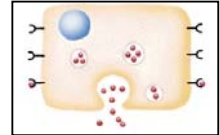


Cell-to-Cell Signaling Receptors



No cell is an island

- Cells communicate with each other
- Cells send and receive information (signals)
- Information is relayed within cell to produce a response (signal transduction)



Signaling process

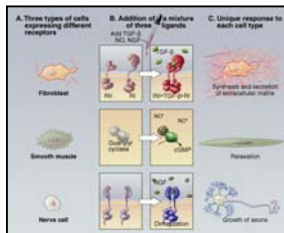
- Recognition of signal
 - Receptors
- Transduction
 - Change of external signal into intracellular message
- Effect
 - Modification of cell behavior

Life is not easy

- The effects of activation of cell surface receptors are more complicated than a simple step-by-step cascade
- Extensive networking and cross talk
- By no means signaling is a linear event
- Key is integration

Recognition

- Performed by receptors
- Ligand will produce response only in cells that have receptors for this particular ligand
- Each cell has a specific set of receptors



Transduction

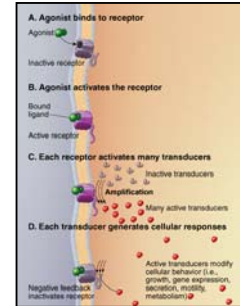
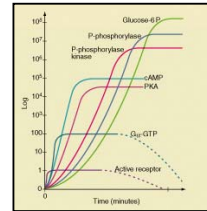
- Activated receptor interacts with other intracellular signaling molecules and
 - Directly changes cellular activity
- or
 - Produces some intermediates (second messengers) that change cellular activity

Cellular effects

- Metabolism
- Gene expression
- Growth and differentiation (cell cycle)
- Secretion
- Structure (cytoskeleton)

Why so complicated?

- Amplification
- Reliability
- Redundance



Receptors

- Molecules specialized in recognizing signals
 - Can be inside the cell or out
- Specific for a signal (they will recognize only a signal that they are made for)
- Energy from the signal (stimulus) or ligand binding alters the structure of the receptor

Receptors

- Ligand – substance that binds to receptor with high affinity
 - Binding of the ligand produces biological response
- Ligands can be endogenous or exogenous
- Agonist – biological response of the same type as the endogenous ligand (can be smaller)
- Antagonist – binds and blocks the response

To be a receptor a molecule

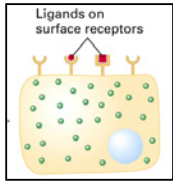
- Has to have an endogenous ligand
 - Has to bind it with high affinity (strength)
 - Has to recognize the biologically active ligand from other similar molecules (specificity)
 - Has to produce the biological response
- All the conditions have to be met!!!**

Definition of a receptor

- Molecules within or on the surface of target cells to which a substance endogenous to the organism attaches itself with high affinity and specificity as an essential step in modifying cellular function

Characterization of the receptors based on localization

- Intracellular receptors
 - For molecules that can enter the cell
- Plasma membrane receptors
 - For molecules that can not



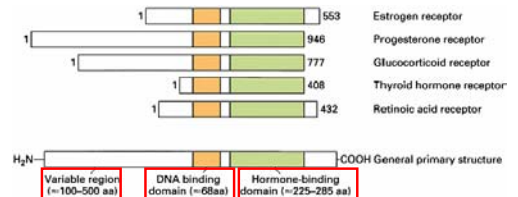
Intracellular receptors

- If a substance can cross the membrane it will bind to intracellular receptors
- Localized in nucleus or cytoplasm
 - Those in cytoplasm translocate to the nucleus upon activation
- Ligand activated transcription factors
- Genomic effects

Structure of nuclear receptors

- Superfamily of ligand-activated transcription factors
- Bind to specific DNA sequences as dimers
- Similar structure and high homology
- Two highly conserved regions

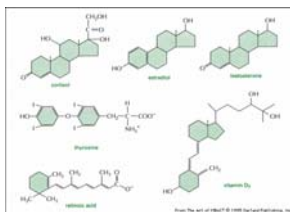
Domain structure of nuclear receptors



Highest homology region – zinc finger motif

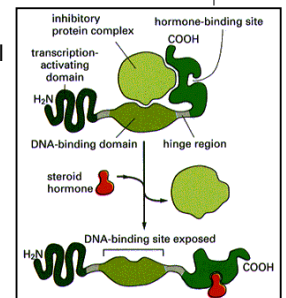
Ligands of intracellular receptors

- Small hydrophobic molecules that can cross the membrane
 - Steroid hormones
 - Thyroid hormones
 - 1,25-dihydroxycholecalciferol (vitamin D3)
 - Retinoic acid



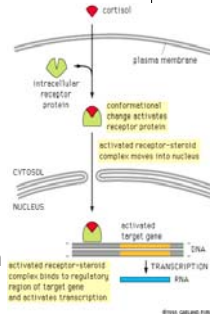
Model of activation of intracellular receptors

- In the absence of hormone, transcriptional activation is inhibited
- Hormone binding relieves inhibition
 - Release of inhibitory complex – hsp
- Exposing of DNA binding domain



Mechanism of intracellular (nuclear) receptor action

- Ligand binding activates the receptor
- Activated receptor binds to regulatory DNA sequences called Hormone Response Elements
 - Localized in the 5' flanking regions of target genes
- N-terminus has a transcription activation domain



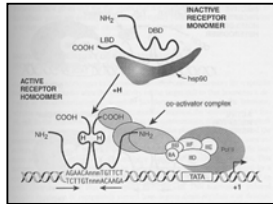
Consensus sequences (Hormone Response Elements)

Estrogen receptor → 5' AGGTCA(N)₃ TGACCT 3'
3' TCCAGT(N)₃ ACTGGA 5'

Retinoic acid receptor → 5' AGGTCA(N)₅ AGGTCA 3'
3' TCCAGT(N)₅ TCCAGT 5'

Structure of nuclear receptors

- Work as dimers
- Directly activate transcription (ligand activated transcription factors)

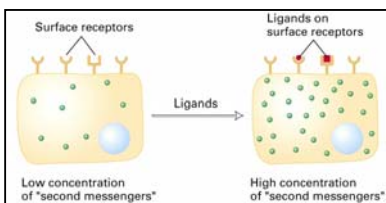


Why do we need cell surface receptors?

- Most signals can not cross the membrane
- It can't work if it can't get in
- But it can send a messenger
- When activated, a receptor on the surface "passes" the signal to intracellular second messengers

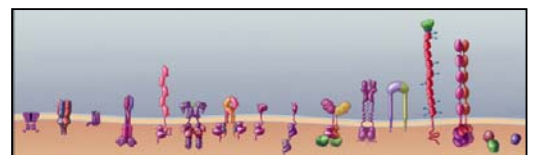
Second messengers

- Molecules inside a cell that
 - Change of function of the cell
 - Signal to the nucleus for genomic effects



Plasma membrane receptors

- About 20 families so far
- Based on similarities in structure, ligand binding and signal transduction strategies



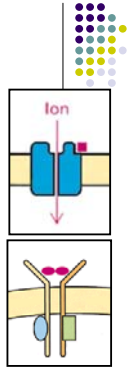
Plasma membrane receptors

- Different sizes and shapes
- Different isoforms within the family arose by gene duplication and divergence
- Selective expression decides about physiology of the cell
- Ligand binding or physical energy (light, pressure, temperature, voltage) activate the receptor



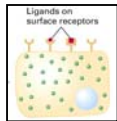
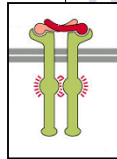
Signaling strategies

- Ion channels receptors
 - Ligand gated ion channels
 - Voltage gated ion channels
- Receptors that are linked to cytoplasmic enzymes
 - Cytokine receptors



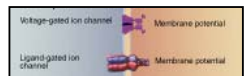
Signaling strategies

- Receptors that have intrinsic enzymatic activity (they are enzymes)
 - Receptor tyrosine kinases
- Receptors that activate intracellular second messengers
 - G protein coupled receptors
- Cell adhesion receptors



Ion channels receptors

- Receptor molecule is an ion channel at the same time
 - [Ligand gated ion channels](#)
 - [Voltage gated ion channels](#)
- Activation of receptor opens a channel and changes excitability of the membrane



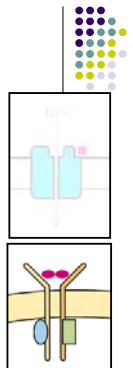
Ligands that use ion channel receptors

- Histamine
- Serotonin
- Heat and cold
- Mechanical deformation of membrane



Signaling strategies

- Ion channels receptors
 - Ligand gated ion channels
 - Voltage gated ion channels
- Receptors that are linked to cytoplasmic enzymes
 - Cytokine receptors



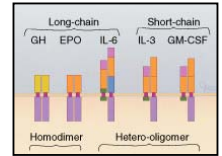
Cytokine receptors

- Receptors for interleukins and polypeptide growth factors
- Do not have enzymatic activity but bind cytoplasmic protein tyrosine kinases
- Signal to nucleus
- Regulate gene expression



Cytokine receptors

- All have 4 subunits
 - Homodimer or heterotrimer/heterodimer
- Single transmembrane region
- Extracellular fibronectin domain (ligand binding site)
- Cytosolic domain binds JAKs (kinases)



Ligands

- Interleukins
- Growth hormone
- Prolactin
- Erythropoietin

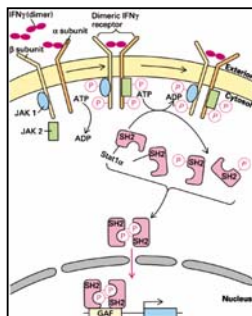


Cytokine receptors activation

- Dimerization or conformational change
- That brings together two JAKs
- JAKs cross-phosphorylate
- Activated JAKs phosphorylate (activate) STATs (transcription factors)
- STATs translocate to the nucleus

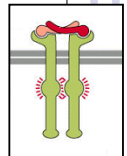


Signaling to the nucleus by JAK/STAT pathway



Signaling strategies

- Receptors that have intrinsic enzymatic activity (they are enzymes)
 - Guanylyl cyclase
 - Receptor tyrosine kinases
- Receptors that activate intracellular second messengers
 - G protein coupled receptors



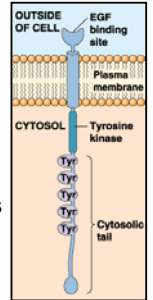
Receptor tyrosine kinases (RTK)

- Cell-surface receptors with intrinsic enzymatic activity (tyrosine kinase)
 - Cytoplasmic domain has tyrosine kinase activity
- Mostly receptors for peptide/protein growth factors
- Regulate growth and differentiation and cell survival

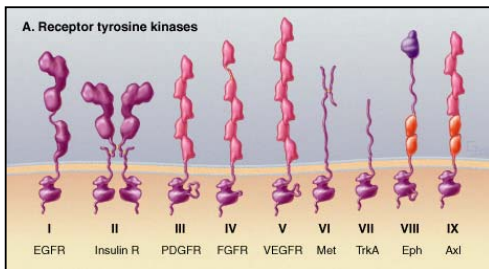


Receptor tyrosine kinases (RTK)

- Single transmembrane domain
 - Usually single polypeptide
 - Insulin family is an exception
- Extracellular binding site has immunoglobulin or fibronectin domains
- Intracellular kinase domain includes tyrosines that can cross-phosphorylate



Subfamilies of receptor tyrosine kinases (RTK)



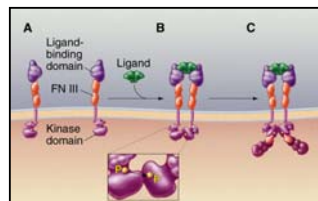
Ligands of receptor tyrosine kinases (RTK)

- EGF
- Insulin
- PDGF
- FGF
- NGF



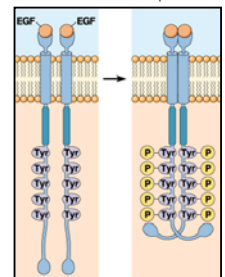
Activation of RTKs

- Ligand binding promotes conformational change and dimerization of the receptor
 - Some RTK are dimers (insulin receptor) but ligand binding is necessary for activity



Activation of RTKs

- Dimerization activates enzymatic activity of the receptor molecule (tyrosine kinase)
- Cross-phosphorylation of the cytosolic domain on the partner

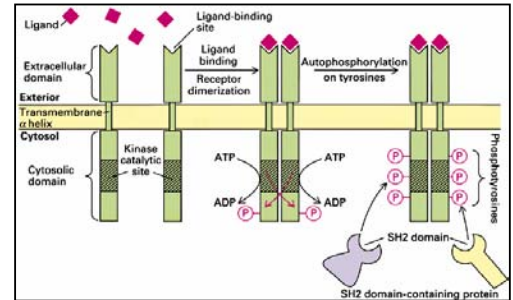


Activation of RTKs

- Phosphotyrosine residues interact with proteins that have SH2 and PTB domains
- Two mechanisms of interactions with the effector
 - Activation of enzymes with SH2 domains
 - Through adapter protein



Ligand binding leads to autophosphorylation of RTKs



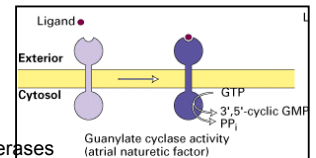
Guanylyl cyclase receptor

- Another receptor with intrinsic enzymatic activity (guanylyl cyclase)
- Binding of the ligand activates the enzymatic activity of the receptor molecule
- Receptor for atrial natriuretic factor and other peptides



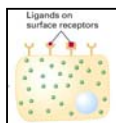
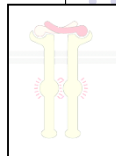
Guanylyl cyclase receptor

- Receptor catalyzes formation of cGMP from GTP
- cGMP regulates
 - cGMP gated ion channels
 - cGMP activated protein kinases
 - cGMP-phosphodiesterases



Signaling strategies

- Receptors that have intrinsic enzymatic activity (they are enzymes)
 - Guanylyl cyclase
 - Receptor tyrosine kinases
- Receptors that activate intracellular second messengers
 - G protein coupled receptors



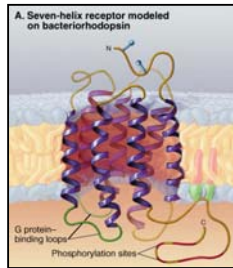
Seven-helix receptors

- A.k.a. G protein coupled receptors
- Plasma membrane receptors
- Involved in a range of signaling pathways, including light detection, odorant detection, and detection of certain hormones and neurotransmitters



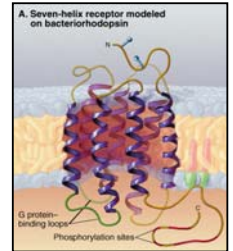
Molecular properties of seven-helix receptors

- Seven transmembrane regions of 22-24 hydrophobic residues
- N-terminus faces outside
 - Often involved in activation or ligand binding



Molecular properties of seven-helix receptors

- C-terminus faces cytosol and has phosphorylation sites
 - Place for regulation
- A cytosolic loop between helices 5 and 6 is the place for interaction with G protein



Ligand binding

Different possibilities for ligand binding

1. Ligand binding site in a pocket among extracellular ends of the helices (1/3 into the membrane)
2. N-terminal binding
3. Truncated N-terminus activates the receptor

Hormones that act through seven-helix receptors

- Epinephrine and norepinephrine
- Glucagon
- Bradykinin
- ACTH
- Vasopressin
- Luteinizing hormone LH
- Thyroid stimulating hormone TSH

Seven-helix receptors

- Activated receptor catalyzes G protein activation
 - Exchange of nucleotide bound to G protein (replacement of GDP with GTP)
- Activated G protein initiates signaling cascade

Signaling by seven-helix receptors

- A typical signal transduction cascade comprises
 - G protein
 - Enzyme
 - Second messengers
 - Target protein - effector
- Not necessary all steps are involved!!!!

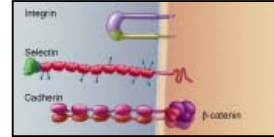


Other receptors

- Receptor serine/threonine kinases
- TNF receptor family
- Notch receptors
- Hedgehog receptors



Cell adhesion receptors



To be discussed later

