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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 or 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 Domains Mediate Interactions Between Intracellular 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 without 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 their specific region of the cell (an antenna like object that projects from the surface of most vertebrate cells).

15.1.5 The Relationship 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 known as **adaptation** to the responsiveness according to prevailing amounts of signal.

- ▷ *Persistence*: 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 $G\alpha$ subunit, releasing G protein from receptor and dissociation of GTP-bound $G\alpha$ 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-binding (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 proteins Signal Via Phospholipids

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

- ▷ **Phosphatidylinositol 4,5-bisphosphate [PI(4,5)P₂]**: a phosphorylated inositol phospholipid (phosphoinositide) that C- β acts on and is present in small amounts in the inner half of the plasma membrane.
- ▷ **G_q**: a G protein that activates the inositol phospholipid signaling pathway.
- ▷ **IP₃** and **diacylglycerol**: products of the cleaved PI(4,5)P₂ and the step at which signaling pathways split.
- ▷ IP₃ is a water soluble molecule that enters the ER and binds there, releasing the stored Ca²⁺ into the cytosol.
- ▷ Diacylglycerol acts as a second messenger embedded in the plasma membrane, with a major function that activates a protein kinase called **PKC** (named due to Ca²⁺ dependency).
- ▷ One activated, PKC activates various proteins depending on cell type.
- ▷ Diacylglycerol can also be cleaved further to release arachidonic acid, which acts as a signal used to make other small lipids called *eicosanoids*, which take part in pain and inflammatory responses.

15.2.5 Ca²⁺ Functions as a Ubiquitous Intracellular Mediator

- ▷ Ca²⁺ has numerous other functions in a variety of cell types.
- ▷ **Ryanodine receptor**: a second type of regulated Ca²⁺ channel located in the ER membrane that opens in response to Ca²⁺ and amplifies the Ca²⁺ signal.

15.2.6 Feedback Generates Ca²⁺ Waves and Oscillations

- ▷ Both IP₃ receptors and ryanodine receptors are stimulated by low to moderate cytoplasmic Ca²⁺ concentrations.
- ▷ If the extracellular signals are sufficiently strong and persistent, then they may activate nearby IP₃ and ryanodine receptors, resulting in a wave of Ca²⁺, similar to action potentials.
- ▷ High concentrations of Ca²⁺ are inhibited and leads to a release of Ca²⁺. This results in an oscillation in Ca²⁺ 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 Regulate Ion Channels

- ▷ **Olfactory receptors:** receptors with specific GPCRs that have modified cilia, which project from the surface of the neuron.
- ▷ Binding orderants activate the G_t which activates adenylyl cyclase, increasing cAMP that in turn opens the cyclic-AMP-gated cation channels.
- ▷ Vision has a similar proccess, but using a different nucleotide—**GMP**.
- ▷ Receptor activation by light causesese a fall rather than a rise in the cyclic nucleotide.
- ▷ Rods are made of a stack of discs that are densley packed with rhodopsin.
- ▷ Unlike most synaptic signaling, cyclic GMP causes hyperpolarization, causing the decrease in GMP and closing of channels.

- ▷ Activated rhodopsin alters the conformation of G_t , causing causing transducin α subunit to activate **cyclic GMP phosphodiesterase**.
- ▷ Rods use several negative feedback loops that allow the cell to quickly revert to a resting state and also help rods adapt to continuously exposed light—allowing small changes in light to be possible.
- ▷ Families of G proteins are determined by amino acid sequence relatedness of the α subunits.

15.2.10 Nitric Oxide is a Gaseous Signaling Mediator that Passes Between Cells

- ▷ **Nitric oxide (NO)**: a signaling molecule in many tissues of plants and animals that can readily cross the plasma membrane.
- ▷ NO acts locally due to a short half-life, about 5-10 seconds in the extracellular space.
- ▷ NO is made by the deamination of arginine and catalyzed by **NO synthases (NOS)**.
- ▷ NO binds reversibly to iron in the active site of guanylyl cyclase, stimulating synthesis of cyclic GMP.
- ▷ NO can increase cyclic GMP in the cytosol within seconds.

15.2.11 GPCR Desensitization Depends on Receptor Phosphorylation

- ▷ There are three general modes of adaptation:
 - *Receptor sequestration*: temporary movement into interior of the cell to remove ligand access.
 - *Receptor down-regulation*: destroyed in lysosomes after internalization.
 - *Receptor inactivation*: altered in order to stop interaction with G protein.
- ▷ All modes depend on the family of **GPCR kinases (GRKs)**

- ▷ GRKs phosphorylates multiple serines and threonines on a GPCR only after ligand binding due to the activated receptor being the one to allosterically activate GRK.
- ▷ Once a receptor has been phosphorylated by GRK, then it binds with high affinity to a member of the arrestin family of proteins.
- ▷ Bound arrestin helps in two ways: by preventing the activated receptor from interacting with G proteins and serves as an adaptor protein to help couple receptors in the clathrin-dependent endocytosis machinery.

15.3 Signaling Through Enzyme-Coupled Receptors

- ▷ **Enzyme coupled receptors:** similar to GPCRs, with are transmembrane proteins with the ligand binding domain on the extracellular side, with the catalytic domain with on the cytosolic side.
- ▷ enzyme-coupled receptors have only a single transmembrane helix.

15.3.1 Activated Receptor Tyrosine Kinases Phosphorylate Themselves

- ▷ **Receptor tyrosine kinases (RTKs):** most common enzyme-coupled receptors for many growth factors, cytokines, and hormones.
- ▷ Most RTKs ligand binding causes receptors to dimerize, bringing cytoplasmic kinase domains closer together and promoting activity.
- ▷ Phosphorylated tyrosines on RTKs serve as docking sites for intracellular signaling proteins.

15.3.2 Proteins with SH2 Domains Bind to Phosphorylated Tyrosines

- ▷ *Interaction domains:* modular domain that mediates protein-protein interactions that relay the signal of activated RTKs.
- ▷ **Phospholipase C- γ (PLC γ):** activates the inositol phospholipid signaling pathway, which allows RTKs to increase cytosolic Ca^{2+} levels that activate PKC.

- ▷ **SH2 domains**, and *PTB domains*: highly conserved phosphotyrosine-binding domains. These interaction domains enable proteins to bind to activated RTKs and other intracellular signaling proteins that have been transiently phosphorylated.
- ▷ Not all proteins that bind to RTKs via SH2 domains relay the signal, some provide negative feedback.

15.3.3 The GTPase Ras Mediates Signaling By Most RTKs

- ▷ **Ras superfamily**: a family of monomeric GTPases that relies on signals from cell-surface receptors and can act as a signaling hub.
- ▷ In general, the Ras family is responsible for cell proliferation or differentiation. With Rho for cell morphology, Ran for nuclear transport, and Rab and Arf for vesicle transport.
- ▷ 30% of human tumors express hyperactive mutant forms of Ras due to locked in of GTP-bound active state.

15.3.4 Ras Activates a MAP Kinase Signaling Module

- ▷ **MAP kinase module**: converts short lived signaling events into longer lasting ones that can relay it downstream to the nucleus in order to alter gene expression.
- ▷ MAP has three well conserved protein kinase components:
 - Raf = MAPKKK
 - Mek = MAPKK
 - Erk = MAPK
- ▷ Scaffold proteins help prevent cross-talk between parallel MAP kinase modules.

15.3.5 Rho Family GTPases Functionally Couple Cell-Surface Receptors to the Cytoskeleton

- ▷ Rho family regulate both the actin and microtubule cytoskeletons in order to control shape, polarity, motility, and adhesion.
- ▷ Rho also regulates cell-cycle progression, gene transcription, and membrane transport.
- ▷ Rho family are often bound to *guanine nucleotide dissociation inhibitors* (GDIs) in the cytosol, preventing interaction with Rho-GEFs at the plasma membrane.
- ▷ **Ephrin**: a family of proteins that serve as the ligand for the eph receptors, which compose the largest known subfamily of RTKs.

15.3.6 The PI 3-Kinase Produces Lipid Docking Sites in the Plasma Membrane

- ▷ **PI 3-kinase**: a kinase that principally phosphorylates inositol phospholipids rather than proteins and plays a central part in promoting cell survival and growth.
- ▷
- ▷

16 The Cytoskeleton

16.1 Function and Origin of the Cytoskeleton

- ▷ The cytoskeleton functions depend on three families: *actin filaments*, *microtubules*, and *intermediate filaments*
- ▷ Actin determines shape, helps in whole-cell locomotion, and cell division.
- ▷ Microtubules determine position of membrane-enclosed organelles, direct intracellular transport, and form mitotic spindles that segregate chromosomes.
- ▷ Intermediate filaments provide mechanical strength and interact with hundreds of accessory proteins that regulate and link the filaments.
- ▷ **Protofilaments**: linear strings of subunits joined end-to-end and associate with one another laterally to form hollow cylinders in order to provide strength and adaptability.
- ▷ Subunit assembly and disassembly constantly remodel all three types of cytoskeletal filaments.

16.1.1 Actin and Actin-Binding Proteins

- ▷ Actin is extraordinarily conserved among eukaryotes.
- ▷ α -actin is expressed in only muscle cells.
- ▷ β and γ actin are found together in almost all non-muscle cells.
- ▷ **minus end**: "pointed" polar side of F-actin that grows slowly.
- ▷ **plus end**: "barbed" polar side that grows faster.
- ▷ Nucleation is the rate limiting step in the formation of actin filaments.
- ▷ **Critical concentration**: concentration of free subunits after equilibrium between subunit dissociation and addition.
- ▷ Cells catalyze filament nucleation at specific sites in order to determine the location at which new actin filaments are assembled.
- ▷ ATP hydrolysis within actin filaments leads to treadmilling at steady state.

- ▷ Polymerization follows as sigmoidal curve due to the lag phase from initial nucleation.
- ▷ ATP caps go on actin filaments while GTP caps go on microtubules.
- ▷ **Dynamic instability:** microtubules depolymerize 100 times faster from an end with GDP-tubulin than GTP, allowing for slow growth and disassembly.

16.1.2 Monomer Availability Controls Actin Filament Assembly

- ▷ **Thymosin:** a small protein that binds to actin monomers, preventing association with the plus or minus end and can neither hydrolyze nor exchange their bound nucleotide.
- ▷ **Profilin:** a protein that binds to face opposite to the ATP-binding cleft, blocking minus end association.

16.1.3 A-Nucleating Factors Accelerate Polymerization and Generate Branched or Straight Filaments

- ▷ **Arp 2/3 complex:** nucleates actin filament growth from the minus end, allowing rapid elongation at the plus end and forms a tree like web.
- ▷ **Formins:** dimeric proteins that nucleate the growth of straight, unbranched filaments that can form parallel bundles.
- ▷ Profilin, arp 2/3, and formins primarily occurs at the plasma membrane.
- ▷ **Cell cortex:** layer just beneath the plasma membrane, and the area where actin filaments determine the shape and movement of the cell surface.

16.1.4 Actin-Filament-Binding Proteins Alter Filament Dynamics

- ▷ **Tropomyosin:** an elongated protein that binds to six or seven adjacent actin subunits along each of the two grooves of the helical actin filament. This stabilizes, stiffens, and prevents actin filament from interacting with other proteins.
- ▷ **CapZ:** stabilizes an actin filament at the plus end, reducing growth and depolymerization.

- ▷ **Tropomodulin:** binds tightly to the minus end of actin filaments. Also can transiently cap pure actin filaments. There is a large family of tropomodulin proteins.

16.1.5 Severing Proteins Regulate Actin Filaments Depolymerization

- ▷ **Gelsolin superfamily:** a class of actin-severing proteins that are activated by high levels of cytosolic Ca^{2+} .
- ▷ After severing, gelsolin remains attached to the actin filament and caps to the new plus end.
- ▷ **Cofilin:** binds along the length of the actin filament, forcing the filament to twist, making it more easily severed by thermal motions.
- ▷ Cofilin preferentially binds to ADP-containing filaments, which results in a tendency to dismantle older filaments in the cell.
- ▷ Tropomyosin binding can protect filaments from cofilin.

16.1.6 Filament Arrays Influence Cellular Mechanical Properties and Signaling

- ▷ Actin filaments are organized into several types of arrays: dendritic networks, bundles, and weblike networks.
- ▷ *bundling proteins:* cross link actin filaments into a parallel array.
- ▷ *Gel-forming proteins:* hold two actin filaments together at a large angle to each other, creating a looser meshwork.
- ▷ **Fimbrin:** excludes myosin which prevents them from contracting.
- ▷ **α -actinin:** cross links oppositely polarized filaments into loose bundles, allowing binding of myosin and formation of contractile actin bundles.
- ▷ **Filamin:** promotes formation of loose and viscous gel by clamping together two actin filaments roughly at right angles.
- ▷ *Lamellipodia:* sheetlike membrane projections that help cells crawl along solid surfaces.

- ▷ **Spectrin:** long flexible protein made out of four elongated polypeptide chains (two α and two β subunits) that concentrate just beneath the plasma membrane, resulting in a network that creates a strong, yet flexible cell cortex, providing mechanical support for the overlying plasma membrane.

16.2 Myosin and Actin

- ▷ Actin-based members of the myosin superfamily.
- ▷ *Myosin II*: the first motor protein identified and is responsible for generating force for muscle contraction.
- ▷ Myosin generates force by coupling ATP hydrolysis to conformational changes.
- ▷ Each step of the movement along actin is generated by the swinging of α helix, or lever arm.
- ▷ Sliding of myosin II along actin filaments causes muscles to contract.
- ▷ **Myofibril:** a cylindrical structure that is often as long as the muscle itself. It consists of *sarcomeres*, which give the striated appearance.
- ▷ Each sarcomere consists of precisely ordered array of partly overlapping thin and thick filaments.
- ▷ *Thin filaments*: are composed of actin and associated proteins with their plus ends attached to Z discs with the minus ends extending toward the middle and overlapping with thick filaments.
- ▷ *Thick filaments*: bipolar assemblies formed from specific muscle isoforms of myosin II.
- ▷ **Nebulin:** a repeating 35-amino-acid actin-binding motif that determines the length of the small filaments.
- ▷ Sudden rise in cytosolic Ca^{2+} concentration initiates muscle contraction.
- ▷ Actin and myosin perform a variety of functions in non-muscle cells.