Johns Hopkins Engineering

Molecular Biology

Receptor-ligand interactions

JOHNS HOPKINS
WHITING SCHOOL
of ENGINEERING

Outline

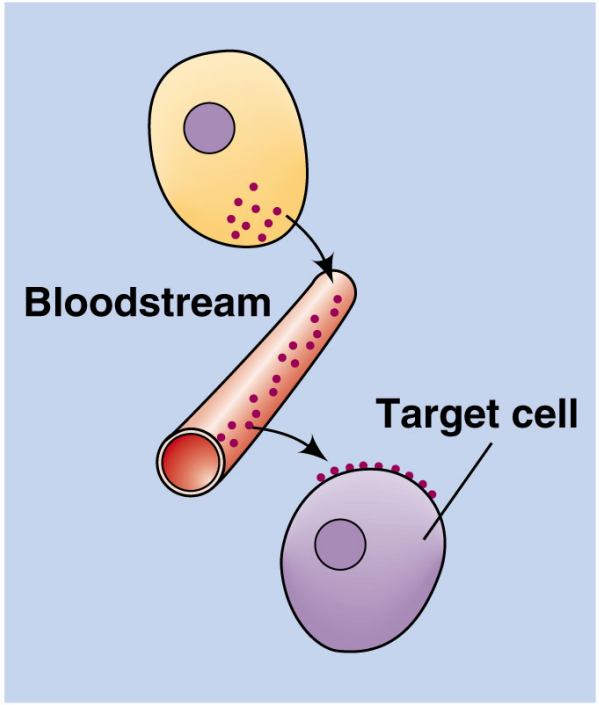
- Signal Transduction
- Receptor-ligand interactions
- Agonists and antagonists
- Signal Amplification

Signal Transduction Mechanisms

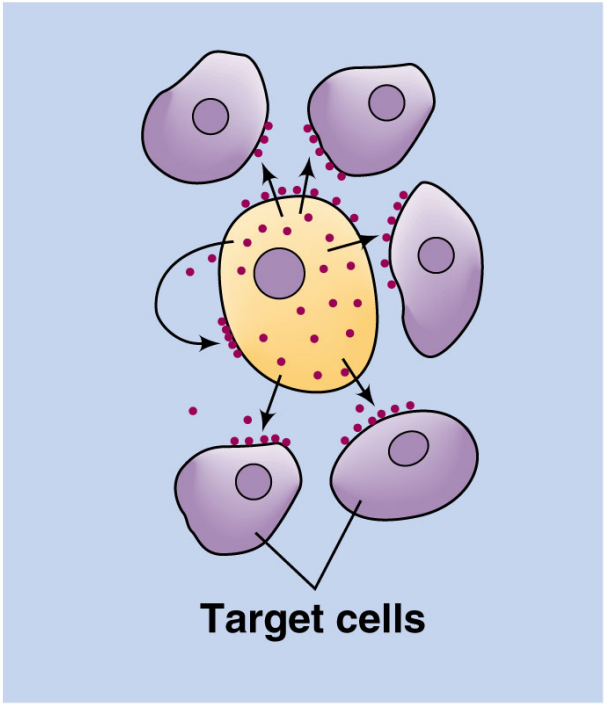
- All cells have some ability to sense and respond to their environments through **chemical signals**
- **Receptors** are located on receiving cells that can be quite distant from the secreting cell
- Cells produce signals, in some cases by displaying molecules on their surfaces or by releasing a chemical signal
- Multicellular organisms can control the activities of specialized cells through release of *chemical messengers*
- The ability of a cell to respond to ligand-receptor binding by altering its behavior or gene expression is called **signal transduction**

Different Types of Chemical Signals Can Be Received by Cells

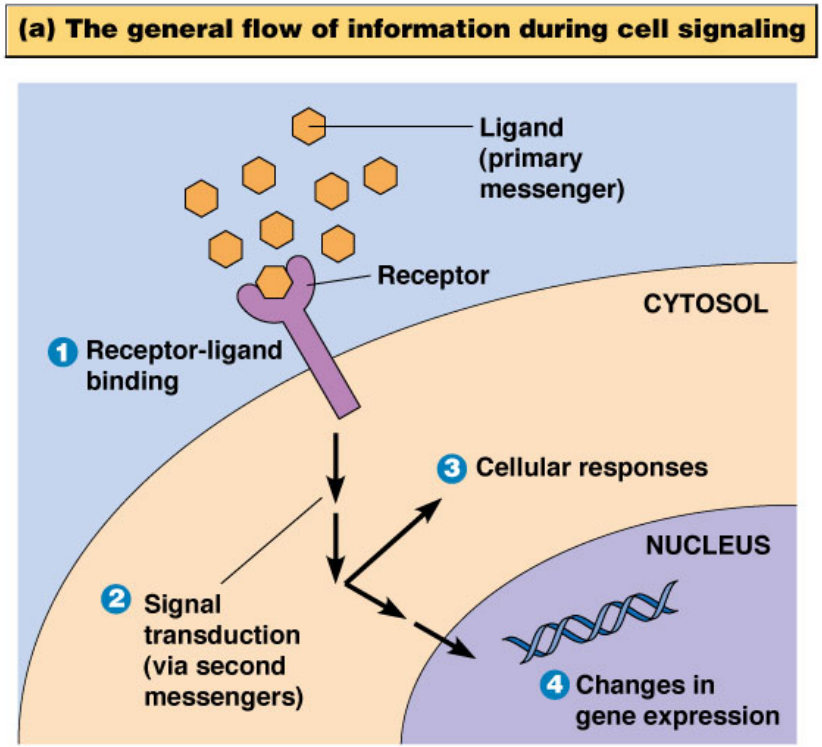
- Signaling molecules are often classified based on the distance between the site of production and the target
  - ***Endocrine signals*** are produced far from the target tissues, which they reach via the circulatory system
  - ***Paracrine signals*** are diffusible and act over a short range
  - ***Juxtacrine signals*** require physical contact between sending and receiving cells
  - ***Autocrine signals*** act on the same cell that produces them



Hormones



Local mediators



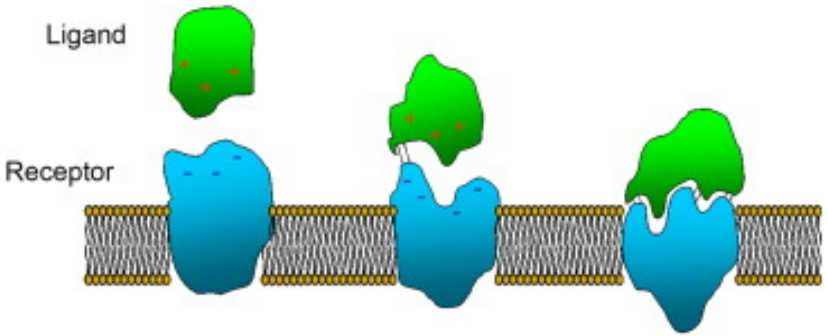
Receptor Binding Involves Specific Interactions Between Ligands and Their Receptors

- Messengers bind to receptors in a highly specific way

- This is achieved through
  - The *binding site* (or *binding pocket*) on the receptor that fits the messenger very closely
  - The necessary amino acid side chains, positioned to form chemical bonds with the messenger

Receptor-ligand interactions

- In most cases the binding of a receptor and ligand resembles the binding of an enzyme and its substrate
- The receptor specific for a certain ligand is called the *cognate receptor*
- A receptor bound to its ligand is said to be *occupied*



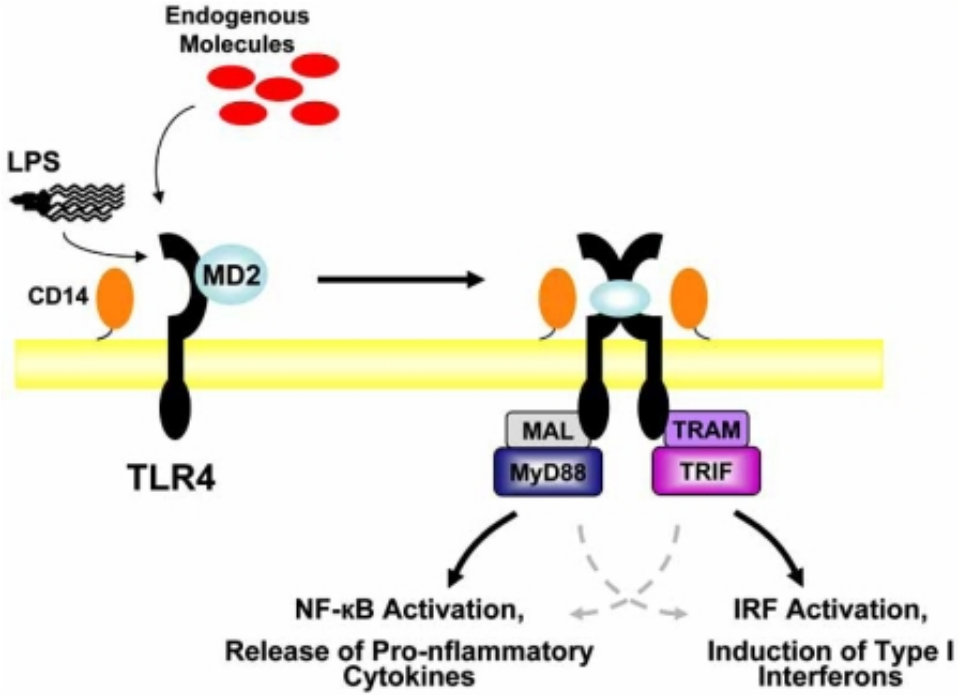
Guryanov, et al., Volume 68, 1 November 2016, Pages 890-903

Receptor Affinity

- The relationship between the ligand in solution and the number of receptors occupied can be described in terms of **receptor affinity**
- When almost all the receptors are occupied at a low concentration of free ligand, we say that a receptor has a high affinity for its ligand and vice versa.
- The **dissociation constant**, K_d, is the [free ligand] needed to produce a state in which half the receptors are occupied
- Receptors with high ligand affinity have low K_d (and vice versa)

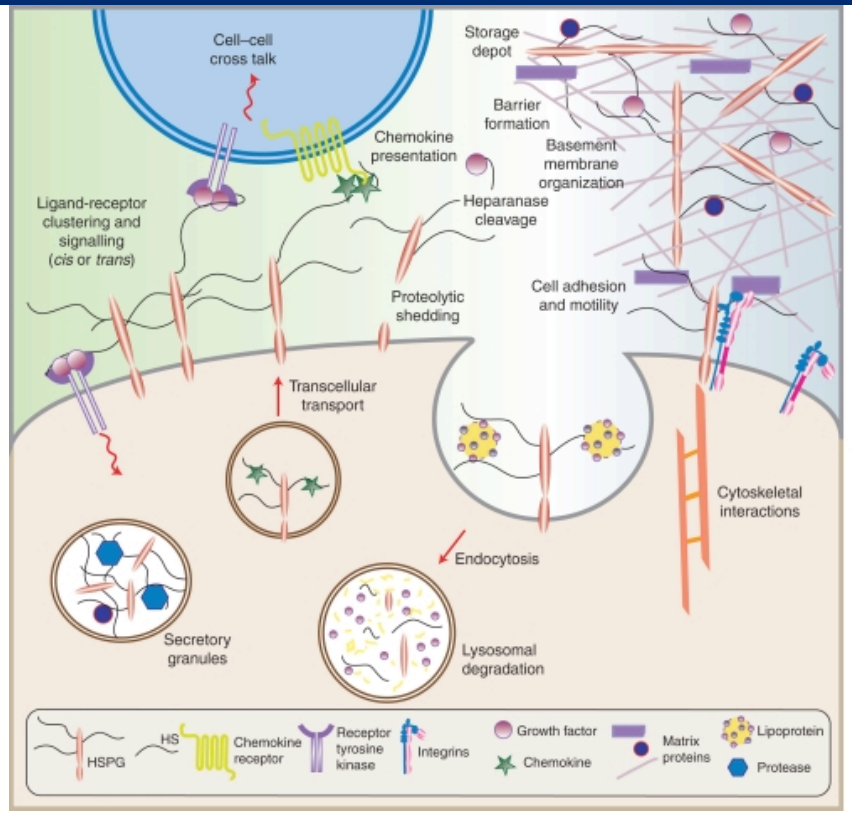
Coreceptors

- Receptor-ligand interactions can be affected by coreceptors on the cell surface
- They help to facilitate receptor-ligation interaction via physical interaction with the receptor
- Coreceptors are often clustered in lipid rafts (microdomains)
  - E.g. Toll-like Receptors



Current Cardiology Reviews 5(3):196-202

One well-studied class of co-receptor molecules is *heparan sulfate proteoglycans (HSPGs)*



Adapted from Bishop et al., Nature Vol 446, 26 April 2007

Receptor Down-regulation

- Cells are geared to sense ligand concentration *changes* rather than fixed concentrations
- When receptors are occupied for prolonged periods, the cell adapts to no longer respond to the ligand
- Such changes are called *receptor down-regulation,* which can be accomplished in two ways:
  - Cells reduce the density of receptors on their cell surfaces via ***receptor-mediated endocytosis***
  - Cells can adapt to signals by ***desensitization***, alterations to the receptor that lower its affinity for the ligand
    - A common method of desensitization is phosphorylation (addition of a phosphate group to a molecule)

Agonists and Antagonists

- **Agonists**: drugs that activate the receptor they are bound to

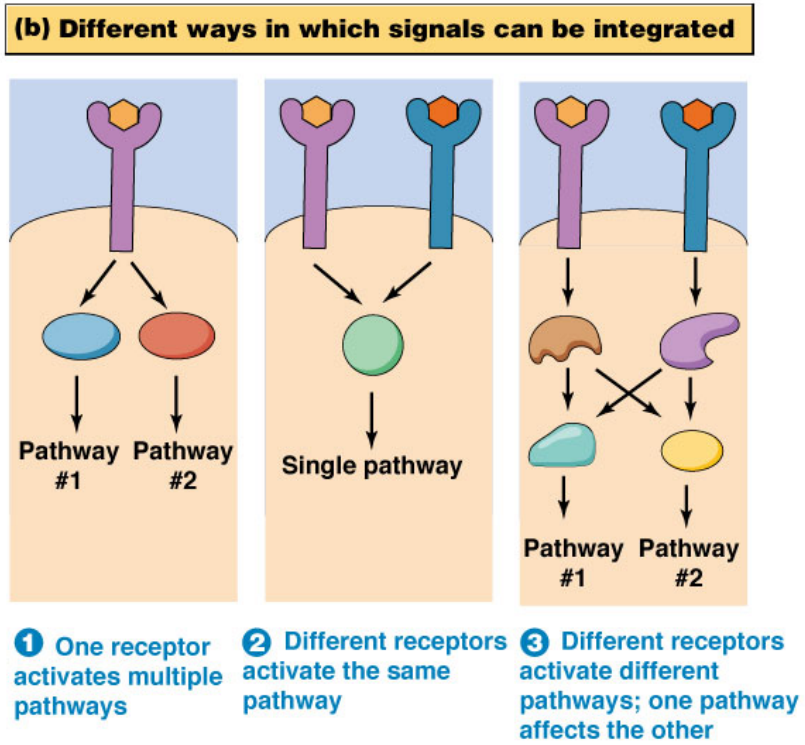
- **Antagonists:** bind receptors without triggering a change, and prevent the naturally occurring messenger from activating the receptor

- It is possible to make synthetic ligands that bind even more tightly or selectively than the real ligand; This is the central mechanism of many treatments for human disease

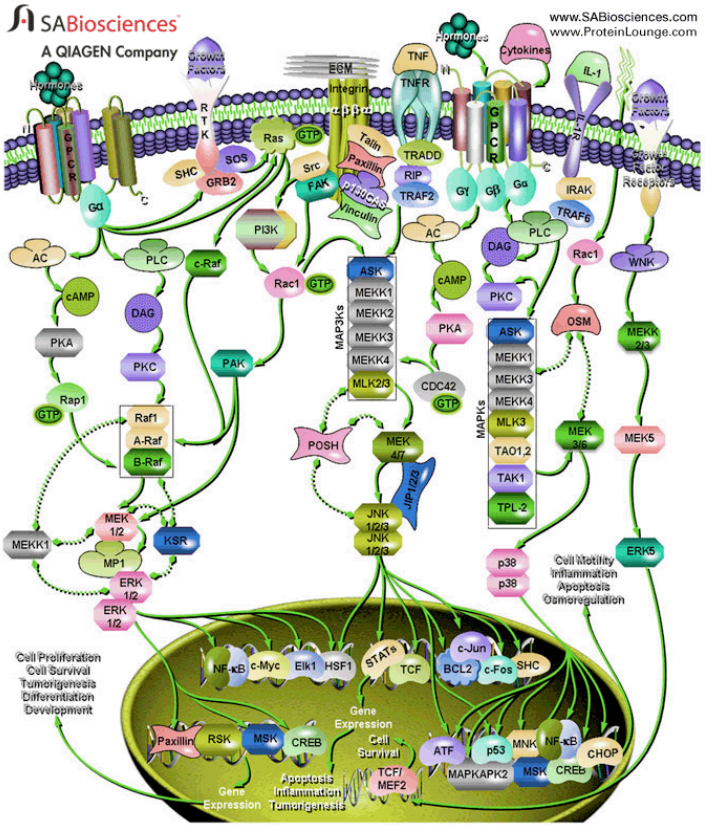
  - e.g: Commercial product “Pepcid” acid controller (famotidine), selectively binds & inhibits a histamine receptor on cells in the stomach

Receptor Binding Activates a Sequence of Signal Transduction Events Within the Cell

- When a ligand binds to its cognate receptor it either induces a change in receptor conformation or causes receptors to cluster
- Once this takes place, a *preprogrammed* sequence of events is initiated inside the cell
- Cells can be exposed to a multitude of signals at any given moment
- Cells must *integrate* these signals to produce appropriate responses (i.e. *signal integration*)
- A single receptor can activate multiple pathways, or multiple pathways can converge onto the same molecules



- Example of a complex signal network: MAP kinase signaling
- MAPKs are activated in response to a cell signal to grow and divide, sometimes called a *mitogen*
- MAPKs phosphorylate transcription factors that enter the nucleus to alter gene expression



Signal Amplification

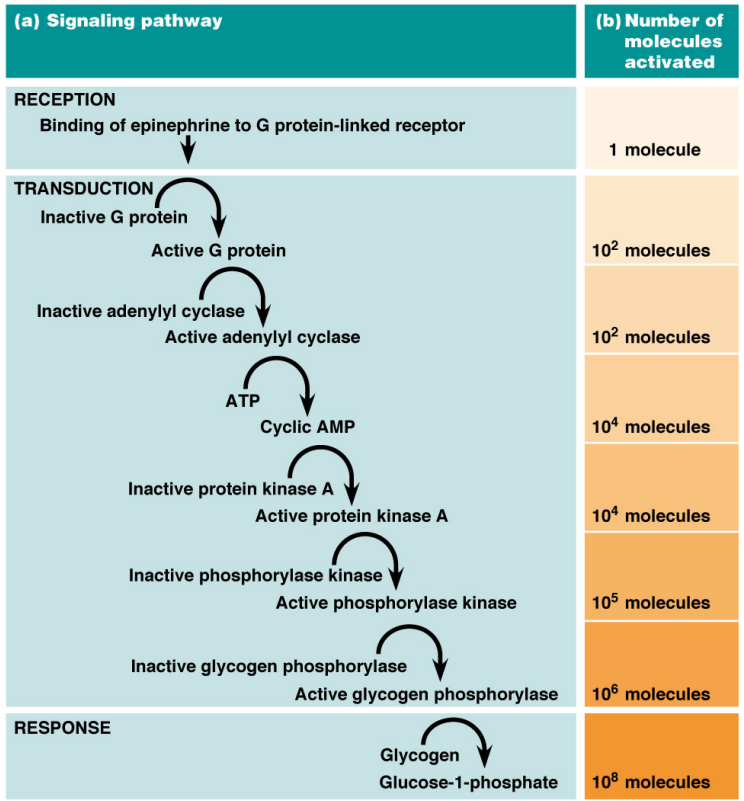
- Very small quantities of ligand are often sufficient to elicit a response from a target cell

- At each step in the resulting cascade of events, a signaling intermediate stimulates the production of many molecules needed for the next step

- This multiplication of the effect of the signal is called signal amplification

Signal Amplification

Example:
liver cell responding to one molecule of epinephrine; triggers hundreds of millions of glucose-1-phosphate molecules



Summary

- Signal Transduction
  - Types of signals
- Receptor-ligand interactions
  - Receptor affinity
  - Coreceptors
- Agonists and antagonists
- Signal Amplification