CMACS
Computational Modeling and Analysis for Complex Systems

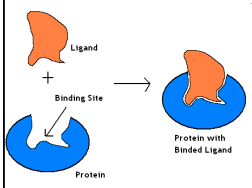
Part II: Signaling pathway

Introduction to ligands, receptors, binding and phosphorylation

Ziping Liu

1. What is a ligand?

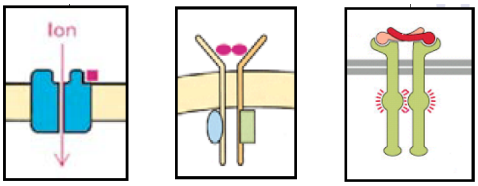
A ligand is a substance that is able to bind to and form a complex with a biomolecule, usually a protein, to function as a whole.



- A ligand has to bind with a certain type of protein, which is usually called its receptor.
- This type of protein has a special domain than can specifically fit the 3D structure of such ligand.

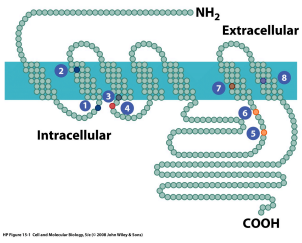
2. What is a receptor?

A receptor is a protein that can specifically recognize the ligand. It can be either inside or outside of the cell.



Different types of ligand-receptor complex work differently. Being an ion channel, link to a enzyme, or work itself as an enzyme.

A closer view of a receptor: There are three parts in a receptor.



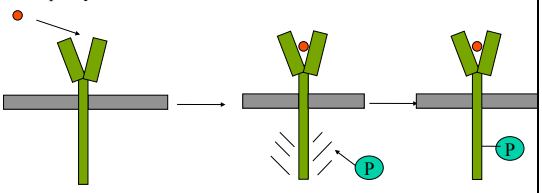
A ligand can be a protein, a hormone, or even an iron. But a receptor is usually a protein.

$$\text{[Ligand]} + \text{[Receptor]} \underset{k2}{\overset{k1}{\rightleftharpoons}} \text{[Ligand * Receptor]}$$

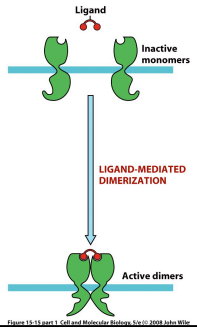
The binding of ligand-protein complex is through non-covalent bond. The reason is that an ligand often works as a messenger. Once it triggers the protein and downstream process, it tends to leave its receptor.

3. What could happen after a ligand binds with its receptor?

Phosphorylation.

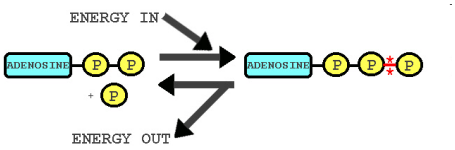


Or Dimerization:

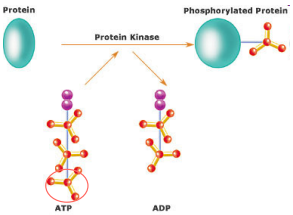


How phosphorylation takes place?

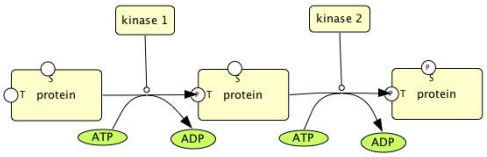
ADP + P + energy ⟶ ATP



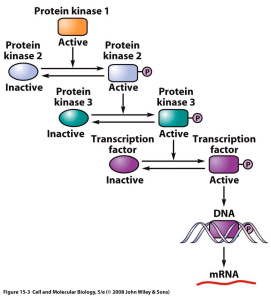
what is a kinase?



A kinase is an enzyme that modifies other proteins by adding a phosphate molecule on them.

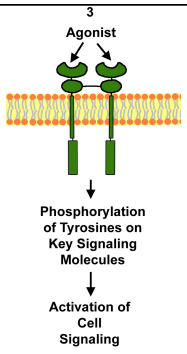


With the help of protein kinase, ATP can add a Phosphate unit on the target protein, and this process is called ***Phosphorylation.***



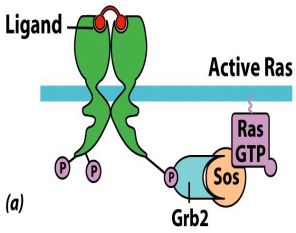
Signal transduction pathway: how protein and protein kinase works together.

A protein can be activated by protein kinase, by being phosphorylated.



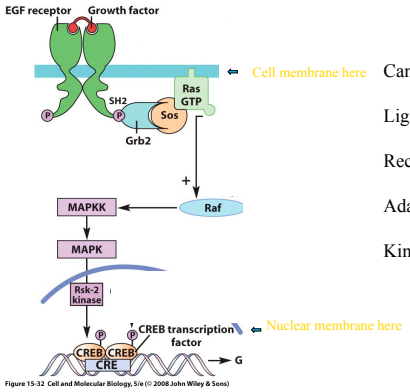
Phosphorylation of ligand receptor dimer is our most discussed model.

4. What is an adaptor.



An adaptor protein functions as a linker that enables two or more signaling proteins to joint together as part of a signaling complex.

Such as Grb2 in the chart.



Can you identify:

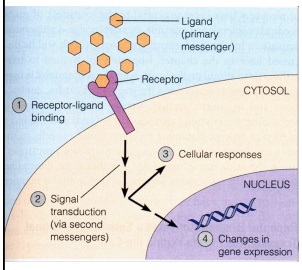
Ligand

Receptor

Adaptor

Kinase

It's not for nothing that the ligand binds with its receptor. They are in order to trigger some reactions or some biological processes.



Ligands are also called "primary messenger" in contrast to secondary messengers such as G protein or Ca2+.

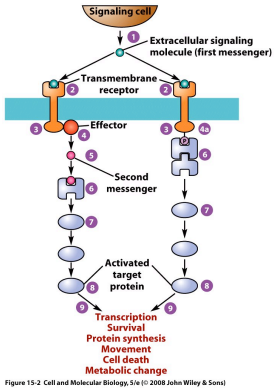


Figure 15-2 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Signaling Pathway:

How extra-cellular messenger elicit intracellular response

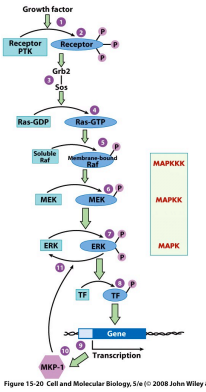


Figure 15-20 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Overview of the signaling pathway of EGF

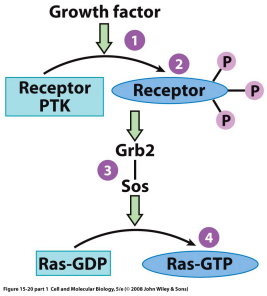
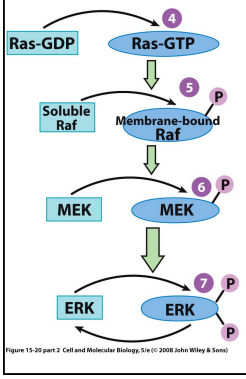


Figure 15-20 part 1 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Step 1: growth factor induce phosphorylation of receptor

Step 2: receptor recruits Grb2-Sos complex and the latter phosphorylate Ras.



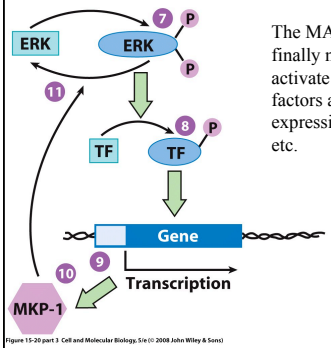
Step 3: Ras then recruit Raf to the membrane to be activated

MAPKKK

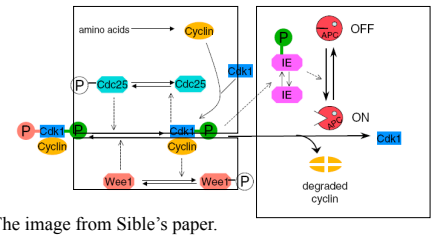
Step 4: MAP kinase cascades

MAPKK

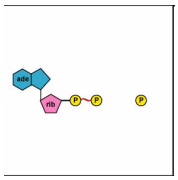
MAPK

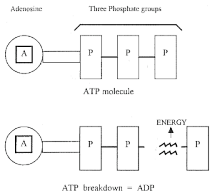


The MAP kinase of the cascade finally move into the nucleus and activate some transcription factors and lead to gene expression, including cyclin D1 etc.



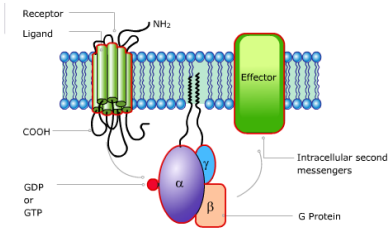
The image from Sible's paper.
Activation block
Inactivation block
Degradation block





http://student.ccbcmd.edu/biotutorials/energy/images/adp.gif

How G protein works as a secondary messenger



Additional: trans-membrane transportation of molecules