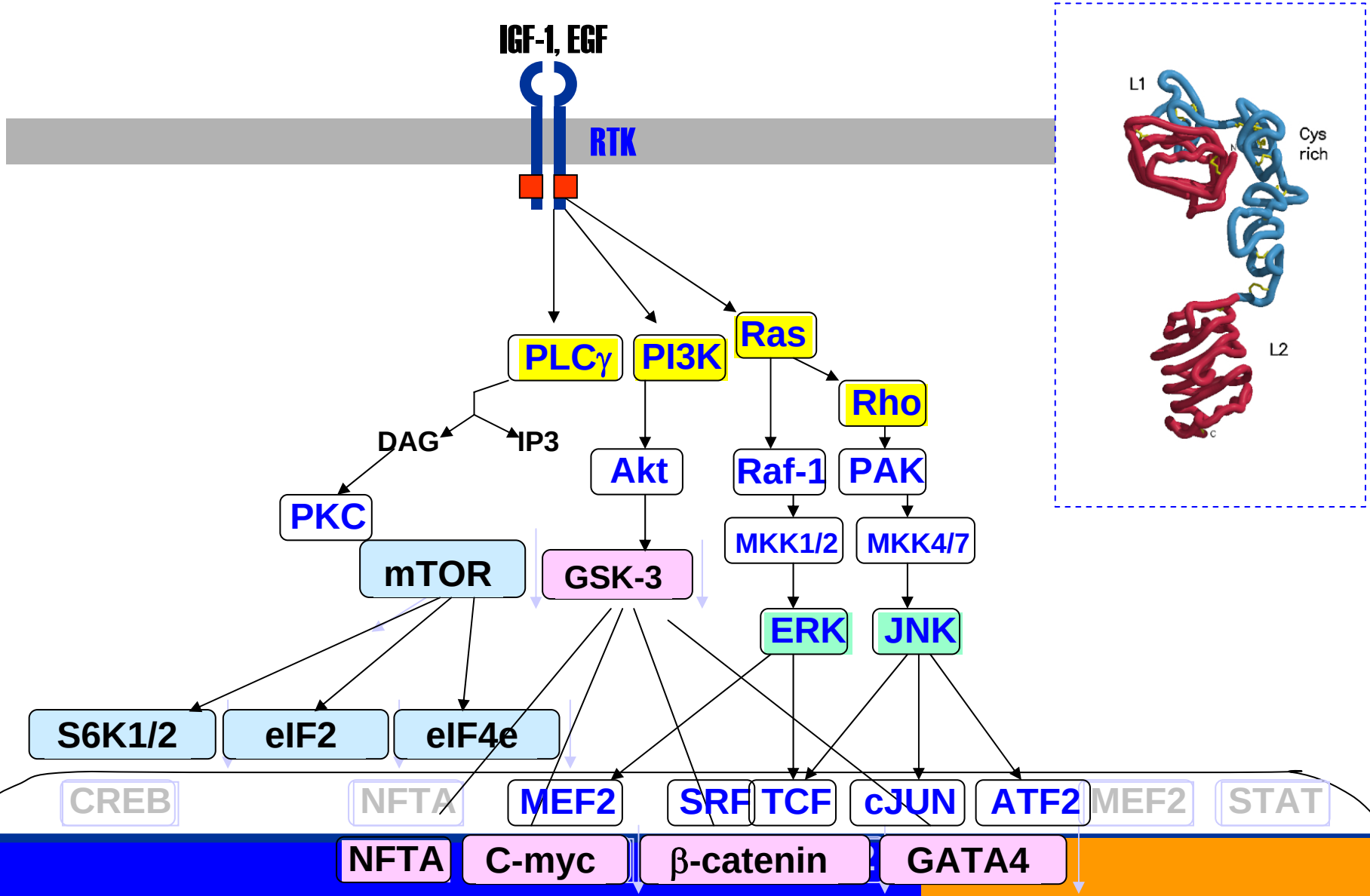


Figura 1. Representação simplificada dos componentes intracelulares do sistema IGF e suas ações.

Growth factors



Ras

4 Ras:

Harvey(Ha)-ras, Ki(4A)-ras, Ki(4B)-ras, and neural(N)-ras

Activation

Classical downstream effector of RTK

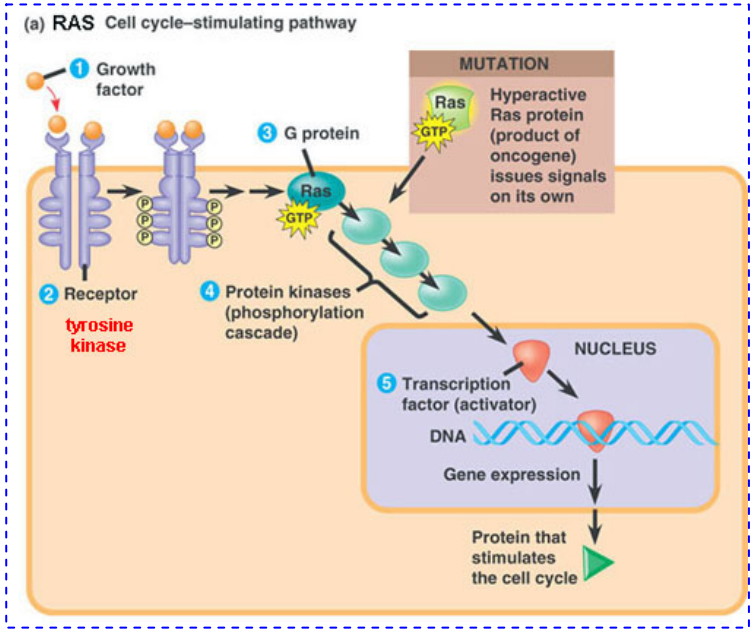
RTK transactivation from GPCR:

via FAK, HB-EGF, Gβγ, Src, PKC

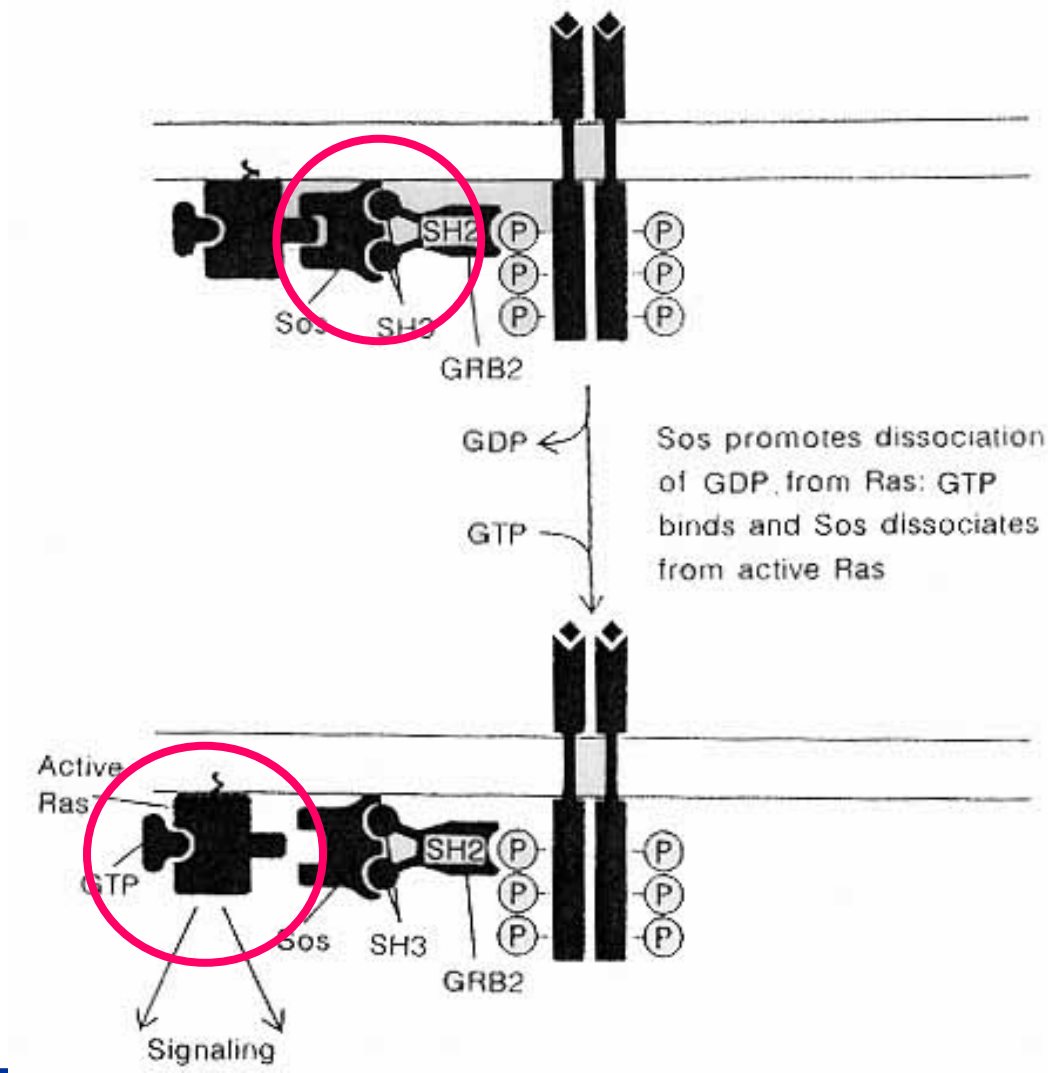
Important hypertrophic signaling of Gq

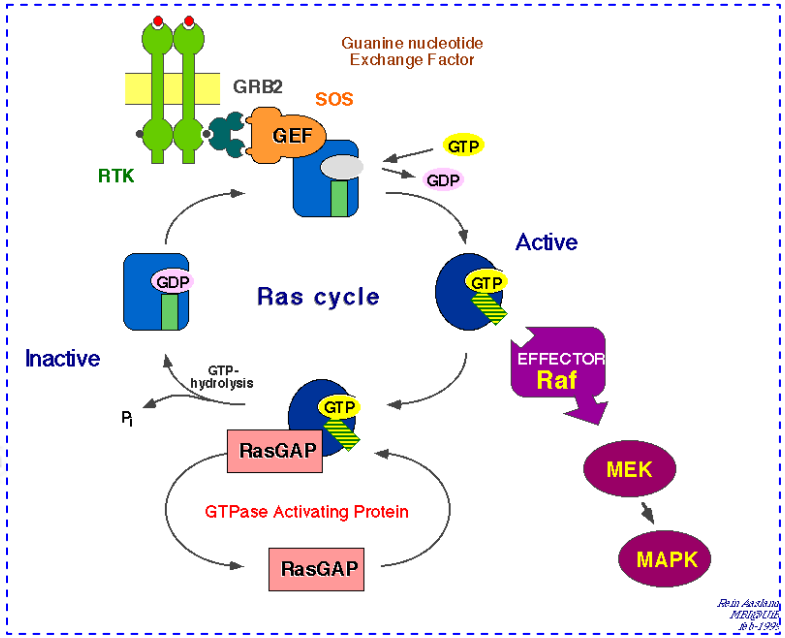
Directly bind to PI3K

Promote other small G proteins

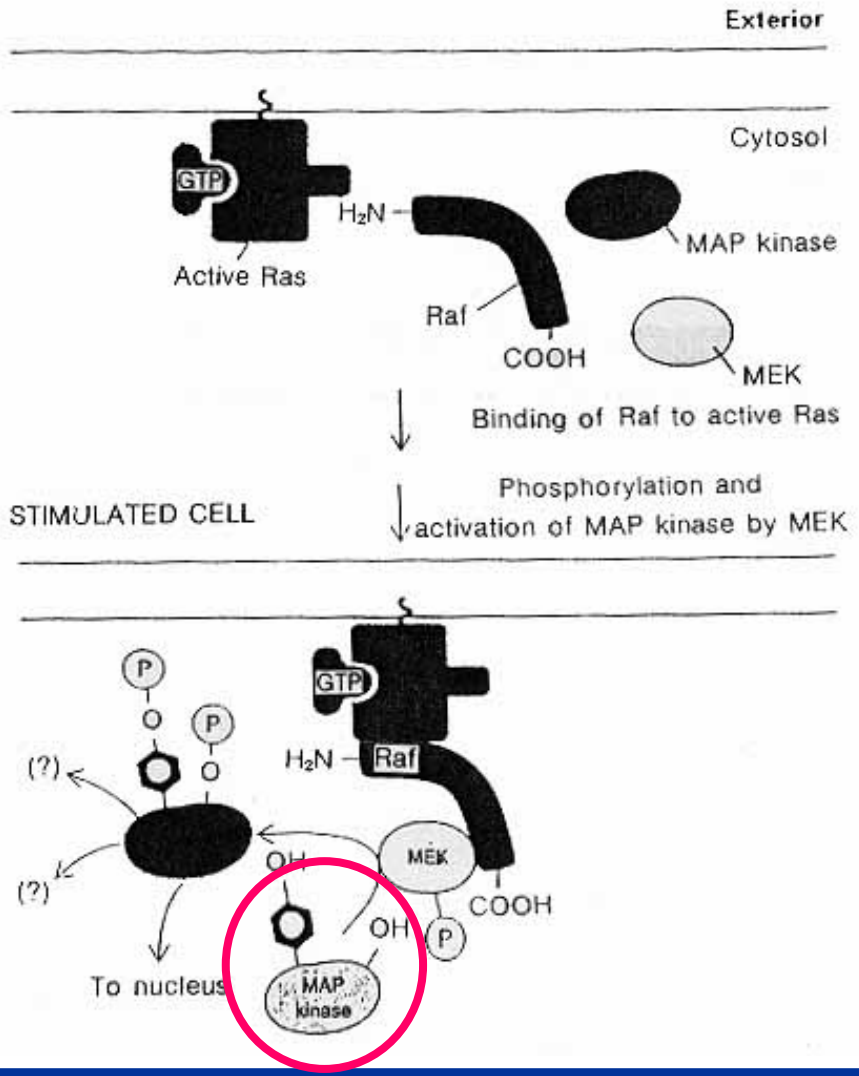


Ras

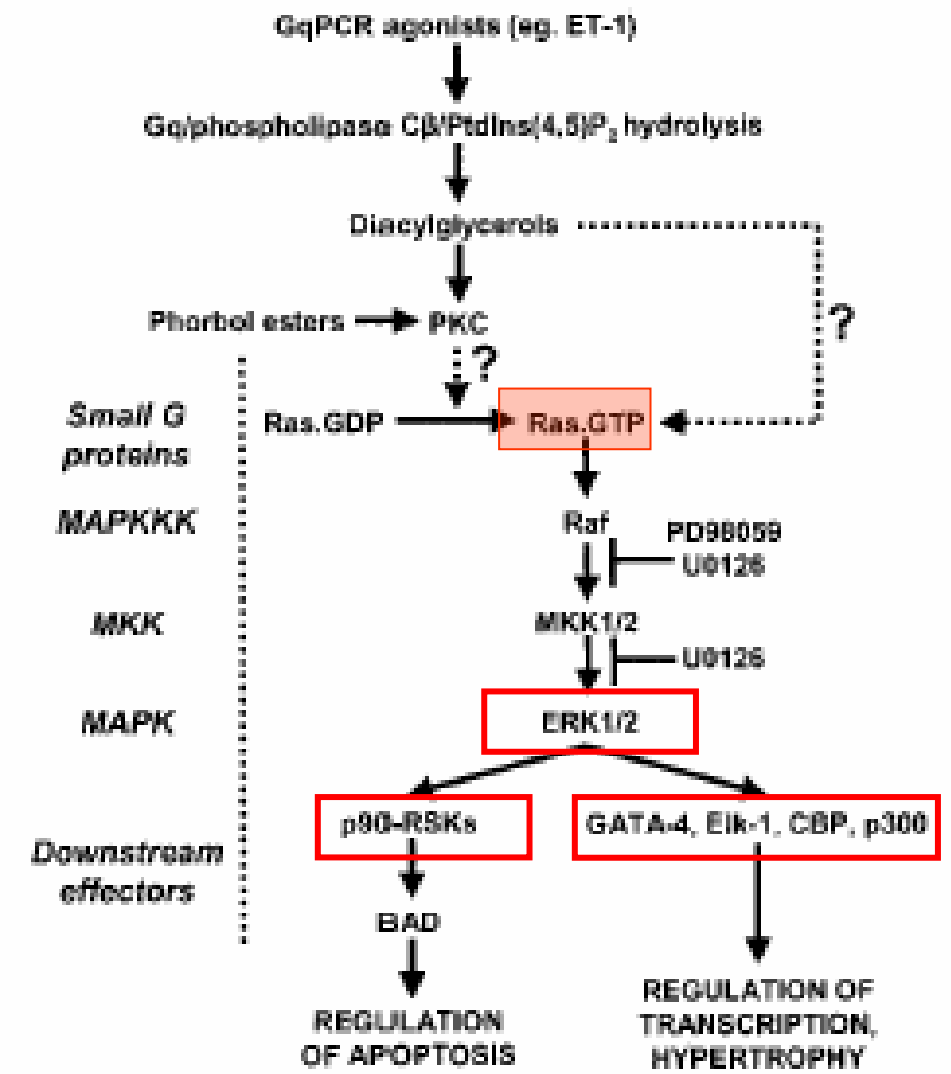

SH2
Sos
SH3
GRB2
GDP
GTP
Sos promotes dissociation of GDP from Ras: GTP binds and Sos dissociates from active Ras
Active Ras
GTP
Sos
SH3
GRB2
Signaling


Guanine nucleotide Exchange Factor
GRB2
SOS
GEF
RTK
GTP
GDP
Active
Ras cycle
Inactive
GTP-hydrolysis
Pi
RasGAP
GTPase Activating Protein
EFFECTOR
Raf
MEK
MAPK

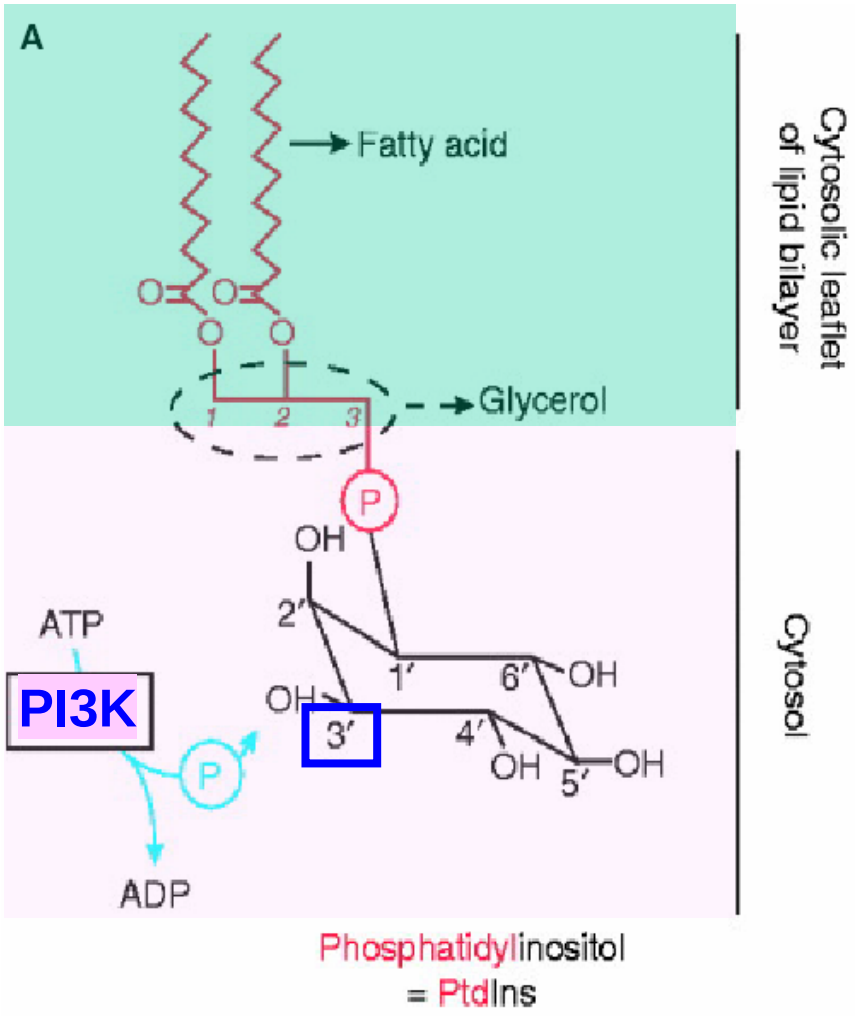
Ras

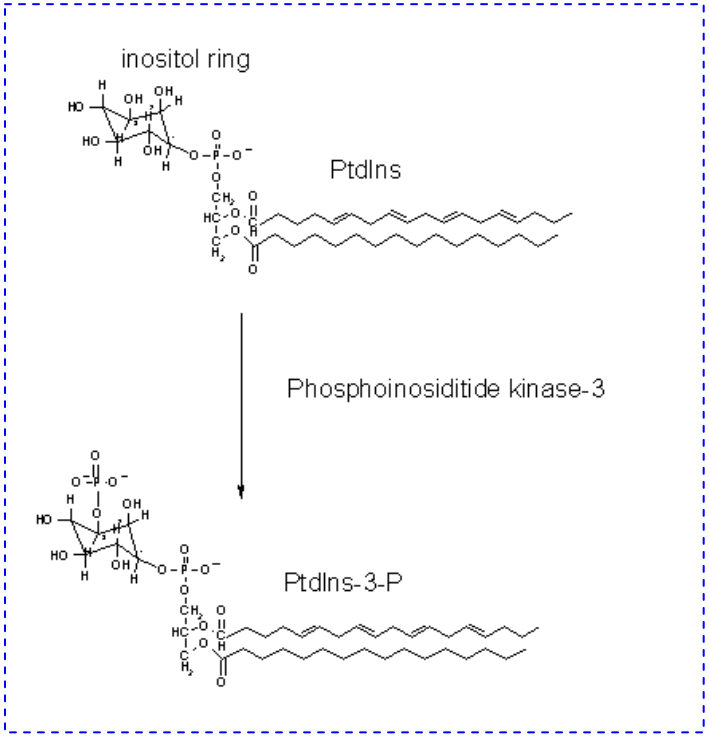

Exterior
Cytosol
GTP
H_2N
Active Ras
Raf
COOH
MAP kinase
MEK
Binding of Raf to active Ras
STIMULATED CELL
Phosphorylation and
activation of MAP kinase by MEK
P
O
(?)
To nucleus
OH
MEK
COOH
MAP kinase

Ras

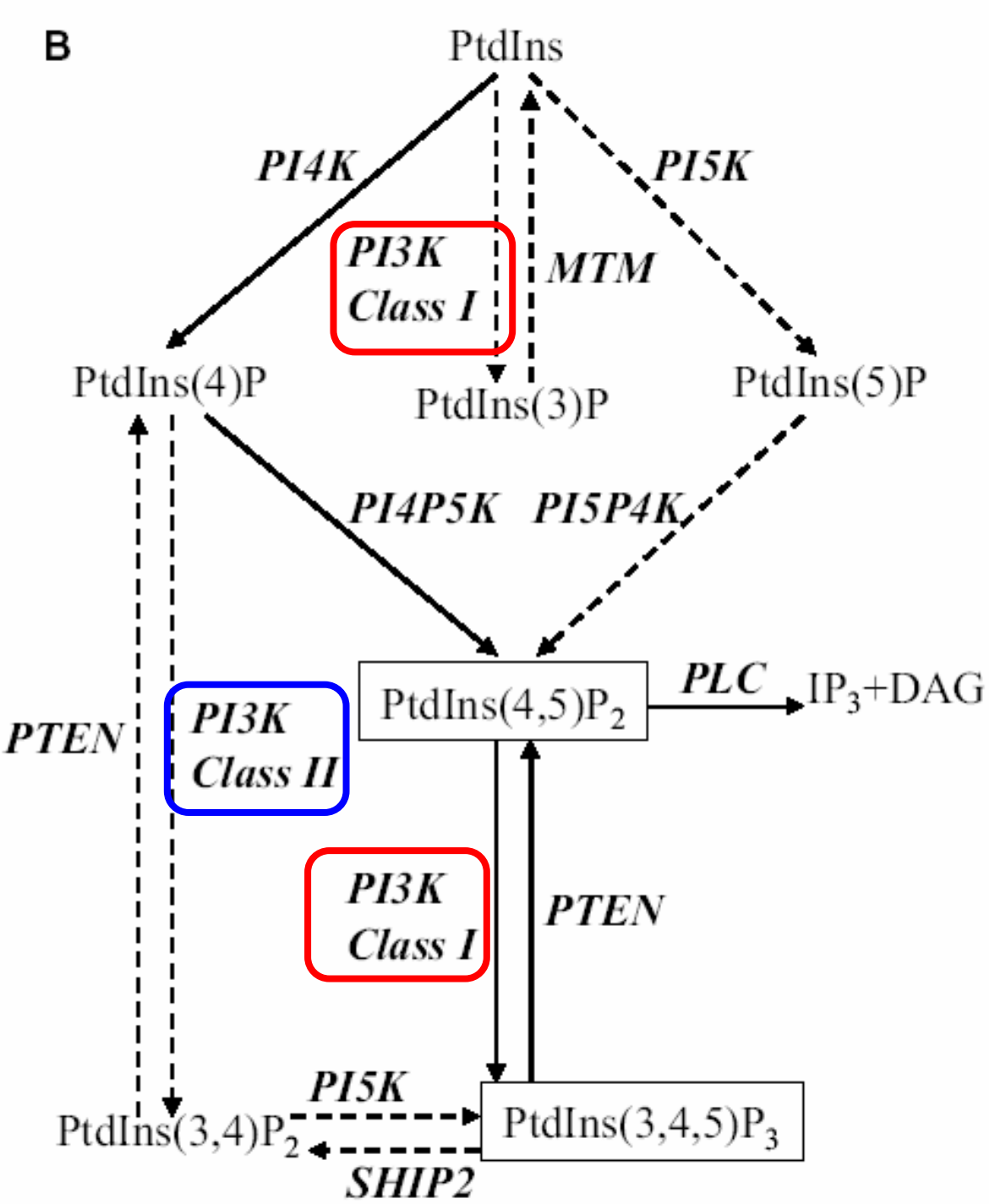

GqPCR agonists (eg. ET-1)
Gq/phospholipase Cβ/PtdIns(4,5)P2 hydrolysis
Diacylglycerols
Phorbol esters
PKC
?
?
Small G proteins
Ras.GDP
Ras.GTP
MAPKKK
Raf
PD98059
U0126
MKK
MKK1/2
U0126
MAPK
ERK1/2
Downstream effectors
p90-RSKs
GATA-4, Elk-1, CBP, p300
BAD
REGULATION OF APOPTOSIS
REGULATION OF TRANSCRIPTION, HYPERTROPHY

PI3K

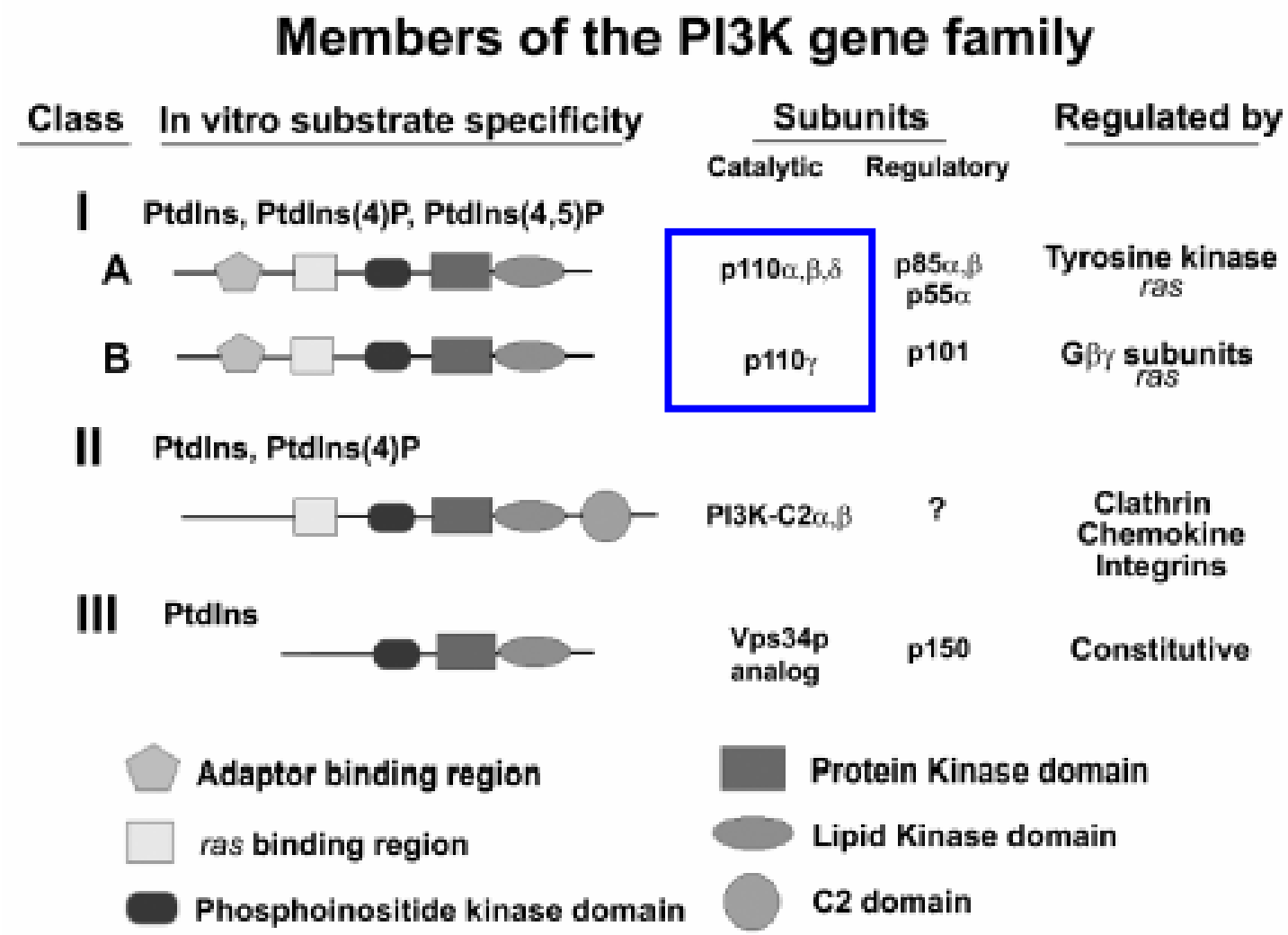

A
Fatty acid
Glycerol
1
2
3
P
OH
2′
1′
6′
OH
OH
3′
4′
OH
5′
OH
ATP
PI3K
P
ADP
Cytosolic leaflet of lipid bilayer
Cytosol
Phosphatidylinositol
= PtdIns


inositol ring
PtdIns
Phosphoinosiditide kinase-3
PtdIns-3-P

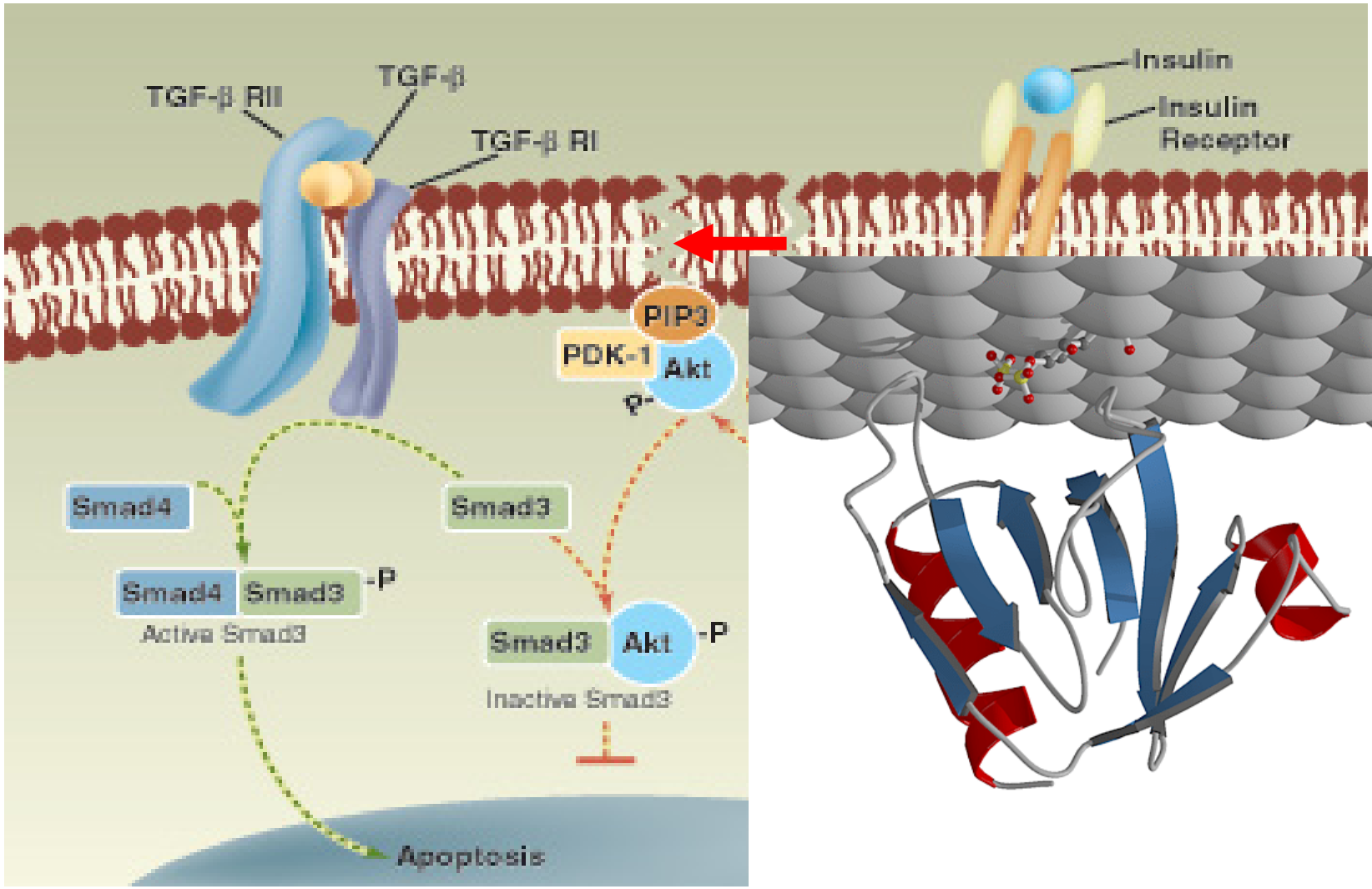
PI3K


B
PtdIns
PI4K
PI5K
PI3K
Class I
MTM
PtdIns(4)P
PtdIns(3)P
PtdIns(5)P
PI4P5K
PI5P4K
PTEN
PI3K
Class II
PtdIns(4,5)P2
PLC
IP3+DAG
PI3K
Class I
PTEN
PI5K
PtdIns(3,4)P2
PtdIns(3,4,5)P3
SHIP2

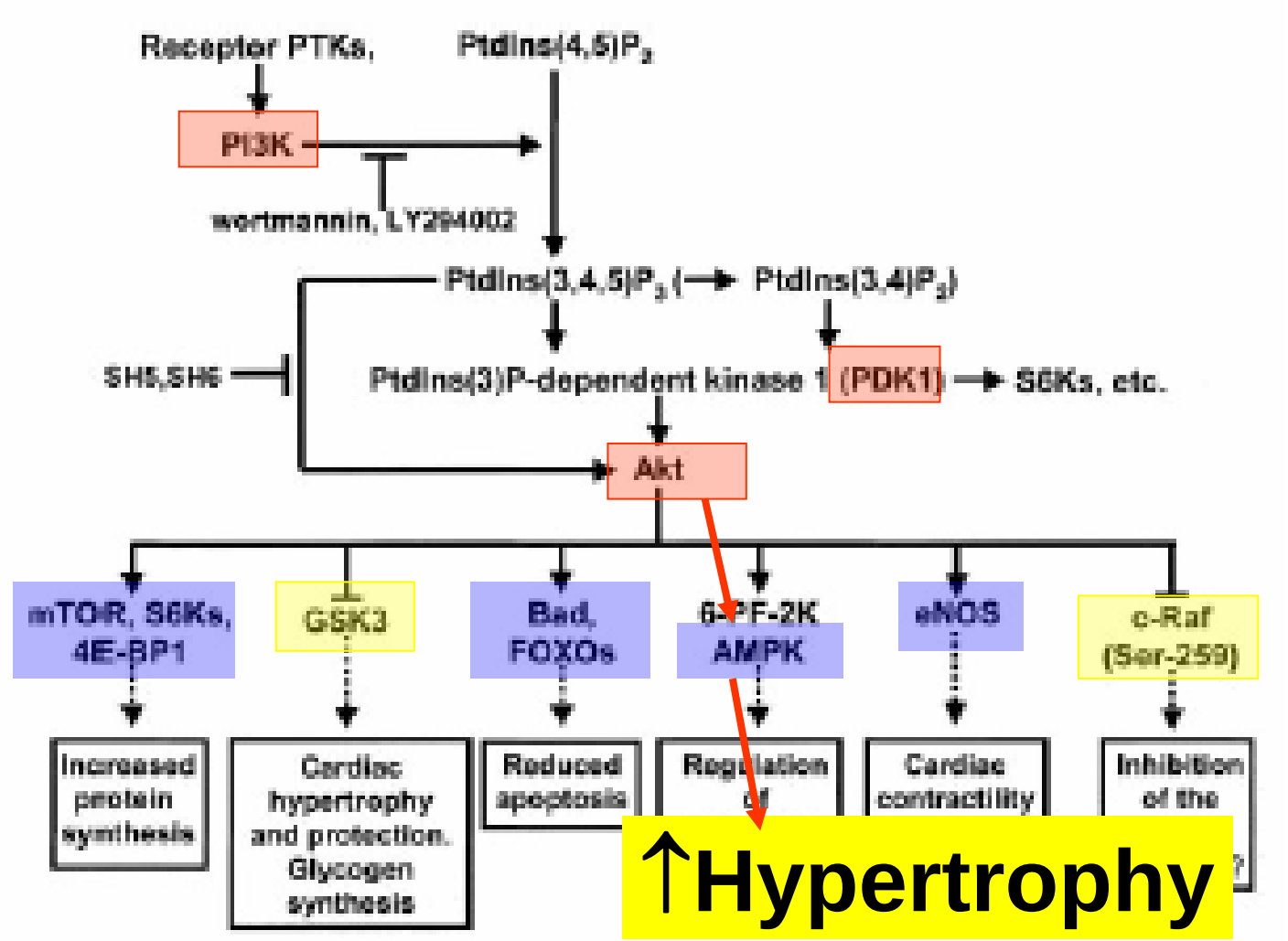
PI3K


Members of the PI3K gene family
Class
In vitro substrate specificity
Subunits
Catalytic
Regulatory
Regulated by
I
PtdIns, PtdIns(4)P, PtdIns(4,5)P
A
p110α,β,δ
p85α,β
p55α
Tyrosine kinase
ras
B
p110γ
p101
Gβγ subunits
ras
II
PtdIns, PtdIns(4)P
PI3K-C2α,β
?
Clathrin
Chemokine
Integrins
III
PtdIns
Vps34p
analog
p150
Constitutive
Adaptor binding region
ras binding region
Phosphoinositide kinase domain
Protein Kinase domain
Lipid Kinase domain
C2 domain

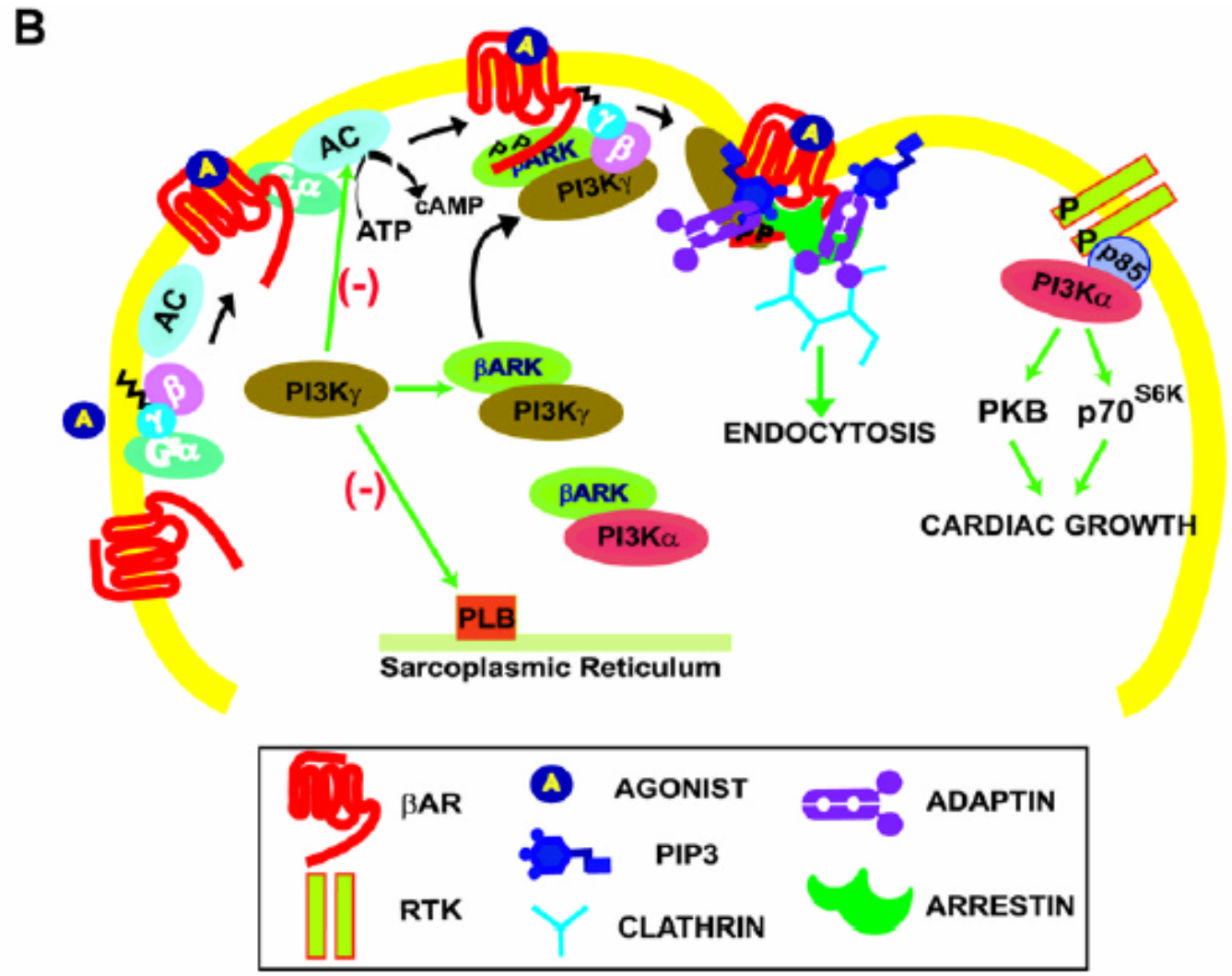
PI3K


TGF-β RII
TGF-β
TGF-β RI
Insulin
Insulin Receptor
PIP3
PDK-1
Akt
P-
Smad4
Smad3
Smad4
Smad3
-P
Active Smad3
Smad3
Akt
-P
Inactive Smad3
Apoptosis

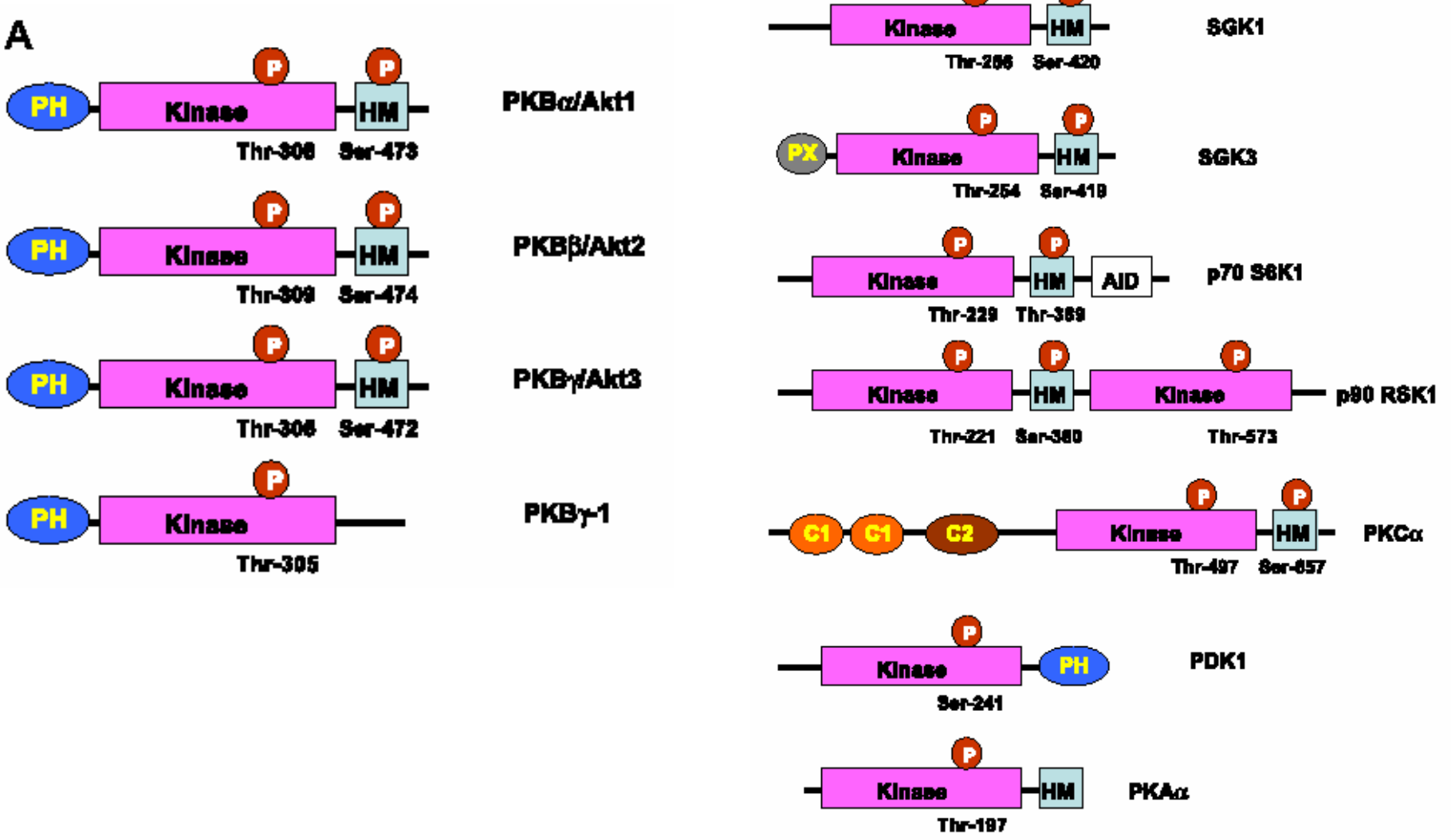
PI3K and Akt


Receptor PTKs,
PtdIns(4,5)P2
PI3K
wortmannin, LY294002
PtdIns(3,4,5)P3
PtdIns(3,4)P2
SH5,SH6
PtdIns(3)P-dependent kinase 1 (PDK1)
S6Ks, etc.
Akt
mTOR, S6Ks, 4E-BP1
GSK3
Bad, FOXOs
6-PF-2K AMPK
eNOS
c-Raf (Ser-259)
Increased protein synthesis
Cardiac hypertrophy and protection. Glycogen synthesis
Reduced apoptosis
Cardiac contractility
Inhibition of the
↑Hypertrophy

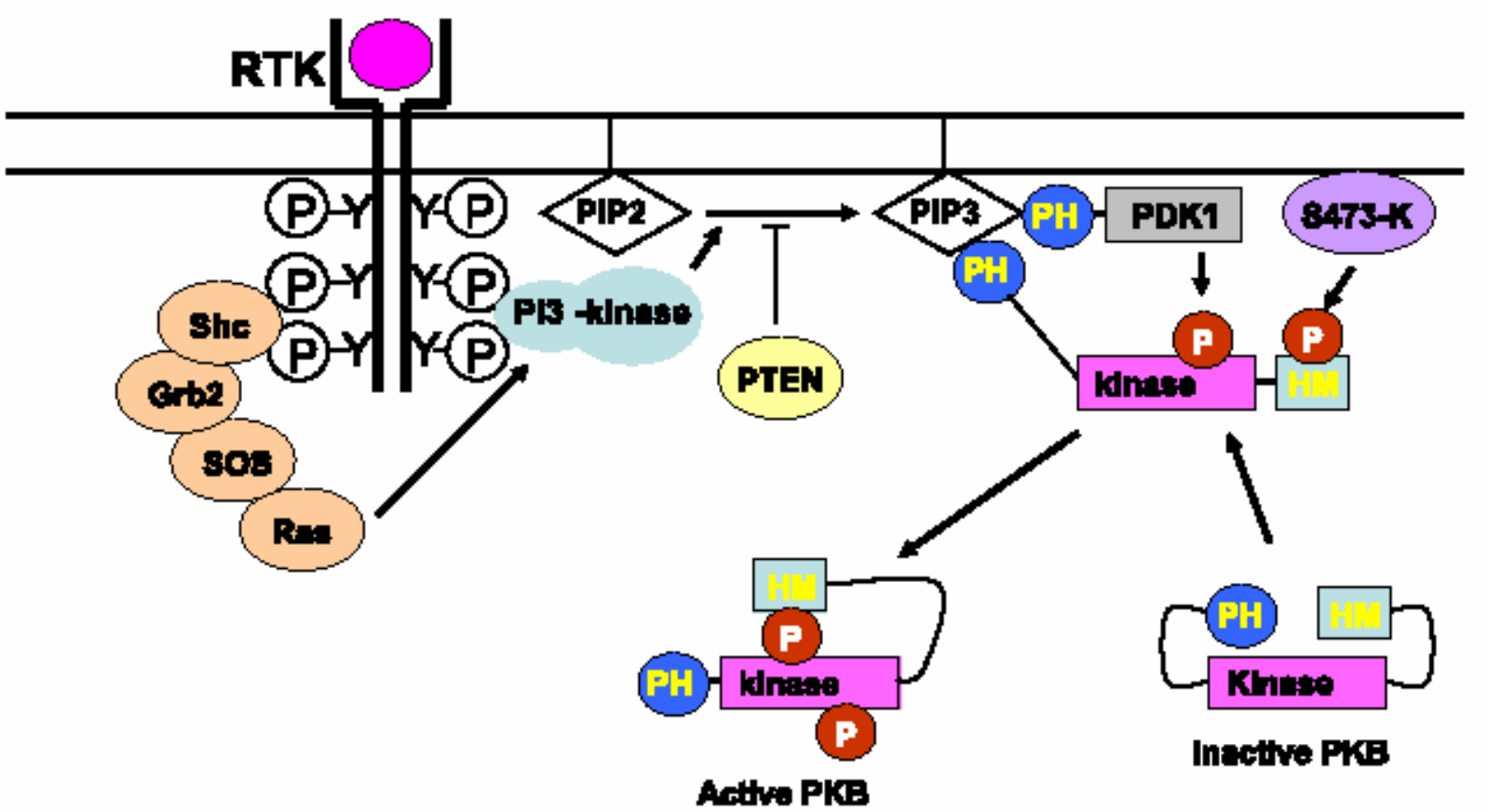
PI3K and βAR


B
AC
ATP
cAMP
(-)
PI3Kγ
βARK
PI3Kγ
βARK
PI3Kα
PLB
Sarcoplasmic Reticulum
ENDOCYTOSIS
P
P
p85
PI3Kα
PKB
p70 S6K
CARDIAC GROWTH
βAR
AGONIST
ADAPTIN
PIP3
RTK
CLATHRIN
ARRESTIN

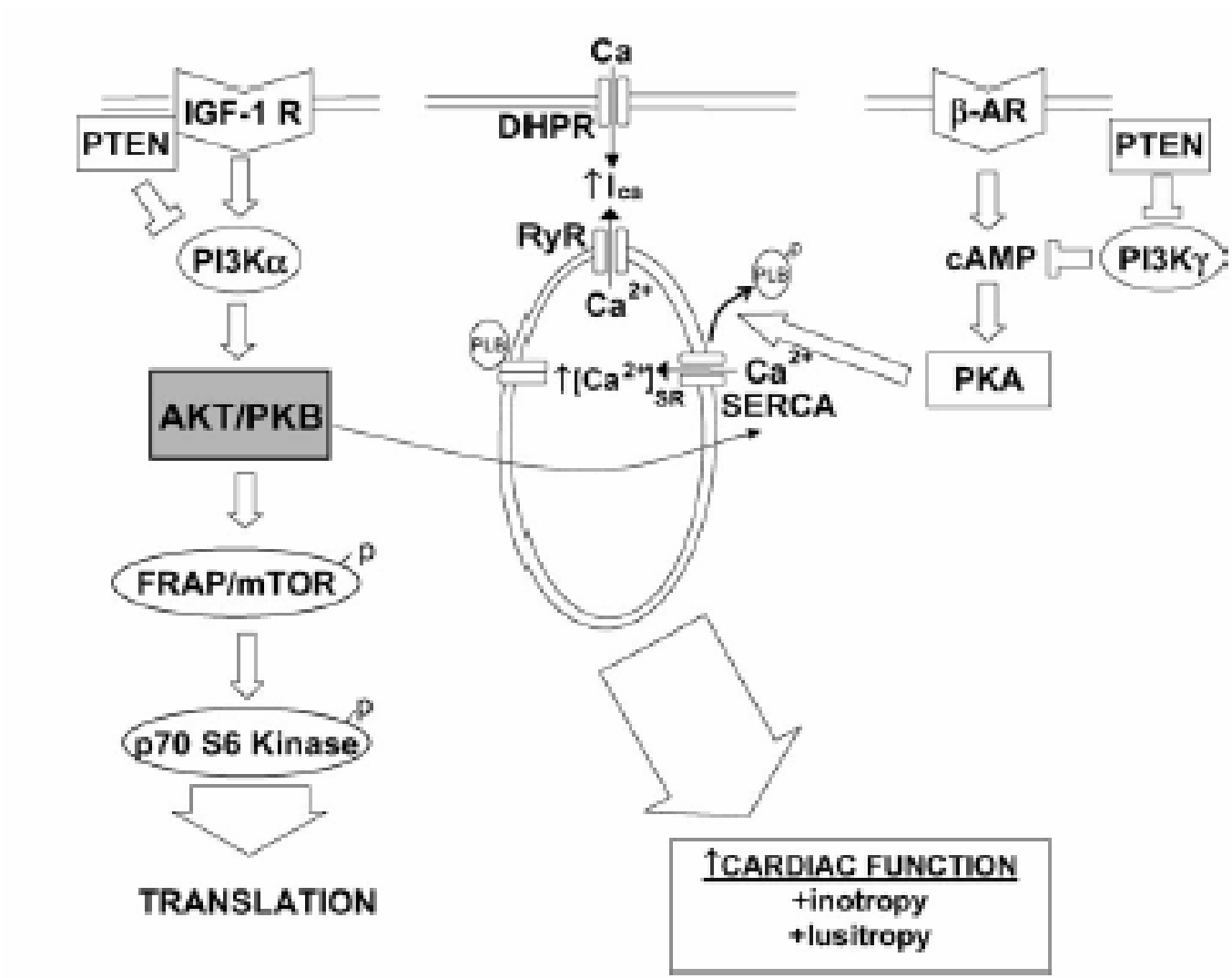
Akt/PKB


A
PH
Kinase
HM
P
Thr-308
Ser-473
PKBα/Akt1
Thr-309
Ser-474
PKBβ/Akt2
Thr-308
Ser-472
PKBγ/Akt3
Thr-305
PKBγ-1
B
Thr-309
Ser-473
PKBα/Akt1
Thr-256
Ser-420
SGK1
PX
Thr-254
Ser-419
SGK3
AID
Thr-229
Thr-389
p70 S6K1
Thr-221
Ser-380
Thr-573
p90 RSK1
C1
C2
Thr-497
Ser-657
PKCα
Ser-241
PDK1
Thr-197
PKAα

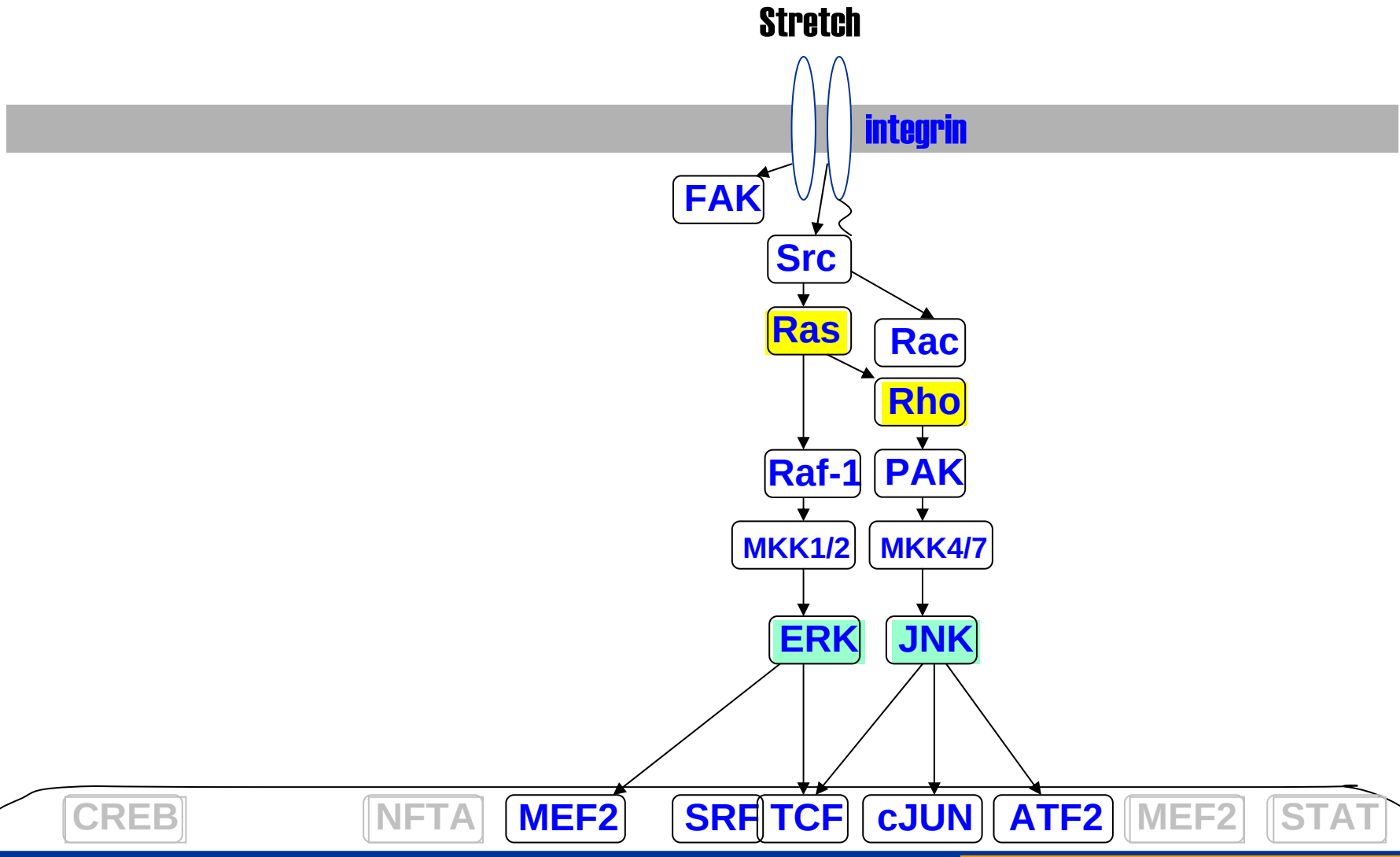
Akt


RTK
P
Y
Y
P
Shc
Grb2
SOS
Ras
PI3 -kinase
PIP2
PTEN
PIP3
PH
PDK1
S473-K
kinase
HM
Active PKB
Inactive PKB

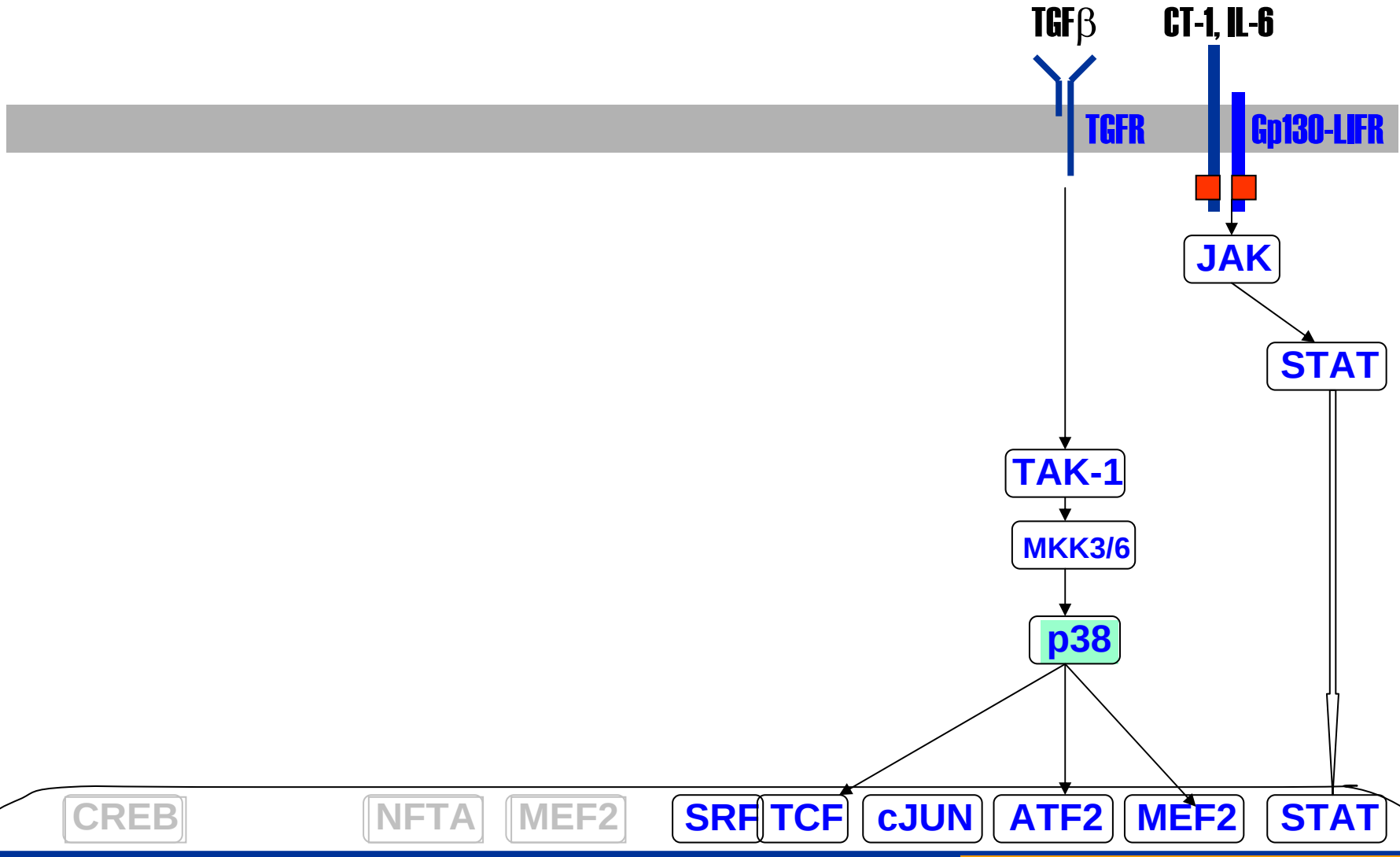
Akt in CMC (Cardiomyocyte)



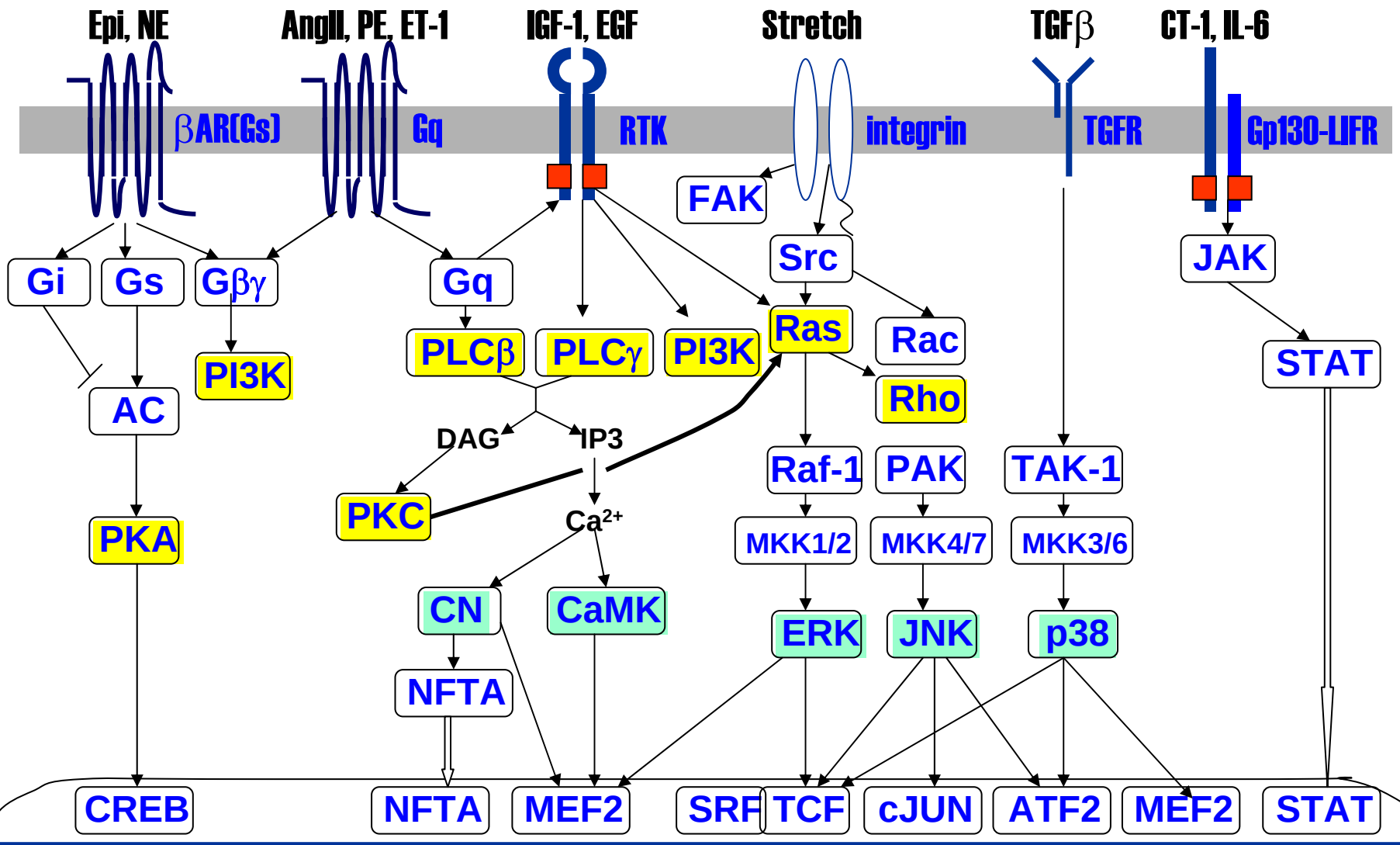
Stretch signal



Cytokines


TGFβ
CT-1, IL-6
TGFR
Gp130-LIFR
JAK
STAT
TAK-1
MKK3/6
p38
CREB
NFTA
MEF2
SRF
TCF
cJUN
ATF2
MEF2
STAT

Signals in cardiac hypertrophy



Downstream effectors

1. Protein synthesis
2. Sarcomeric organization
3. Transcriptional regulation

Downstream effectors

Protein synthesis

Hallmark of hypertrophy with cell size

– Initiation of translation

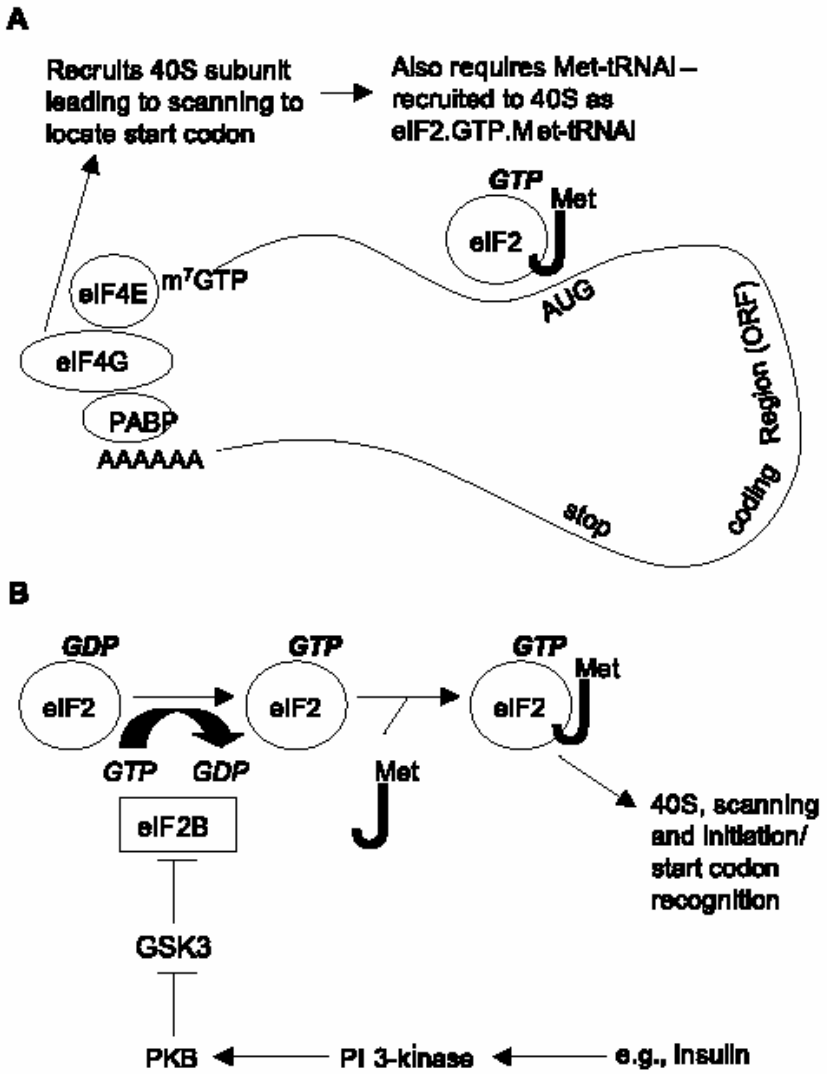
S6K, TSC

PI3K-Akt-mTOR-S6K pathway

– Translational efficacy

eIF4

mRNA translation



Downstream effectors

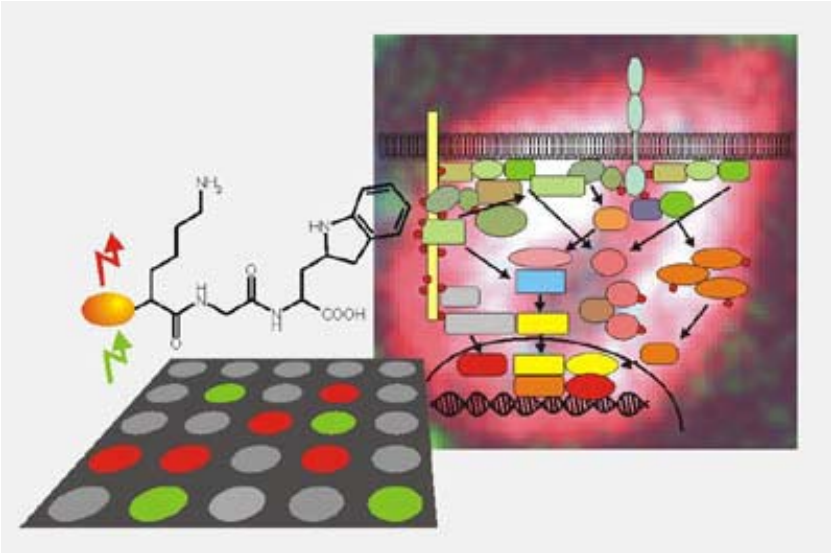
Sarcomeric organization

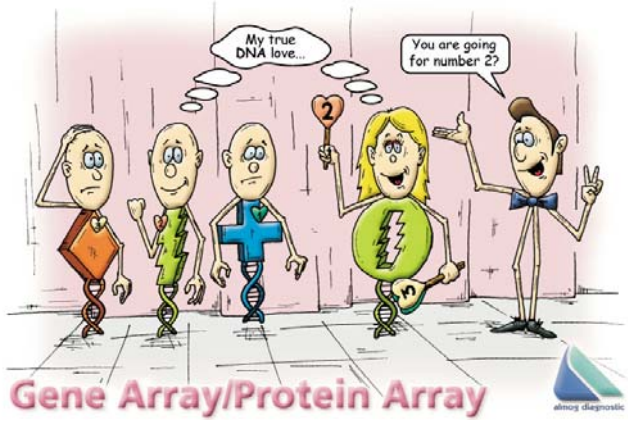
- Enhanced sarcomeric organization by hypertrophic stimuli, but decrease in decompansation and HF
- **Rho family , small G protein stimulate organization**
- MLC kinase is **critical for MLC-2** phosphorylation

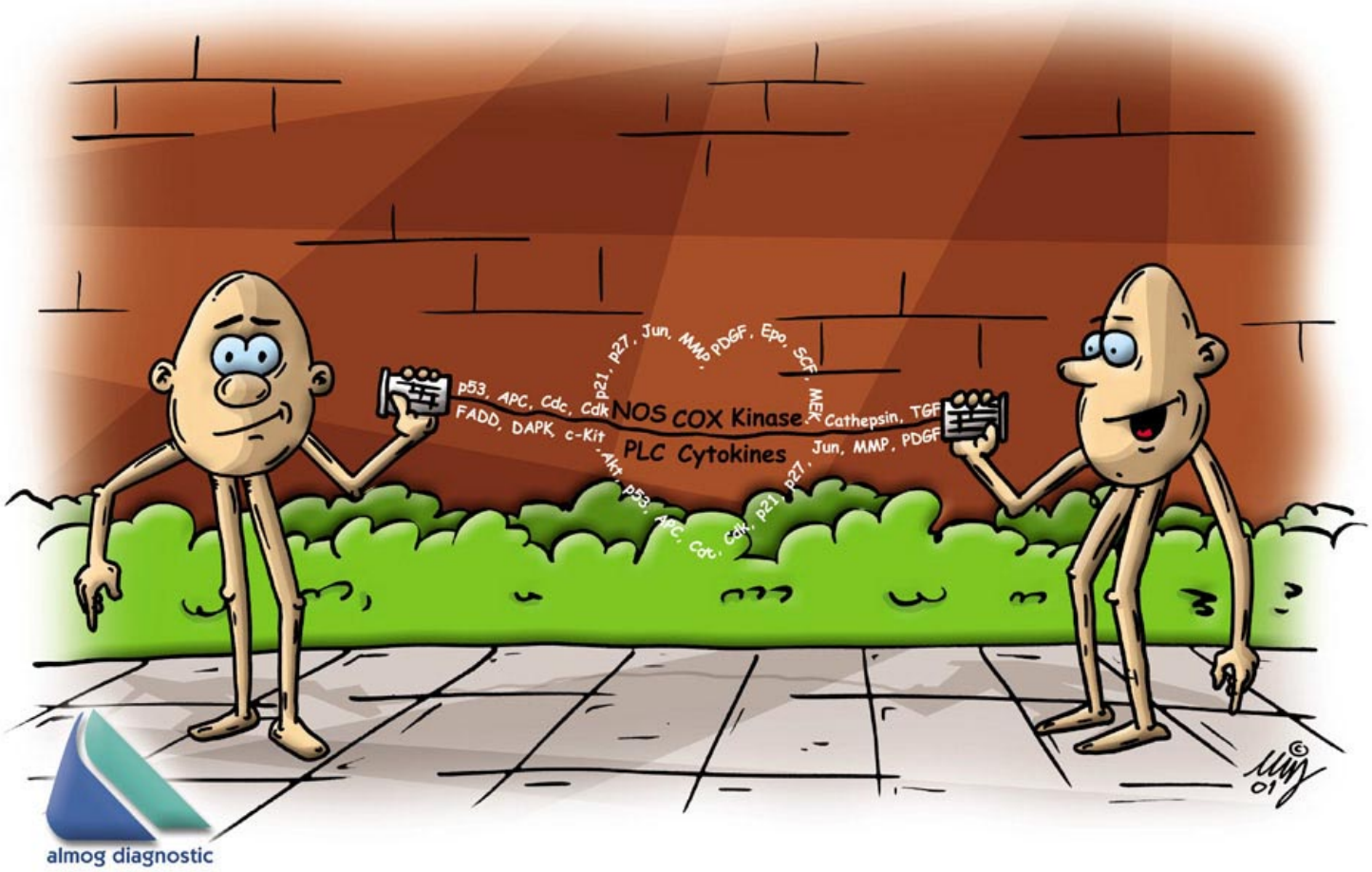
Downstream effectors

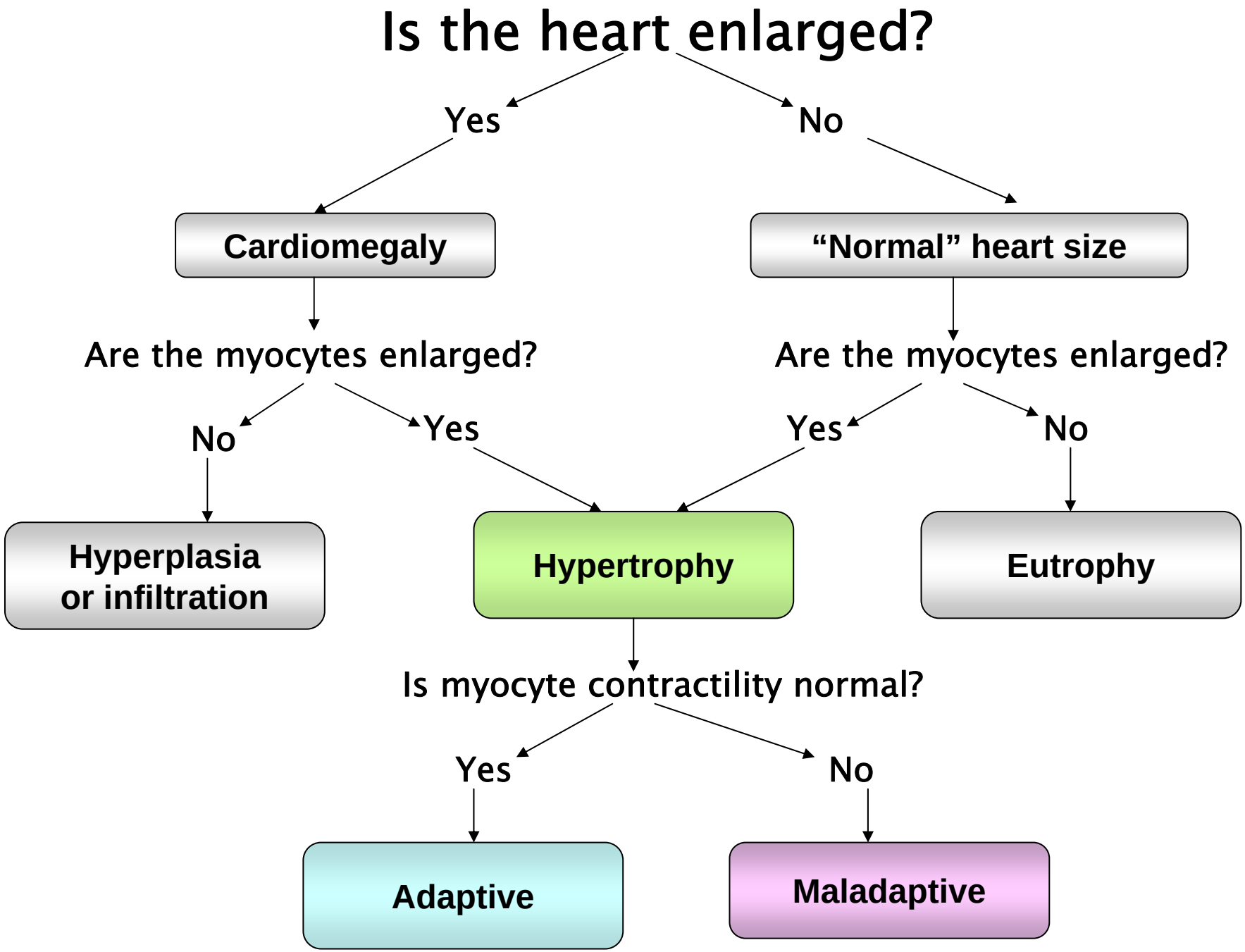
Transcriptional regulation

- Analysis of gene expression in response under diverse condition.
- www.cardiogenomics.org






p53, APC, Cdc, Cdk
FADD, DAPK, c-Kit
p21, p27, Jun, MMP, PDGF, Epo, SCF, MEK
NOS COX Kinase
PLC Cytokines
Cathepsin, TGF
Jun, MMP, PDGF
Akt, p53, APC, Cdc, Cdk, p21, p27,
almog diagnostic


Is the heart enlarged?
Yes
No
Cardiomegaly
"Normal" heart size
Are the myocytes enlarged?
Are the myocytes enlarged?
No
Yes
Yes
No
Hyperplasia or infiltration
Hypertrophy
Eutrophy
Is myocyte contractility normal?
Yes
No
Adaptive
Maladaptive

Classification of Cardiac Hypertrophy

1. **Physiologic (adaptive) hypertrophy:**
   - **Resulting from exercise**
2. **Pathologic (maladaptive) hypertrophy:**
   - **Compensated or decompensated (HF)**
3. **Hypertrophy by genetic mutation**

Maladaptive hypertrophy

1. **AngII, PE, ET-1, etc:**

   activate Gq(G11)

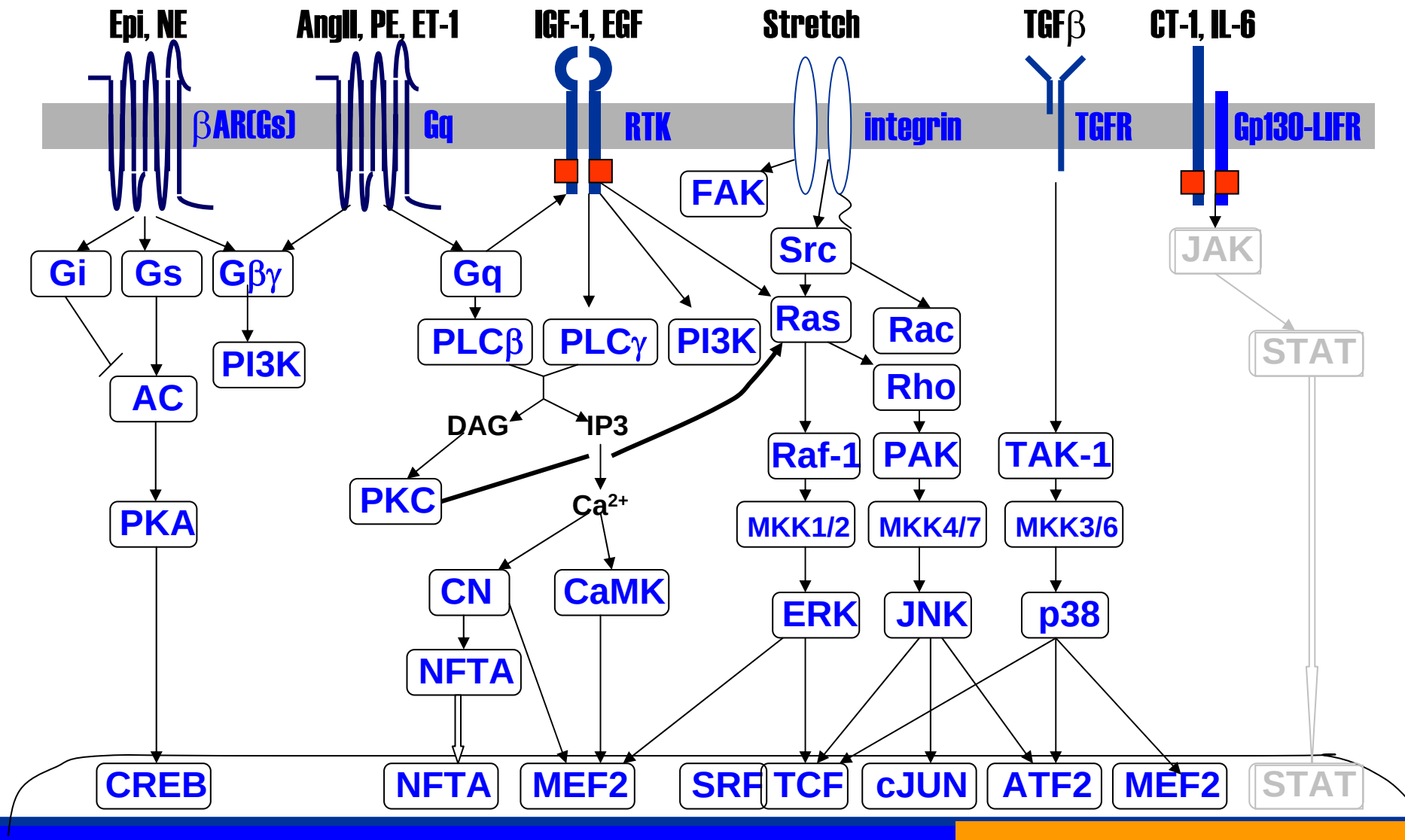
2. **Gq activation**

→ 1) **PKC activation**

→ 2) IP3-mediated **Ca^{2+} release**

→ 3) PI3K(**p110**γ: subgroup IB)

Maladaptive hypertrophy

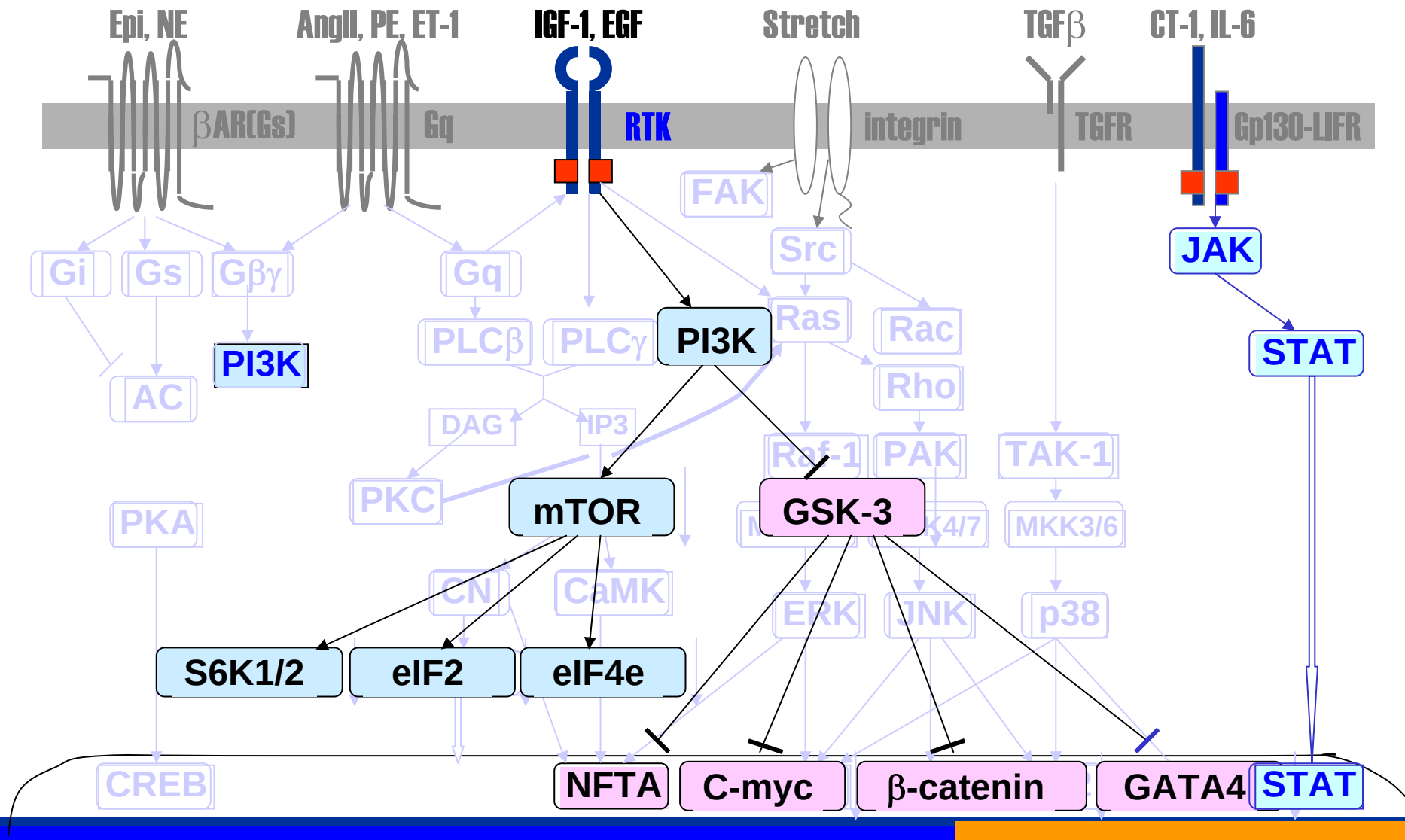


Physiologic hypertrophy

1. Largely mediated by signaling through **IGF-1** and GH

2. **PI3K(p110α**: subgroup IA)
   $\rightarrow$phosphorylae PIP_2 at 3'P $\rightarrow PIP_3$
   $\rightarrow$colocalize Akt, PDK1 of PH domain
   $\rightarrow$phospholylate **Akt**

Physiologic hypertrophy



Conclusions

1. **Signals and effectors regulate the growth** of cardiomyocytes in response to hypertrophic stimuli.
2. The hypertrophic reponse is **a complex phenomenon with multiple networks** of signaling cascade.
3. **Sustained activation leads to declines** in number and function of cardiomyocyte and results in HF.

Conclusions

4. Because of the complexity and interacing nature of signal pathway, **any single pathway will not be** found that mediates the detrimental changes of HF.
5. However, therapy will be improved through the **identification and modulation of critical points** in signal network.

   (Ex: Use of beta-blocker for BSH guide)