Contents

15 Cell Signaling

15.1 Principles of Cell Signaling

- Extracellular signaling → Receptor protein → Intracellular signaling proteins → Effector proteins.
- Effector proteins consists transcription regulators, ion channels, or metabolic enzymes.a
- More than 1500 genes encode for receptor proteins, and variation in the proteins are increased even more due to alternative RNA splicing and post-translational modifications.

15.1.1 Extra Signals Can Act Over Short or Long Distances

- **Contact dependent signaling**: many extracellular signals are bound to the surface of cells that require direct contact from other membrane bound signaling cells in order for activation.
- **Local mediators**: secreted molecules that generally only act on cells in the local environment.
- **Paracrine signaling**: result of signaling using local mediators, and generally acts on cells of different types.
- *Autocrine signaling*: results of local mediators acting on the cells that secret them.
- **Endocrine cells**: signaling over long distance using hormones that travel through the bloodstream.

15.1.2 Classes of Cell-Surface Receptor Proteins

- Most extracellular signals do not enter the nucleus, instead they act as signal transducers of extracellular ligand-binding events.
- **Ion-channel-coupled receptors**: or ionotropic receptors, are involved in rapid synaptic signaling between nerve cells of other electronically excitable cells.

- **G-protein-coupled receptors**: indirectly regulating separate membrane-bound target proteins, usually using enzymes or ion channels, resulting in small intracellular signaling molecules to alter the behavior of different signaling proteins in the cell.
- **Enzyme-coupled receptors**: either function as or directly associate with enzymes they activate. Usually are single pass transmembrane proteins that have ligand-binding site outside the cell and the catalytic site inside.
- Majority of enzyme are either protein kinases of associate with protein kinases.

15.1.3 Cell-Surface Receptors Relay Signals Via Intracellular Signaling Molecules

- **Second messengers**: small chemicals involved in intracellular signaling that are generated in large amounts in response to receptor activation and diffuse to spread signals to other parts of the cell.
- Either water soluble or lipid soluble, resulting in an extension of the signal by binding/altering the behavior of selected signaling or effector proteins.
- Most intracellular molecules are proteins that act like a chain of molecular switches to transmit signals.
- **Protein kinase**: covalently adds one or more phosphate groups.
- **Protein phosphatase**: removes phosphate groups.
- 30-50% of human proteins contain covalently attached phosphate.
- Many intracellular proteins are protein kinases themselves, resulting in **kinase cascades**.
- *trimeric GTP-binding proteins*: help relay signals from G-proteins-coupled receptors that activate them.
- **monomeric GTPases** help relay signals from many classes of cell-surface receptors.
- **GTPase-activating proteins (GAPs)**: drive proteins into an "off" state by increasing rate of hydrolysis of bound GTP.

- **Guanine nucleotide exchange factors (GETs)**: promote the release of bound GDP, allowing new GTP to bind, which activates the proteins.

15.1.4 Modular Interaction Domans Mediate Interactions Between Inracellular Signaling Proteins

- *Induced proximity*: the result of a signal triggering the assembly of a signaling complex, which can activate other proteins simply due to proximity.
- **Interaction domains**: highly conserved domains that are found in many intracellular signaling proteins and highly affect assembly of proximity complexes.
- The modular function helped evolution because the new pathways can be inserted with out disturbing the proteins folding of function.
- **Adaptors**: two or more interaction domains that link two proteins together in a signaling pathway.
- **Primary cilium**: an example of how to bring receptors and intracellular signaling together by concentrating them in them specific region of the cell (an antenna like object that projects from the surface of most vertebrate cells).

15.1.5 The Reelationship Between Signal and Response Varies in Different Signaling Pathways

- All signaling systems do not work in the same way and have a variety of response factors.
- *Response timing*: can range from milliseconds to hours or days.
- *Sensitivity*: controlled by changes to numbers or affinity of the receptors on the target cell and often further influenced by amplification factors.
- *Dynamic range*: related to sensitivity. More focused on the broader range sensitivity, responding to the changes in sensitivity itself, which is know as **adaptation** to the responsiveness according to prevailing amounts of signal.

- *Persistance*: how long signaling is active, regulated by numerous mechanisms, including positive feedback.
- *Signal processing*: converting simple signals into complex responses; regulated by switch like or oscillatory responses.
- *Integration*: allows a response to be governed by multiple inputs; equivalent to AND gates.
- *Coordination*: multiple responses due to a single extracellular signal. Depends on mechanisms for distributing a signal to multiple effectors, even sometimes modulating the strength of a response to other signals.

15.2 Signaling Through G-Protein-Coupled Receptors

- **G-protein-coupled receptors (GPCRs)**: the largest family of cell-surface receptors and the mediators of most responses to cell signaling.
- The same signal molecule can activate many different GPCR family members.
- GPCRs consists of a single polypeptide chain that threads across the membrane layer seven times, forming a cylindrical structure, often with a ligand binding site in the center.

15.2.1 Trimeric G Proteins Relay Signals From GPCRs

- **trimeric GTP-binding protein (G protein)**: activated when a receptor undergoes a conformational change and couples the receptor to enzymes or ion channels in the membrane.
- The G protein can be associated with the receptors before of after activation depending on the type.
- G proteins are composed of three subunits —α, β, and γ.
- Unstimulated state: α subunit has GDP bound and G protein is inactive.
- When GPCR is activated it acts like GEF and induces α subunit to release bound GDP.

- GTP binding induces conformational change in Gα subunit, releasing G protein from receptor and dissociation of GTP-bound Gα from G$\beta\gamma$ pair.
- **regulator of G protein signaling (RGS)**: proteins that act as a α-subunit-specific GAPs and help shut off G-protein-mediated responses.

15.2.2 Some G Proteins Regulate the Production of Cyclic AMP

- **Cyclic AMP (cAMP)**: acts as a second messenger in some pathways and helps with signal transduction.
- cAMP is synthesized from ATP by **adenylyl cyclase** and destroyed by **cyclic AMP phosphodiesterase**.
- Many extracellular signals work by increasing cAMP.

15.2.3 Cyclic-AMP-Dependent Protein Kinase (PKA) Mediates Most of the Effects of Cyclic AMP

- **Cyclic-AMP-dependent protein kinase (PKA)**: activated by cAMP and used to regulates selected proteins through phosphorylating specific serines of threonines.
- PKA consists of a complex of two catalytic subunits and two regulatory subunits.
- Binding of cAMP causes the regulatory subunits to dissociate and are free to phosphorylate specific target proteins.
- **CRE-biding (CREB) protein**: a transcription regulator that recruits a transcriptional coactivator called *CREB-binding protein (CBP)*. Thus, CREB can transform a short cAMP signal into a long-term change in the cell. (May play a role in some forms of learning and memory)

15.2.4 Some G protins Signal Via Phospholipids

- **Phospholipase C-β (PLCβ)**: plasma membrane bound enzyme that many GPCRs exert their effects through.

- **Phosphatidyblinositol 4,5-bisphosphate [PI(4,5)P_2]**: a phosphorylated inositol phospholipid (phosphoinositide) that C-β acts on and is present in small amounts in the inner half ot the plasma membrane.
- **G_q**: a G protein that activate the inositol phospholipid signaling pathway.
- **IP_3** and **diacylglycerol**: products of the cleaved PI(4,5)P_2 and the step at which signaling pathways split.
- IP_3 is a water soluble molecule that enters the ER and binds there, releasing the stored Ca^{2+} into the cytosol.
- Diacylglycerol acts as as second messengers embedded in the plasma membrane, with a major function that activates a protein kinase called **PKC** (named due to Ca^{2+} dependency).
- One activated, PKC various proteins depending on cell type.
- Diacylglycerol can also be cleaved further to release arachiconic acid, which acts a signal of used to make other small lipids caleld *eicosanoinds*, which take part in pain and inflammatory responses.

15.2.5 Ca^{2+} Functions as a Ubiquitous Intracellular Mediator

- Ca^{2+} has numerous other functions in a variety of cell types.
- **Ryanodine receptor**: a second type of regulated Ca^{2+} channel located in the ER membrane that opens in response to Ca^{2+} and amplifies the Ca^{2+} signal.

15.2.6 Feedback Generates Ca^{2+} Waves and Oscillations

- Both IP_3 receptors and ryanodine receptors are stimulated by low to moderate cytoplasmic Ca^{2+} concentrations.
- If the extracellular signals are sufficiently strong and persistant, then they may activate nearby IP_3 and ryanodine receptors, resulting in a wave of Ca^{2+}, similar to actions potentials.
- High concentrations of Ca^{2+} are inhibited and leads to a release of Ca^{2+}. This results in an oscillations in Ca^{2+} concentrations.
- Frequency dependent responses can also be oscillatory or non-oscillatory.

15.2.7 Ca^{2+}/Calmodulin-Dependent Protein Kinases Mediate Many Responses to Ca^{2+} Signals

- **Calmodulin**: a multipurpose intracellular Ca^{2+} receptor found in all eukaryotic cells and constitute as much as 1% of the cell's total protein mass.
- Calmodulin displays a sigmoidal response to increasing concentrations of Ca^{2+}.
- **CaM-kinase II**: found in most animal cells and is especially enriched in the nervous system–highly concentrated in synapses.
- Mutant mice lacking the enzyme have specific defects in memory, suggesting it plays a significant role in memory and learning.
- CaM-kinase II can use its intrinsic memory mechanism to decode the frequency of Ca^{2+} oscillations.

15.2.8 Some G Proteins Directly Regulate Ion Channels

- G proteins to not exclusively regulate membrane-bound enzymes.
- G proteins can directly activate ion channels in the plasma membrane of target cells–thereby altering ion electrical excitability of the membrane.

15.2.9 Smell and Vision Depend on GPCRs That Rgulate Ion Channels

15.3 Signaling Through Enzyme-Coupled Receptors

-

15.4 Alternative Signaling Routes in Gene Regulation

-

16 Chapter

16.1 Section

- **Word**: the part of the cell that separates the exterior and the interior of a cell with a semipermeable lipid bilayer. The plasma membrane regulates import and export of materials for the cell and includes various proteins that interact with other cells.
    - relates to word
- *Also Important*: the resulting structure of the spontaneous alignment of mostly amphiphilic phospholipids.