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Chapter 1 : Signal Transduction | Tocris Bioscience

Authoritative and up-to-date, Receptor Signal Transduction Protocols, Third Edition serves the scientific community with a broad collection of the current, practical methodologies in this highly promising field.

Extracellular receptors Extracellular receptors are integral transmembrane proteins and make up most receptors. They span the plasma membrane of the cell, with one part of the receptor on the outside of the cell and the other on the inside. Signal transduction occurs as a result of a ligand binding to the outside region of the receptor the ligand does not pass through the membrane. Ligand-receptor binding induces a change in the conformation of the inside part of the receptor, a process sometimes called "receptor activation". A molecular model for receptor activation This results in either the activation of an enzyme domain of the receptor or the exposure of a binding site for other intracellular signaling proteins within the cell, eventually propagating the signal through the cytoplasm. Often such enzymes are covalently linked to the receptor. Some of them create such as cyclic AMP and IP3, the latter controlling the release of intracellular calcium stores into the cytoplasm. Other activated proteins interact with adaptor proteins that facilitate signaling protein interactions and coordination of signaling complexes necessary to respond to a particular stimulus. Enzymes and adaptor proteins are both responsive to various second messenger molecules. Many adaptor proteins and enzymes activated as part of signal transduction possess specialized protein domains that bind to specific secondary messenger molecules. For example, calcium ions bind to the EF hand domains of calmodulin , allowing it to bind and activate calmodulin-dependent kinase. PIP3 and other phosphoinositides do the same thing to the Pleckstrin homology domains of proteins such as the kinase protein AKT. G proteinâ€"coupled receptors G proteinâ€"coupled receptors GPCRs are a family of integral transmembrane proteins that possess seven transmembrane domains and are linked to a heterotrimeric G protein. With nearly members, this is the largest family of membrane proteins and receptors in mammals. Counting all animal species, they add up to over Mammalian GPCRs are classified into 5 major families: Other classes exist in eukaryotes, such as the Dictyostelium cyclic AMP receptors and fungal mating pheromone receptors. The dissociation exposes sites on the subunits that can interact with other molecules. ISBN The activated G protein subunits detach from the receptor and initiate signaling from many downstream effector proteins such as and ion channels , the latter permitting the release of second messenger molecules. The total strength of signal amplification by a GPCR is determined by the lifetimes of the ligand-receptor complex and receptor-effector protein complex and the deactivation time of the activated receptor and effectors through intrinsic enzymatic activity; e. A study was conducted where a point mutation was inserted into the gene encoding the chemokine receptor CXCR2; mutated cells underwent a malignant transformation due to the gene expression of CXCR2 in an active conformation despite the absence of chemokine-binding. This meant that chemokine receptors can contribute to cancer development. Receptor tyrosine kinases RTKs are transmembrane proteins with an intracellular kinase domain and an extracellular domain that binds ; examples include growth factor receptors such as the insulin. To perform signal transduction, RTKs need to form protein dimer in the plasma membrane ; the dimer is stabilized by ligands binding to the receptor. The interaction between the cytoplasmic domains stimulates the auto phosphorylation of tyrosine residues within the intracellular kinase domains of the RTKs, causing conformational changes. The process of signal transduction involves around known protein kinases and pseudokinases , encoded by the human kinome As is the case with GPCRs, proteins that bind GTP play a major role in signal transduction from the activated RTK into the cell. In this case, the G proteins are members of the Ras superfamily , Rho, and Raf families, referred to collectively as small G proteins. They act as molecular switches usually tethered to membranes by isoprenyl groups linked to their carboxyl ends. Upon activation, they assign proteins to specific membrane subdomains where they participate in signaling. The mutation of certain RTK genes, as with that of GPCRs, can result in the gene expression of receptors that exist in a constitutively activated state; such mutated genes may act as oncogenes. Histidine kinase are structurally distinct from other protein kinases and are found in prokaryotes, fungi, and plants as part of a two-component signal transduction mechanism: Integrins Integrins are produced by a wide variety of cells; they play a role in

cell attachment to other cells and the extracellular matrix and in the transduction of signals from extracellular matrix components such as fibronectin and collagen. Integrins lack kinase activity; hence, integrin-mediated signal transduction is achieved through a variety of intracellular protein kinases and adaptor molecules, the main coordinator being integrin-linked kinase. As shown in the adjacent picture, cooperative integrin-RTK signaling determines the timing of cellular survival, apoptosis , cell growth , and differentiation. Important differences exist between integrin-signaling in circulating blood cells and non-circulating cells such as ; integrins of circulating cells are normally inactive. For example, cell membrane integrins on circulating leukocytes are maintained in an inactive state to avoid epithelial cell attachment; they are activated only in response to stimuli such as those received at the site of an inflammation. In a similar manner, integrins at the cell membrane of circulating platelets are normally kept inactive to avoid thrombosis. Epithelial cells which are non-circulating normally have active integrins at their cell membrane, helping maintain their stable adhesion to underlying stromal cells that provide signals to maintain normal functioning. In plants, there are no bona fide integrin receptors identified to date; nevertheless, several integrin-like proteins were proposed based on structural homology with the metazoan receptors. Plants contain integrin-linked kinases that are very similar in their primary structure with the animal ILKs. In the experimental model plant Arabidopsis thaliana, one of the integrin-linked kinase genes, ILK1, has been shown to be a critical element in the plant immune response to signal molecules from bacterial pathogens and plant sensitivity to salt and osmotic stress. Toll-like receptors When activated, toll-like receptors TLRs take adapter molecules within the cytoplasm of cells in order to propagate a signal. Thousands of genes are activated by TLR signaling, implying that this method constitutes an important gateway for gene modulation. Ligand-gated ion channels A ligand-gated ion channel, upon binding with a ligand, changes conformation to open a channel in the cell membrane through which ions relaying signals can pass. An example of this mechanism is found in the receiving cell of a neural synapse. The influx of ions that occurs in response to the opening of these channels induces action potentials, such as those that travel along nerves, by depolarizing the membrane of post-synaptic cells, resulting in the opening of voltage-gated ion channels. This results in amplification of the synapse response between synaptic cells by remodelling the dendritic spines involved in the synapse. Intracellular receptors Intracellular receptors, such as and cytoplasm , are soluble proteins localized within their respective areas. The typical ligands for nuclear receptors are non-polar hormones like the steroid hormones testosterone and progesterone and derivatives of vitamins A and D. To initiate signal transduction, the ligand must pass through the plasma membrane by passive diffusion. On binding with the receptor, the ligands pass through the nuclear membrane into the cell nucleus , altering gene expression. Activated nuclear receptors attach to the DNA at receptor-specific hormone-responsive element HRE sequences, located in the promoter region of the genes activated by the hormone-receptor complex. Due to their enabling gene transcription, they are alternatively called inductors of gene expression. All hormones that act by regulation of gene expression have two consequences in their mechanism of action; their effects are produced after a characteristically long period of time and their effects persist for another long period of time, even after their concentration has been reduced to zero, due to a relatively slow turnover of most enzymes and proteins that would either deactivate or terminate ligand binding onto the receptor. Nucleic receptors have DNA-binding domains containing and a ligand-binding domain; the zinc fingers stabilize DNA binding by holding its phosphate backbone. DNA sequences that match the receptor are usually hexameric repeats of any kind; the sequences are similar but their orientation and distance differentiate them. The ligand-binding domain is additionally responsible for protein dimer of nucleic receptors prior to binding and providing structures for transactivation used for communication with the translational apparatus. In the absence of steroids, they associate in an aporeceptor complex containing chaperone or heatshock proteins HSPs. The HSPs are necessary to activate the receptor by assisting the protein to protein folding in a way such that the signal peptide enabling its passage into the nucleus is accessible. Steroid receptors, on the other hand, may be repressive on gene expression when their transactivation domain is hidden. Receptor activity can be enhanced by phosphorylation of serine residues at their N-terminal as a result of another signal transduction pathway, a process called crosstalk. Retinoic acid receptors are another subset of nuclear receptors. They can be activated by an endocrine-synthesized ligand that entered the cell by

diffusion, a ligand synthesised from a precursor like retinol brought to the cell through the bloodstream or a completely intracellularly synthesised ligand like prostaglandin. These receptors are located in the nucleus and are not accompanied by HSPs. They repress their gene by binding to their specific DNA sequence when no ligand binds to them, and vice versa. Certain intracellular receptors of the immune system are cytoplasmic receptors; recently identified NOD-like receptors NLRs reside in the cytoplasm of some eukaryotic cells and interact with ligands using a leucine-rich repeat LRR motif similar to TLRs. Second messengers are the substances that enter the cytoplasm and act within the cell to trigger a response. In essence, second messengers serve as chemical relays from the plasma membrane to the cytoplasm, thus carrying out intracellular signal transduction. Calcium The release of calcium ions from the endoplasmic reticulum into the cytosol results in its binding to signaling proteins that are then activated; it is then sequestered in the smooth endoplasmic reticulum and the mitochondria. The nature of calcium in the cytosol means that it is active for only a very short time, meaning its free state concentration is very low and is mostly bound to organelle molecules like calreticulin when inactive. Calcium is used in many processes including muscle contraction, neurotransmitter release from nerve endings, and cell migration. The three main pathways that lead to its activation are GPCR pathways, RTK pathways, and gated ion channels; it regulates proteins either directly or by binding to an enzyme.

Chapter 2 : Wiki: Signal transduction - upcScavenger

In Receptor Signal Transduction Protocols, a diverse array of meth- ologies employed to interrogate ligand--receptor and receptor-effector int- actions are described by authors who have devised and successfully applied them.

Extracellular receptors[edit] Extracellular receptors are integral transmembrane proteins and make up most receptors. They span the plasma membrane of the cell, with one part of the receptor on the outside of the cell and the other on the inside. Signal transduction occurs as a result of a ligand binding to the outside region of the receptor the ligand does not pass through the membrane. Ligand-receptor binding induces a change in the conformation of the inside part of the receptor, a process sometimes called "receptor activation". Often such enzymes are covalently linked to the receptor. Some of them create second messengers such as cyclic AMP and IP3 , the latter controlling the release of intracellular calcium stores into the cytoplasm. Other activated proteins interact with adaptor proteins that facilitate signaling protein interactions and coordination of signaling complexes necessary to respond to a particular stimulus. Enzymes and adaptor proteins are both responsive to various second messenger molecules. Many adaptor proteins and enzymes activated as part of signal transduction possess specialized protein domains that bind to specific secondary messenger molecules. For example, calcium ions bind to the EF hand domains of calmodulin , allowing it to bind and activate calmodulin-dependent kinase. PIP3 and other phosphoinositides do the same thing to the Pleckstrin homology domains of proteins such as the kinase protein AKT. G proteinâ€"coupled receptors[edit] Main article: G proteinâ€"coupled receptor G proteinâ€"coupled receptors GPCRs are a family of integral transmembrane proteins that possess seven transmembrane domains and are linked to a heterotrimeric G protein. With nearly members, this is the largest family of membrane proteins and receptors in mammals. Counting all animal species, they add up to over The dissociation exposes sites on the subunits that can interact with other molecules. A study was conducted where a point mutation was inserted into the gene encoding the chemokine receptor CXCR2; mutated cells underwent a malignant transformation due to the expression of CXCR2 in an active conformation despite the absence of chemokine-binding. This meant that chemokine receptors can contribute to cancer development. The interaction between the cytoplasmic domains stimulates the auto phosphorylation of tyrosine residues within the intracellular kinase domains of the RTKs, causing conformational changes. The process of signal transduction involves around known protein kinases and pseudokinases , encoded by the human kinome [33] [34] As is the case with GPCRs, proteins that bind GTP play a major role in signal transduction from the activated RTK into the cell. In this case, the G proteins are members of the Ras , Rho , and Raf families, referred to collectively as small G proteins. They act as molecular switches usually tethered to membranes by isoprenyl groups linked to their carboxyl ends. Upon activation, they assign proteins to specific membrane subdomains where they participate in signaling. The mutation of certain RTK genes, as with that of GPCRs, can result in the expression of receptors that exist in a constitutively activated state; such mutated genes may act as oncogenes. Integrin An overview of integrin-mediated signal transduction, adapted from Hehlgens et al. Integrins lack kinase activity; hence, integrin-mediated signal transduction is achieved through a variety of intracellular protein kinases and adaptor molecules, the main coordinator being integrin-linked kinase. Important differences exist between integrin-signaling in circulating blood cells and non-circulating cells such as epithelial cells ; integrins of circulating cells are normally inactive. For example, cell membrane integrins on circulating leukocytes are maintained in an inactive state to avoid epithelial cell attachment; they are activated only in response to stimuli such as those received at the site of an inflammatory response. In a similar manner, integrins at the cell membrane of circulating platelets are normally kept inactive to avoid thrombosis. Epithelial cells which are non-circulating normally have active integrins at their cell membrane, helping maintain their stable adhesion to underlying stromal cells that provide signals to maintain normal functioning. In the experimental model plant Arabidopsis thaliana , one of the integrin-linked kinase genes, ILK1, has been shown to be a critical element in the plant immune response to signal molecules from bacterial pathogens and plant sensitivity to salt and osmotic stress. Toll-like receptor When activated, toll-like receptors TLRs take adapter molecules within

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lipids residing in cellular membranes; enzymes stimulated by activated receptors activate the lipids by modifying them. Examples include diacylglycerol and ceramide , the former required for the activation of protein kinase C. Nitric oxide[edit] Nitric oxide NO acts as a second messenger because it is a free radical that can diffuse through the plasma membrane and affect nearby cells. It is synthesised from arginine and oxygen by the NO synthase and works through activation of soluble guanylyl cyclase , which when activated produces another second messenger, cGMP. NO can also act through covalent modification of proteins or their metal co-factors; some have a redox mechanism and are reversible. It is toxic in high concentrations and causes damage during stroke , but is the cause of many other functions like relaxation of blood vessels, apoptosis , and penile erections. Redox signaling[edit] In addition to nitric oxide, other electronically activated species are also signal-transducing agents in a process called redox signaling. Examples include superoxide , hydrogen peroxide , carbon monoxide , and hydrogen sulfide. Redox signaling also includes active modulation of electronic flows in semiconductive biological macromolecules. Gene activation leads to further cellular effects, since the products of responding genes include instigators of activation; transcription factors produced as a result of a signal transduction cascade can activate even more genes. Hence, an initial stimulus can trigger the expression of a large number of genes, leading to physiological events like the increased uptake of glucose from the blood stream [50] and the migration of neutrophils to sites of infection. The set of genes and their activation order to certain stimuli is referred to as a genetic program. Such requirements for extracellular stimulation are necessary for controlling cell behavior in unicellular and multicellular organisms; signal transduction pathways are perceived to be so central to biological processes that a large number of diseases are attributed to their disregulation. Three basic signals determine cellular growth: Stimulatory growth factors Transcription dependent response For example, steroids act directly as transcription factor gives slow response, as transcription factor must bind DNA, which needs to be transcribed. Major pathways[edit] Following are some major signaling pathways, demonstrating how ligands binding to their receptors can affect second messengers and eventually result in altered cellular responses. A pathway that couples intracellular responses to the binding of growth factors to cell surface receptors. This pathway is very complex and includes many protein components. DAG remains bound to the membrane, and IP3 is released as a soluble structure into the cytosol. IP3 then diffuses through the cytosol to bind to IP3 receptors , particular calcium channels in the endoplasmic reticulum ER. These channels are specific to calcium and allow the passage of only calcium to move through. This causes the cytosolic concentration of Calcium to increase, causing a cascade of intracellular changes and activity. End-effects include taste, manic depression, tumor promotion, etc. The earliest notion of signal transduction can be traced back to , when Claude Bernard proposed that ductless glands such as the spleen , the thyroid and adrenal glands , were responsible for the release of "internal secretions" with physiological effects. The discovery of nerve growth factor by Rita Levi-Montalcini in , and epidermal growth factor by Stanley Cohen in , led to more detailed insights into the molecular basis of cell signaling, in particular growth factors. Thus, he deduced that the G-protein is a transducer that accepts glucagon molecules and affects the cell. Thus, the characterization of RTKs and GPCRs led to the formulation of the concept of "signal transduction", a word first used in

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In Receptor Signal Transduction Protocols, a diverse array of method- ologies employed to interrogate ligand--receptor and receptor-effector inter- actions are described by authors who have devised and successfully applied.

Chapter 4 : Receptor Transduction Mechanisms

[Publisher-supplied data] As our understanding of G protein-coupled receptor (GPCR) signal transduction continues to grow, we cannot help but be struck by the emerging complexity and the ability of this receptor superfamily to continually surprise us as new facets are discovered.

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Chapter 5 : Signal transduction - Wikipedia

Receptor signal transduction protocols is an experimental aid to anyone who is engaged in ligand-receptor and receptor-effector research. This book comprises many protocols written by those who have successfully developed or applied them to study cellular signal transduction.

Chapter 6 : Receptor signal transduction protocols (eBook,) [blog.quintoapp.com]

Receptor Signal Transduction Protocols: Third Edition by Gary B. Willars As our understanding of G protein-coupled receptor (GPCR) signal transduction continues to grow, we cannot help but be struck by the emerging complexity and the ability of this receptor superfamily to continually surprise us as new facets are discovered.

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In this second edition of a widely appreciated work, Receptor Signal Transduction Protocols, a panel of internationally recognized investigators presents their best methods for studying G-protein-coupled receptors (GPCRs) and events immediately downstream of their activation.

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