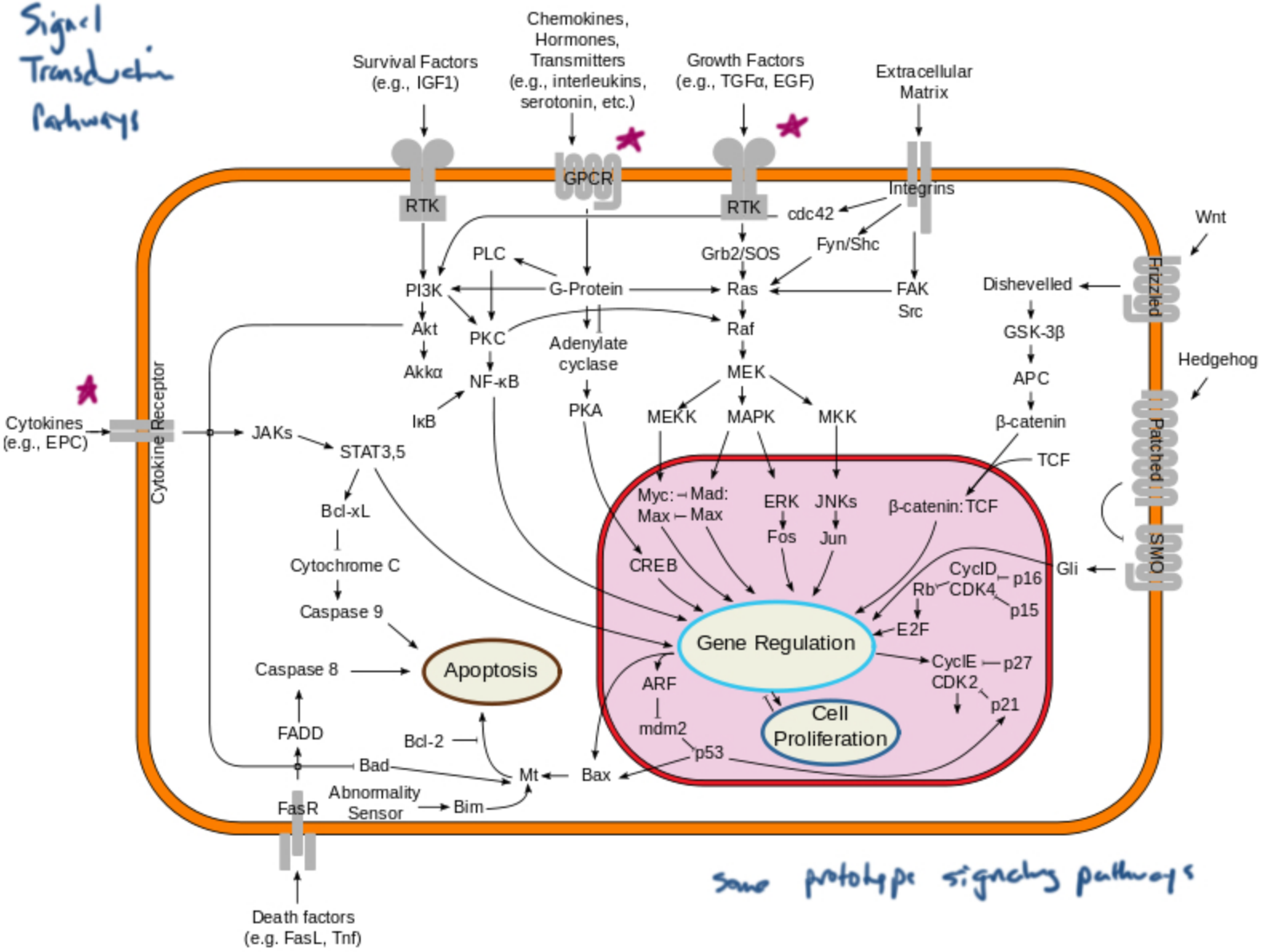
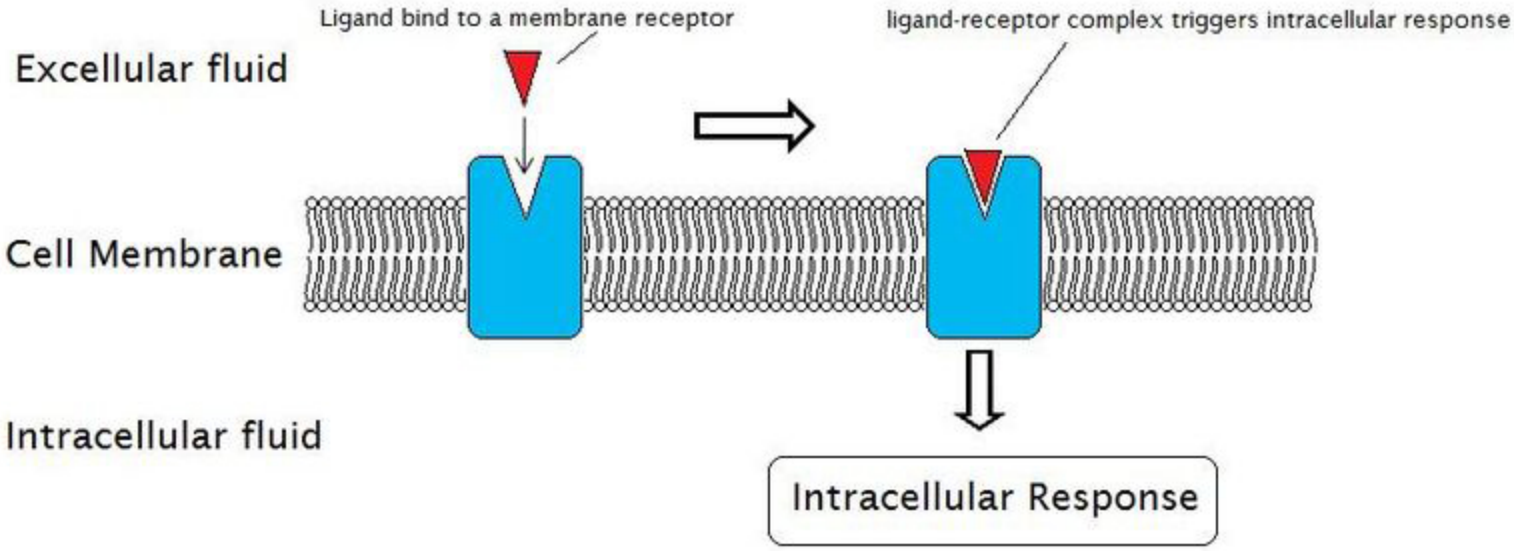
Signal Transduction Pathways

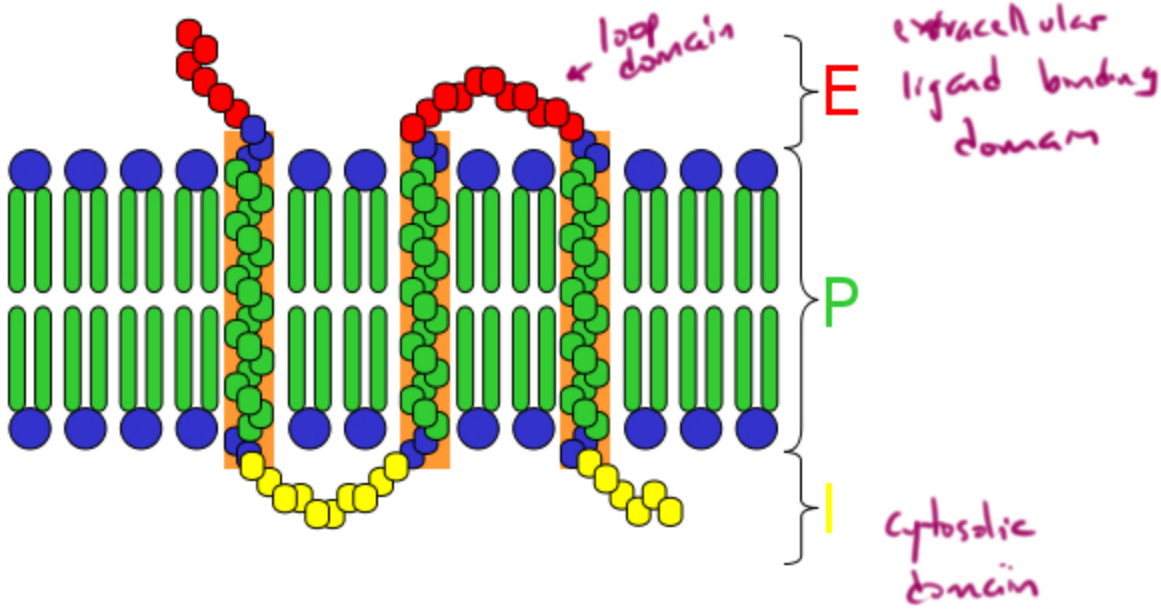
Session Slides with Notes

Signal Transduction Pathways

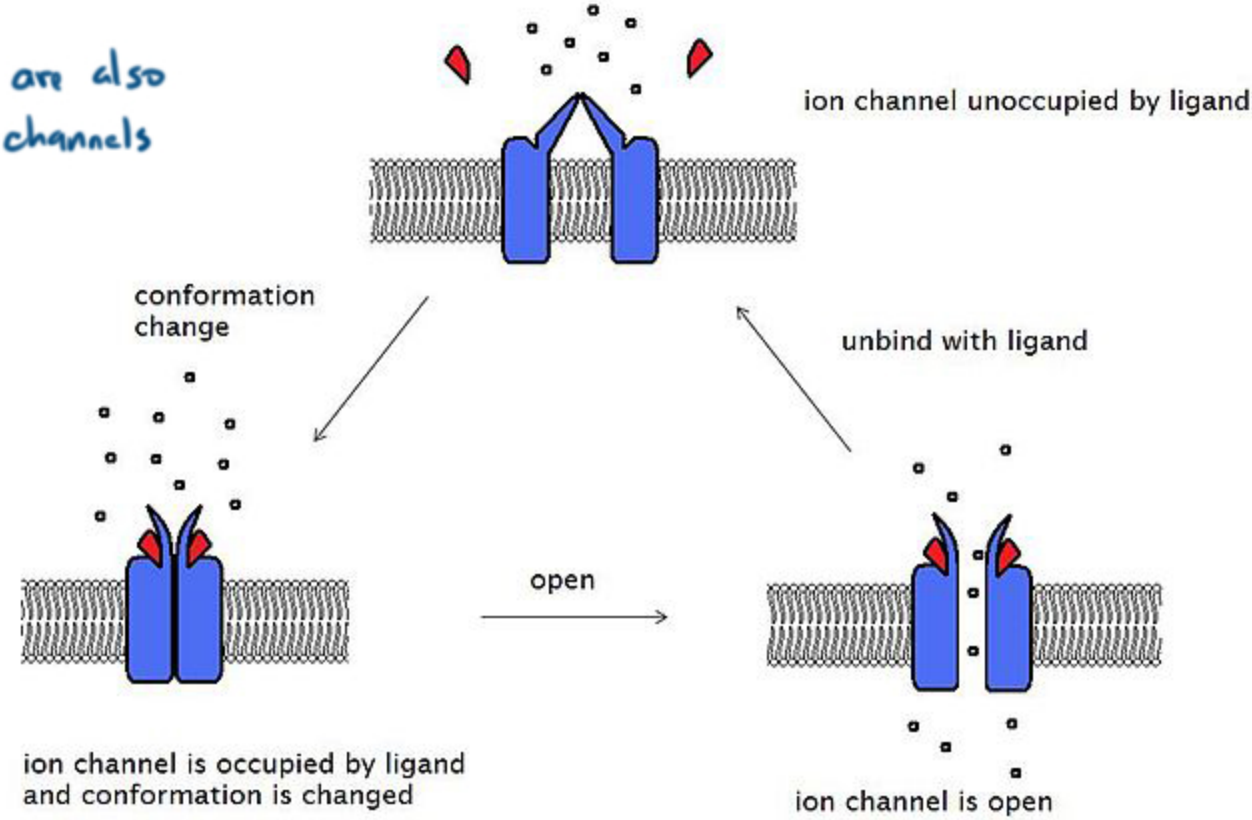


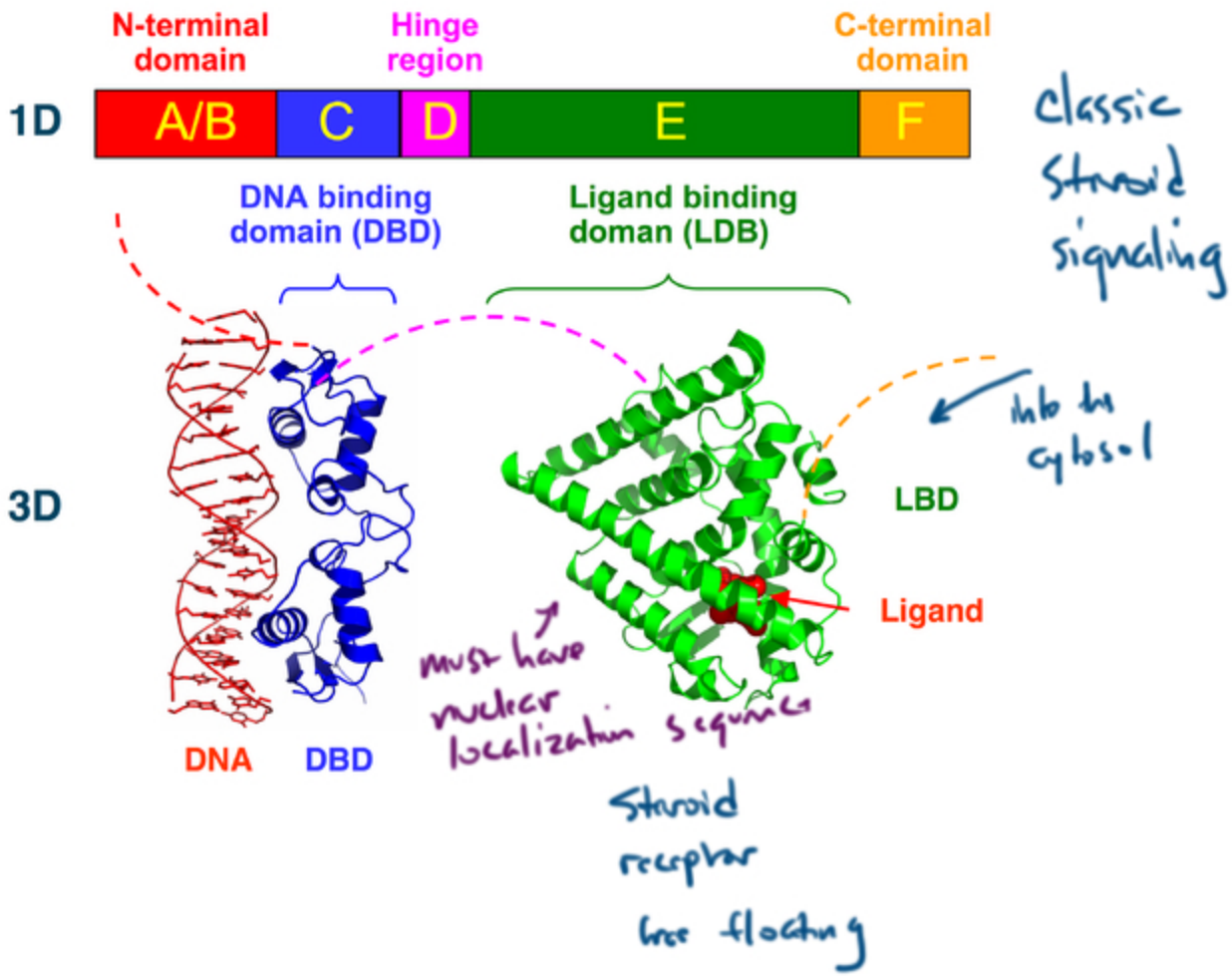
some prototype signaling pathways


Ligand bind to a membrane receptor
ligand-receptor complex triggers intracellular response
Excellular fluid
Cell Membrane
Intracellular fluid
Intracellular Response

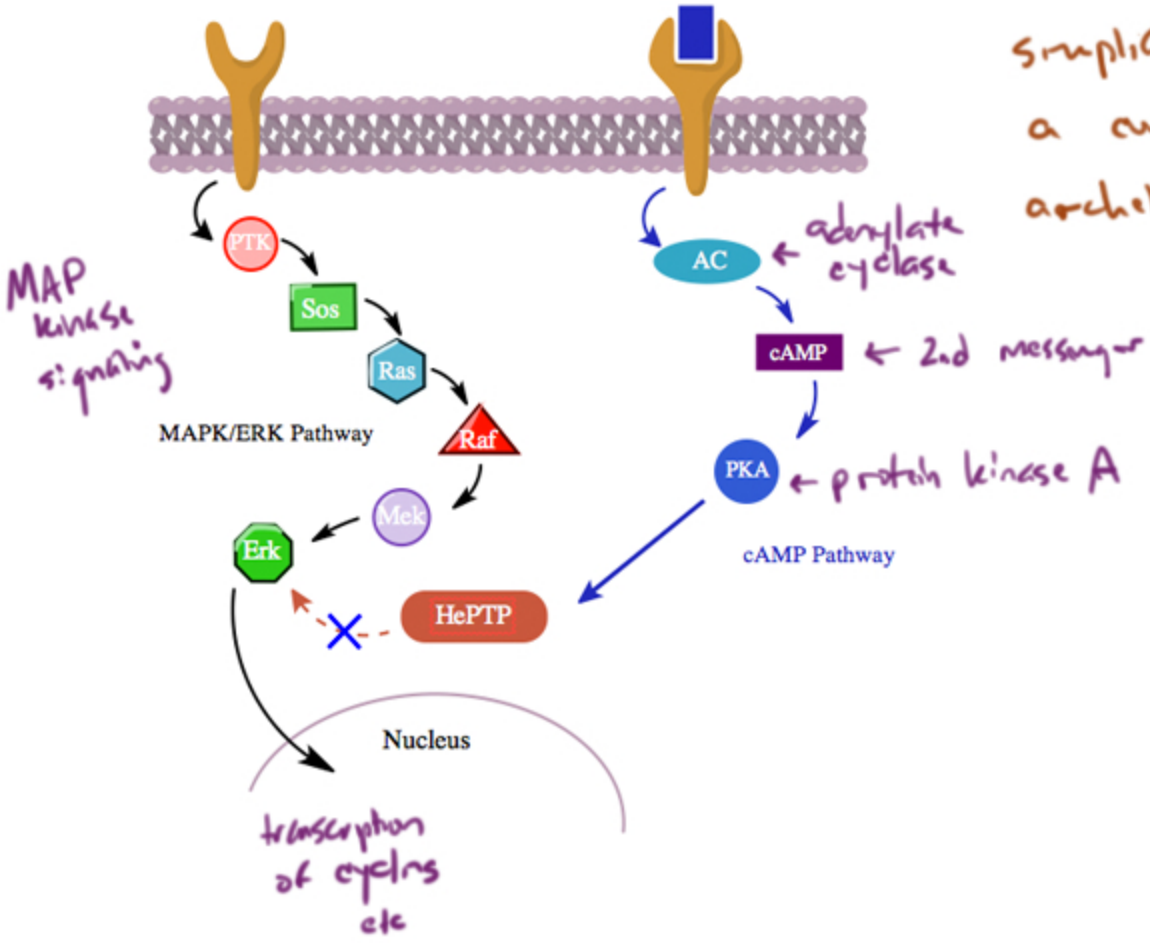

loop domain
extracellular ligand binding domain
E
P
I
cytosolic domain

There are also ion channels



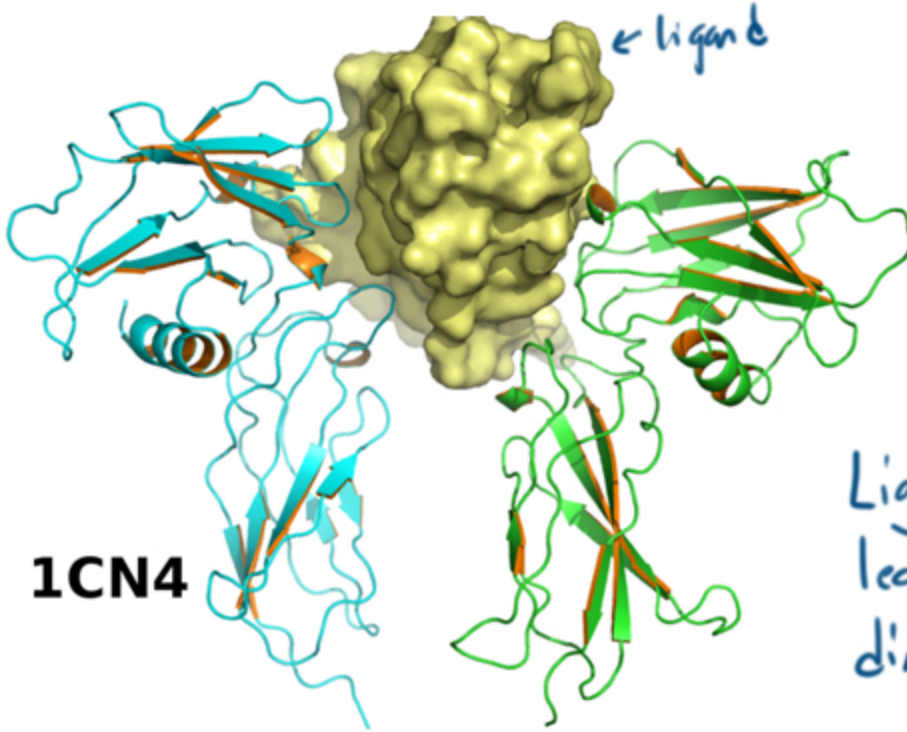

N-terminal domain
Hinge region
C-terminal domain
1D
A/B
C
D
E
F
DNA binding domain (DBD)
Ligand binding doman (LDB)
3D
LBD
Ligand
DNA
DBD
must have nuclear localization sequence
classic steroid signaling
into the cytosol
steroid receptor free floating

simplified pictures of a couple of archetypal pathways



Catalytic receptors

(growth factor receptors ; cytokine receptors)

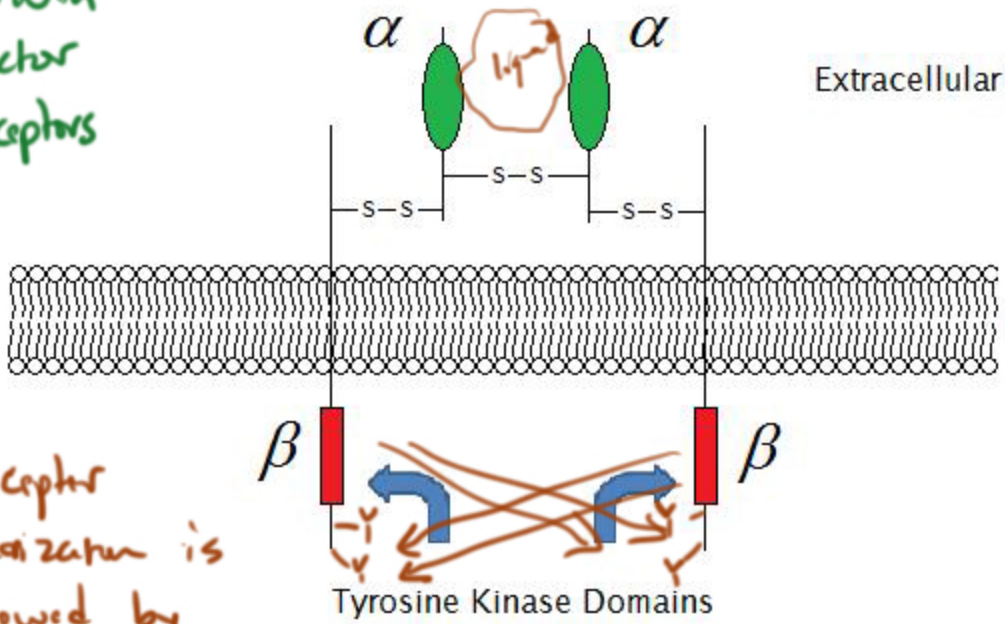


Ligand binding leads to dimerization

EPOR-EPO

erythropoetin receptor
- a cytokine receptor

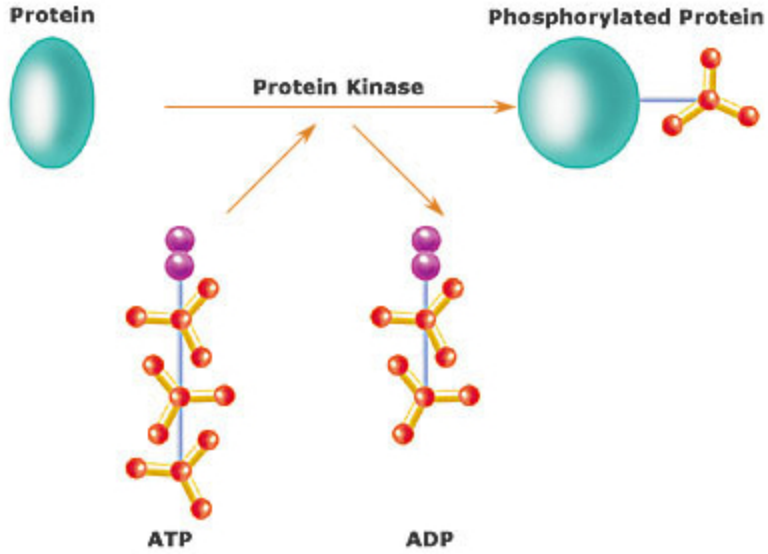
Growth Factor Receptors



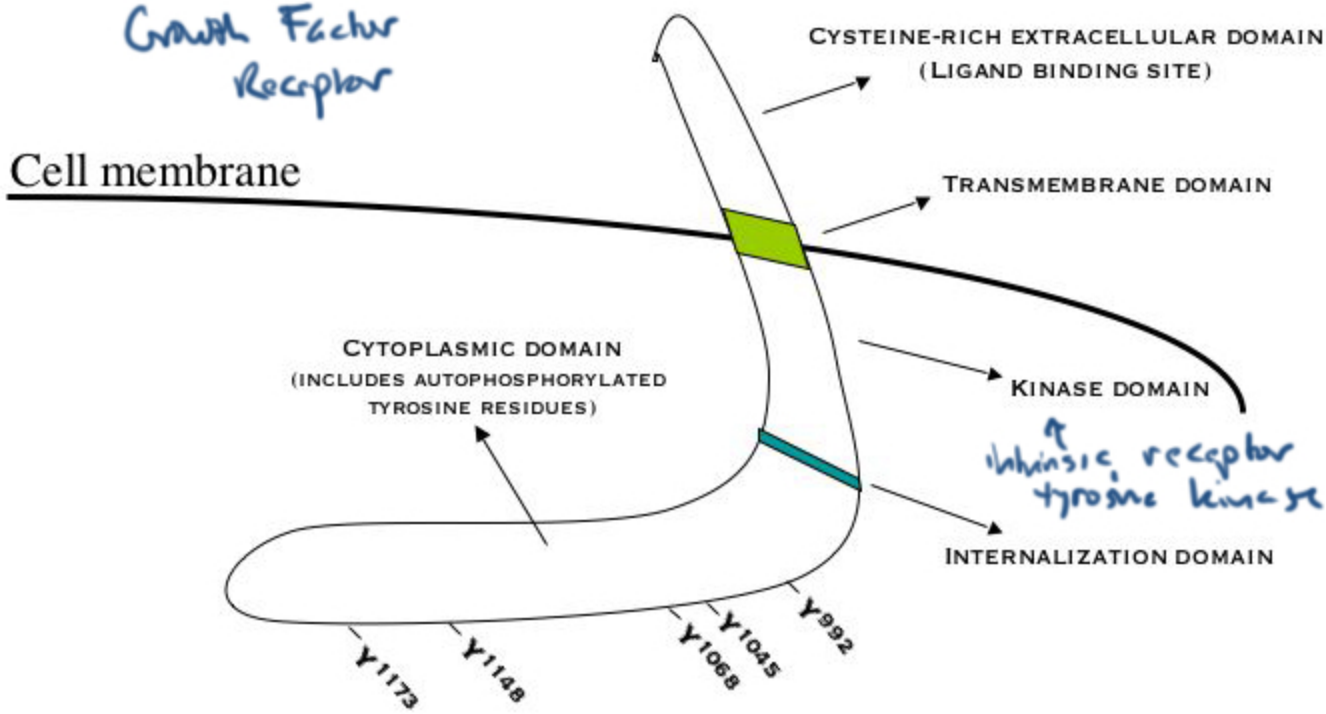
- Receptor dimerization is followed by transautophosphorylation
- Phosphorylated tyrosines serve as docking sites for signaling proteins (with SH2 domains)

Growth factor receptors possess intrinsic receptor tyrosine kinase.

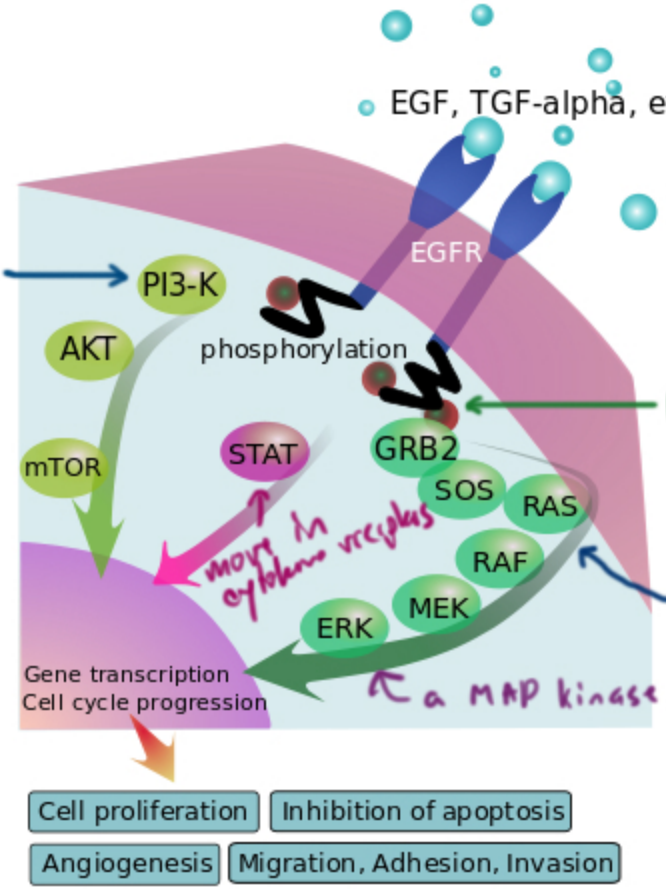
(cytokine receptors are just like this but they utilize a non receptor tyrosine kinase)


Protein
Phosphorylated Protein
Protein Kinase
ATP
ADP

Growth Factor Receptor



Some simplified archetypal pathways



phosphatidyl inositol 3-kinase (don't confuse with phospholipase C)

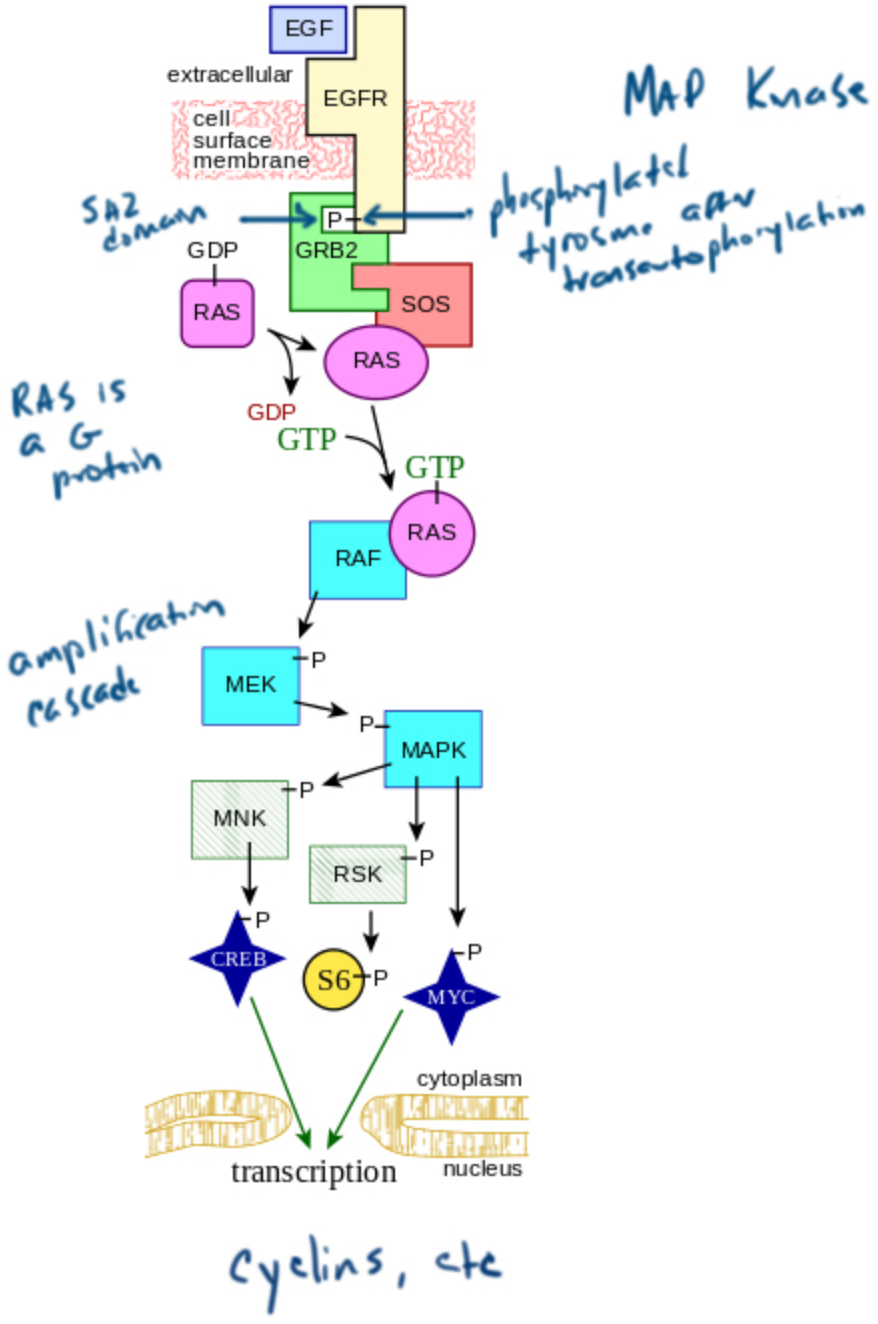
phosphorylated tyrosine

moves in cytokine receptors

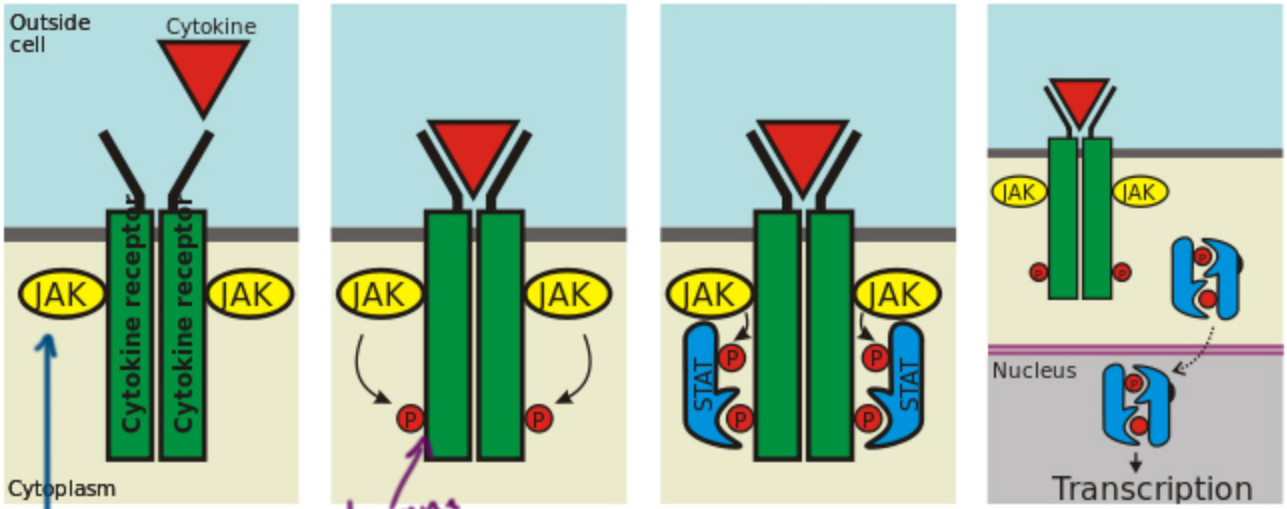
a MAP kinase

RAS is a G protein (don't confuse with GPCR) activated by exchange of GDP with GTP

deactivated by GTPase activity


MAP Kinase
EGF
extracellular
EGFR
cell surface membrane
SH2 domain
P
phosphorylated tyrosine after transautophosphorylation
GDP
GRB2
RAS
SOS
RAS
RAS is a G protein
GDP
GTP
GTP
RAS
RAF
amplification cascade
MEK
P
P
MAPK
MNK
P
RSK
P
P
CREB
S6
P
P
MYC
cytoplasm
transcription
nucleus
cyclins, etc

Cytokine Receptor



tyrosine

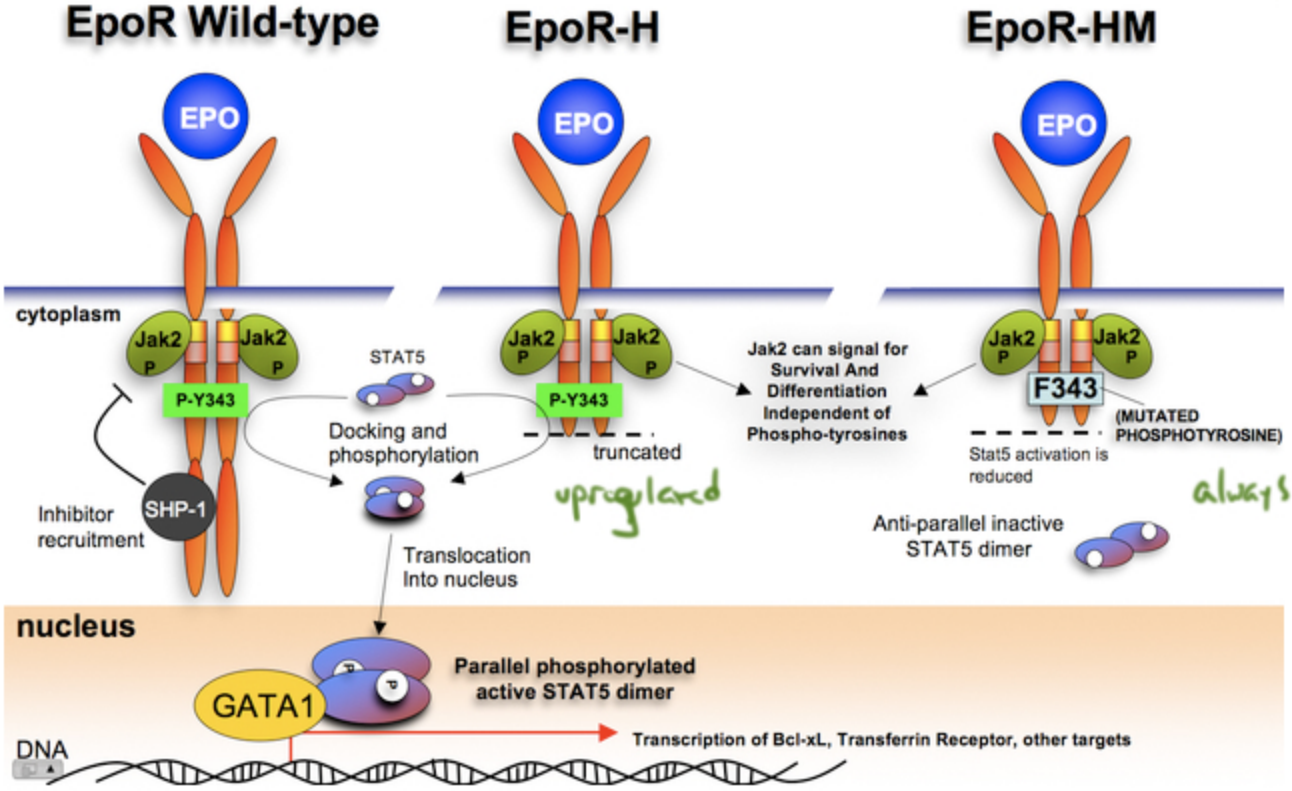
JAK STAT

non receptor tyrosine kinase

Janus Kinase

Truncated Epo Receptors

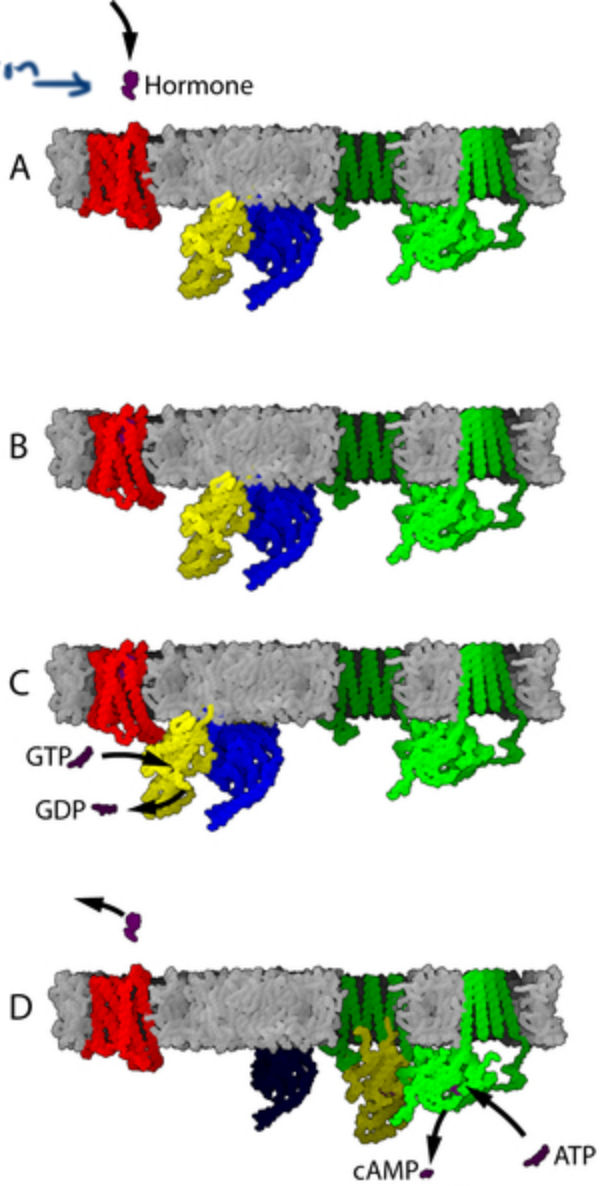
MCAT logic



example in liver

glucagon → Hormone

2nd Messengers



cAMP

↓

PKA → phosphorylase kinase (ON)

↓

glycogen phosphorylase

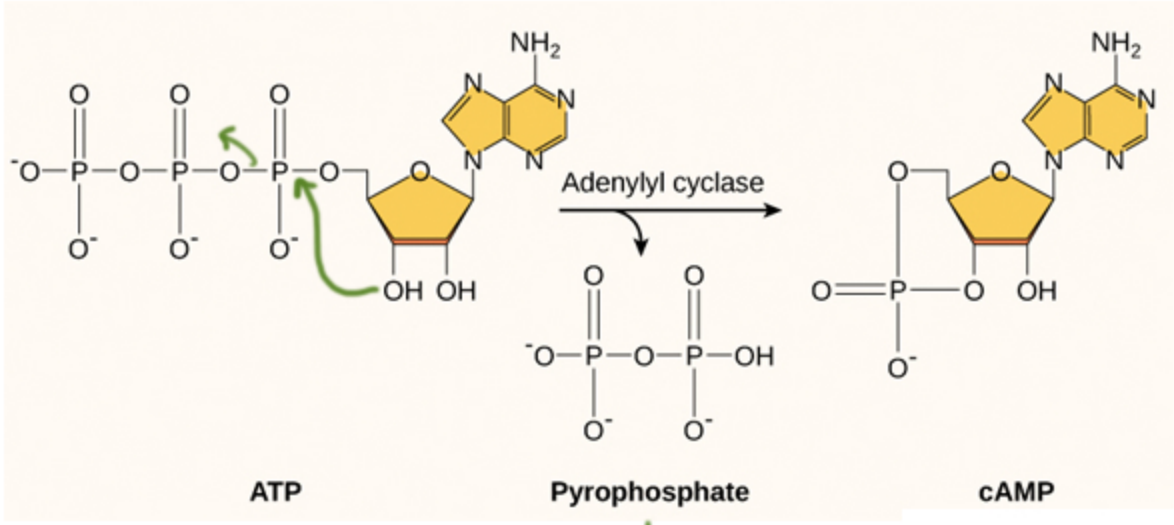
PKA → CREB

↓

PEP carboxykinase

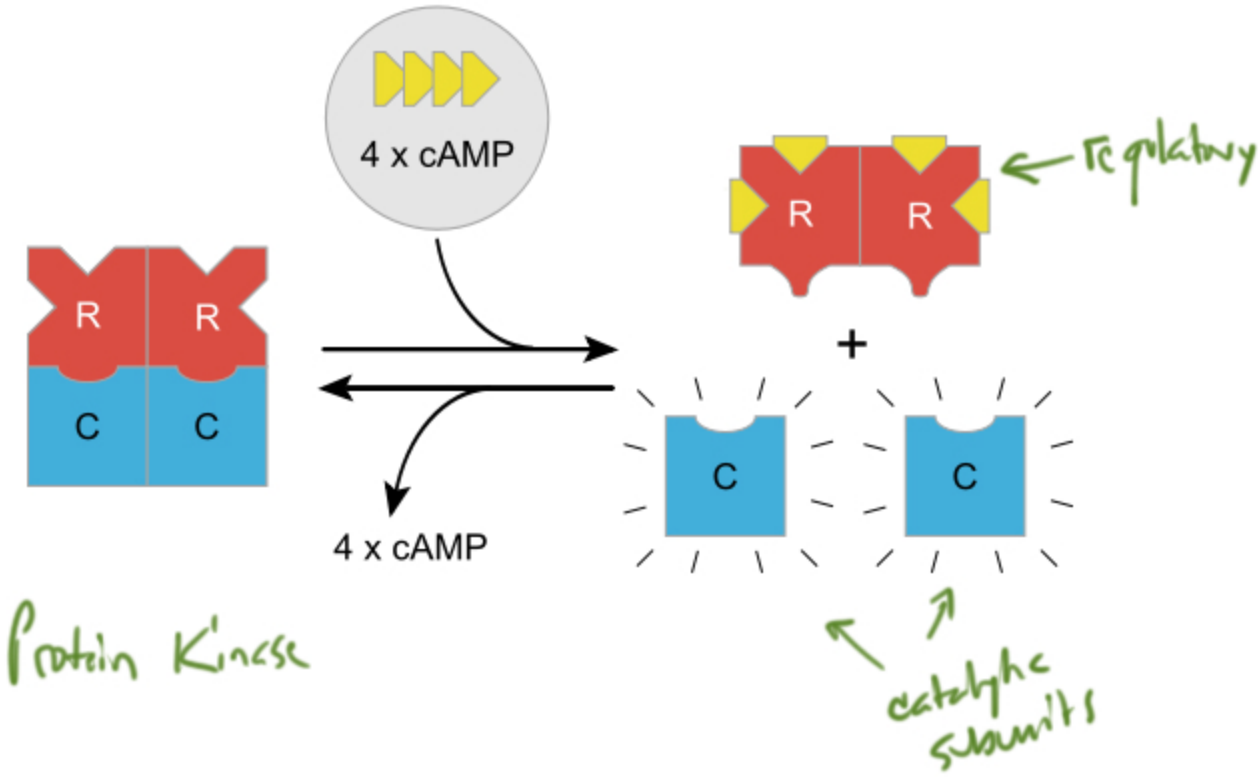
PKA → transcription factor

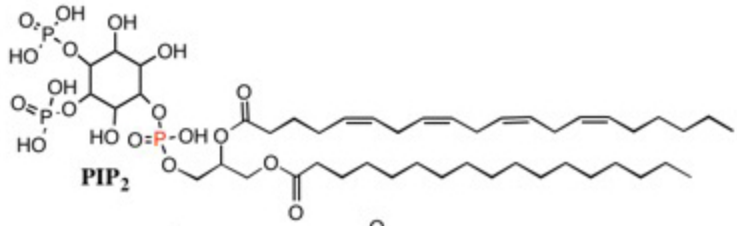
PFK II OFF



more $-\Delta G$

$2P_i$


4 x cAMP
R
R
C
C
4 x cAMP
R
R
+
C
C
Protein Kinase
regulatory
catalytic subunits

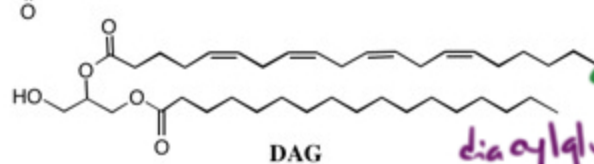


PIP$_2$

Phosphatidyl inositol diphosphate

Phospholipase C

PLC

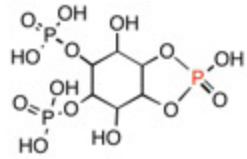


DAG

stays in membrane

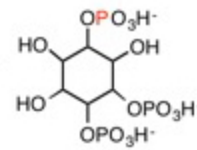
diacylglycerol

2nd messengers



Cyclic-IP$_3$

H_2O



IP$_3$

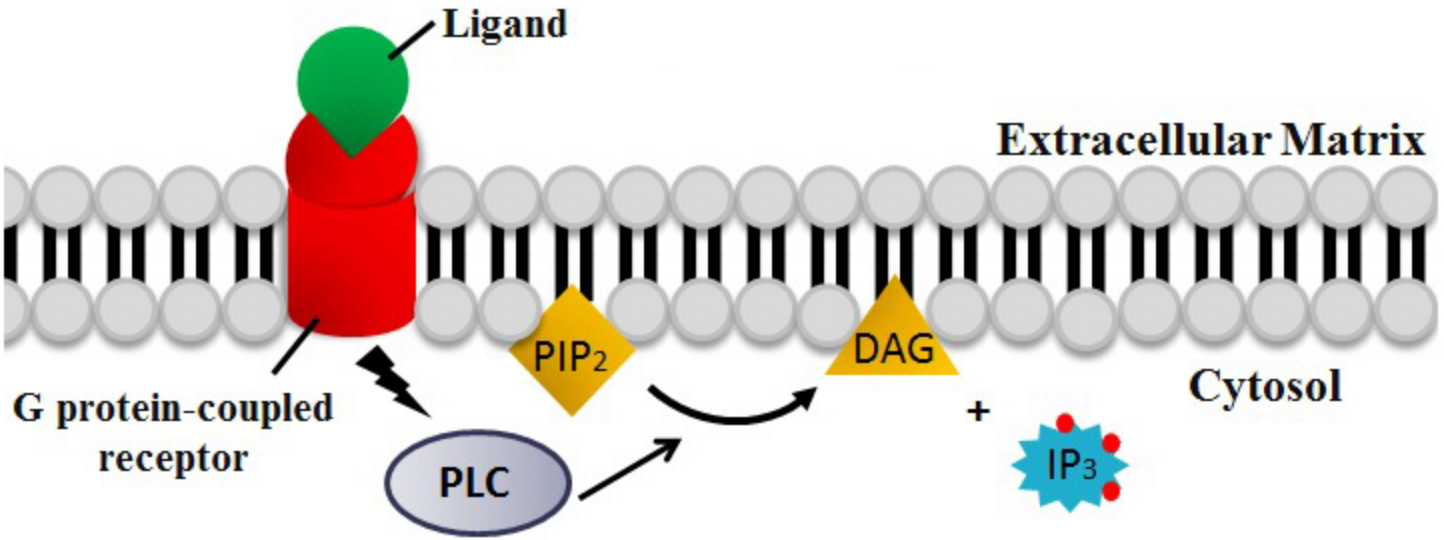
inositol triphosphate

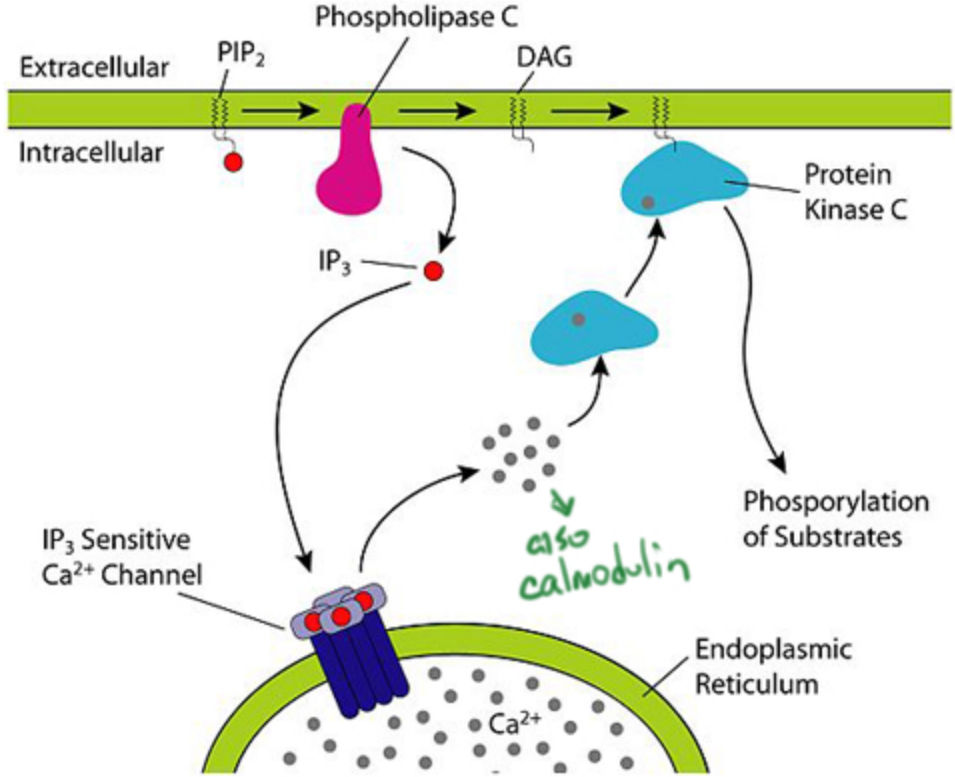
cytosol

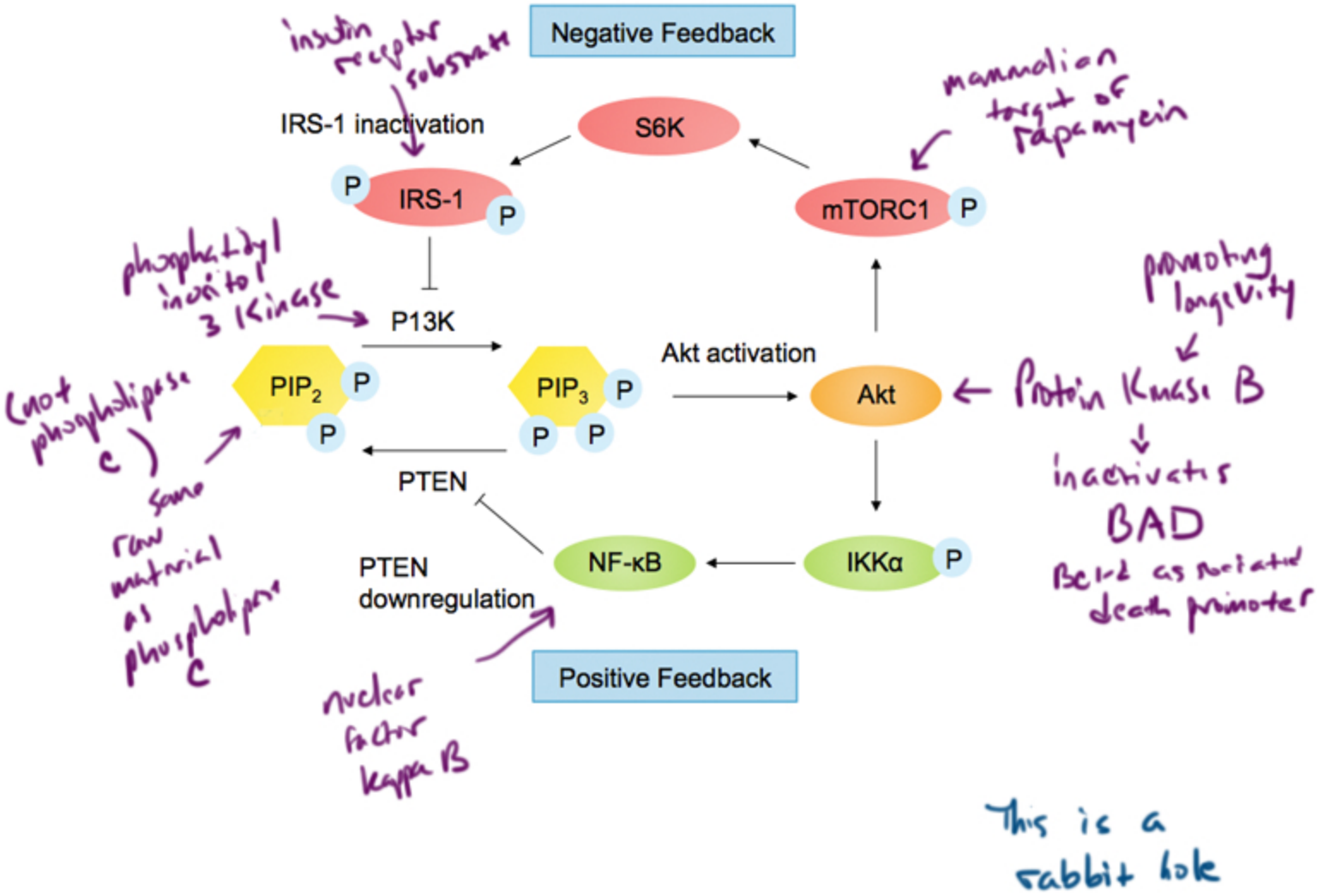
ER → Ca^{2+} + DAG → protein kinase C

↓

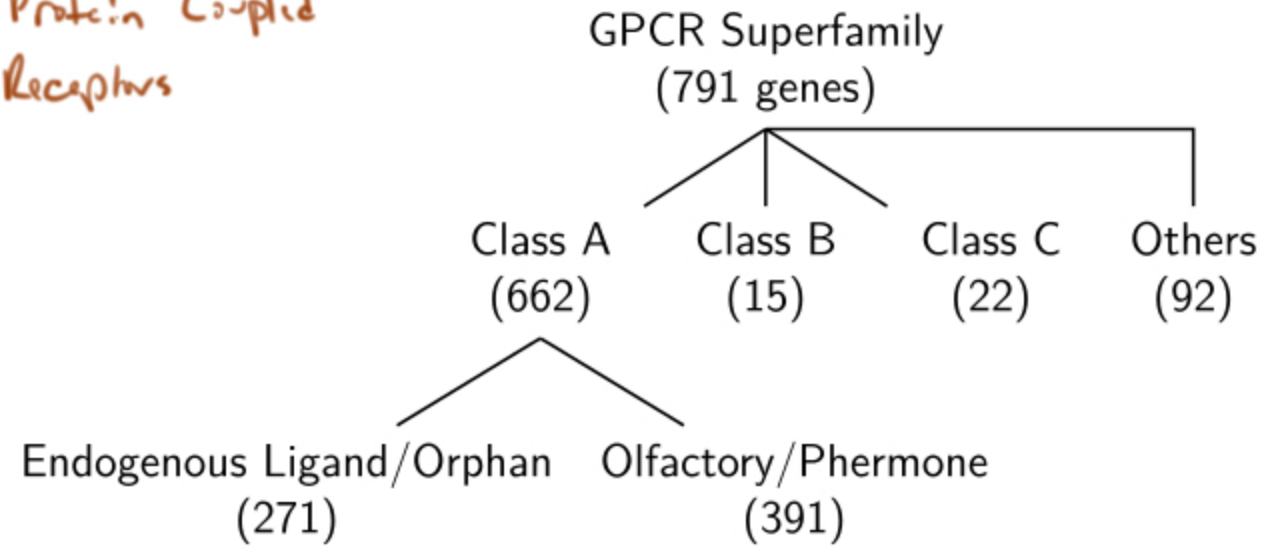
Calmodulin

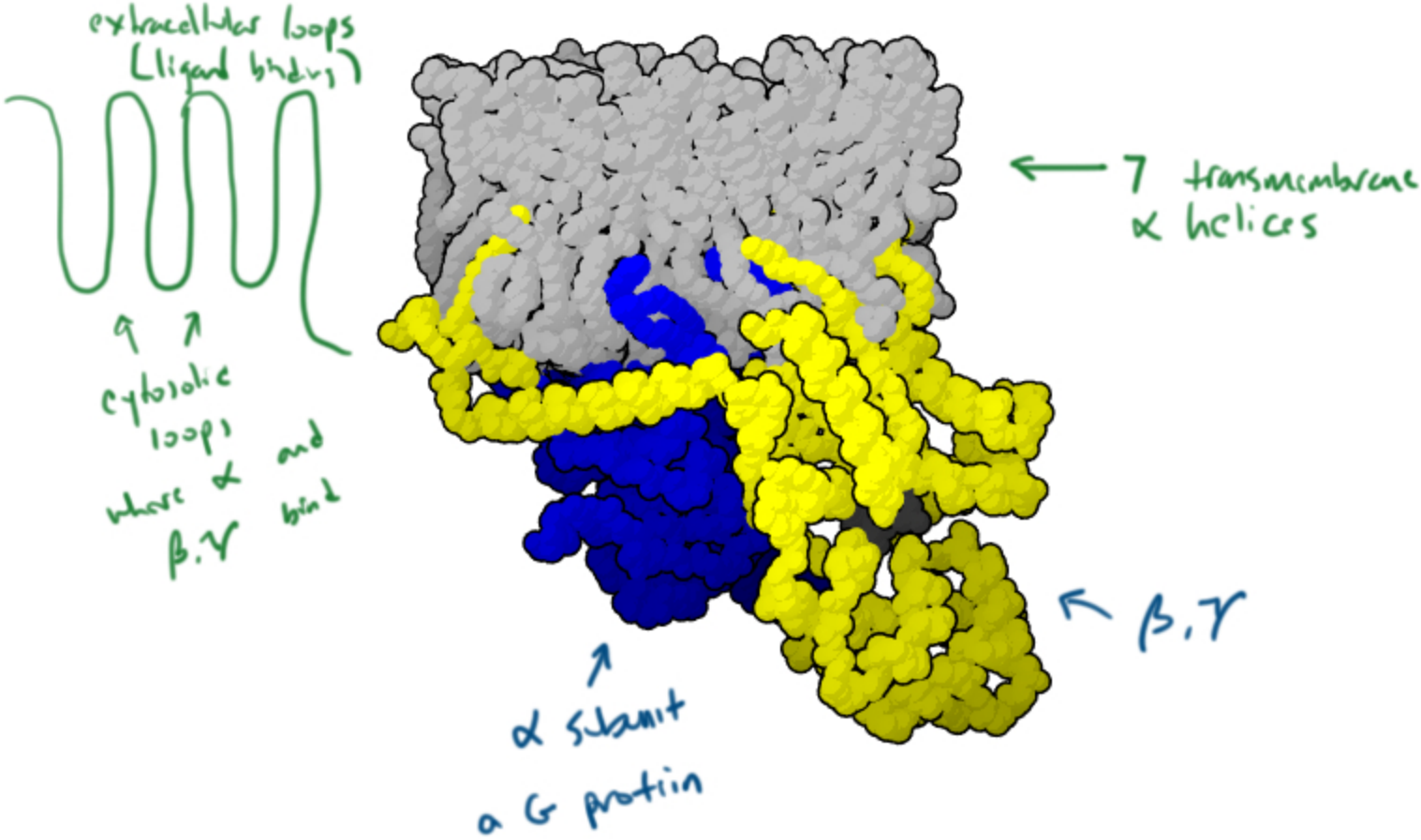

Ligand
Extracellular Matrix
PIP2
DAG
Cytosol
G protein-coupled
receptor
PLC
+
IP3

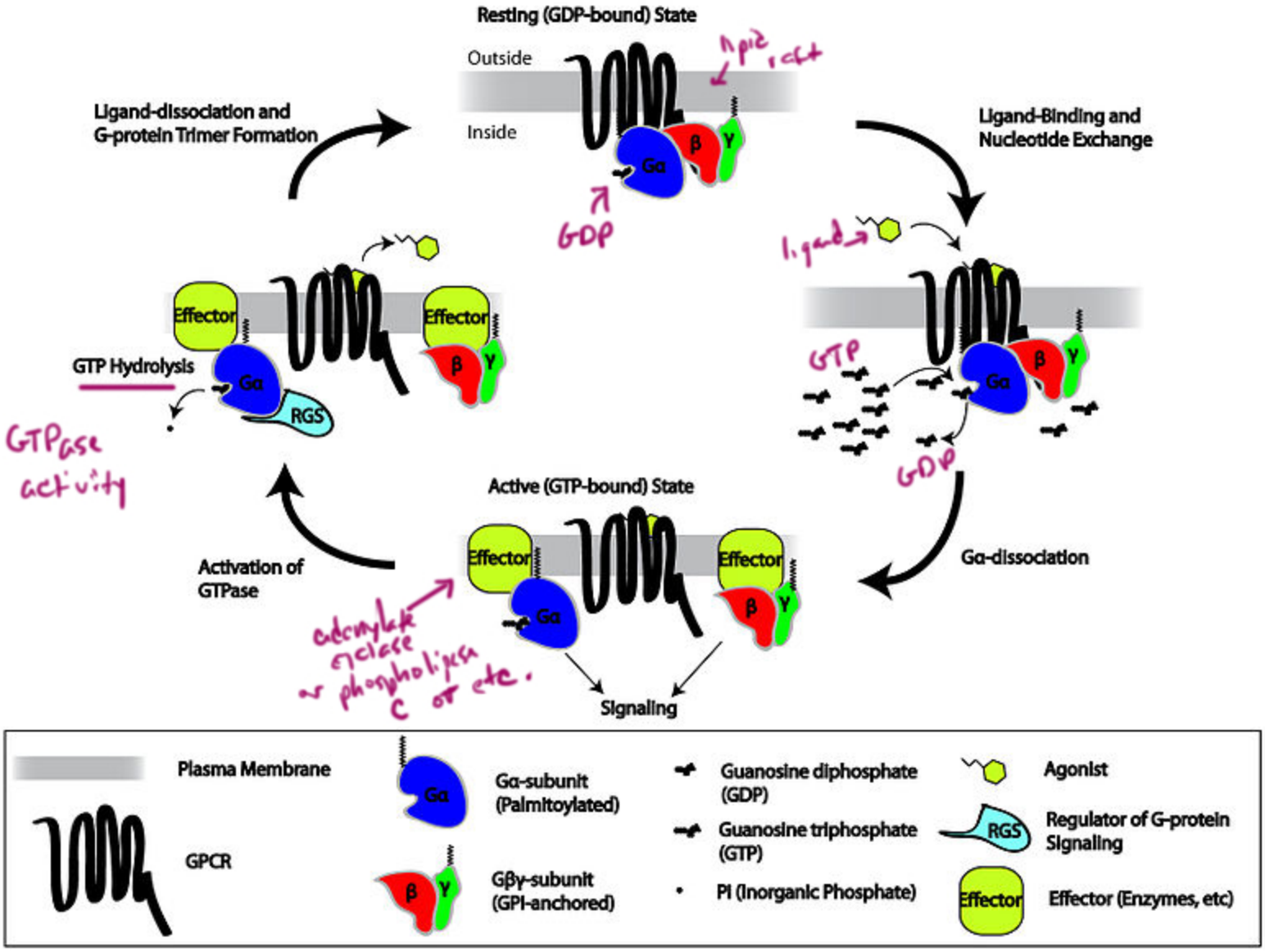

Phospholipase C
Extracellular
PIP2
DAG
Intracellular
Protein
Kinase C
IP3
IP3 Sensitive
Ca2+ Channel
also
calmodulin
Phosporylation
of Substrates
Endoplasmic
Reticulum
Ca2+

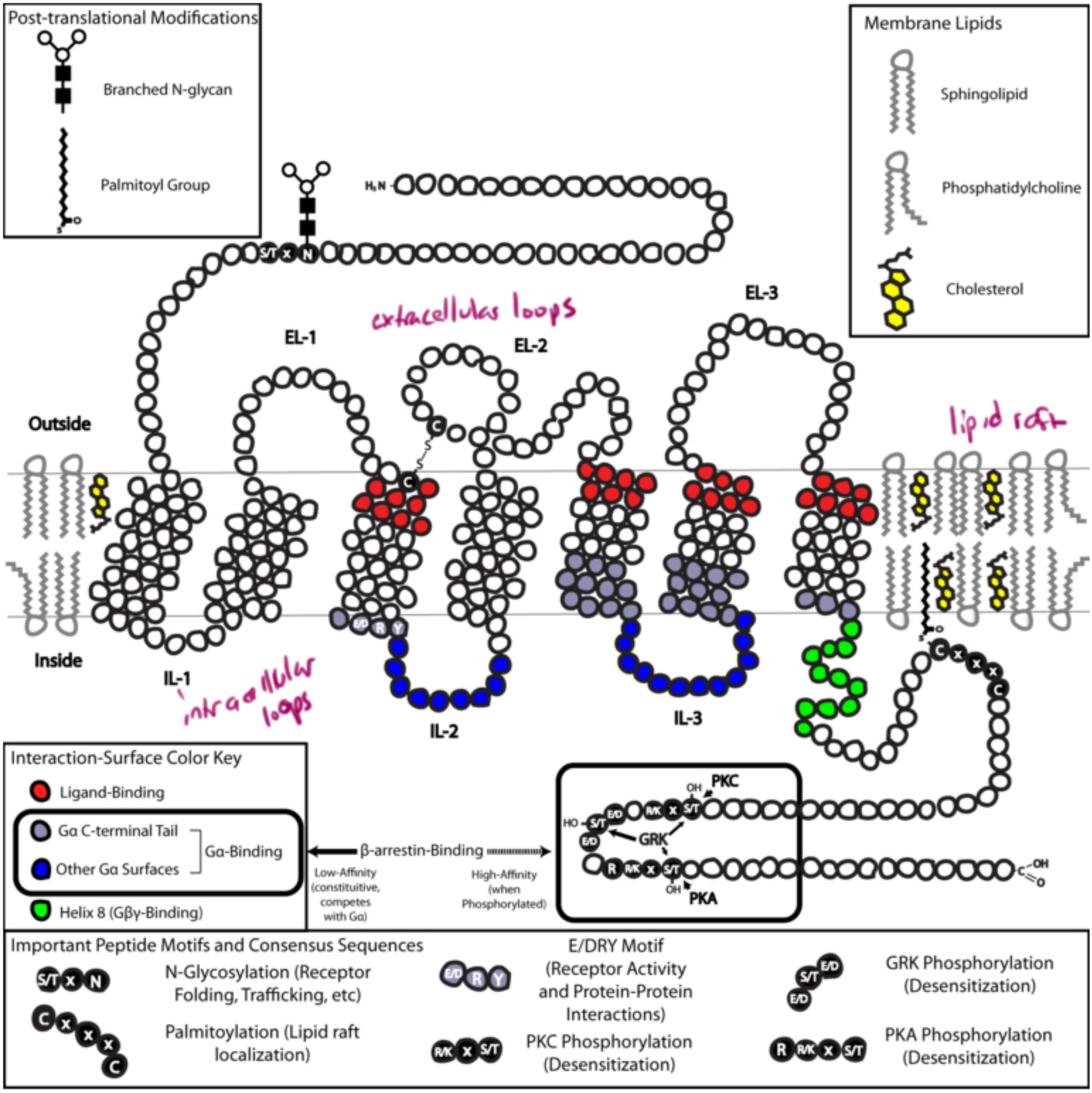

Negative Feedback
IRS-1 inactivation
S6K
IRS-1
P
mTORC1
P
P13K
PIP2
PIP3
Akt activation
Akt
PTEN
NF-κB
IKKα
PTEN downregulation
Positive Feedback

G Protein Coupled Receptors

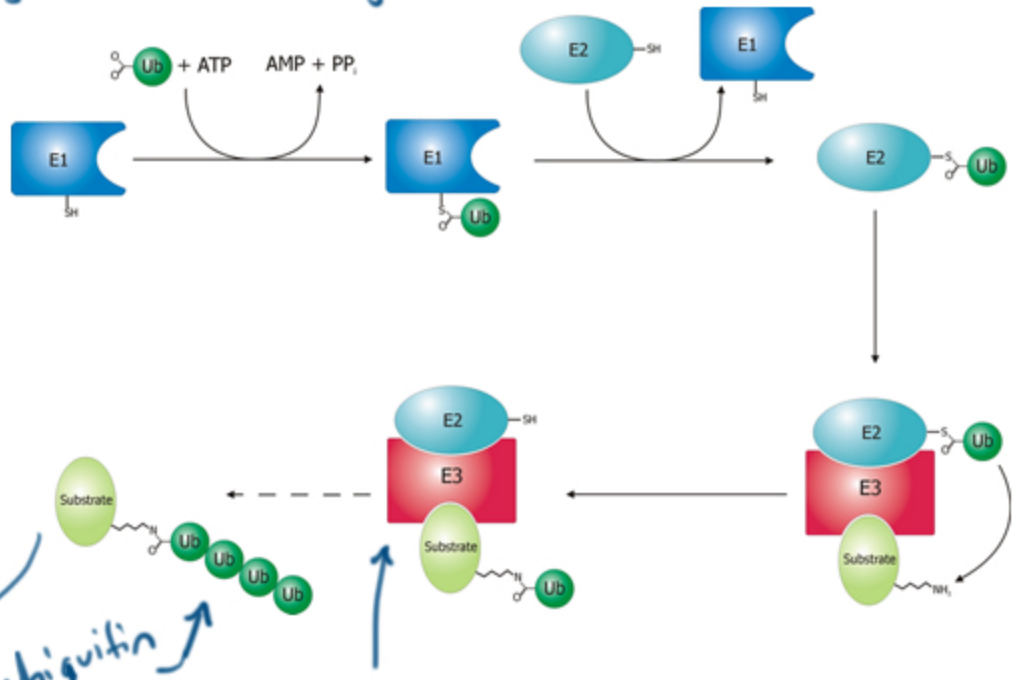



extracellular loops
(ligand binding)
cytosolic loops where α and β,γ bind
7 transmembrane α helices
β,γ
α subunit a G protein


Resting (GDP-bound) State
Outside
Inside
Gα
β
γ
GDP
Ligand-Binding and Nucleotide Exchange
Ligand
GTP
GDP
Gα-dissociation
Active (GTP-bound) State
Effector
Effector
Signaling
Activation of GTPase
adenylate cyclase or phospholipase C or etc.
GTP Hydrolysis
RGS
GTPase activity
Ligand-dissociation and G-protein Trimer Formation
Plasma Membrane
GPCR
Gα-subunit (Palmitoylated)
Gβγ-subunit (GPI-anchored)
Guanosine diphosphate (GDP)
Guanosine triphosphate (GTP)
PI (Inorganic Phosphate)
Agonist
Regulator of G-protein Signaling
Effector (Enzymes, etc)


Post-translational Modifications
Branched N-glycan
Palmitoyl Group
Membrane Lipids
Sphingolipid
Phosphatidylcholine
Cholesterol
H2N
S/T X N
extracellular loops
EL-1
EL-2
EL-3
Outside
Inside
lipid raft
C
C
E/D R Y
C X X X C
IL-1
intracellular loops
IL-2
IL-3
Interaction-Surface Color Key
Ligand-Binding
Gα C-terminal Tail
Other Gα Surfaces
Gα-Binding
Helix 8 (Gβγ-Binding)
β-arrestin-Binding
Low-Affinity (constituitive, competes with Gα)
High-Affinity (when Phosphorylated)
PKC
GRK
PKA
OH
HO
R/K X S/T
E/D
Important Peptide Motifs and Consensus Sequences
S/T X N
N-Glycosylation (Receptor Folding, Trafficking, etc)
C X X X C
Palmitoylation (Lipid raft localization)
E/D R Y
E/DRY Motif (Receptor Activity and Protein-Protein Interactions)
R/K X S/T
PKC Phosphorylation (Desensitization)
S/T E/D E/D
GRK Phosphorylation (Desensitization)
R R/K X S/T
PKA Phosphorylation (Desensitization)

Targeted Protein Degradation



Proteosome

ubiquitin

E3 ligase
(lots of these
for many specific
target proteins)