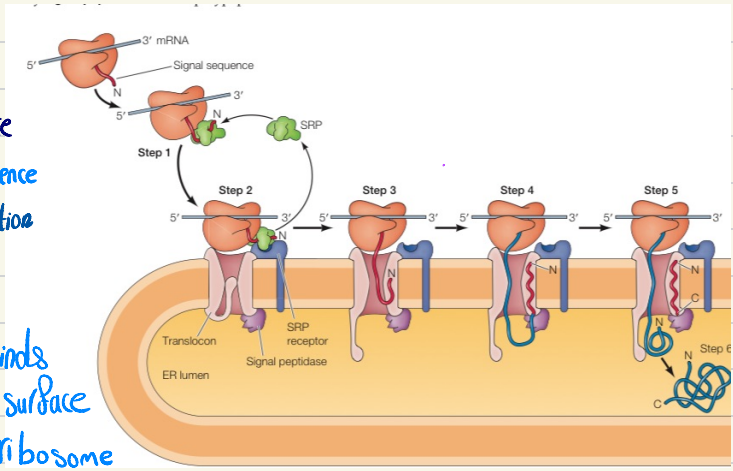
Pathways / Mechanisms / regulation - Cyto

H·S

Protien Sorting



Step 1 : recognition of signal sequence
as ribosomes being translated, signal sequence is produced & recognized by signal recognition particle (SRP)

Step 2 : SRP-ribosome complex binds with SRP receptor located on surface of RER ⟶ positions the ribosome over a channel called translocon

Step 3 : Translocon opens allowing growing polypeptide chain to be inserted into ER lumen

Steps 4 & 5 : sequence is removed by signal peptidase

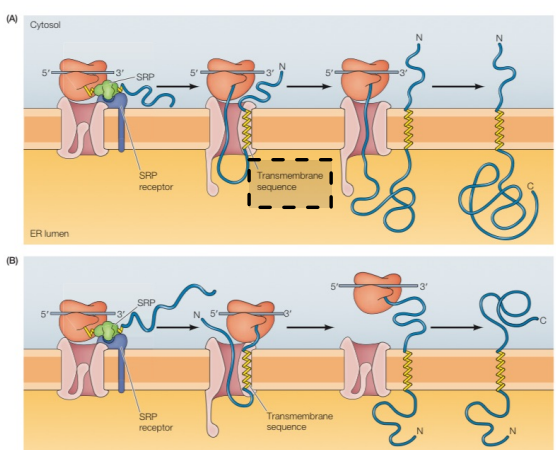
Step 6: Continue translation & PPC embedded into ER lumen

Insertion of membrane Proteins via trans-membrane sequence

The Translocon recognizes transmembrane sequence

Acts as a stop ! - transfer signal anchoring the protien in the ER membrane

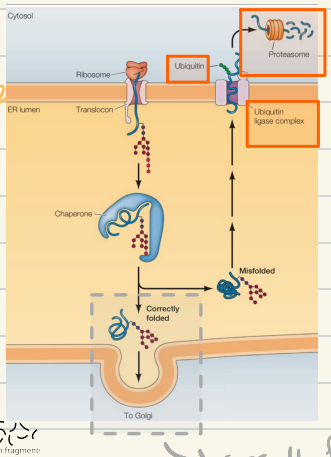
Note : orientation of N-terminus & C-terminus depends on the direction of internal transmembrane sequence



Note 2: Multiple transmembrane domain proteins have multiple transmembrane sequence

Protien folding & ER-associated degredation (ERAD)

acts as a sensor - if a protien is misfolded ⇝ unfolded then folded again



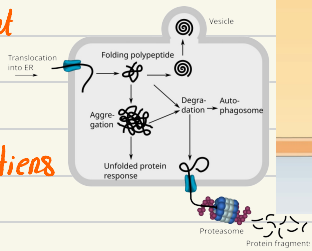
if protien is misfolded again so the protien is sent outside ER

↓

in cytosol, protien is tagged with small proteins called ubiquitins

↓

ubiquinated proteins recognized & degreded by (proteasome)

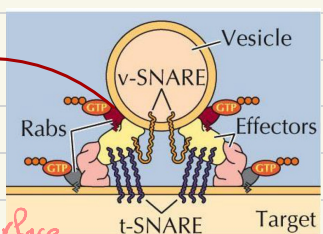


→ correctly folded proteins move on

Delivery of vesicles: Targeting & fusion

Rab: Guide vesicles to corret target membrane; each Rab specific to a transport route

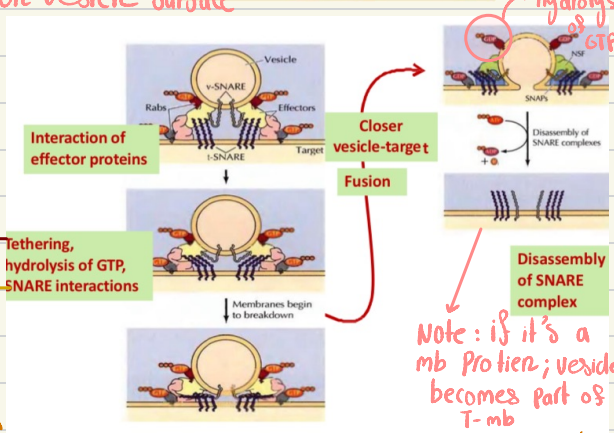
Rab is activated ⇝ (GTP-bound) on vesicle surface



Active Rab interact with tethering factors or effector protien on target membrane, bringing the vesicle closer to the target

Each v-SNARE specific to a t-SNARE

V-SNARE & t-SNARE interact & forms a stable complex, bringing vesicle & target membrane togather ⇝ The SNAREs drives fusion of V-mb with T-mb cargo delivery



Protien import & mitochondrial assembly

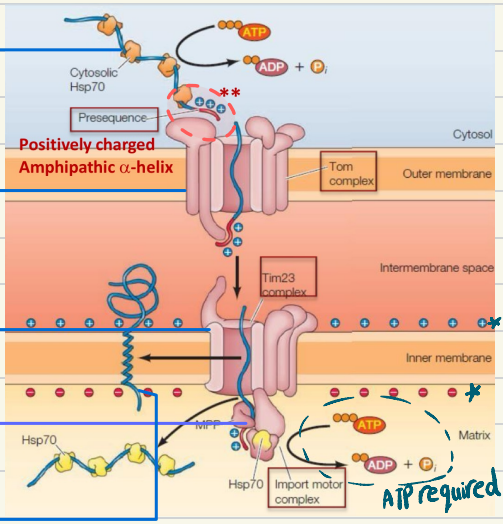
* protiens destined for mt have N-terminal Presequence ; it's + charged & amphipathic α-helices

* Translocation through TOM complex
  - Translocase of outer membrane

* Translocation through TIM complex

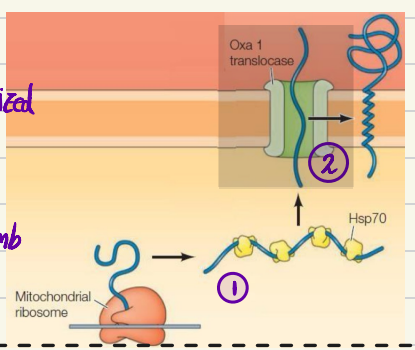
* presequence is removed during Translocation

* some protiens with transmembrane domains exit laterally into inner membrane



Targeting of inner membrane protiens

* inner mt membrane protiens encoded by mtDNA are synthesized directly on mitochonderial ribosomes in matrix
  ↓
* Oxa1 translocase recognize & integrates these protiens into the mb

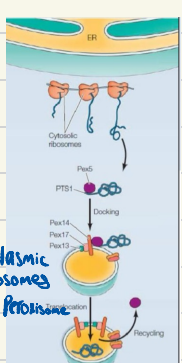


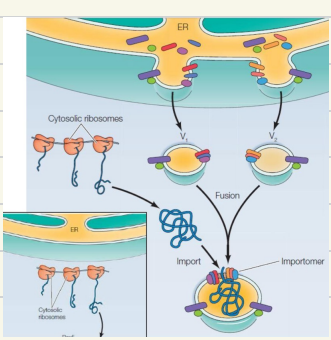
Assembly of peroxisomes

Transmembrane protiens are derived from ER, specific peroxisomal transmembrane are involved in creating a functional peroxisome

* Matrix/internal protiens are synthesized in cytoplasm on cytoplasmic ribosomes
* They contain peroxisomal targeting signal (PTS1) direct them to peroxisome

* peroxins help in translocating peroxisomal protiens into peroxisome by functioning in carrying & importing them

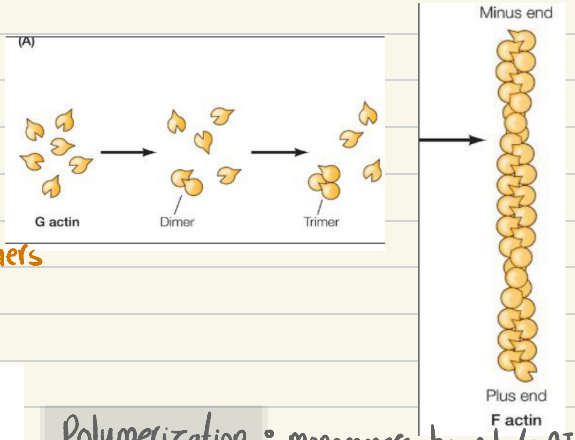


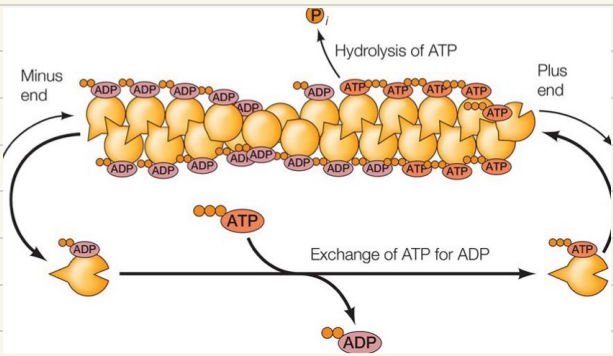


Actin Polymerization

Nucleation : start of actin polymerization ← where a trimer of G-actin protien is formed

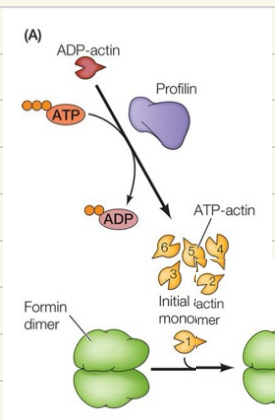
*Actin filamen then grow by adding monommers to both ends





Polymerization : monommers bound to ATP

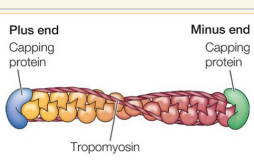
Treadmilling : filaments dissociated from ADP actin

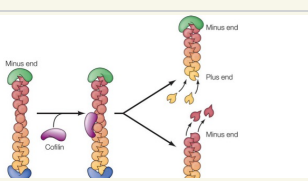


Formin : promotes nucleation of actin

ARP 2/3 : initiates branching

Profilin : exchange ADP for ATP





Tropomyosis : stabilizes ends by binding to capping protiens

Cofilin : breaks up acting filaments

Microtubul-associated Proteins (MAPs) - Regulate dynamic behavior of microtubuls

Regulating

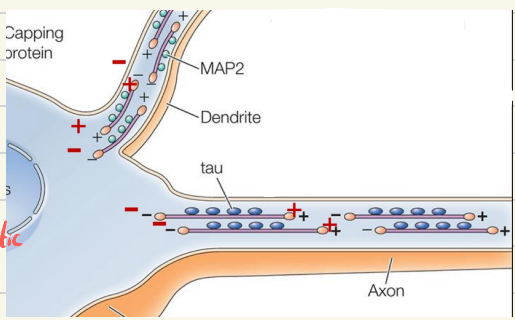
* growth by Polymerases
* shrinkage by depolymerases at + ends of microtubuls

Suppressing microtubule catastrophe & Promoting rescue :

* CLASP proteins rescue microtubul from catastrophe

Organization of microtubules within cells - Neuron

(+) & (-) ends in nerve cells terminate in cytoplasm



dendrites : Microtubuls are oriented in both directions, meaning some have their + end facing dendritic tip, others have - end at dendritic tip

axons : organized with their + end consistenly pointing towards axon tip

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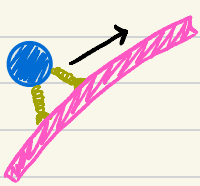
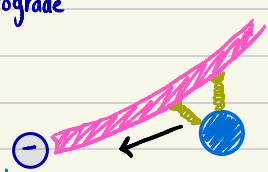
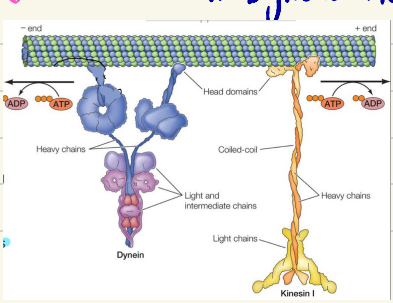
Microtubuls - motor Proteins → Kinesin & dynein → Microtubuls - motor proteins uses ATP to move along microtubuls in opposite directions



* Kinesin moves towards +ve end ⇝ anterograde

* Dynein moves toward the minus end





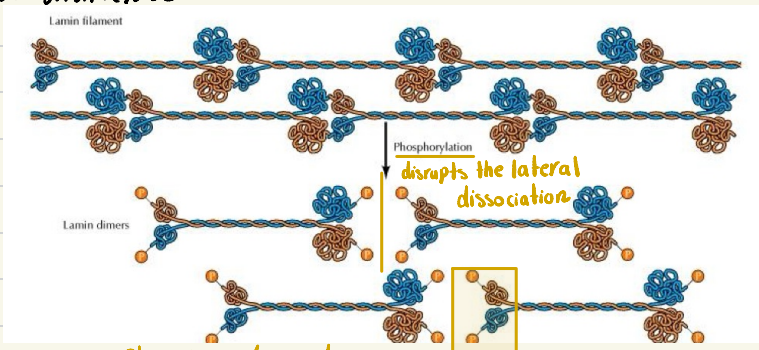
Each motor protein has two head domains they alternately bind to & release from microtubul

↓

when it binds to ATP it attatches strongly to microtubule, when ATP is hydrolyzed it triggers a shape change, causing it to release from microtubule & swing forward

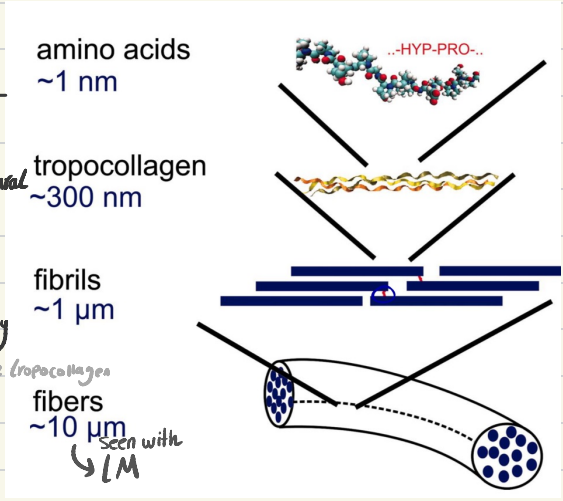
Regulation of intermediate filaments

When intermediate filaments like nuclear lamin & vimentins are phosphorylated (P) → they disassemble into dimers or protofilament



Phosphorylation at globular head

Assembly of fibrillar collagen



begins with a single α chain

↓

formation of a triple-stranded molecule, basic structural unit

↓

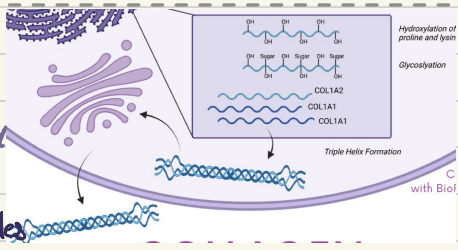
outside, they assemble into fibrils, stabilized by cross-linking - can be between 3 diff tropocollagen or 3 same tropocollagen

↓

fibrils aggregate to form fibers

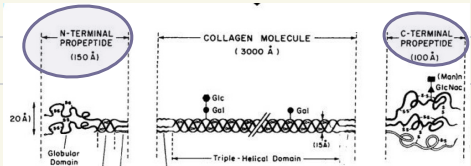
Synthesis of collagen

Note: Procollagen I intact N-Terminal considered most sensitive marker of bone formation



molecule is synthesized as a procollagen, where N-terminal & C-terminal propeptides inhibit intracellular fibril formation

lysyl oxidase, which catalyzes formation of reactive aldehydes

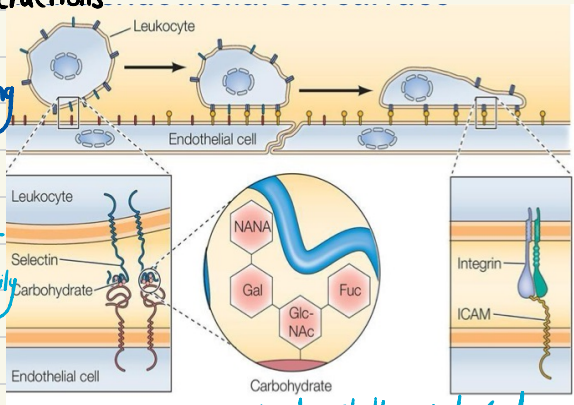


Following exocytosis, procollagen peptidases remove propeptides

Role of Selectins in leukocyte - endothelial cell interactions

leukocytes interact with endothelial cells via binding of leukocyte selectin to carb on endothelial cell

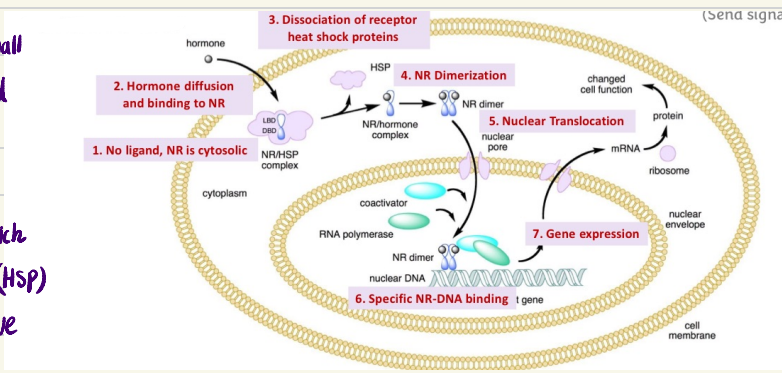
More stable interaction between leukocyte integrins & inter-cellular adhesion molecule (ICAM) - members of Ig family



Hetrophillic interactions

Mechanism of action of steroid nuclear receptor (NR)

1. steriod diffuses, because they are small they diffuse through without the need of a carrier



2. They bind to intracellular receptor which is cytosolic & bound to heat shock protien (HSP) which prevent receptor from being active

3. HSP released

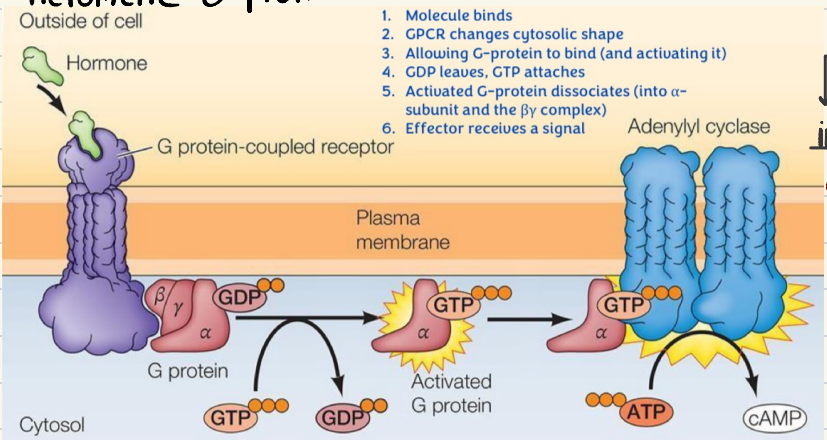
4. receptor dimerizes

5. Receptor gets translocated into nucleus

6. Receptor binds to DNA

7. controls gene expression

Hetomeric G-Protien

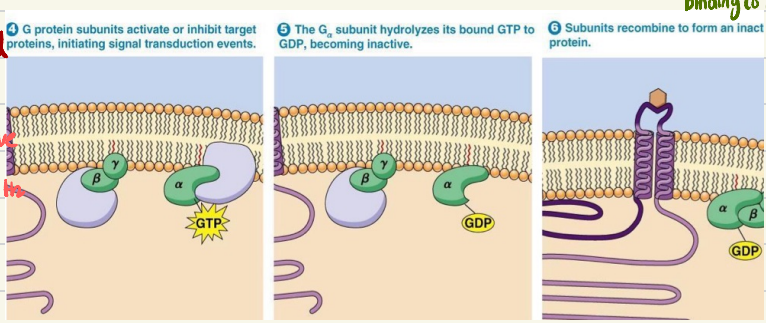


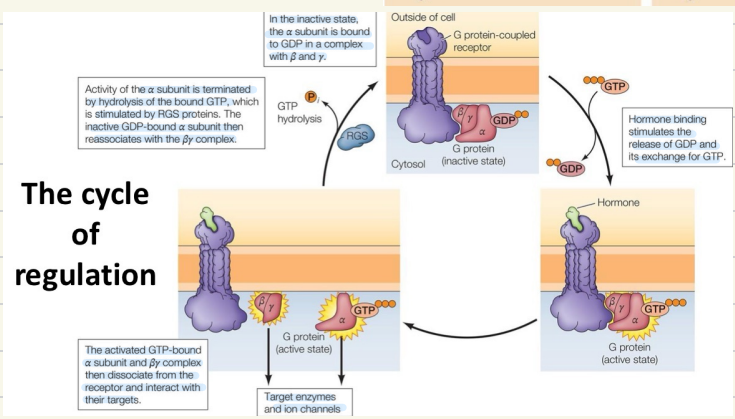
G-Protien regulations

- (RGS)
- inhibitors
  - GTPase which is regulated by
  - GAPs
  - GTPase Activating Proteins
- Activators
  - (GEFs)
  - Guanine nucleotide exchange factors
  - ↓
  - facilitate release of GDP & binding to GTP

G-protien inactivation

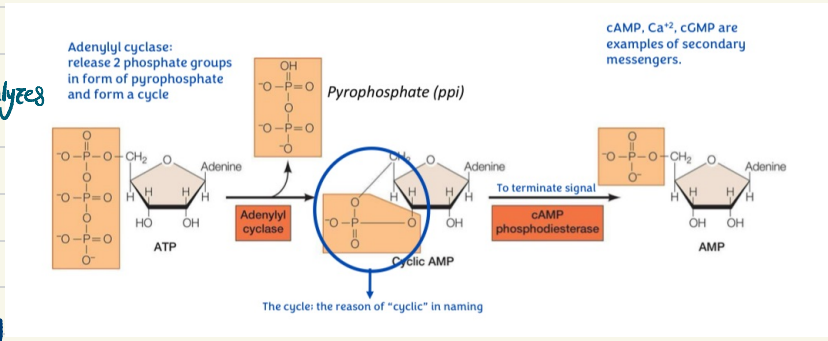
activity of α-subunit is terminated by hydrolysis of the bound by intrinsic GTPase activity, the inactive α subunit now re-associates with βγ





cAMP synthesis

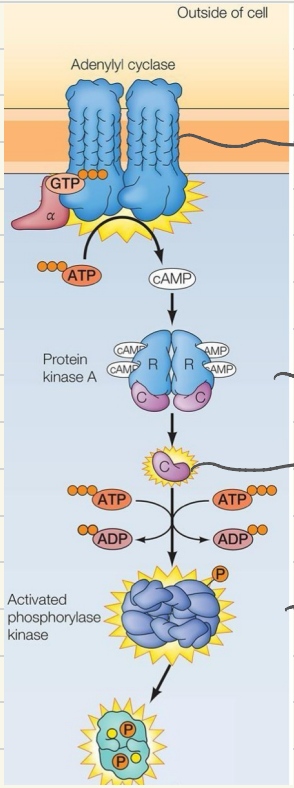
* process begins with ATP
* Adenylyl cyclase, an enzyme catalyzes conversion of ATP into cAMP
* PPi released



cAMP degredation:

cAMP is degraded into AMP by cAMP Phosphodiesterase

Regulation of PKa by cAMP

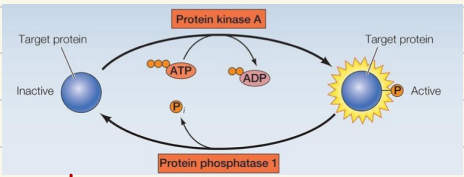


→ it's a seriene/therionine kinase

→ 2 subunits R & C

→ Catalytic subunit release → phosphorylate other enzymes or molecules → Glycogen synthase & Glycogen Phosphorylase

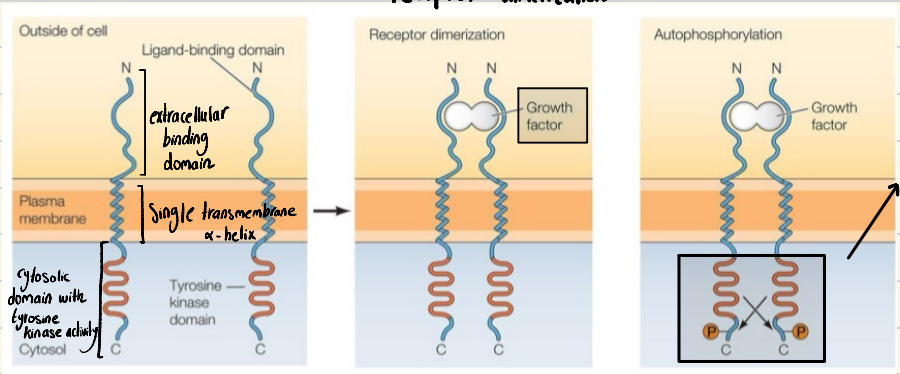
→ phosphorylate other molecules → Translocate into nucleus & Phosphorylates transcription factors like CREB leading to expression of cAMP inducible genes



→ phosphorylation of PKA is reversed by Phosphatase 1

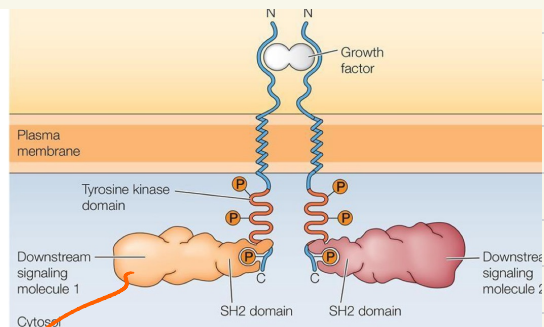
Mechanisms of action of receptor-tyrosine kinase

Growth factor binding induces receptor dimerization



Dimerization results in receptor autophosphorylation as the two polypeptide chains now phosphorylate one another

receptor is now active



Autophosphorylation effects

① increases protien kinase activity

② creates specific binding sites "docking sites" for additional protiens that transmit signals downstream of activated receptors

They localize to plasma mb

↓

associate with other Protiens

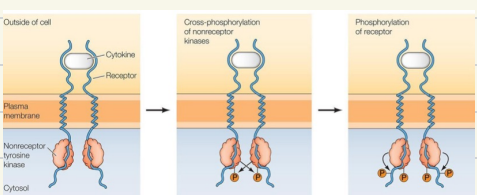
↓

phosphorylation of further protiens

↓

Stimulates enzymatic activity

Non receptor protien tyrosine kinases - cytokines receptor superfamily



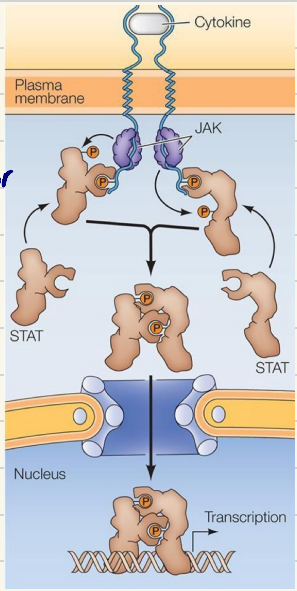
ligand binding induces receptor dimerization → cross-phosphorylation of non receptor TR

↓

activated kinases phosphorylates tyrosine residues on receptor → creating phosphotyrosine binding sites for downstream signaling molecules

JAK/STAT Pathway

1. cytokines bind to receptor, dimerization
2. JAK cross phosphorylates & then phosphorylate receptor
3. Transcription factor (STAT) binds on phosphotyrosine binding sites
4. STAT phosphorylated by JAK
5. JAK dimerizes & goes to nucleus
6. Affecting gene expression



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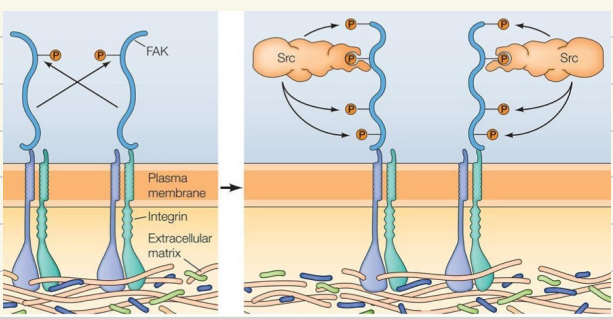
integrin signaling

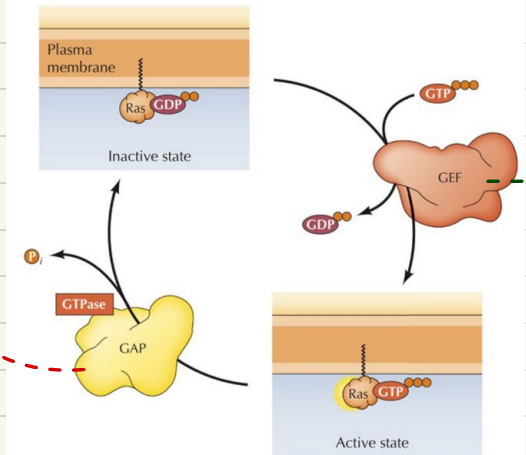
1. integrin bind to ECM; they cluster together on cell surface
2. activation of FAK (focal adhesion kinase) by autophosphorylation



3. binding of Src ⟶ phosphorylates FAK on additional tyrosine residue
4. creating binding sites for other signal molecules ⟿ Ras

Other receptors, such as cadherins & Ig superfamily can also transmit signals in a related way

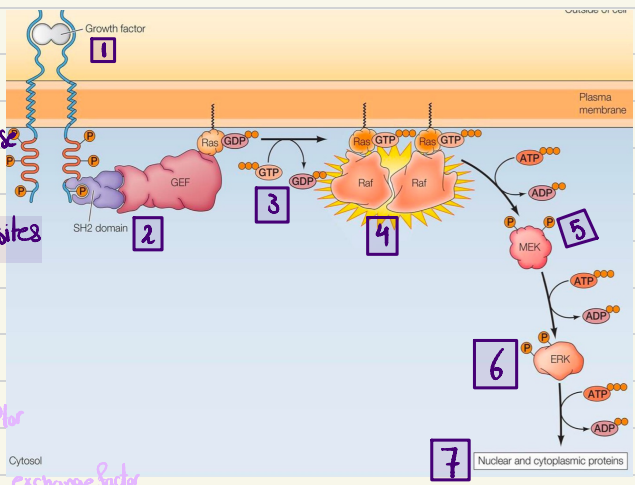
Ras Regulation



inhibited by GTPase activating factors (GAPs)

Stimulated by Guanine nucleotide exchange factors

Ras/Raf/MAPK Signaling Pathway



1. growth factor binds to a receptor tyrosine kinase this binding activates the receptor causing it to undergo autophosphorylation, creating docking sites for specific proteins

2. phosphorylated receptor recruits a docking protien called Grb - Growth factor bound receptor it brings another molecule GEF - Guanine nucleotide exchange factor

3. GEF interact with Ras, inactive at this stage bound to GDP, GEF cause Ras to release GDP & bind GTP

4. Active Ras interacts with Raf

5. Raf phosphorylates another kinase called MEK

6. MEK activates ERK

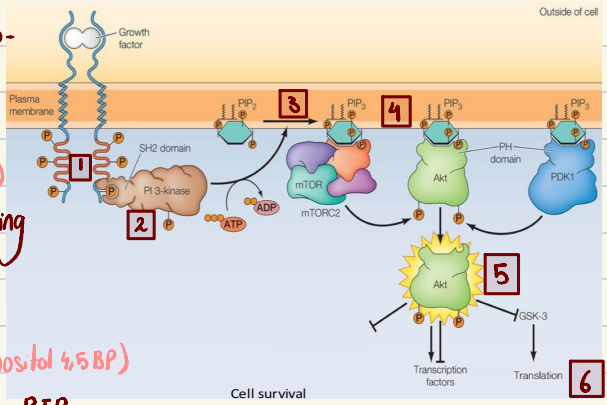
7. ERK enters nucleus & activate transcription factors
   - Proliferation
   - Survival
   - differentiation

PI_3K/Akt Pathway

1. growth factor binds to RTK ⇝ it undergoes auto-phosphorylation which creates docking sites

2. PI3-Kinase (Phosphatidyl inositol 3-kinase) is recruited to the receptor, it binds to docking site & becomes activated

3. PI3-kinase targets PIP_2 (Phosphatidylinositol 4,5 BP) PIP_3-K adds a Ⓟ group to PIP_2 converting it to PIP_3



4. PIP_3 remains in cytoplasm & acts as docking site for (AKt, PDK1, mTOR)

5. AKt is phosphorylated by PDK1 & $mTORC_2$ & fully activate it

6. AKt carries out its function ⇝ Protien synthesis & cell growth

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NF/KB signaling pathway

1. NF/Kb is bound to IKb (inhibitor), which traps NF-Kb in cytoplasm

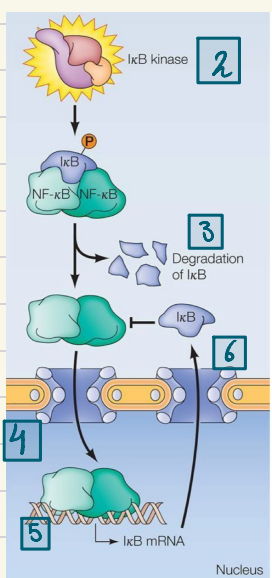
2. Cell recieves a signal → IKB kinase active ⟶ Phosphorylates IKB

3. degredation of IKB, NF-KB is now released

4. NF-KB enters nucleus & binds to specific DNA sequences

5. Gene activation, activation of certain genes ⟶ cell survival

6. Feedback-loop ⇜ one of the genes act by NF-KB encodes IKB itself



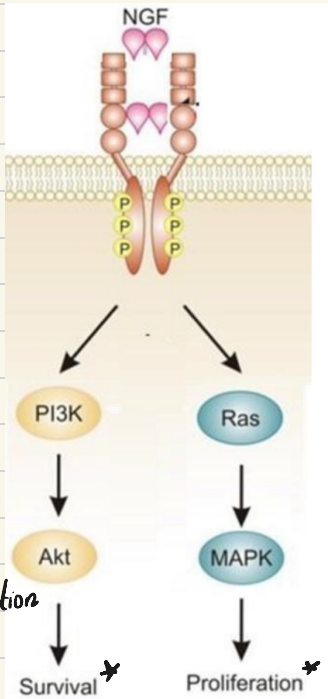
NGF

NGF binds to specific receptors on cell mb. activating Signaling pathways

Activation of Pathway depends on ERK activity duration

Short duration
↓
30-60 mins
↓
cell proliferation

Sustained ERK activation
↓
2-3 hours
↓
neuronal differentiation



Cross-talk

Ras activates PI3K

AKt inhibits Raf

ERK activate MTORC.