Signaling pathways

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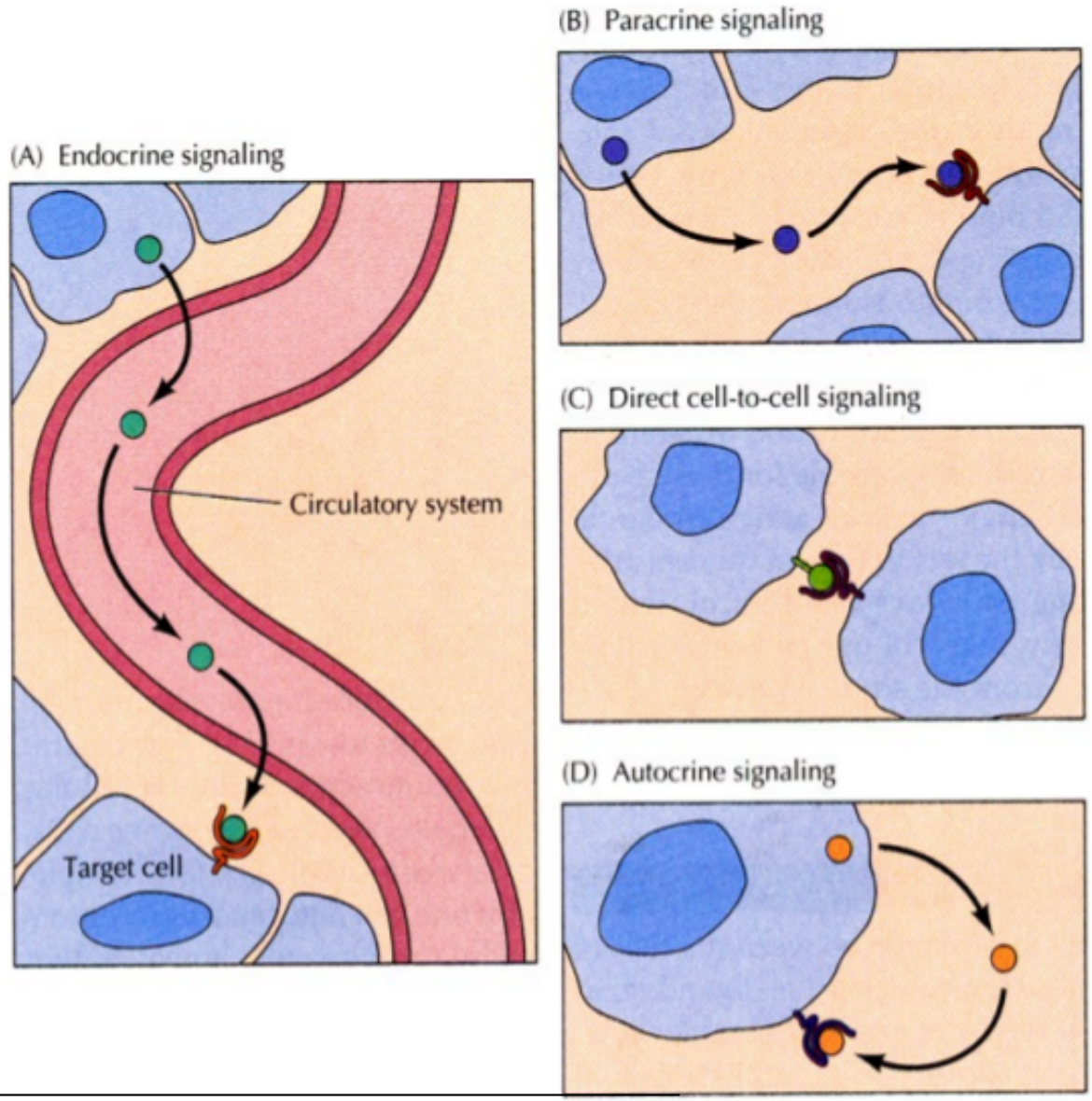
March 20, 2014

1. **Signaling pathways**
2. **FGFR pathway**
3. **Yamada *et al.* model**

Signals



Cooper et al., The Cell: A Molecular Approach, 4th edition, 2006

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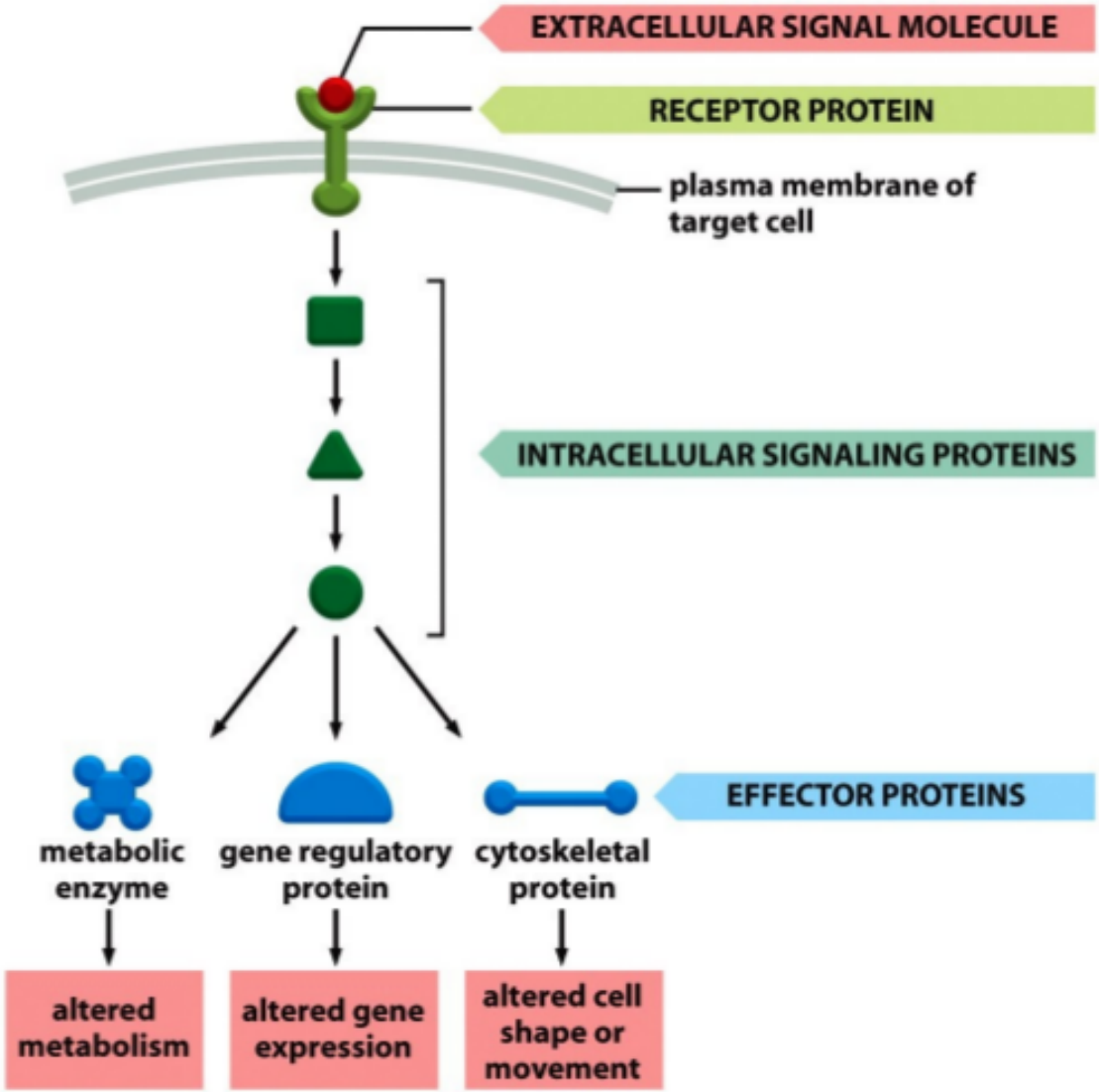
Cell signaling



Alberts et al., Molecular biology of the Cell, 5th edition, 2007

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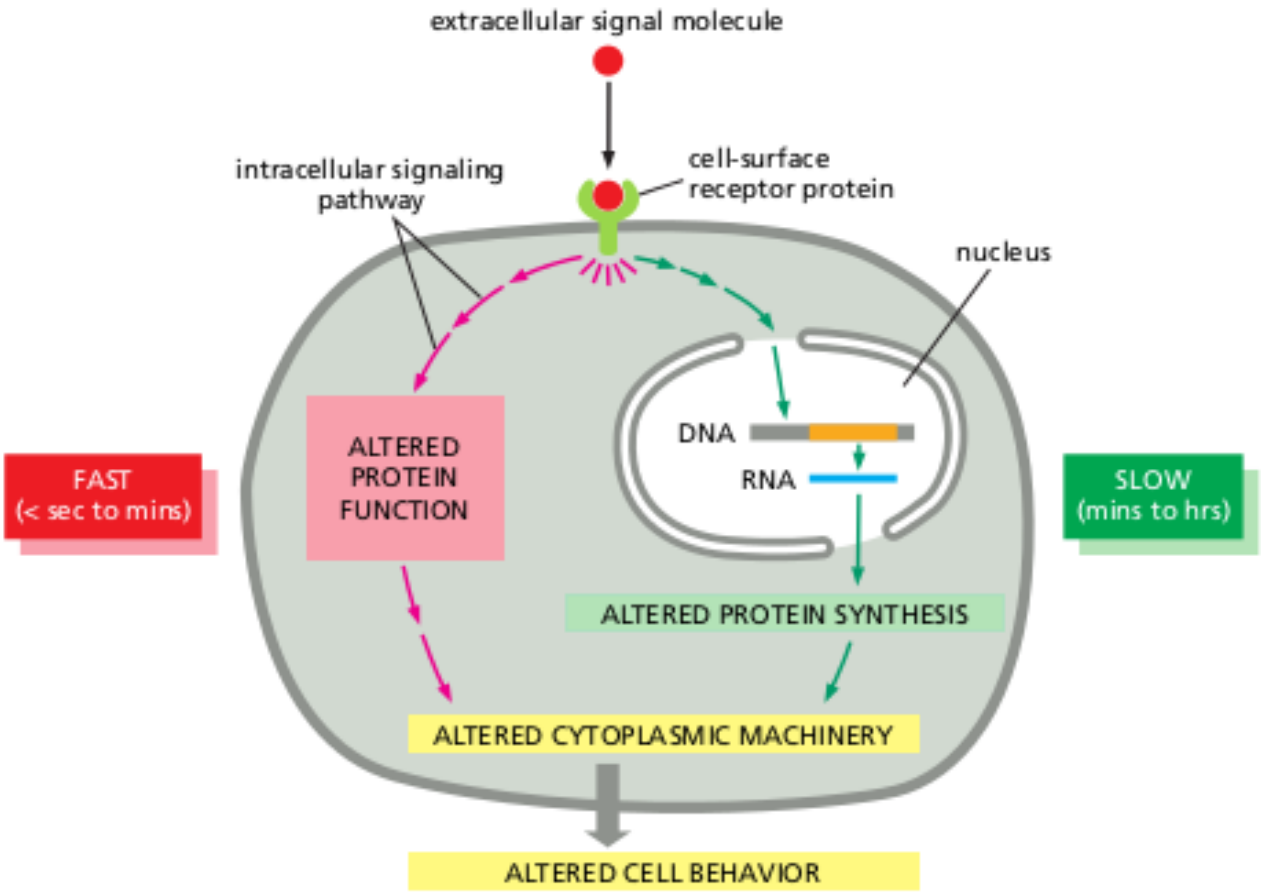
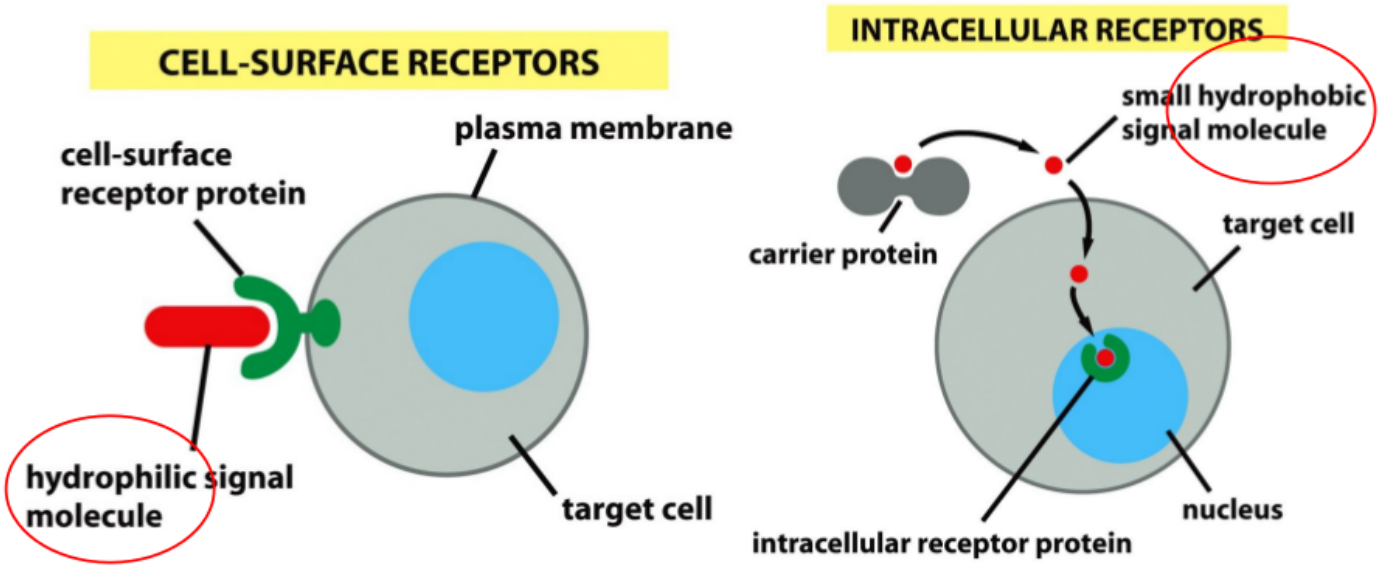
Response time



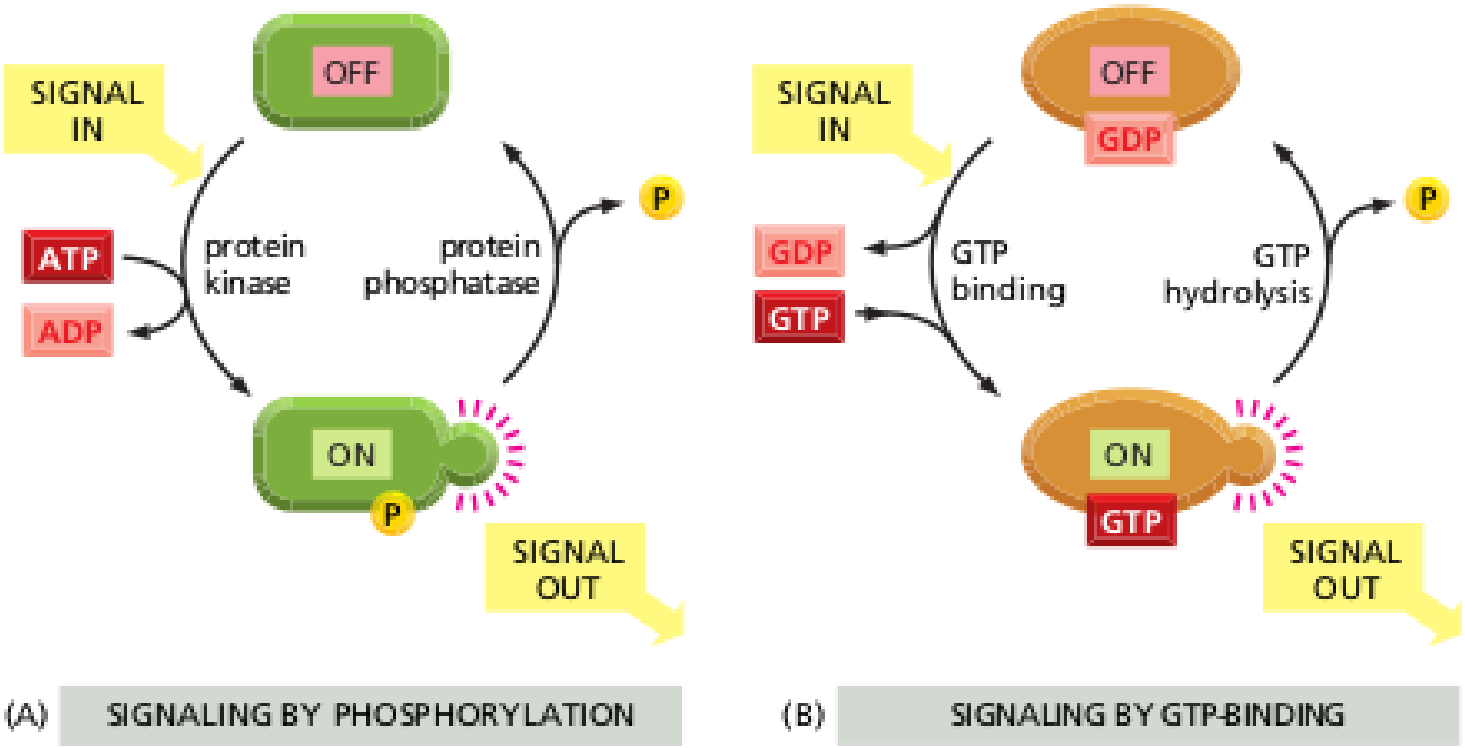
Alberts et al., Molecular biology of the Cell, 5th edition, 2007

Receptors



Alberts et al., Molecular biology of the Cell, 5th edition, 2007

Signal transduction through molecular switches

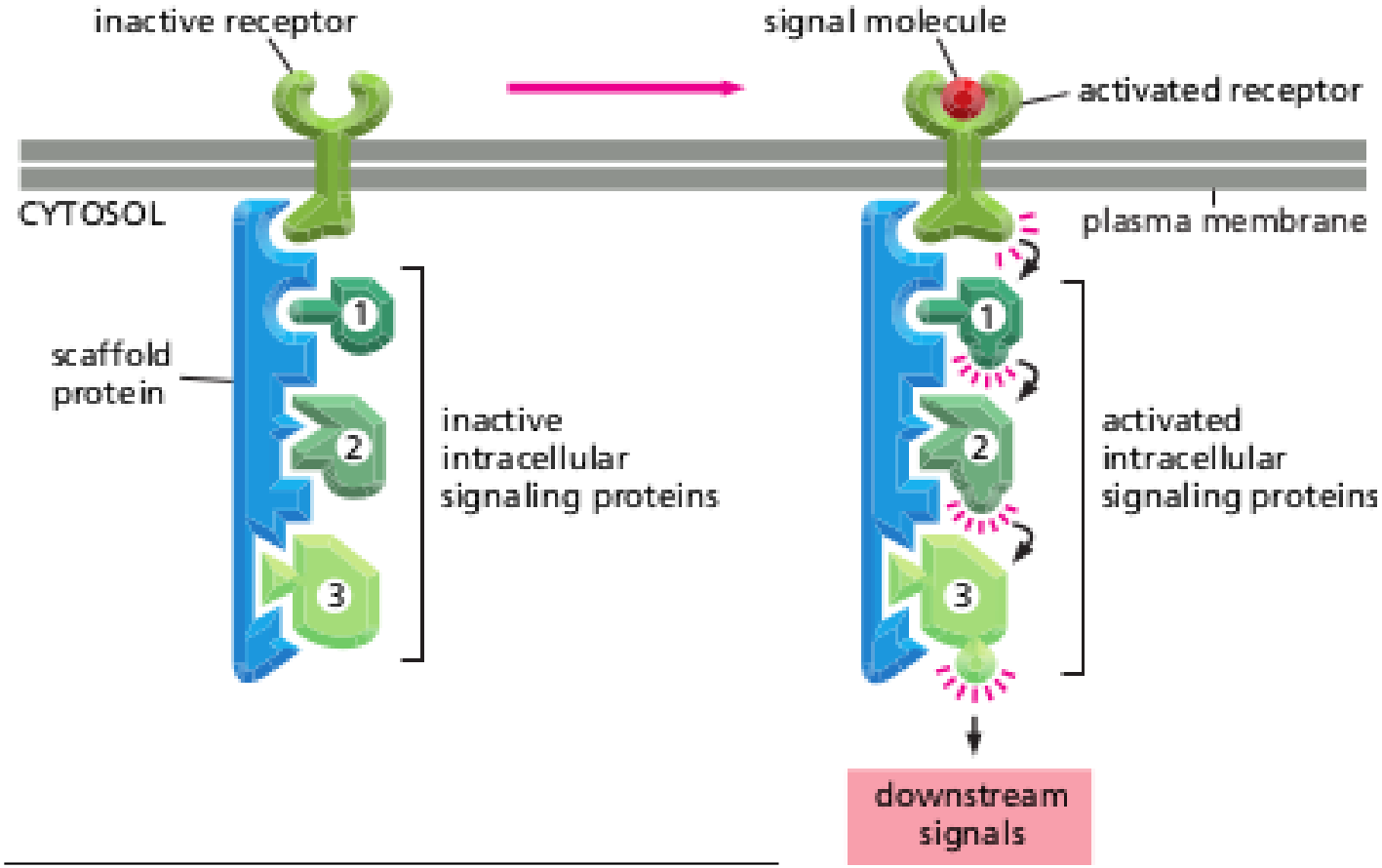


- Other ways to switch a protein on/off: binding of another signaling protein, cAMP, Ca^{2+} or by another modification (e.g. ubiquitylation)

Alberts et al., Molecular biology of the Cell, 5th edition, 2007

Scaffold proteins

- Signaling proteins in close proximity
- Fast, efficient, selective response to an extracellular signal
- Avoiding unwanted cross-talk



Alberts et al., Molecular biology of the Cell, 5th edition, 2007

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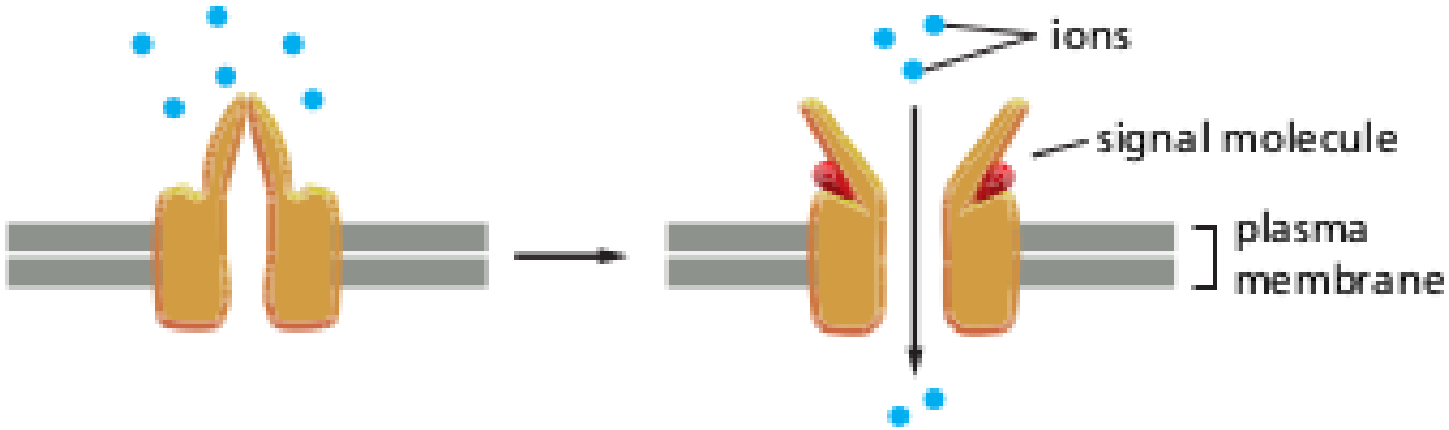
The three largest classes of cell-surface receptor

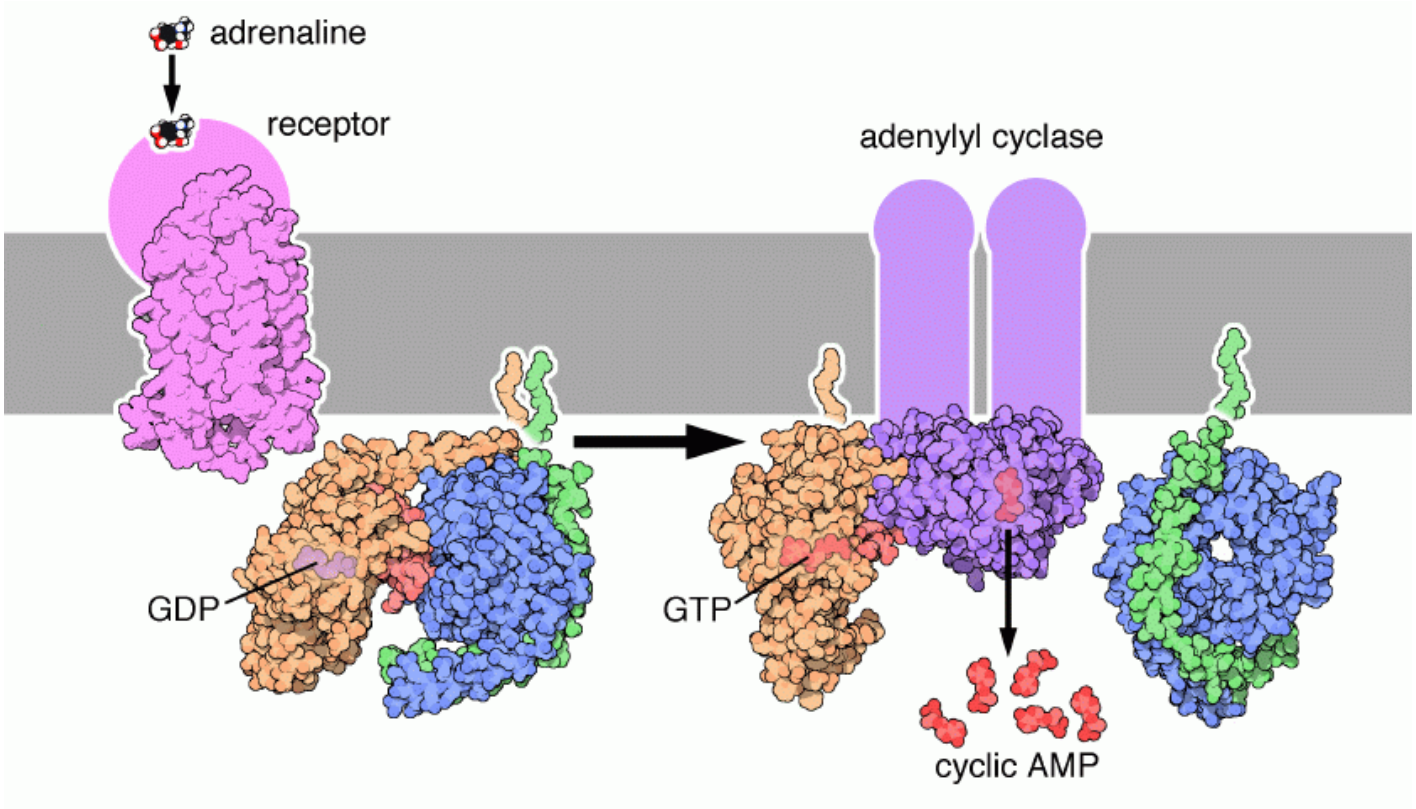
- Ion-channel-coupled receptors
- G-protein-coupled receptors
- Enzyme-coupled receptors

Ion-channel-coupled receptors



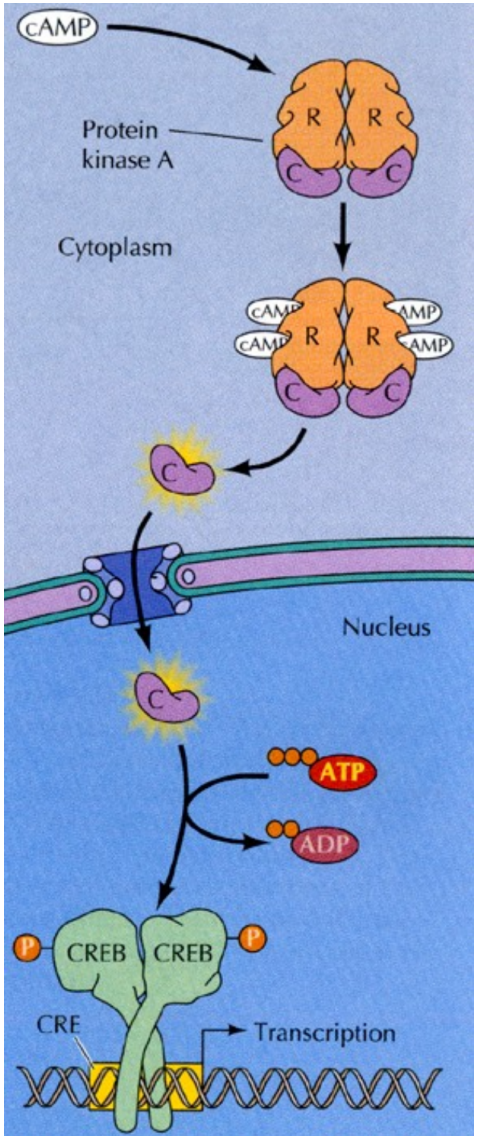
Alberts et al., Molecular biology of the Cell, 5th edition, 2007

G-protein coupled receptors



http://www.rcsb.org/pdb/101/motm.do?momID=58

cAMP activates Protein kinase A



Cooper et al., The Cell: A Molecular Approach, 4th edition, 2006

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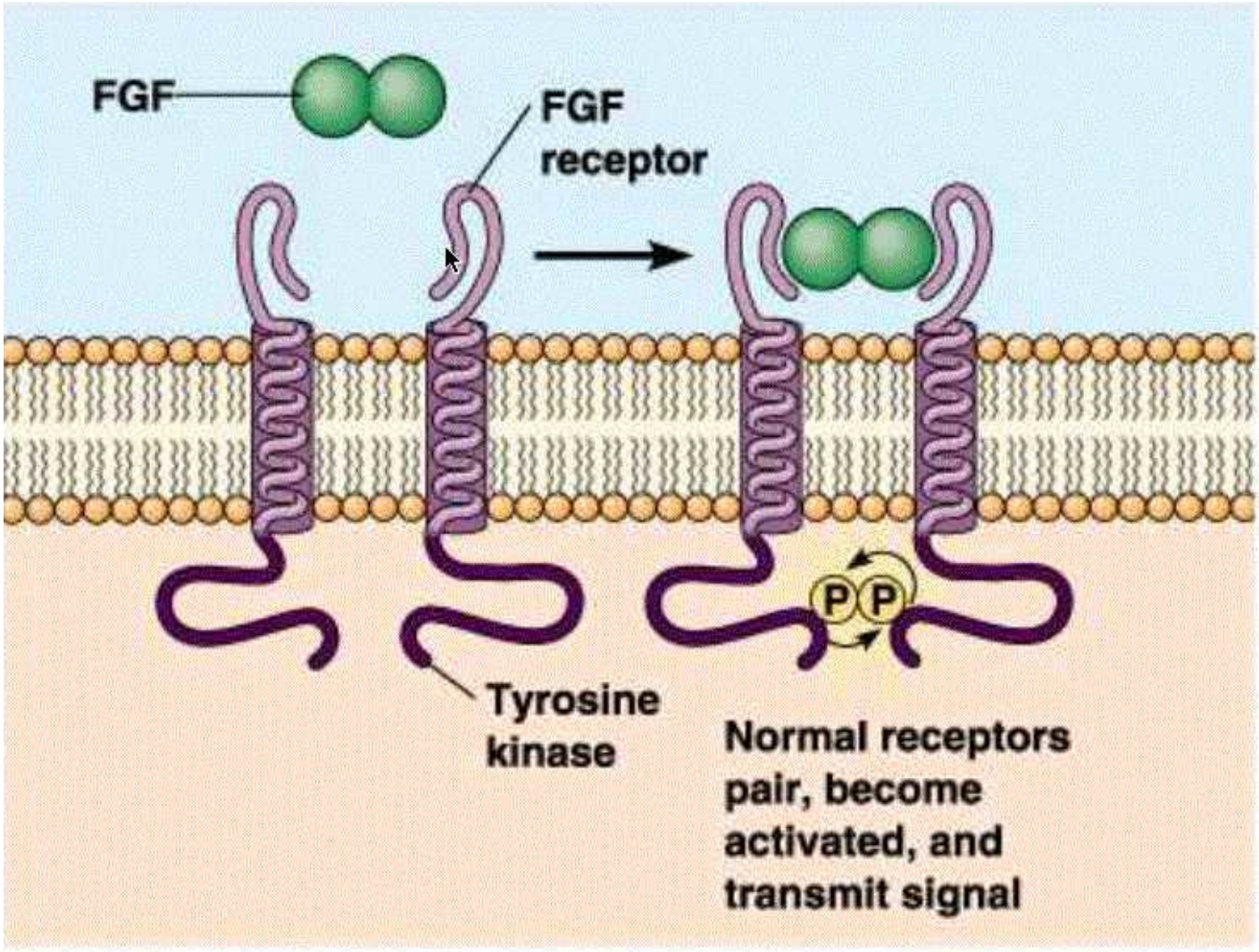
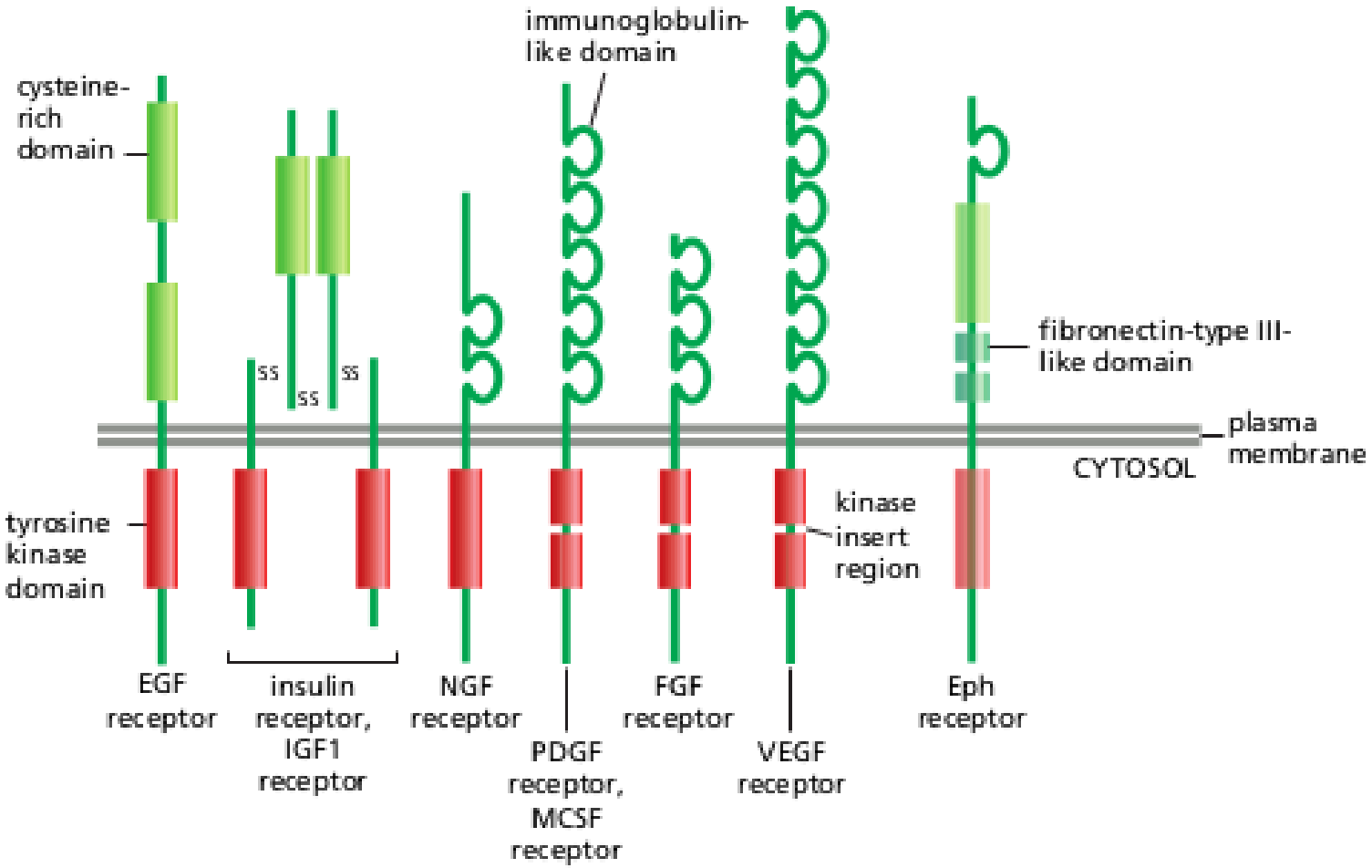
Enzyme-coupled recepetors



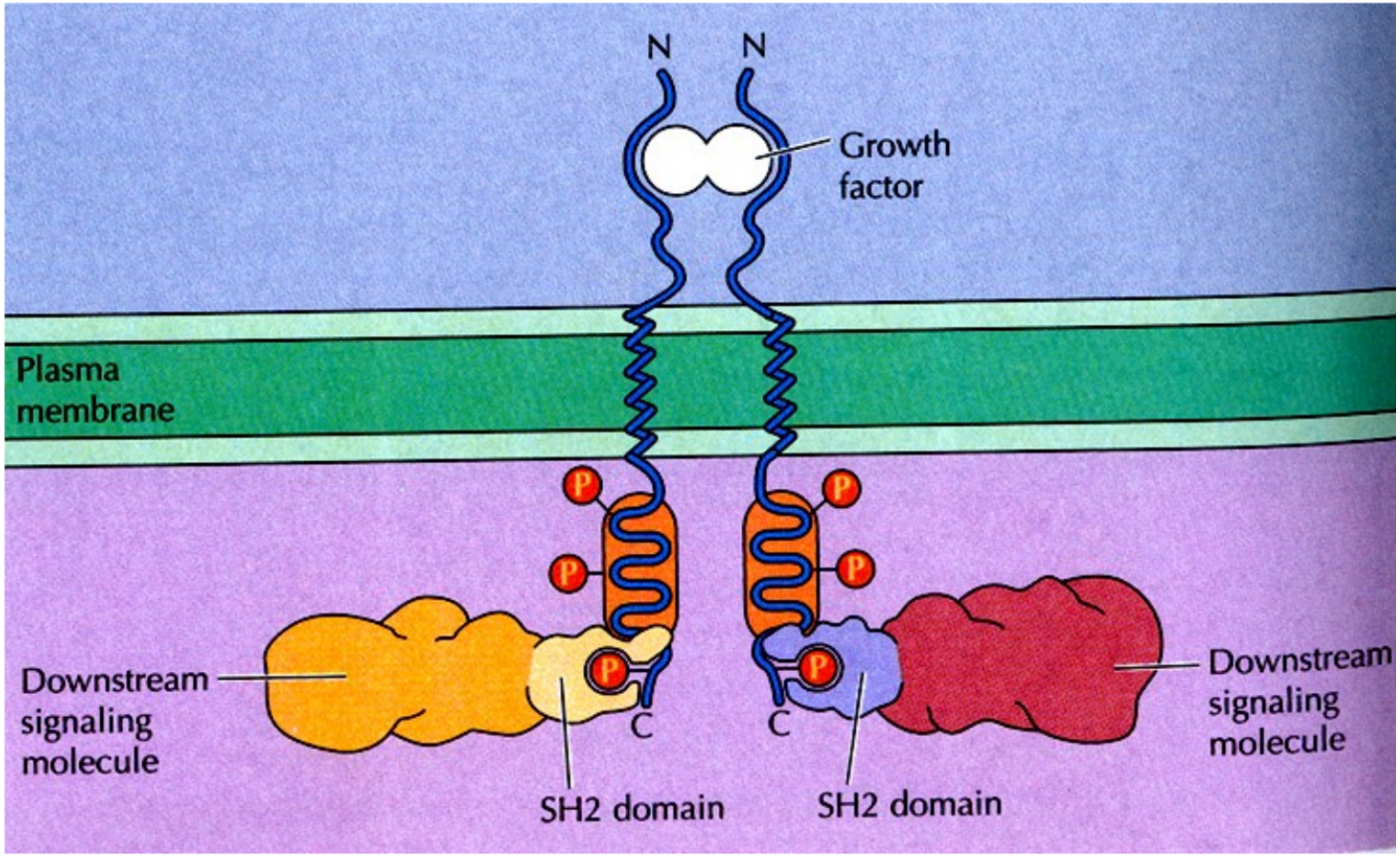
Campbell N., Biology, 5th edition, 2000

Enzyme-coupled recepetors



Alberts et al., Molecular biology of the Cell, 5th edition, 2007

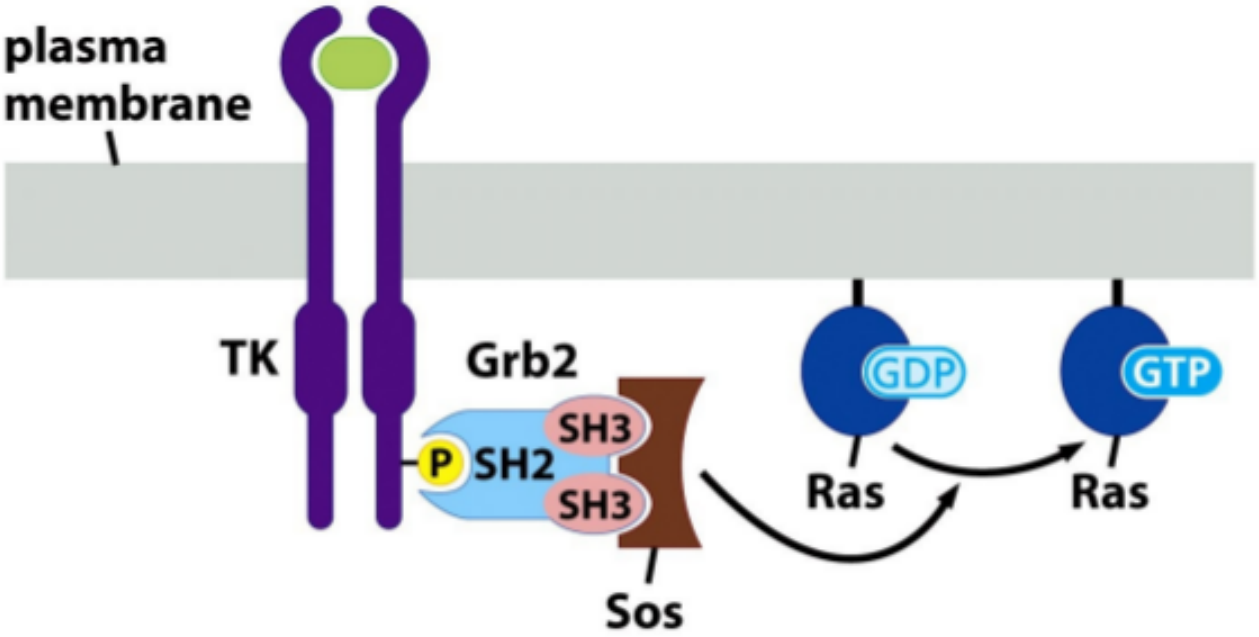
SH2 domain ("SRC-Homology 2 domain")



- crucial part of adaptors (Grb2, Shc, Crk, ...)

Cooper et al., The Cell: A Molecular Approach, 4th edition, 2006

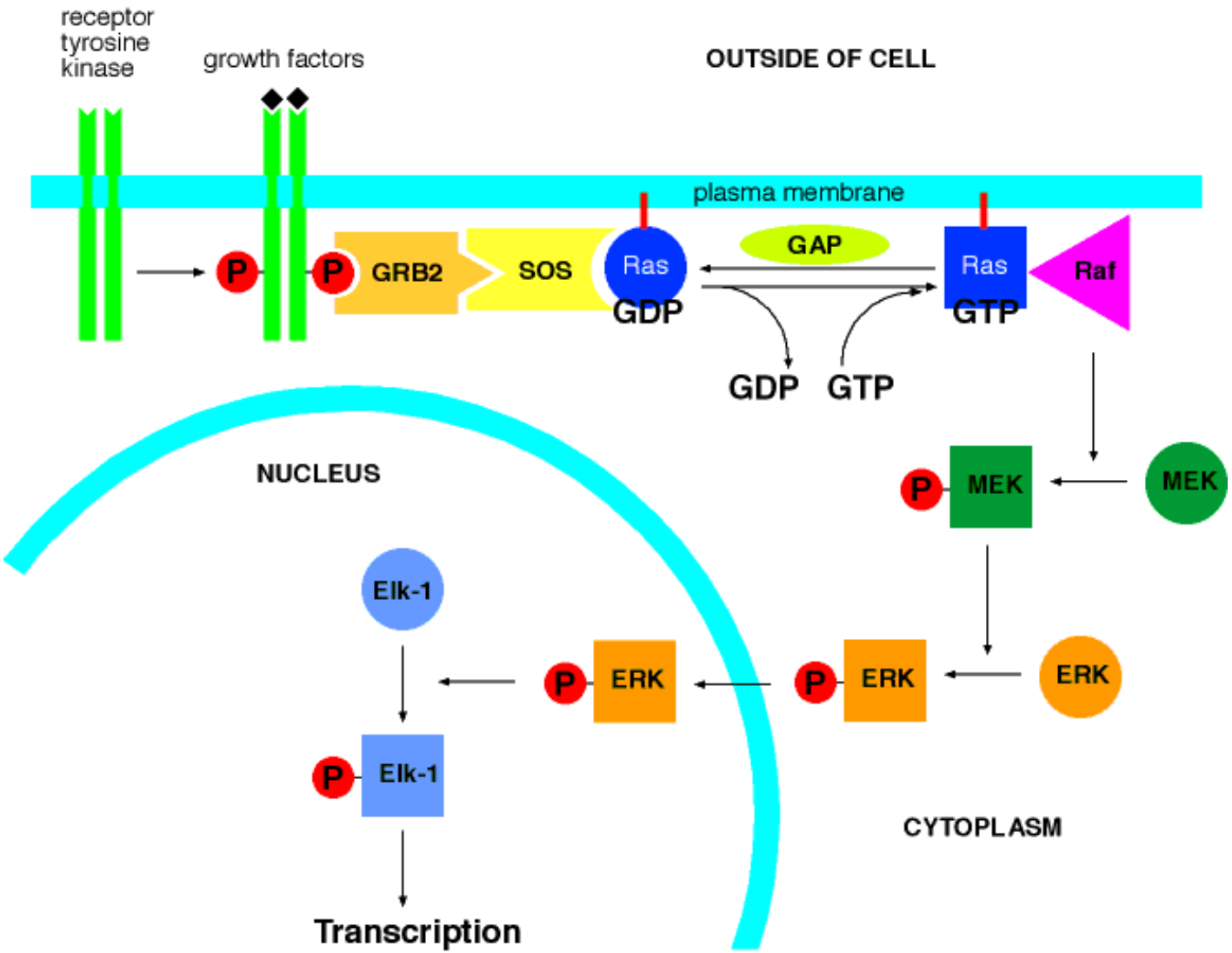
Grb2 and Ras pathway



- Grb2-SOS complex preexist in cytoplasm

Weinberg, R., The Biology of Cancer, Garland Science, 2007

Ras pathway (MAPK pathway)



http://oregonstate.edu/instruct/bb492/fignames/ras3.html

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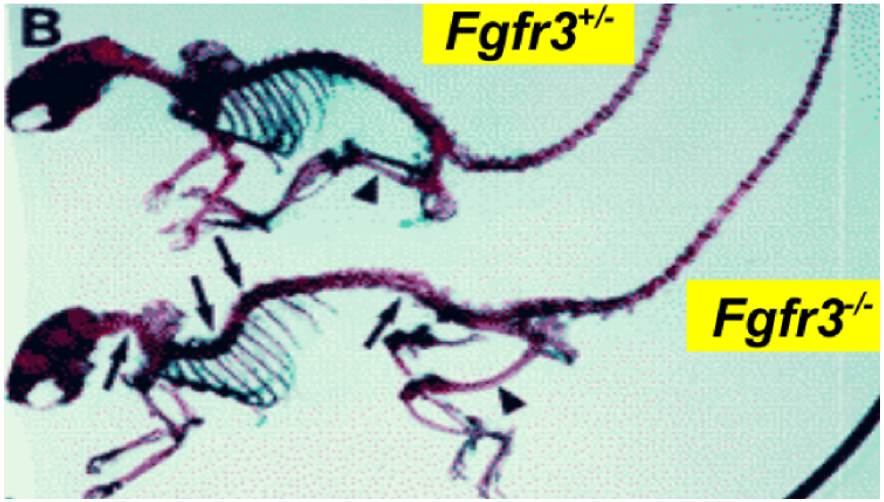
Fibroblast growth factor receptor 3 (FGFR3)

- Enzyme-coupled receptor
- Growth and proliferation inhibition
- Mutation that cause achondroplasia act by exaggerating the negative regulatory functions of FGFR3

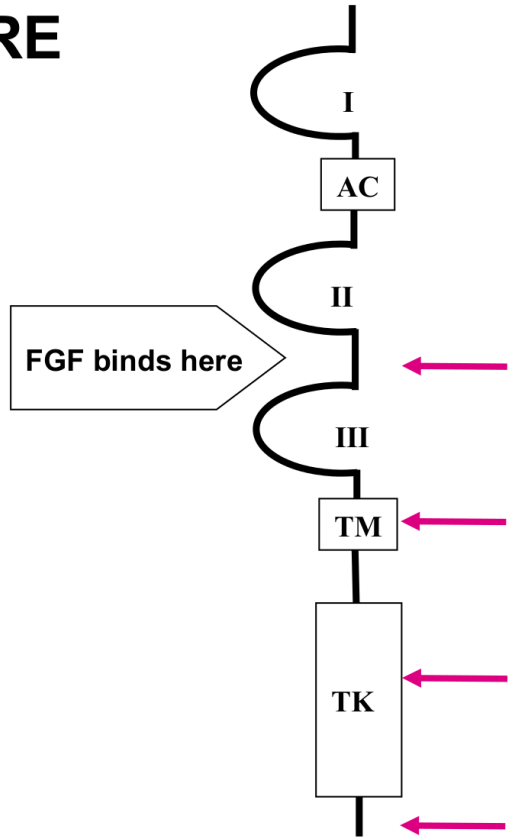


Deng et al.,Fibroblast Growth Factor Receptor 3 Is a Negative Regulator of Bone Growth, Cell, 1996

FGFR3-related skeletal dysplasia

STATURE

Hypochondroplasia
Achondroplasia
SADDAN
Thanatophoric Dysplasia



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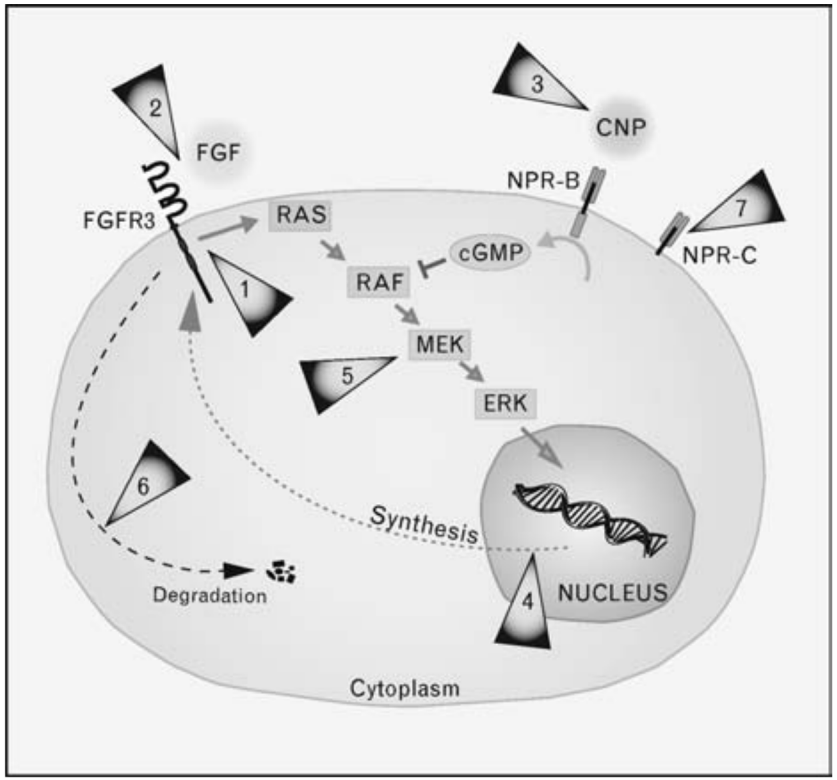
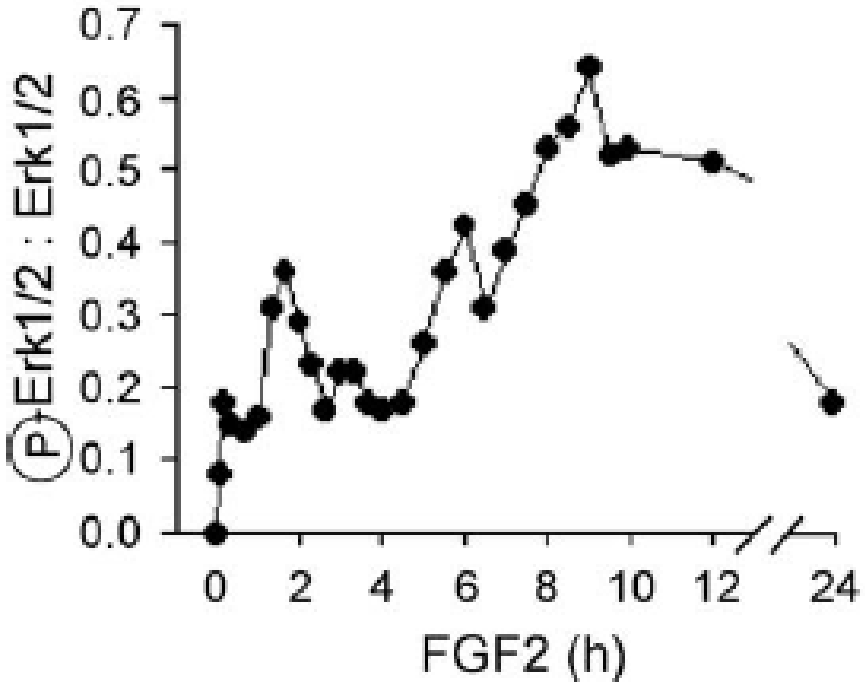


1, FGFR3 tyrosine kinase; 2, ligand-mediated receptor activation; 3, CNP-mediated antagonism of signals downstream of receptor; 4, expression or synthesis of mutant FGFR3; 5, tyrosine kinase mediators of MAPK signaling pathway; 6, degradation of activated receptor. See text for discussion.

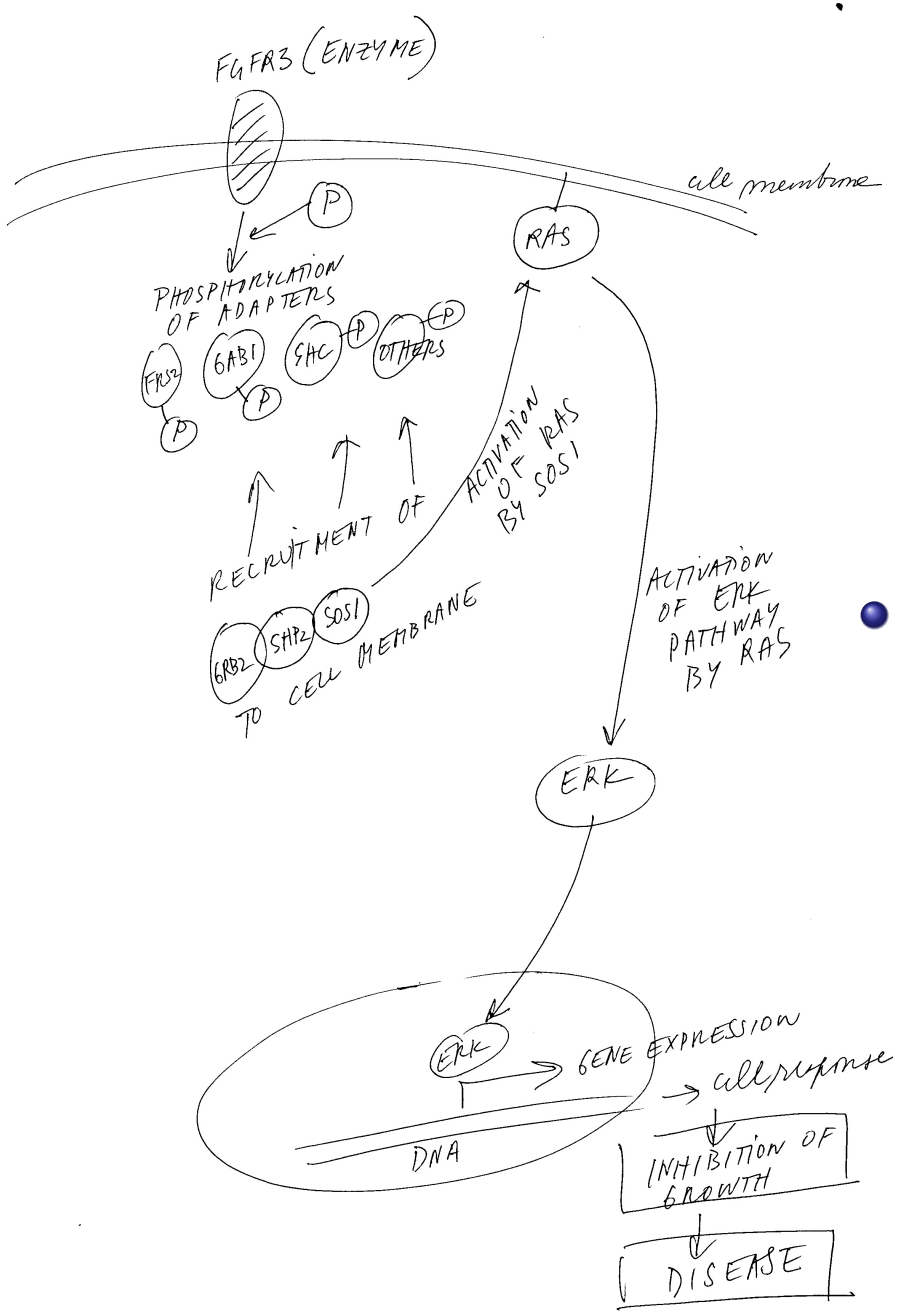
- FGFRs employ several signaling pathways, MAPK pathway is one of them

Leaderich M. B., Horton W. A., Achondroplasia: pathogenesis and implications for future treatment, Curr Opin Pediatr, 2010

Constitutive activation of ERK

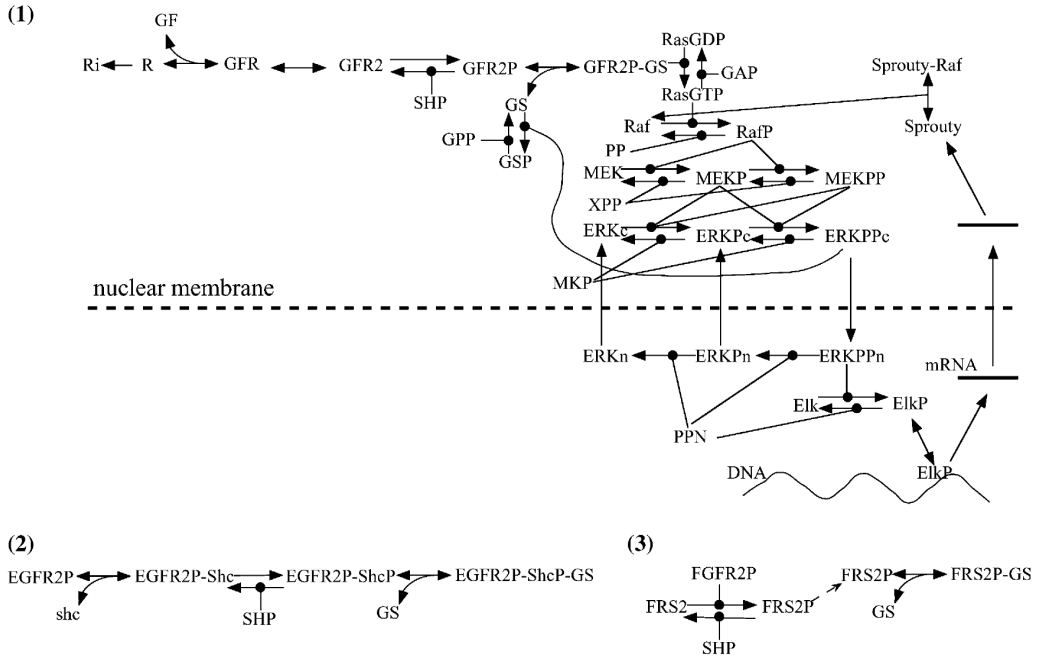


- Mutated FGFR3 induces constitutive activation of the MAPK pathway in chondrocytes
- Disease results from increased signal from the mutant receptor



- FGFRs recruit their downstream adaptors (GAB1, SHC, FRS2, etc.)

EGF vs. FGF pathway model schema (Yamada *et al.*, 2004)

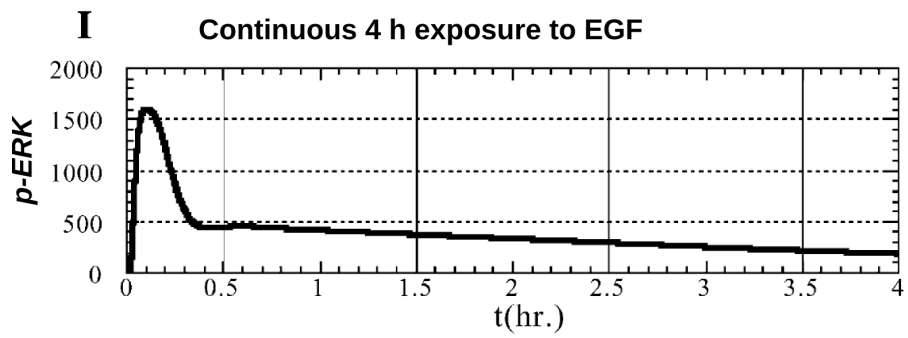


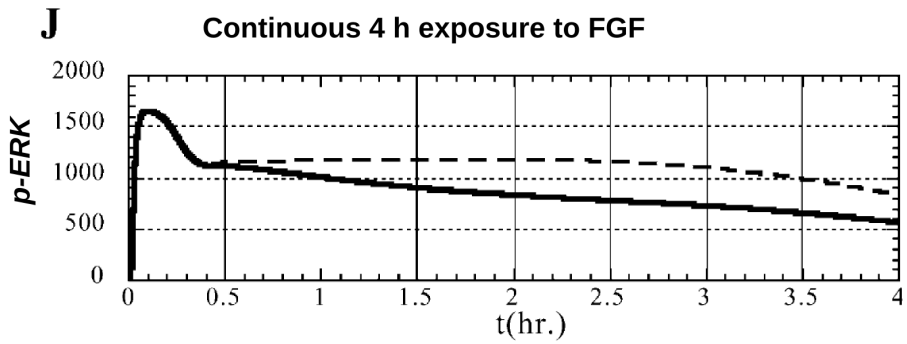
- Grb2-SOS binds EGFR directly or through Shc
- Grb2-SOS binds FGFR through FRS2

Yamada S., Taketomi T., Yoshimura A., Model analysis of difference between EGF pathway and FGF pathway, BBRC, 2004

EGF vs. FGF pathway (Yamada *et al.*, 2004)

- Duration of ERK activation determines the cell response
- EGF induces transient ERK activation
- FGF induces transient and sustained ERK activation
- What is the reason for difference in time course?





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Dependency on Shc and FRS2 initial concentration

- Grb2-SOS binds EGFR directly or through Shc $\rightarrow$ ERK activation is limited by concentration of receptor
  - $[EGFR2P] + [Grb2\text{-}SOS] \leftrightarrow [EGFR2P\text{-}Grb2\text{-}SOS]$
  - $[EGFR2P\text{-}ShcP] + [Grb2\text{-}SOS] \leftrightarrow [EGFR2P\text{-}ShcP\text{-}Grb2\text{-}SOS]$
- Grb2-SOS binds FGFR through FRS2 $\rightarrow$ signal amplification
  - $[FGFR2P] + [FRS] \leftrightarrow [FGFR2P\text{-}FRS]$
    $[FGFR2P\text{-}FRS] \rightarrow [FGFR2P] + [FRSP]$
    $[FRSP] + [Grb2\text{-}SOS] \leftrightarrow [FRSP\text{-}Grb2\text{-}SOS]$

EGF vs. FGF pathway summary

- Differences in mechanism of interaction between receptors and first adapters
- FRS2 and sustained ERK activation (more Grb2-SOS complexes are recruited)