SIGNAL TRANSDUCTION IN CANCER pdf

1: Signal Transduction | CancerIndex

Cancer is driven by genetic and epigenetic alterations that allow cells to overproliferate and escape mechanisms that normally control their survival and migration. Many of these alterations map to signaling pathways that control cell growth and division, cell death, cell fate, and cell motility.

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 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[edit] Main article: Ligand-gated ion channel 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 receptor Intracellular receptors, such as nuclear receptors and cytoplasmic receptors , 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 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 zinc fingers 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 dimerization of nucleic receptors prior to binding and providing structures for transactivation used for communication with the translational apparatus. Steroid receptors are a subclass of nuclear receptors located primarily within the cytosol. 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 fold in a way such that the signal sequence 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[edit] 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 [47] 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. Lipid messengers[edit] Lipophilic second messenger molecules are derived from 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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2: Signal Transduction Modulators for Cancer Therapy: From Promise to Practice?

In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel.

W H Freeman ; Search term Section Cancer, a set of diseases characterized by uncontrolled or inappropriate cell growth, is strongly associated with defects in signal-transduction proteins. Indeed, the study of cancer, particularly cancer caused by certain viruses, has contributed greatly to our understanding of signal-transduction proteins and pathways. For example, Rous sarcoma virus is a retrovirus that causes sarcoma a cancer of tissues of mesodermal origin such as muscle or connective tissue in chickens. In addition to the genes necessary for viral replication, this virus carries a gene termed v-src. The v-src gene is an oncogene; it leads to the transformation of susceptible cell types. The protein encoded by v-src is a protein tyrosine kinase that includes SH2 and SH3 domains Figure Indeed, the names of these domains derive from the fact that they are Src homology domains. The v-Src protein is similar in amino acid sequence to a protein normally found in chicken muscle cells referred to as c-Src for cellular Src. The c-src gene does not induce cell transformation and is termed a proto-oncogene. The protein that it encodes is a signal-transduction protein that regulates cell growth. A Cellular Src includes an SH3 domain, an SH2 domain, a protein kinase domain, and a carboxyl-terminal tail that includes a key tyrosine residue. B Structure of c-Src in an inactivated form with the key tyrosine residue phosphorylated. An examination of the structure of c-Src in an inactive conformation reveals an intricate relation between the three major domains. The SH3 domain lies nearest the amino terminus, followed by the SH2 domain and then the kinase domain. There is also an extended carboxyl-terminal stretch that includes a phosphotyrosine residue. The phosphotyrosine residue is bound within the SH2 domain, whereas the linker between the SH2 domain and the kinase domain is bound by the SH3 domain. These interactions hold the kinase domain in an inactive conformation. The Src protein in this form can be activated by three distinct processes Figure Thus, Src responds to the presence of one of a set of distinct signals. Why does it have such a different biological activity? The C -terminal 19 amino acids of c-Src are replaced by a completely different stretch of 11 amino acids, and this region lacks the key tyrosine residue that is phosphorylated in inactive c-Src. Since the discovery of Src, many other mutated protein kinases have been identified as oncogenes. Inactive c-Src can be activated by one of at least three distinct pathways: How did the Rous sarcoma virus acquire the mutated version of src? In an infection, a viral genome may pick up a gene from its host in such a way that the region encoding the last few amino acids is missing. Such a modified gene may have given the Rous sarcoma virus a selective advantage because it will have favored viral growth when introduced with the virus into a host cell. Impaired GTPase activity in a regulatory protein also can lead to cancer. Indeed, ras is one of the genes most commonly mutated in human tumors. The most common mutations in tumors lead to a loss of the ability to hydrolyze GTP. Protein Kinase Inhibitors May Be Effective Anticancer Drugs The widespread occurrence of over active protein kinases in cancer cells suggests that molecules that inhibit these enzymes might act as antitumor agents. Recent results have dramatically supported this concept. The translocation of genetic material between chromosomes 9 and 22 causes the c-abl gene, which encodes a tyrosine kinase, to be inserted into the bcr gene on chromosome The result is the production of a fusion protein called Bcr-Abl that consists primarily of sequences for the c-Abl kinase. However, the bcr-abl gene is not regulated appropriately; it is expressed at higher levels than the gene encoding the normal c-Abl kinase. In addition, the Bcr-Abl protein may have regulatory properties that are subtly different from those of the c-Abl kinase itself. Thus, leukemia cells express a unique target for chemotherapy. This approach to cancer chemotherapy is fundamentally distinct from most approaches, which target cancer cells solely on the basis of their rapid growth, leading to side effects because normal rapidly growing cells also are affected. Thus, our understanding of signal-transduction pathways is leading to conceptually new disease treatments. In chronic myologenous leukemia, parts of chromosomes 9 and 22 are reciprocally exchanged, causing the bcr and abl genes to fuse. The protein kinase encoded by the bcr-abl gene

is expressed at higher levels more Let us first consider the mechanism of action of the cholera toxin, secreted by the intestinal bacterium Vibrio cholera. Cholera is an acute diarrheal disease that can be life threatening. It causes voluminous secretion of electrolytes and fluids from the intestines of infected persons. The cholera toxin, choleragen, is a protein composed of two functional unitsâ€”a B subunit that binds to GM1 gangliosides of the intestinal epithelium and a catalytic A subunit that enters the cell. The active G protein, in turn, continuously activates protein kinase A. The net result of the phosphorylation of these channels is an excessive loss of NaCl and the loss of large amounts of water into the intestine. Patients suffering from cholera for 4 to 6 days may pass as much as twice their body weight in fluid. Treatment consists of rehydration with a glucose-electrolyte solution. Whereas cholera is a result of a G protein trapped in the active conformation, causing the signal-transduction pathway to be perpetually stimulated, pertussis, or whooping cough, is a result of the opposite situation. Pertussis toxin is secreted by Bordetella pertussis, the bacterium responsible for whooping cough. Cholera and pertussis are but two examples of diseases caused by defects in G proteins. In light of the fact that G proteins relay signals for more than receptors, it is likely that this list will continue to grow. Diseases of heterotrimeric G proteins. By agreement with the publisher, this book is accessible by the search feature, but cannot be browsed.

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3: Signal Events: Cell Signal Transduction and Its Inhibition in Cancer

Signal Transduction and Cancer The Postdoctoral Training Program in Signal Transduction and Cancer enables four postdoctoral fellows per year to receive state-of-the-art training in signal transduction pathways and the role of aberrant signaling pathways in human cancer.

Receptor tyrosine kinases Cancer cells receive signals from their environment, stimulating them to grow and to proliferate. These signals are carried by autocrine, paracrine, and endocrine growth factors that activate surface receptors on the outside of cells. To translate activation of a membrane-bound receptor into a biological response, the signal generated by receptor activation needs to be carried to the nucleus to trigger protein synthesis. This is achieved by the activation of a cascade of intracellular biochemical reactions, the so-called signal transduction pathways. In cancer cells, elements of signal transduction pathways are often mutated or overexpressed compared with normal cells. Oncogenic gene mutations frequently lead to constitutive activation of signal transduction elements, such as growth factor receptor tyrosine kinases, mimicking a situation of continuous activation of the receptor, even in the absence of the relevant growth factor. Also, more downstream signal transduction elements may be mutated or overexpressed, contributing to the malignant phenotype. The elucidation of signal transduction pathways in cancer cells, both at the proteomic and the genomic levels, has fueled the design of drug molecules intended to act at specific proteins of the signal transduction cascade, often referred to as signal transduction modulators STMs. STMs may interfere with signal transduction processes by blocking cell surface receptors, inhibiting growth factor receptor tyrosine kinases, or inhibiting the effects of further downstream genes, such as the mitogen-activated protein kinases. Several STMs are currently in clinical trials; others are still in preclinical research and development. Two anticancer drugs, trastuzumab and imatinib, which can be considered STMs, have already received worldwide regulatory approval in several cancer indications. Thus, the area of signal transduction modulation in cancer therapy has reached a state of maturity warranting a dedicated international scientific meeting. They reviewed various aspects of STMs in experimental cancer therapy including: John Mendelsohn, Director of the M. The focus of his work has been on the epidermal growth factor receptor EGFR and its signaling mechanisms. EGRF is expressed at high levels in about one-third of epithelial cancers. Autocrine activation of the EGFR appears to be critical for tumor growth. Mendelsohn and his group developed a murine antibody, the human: This drug is known as C or cetuximab. Jose Baselga Barcelona, Spain , were reported during the meeting. Baselga could not attend the symposium in Amsterdam for a very good reasonâ€”he was presenting clinical data on ZD gefitinib to the U. ZD and several other small-molecule EGFR inhibitors under development were reviewed in an excellent comprehensive overview by Dr. OSI has a high degree of similarity with ZD in its preclinical profile and is developed clinically much the same way as ZD OSI has shown clinical activity in pretreated NSCLC patients and is currently being evaluated in randomized phase III studies in combination with chemotherapy as first-line treatment. The results of these studies are awaited anxiously, since the results of very similar studies with ZD reportedly have failed in demonstrating a survival benefit for the EGFR tyrosine kinase inhibitor. Both drugs are being evaluated in phase II clinical studies in various tumor types. A prominent feature of the toxicity profile of all these receptor tyrosine kinase inhibitors is skin toxicity in the form of rash and acneic reactions. However, their overall toxicity profiles are relatively mild, allowing their chronic daily administration, also in combination with standard chemotherapy. In his keynote lecture, Dr. Axel Ullrich Martinsried, Germany reviewed the exploitation of genetic alterations in tumor cells as the basis for anticancer drug design and development. This concept was employed successfully in the design of the humanized anti-HER2 monoclonal antibody trastuzumab, the first oncogene-based therapeutic for breast cancer. The developing tumor vasculature has become the target of a range of experimental anticancer agents, many of which are STMs interfering with the process of angiogenesis. The drug is currently being evaluated in phase III trials Dr. Exciting data on a synthetic small-molecule antiangiogenic STM were reported by Dr. SU is an orally active inhibitor of multiple receptor tyrosine kinases. The drug is active against four different tyrosine kinases in the nanomolar concentration range.

Although the results of an ongoing phase I study at Institut Gustave Roussy Villejuif, France were reported in a condensed form, they clearly impressed the audience by reports on a few impressive clinical responses. A later report on the same study, presented at the European Organization for the Research and Treatment of Cancer-National Cancer Institute-American Association for Cancer Research Conference on Molecular Targets and Cancer Therapeutics Frankfurt, November , confirmed the relatively high response rate in this study in patients with advanced cancer. These and many other drug molecules discussed during the symposium illustrate the wealth of the signal transduction machinery as a source of molecular anticancer drug targets. So, to come back to the question posed by the title of this report, the 1st International Symposium on Signal Transduction Modulators has definitely confirmed the promise that signal transduction pathways and STMs hold for the future of cancer therapy. However, the translation of these promises into the reality of superior drugs for use in daily practice may be harder than anticipated when the first STMs received regulatory approval in cancer indications. An important question is whether the lack of efficacy in these pivotal trials was due to failure of the STM concept or failure of the methods employed to test the drug in patients. It cannot be denied that ZD and other STMs in advanced clinical development are being subjected to conventional drug development methodology, which worked for cytotoxic chemotherapy in the past. However, being relatively nontoxic, molecularly targeted agents directed against tumor-specific aberrations, these drugs may require innovative drug development strategies and trial designs in order to reveal their true potential. Elizabeth Eisenhauer of the National Cancer Institute of Canada Clinical Trials Group Kingston, Canada presented an excellent review of the challenges facing those involved in the clinical development of STMs and the lessons already learned from ongoing programs. From the clinical trials of STMs completed or ongoing to date, a number of lessons can be learned: Conventional phase II studies looking at tumor regression in response to single-agent STM administration have been relatively predictive for efficacy in phase III studies. Of the six agents inducing tumor regression in phase II, four have yielded positive results in phase III thus far. Chronic dosing is widely used in ongoing STM drug development programs, but there is no evidence that this is the preferred strategy. Current evidence speaks against the use of STMs in combination with conventional chemotherapy as the only approach for a successful outcome. An alternative strategy that may be considered is to combine different STMs. Little information has been collected thus far on tumor target effects. It is advisable to collect this type of information in future trials as it may teach us, in case a new STM fails in clinical trials, whether the drug was inappropriate and did not affect the tumor target or the selected target was irrelevant for efficacy. Also, little information has been collected on tumor characteristics in terms of target mutation and amplification levels which tumors are more vulnerable or molecular patterns what patterns in tumors lead to efficacy. Study populations in STM clinical development programs have all been patients with recurrent metastatic disease thus far. By putting these agents in the worst possible scenario first, their real impact may have been underestimated so far. Eisenhauer, STMs should not only be tested in advanced disease, but also in the adjuvant setting. Only properly designed drug development programs and clinical trials will be able to provide more definitive answers about the potential of STMs in cancer indications. Also, the selection of STMs as candidates for clinical development may need revision. In view of the complexity of intracellular signaling cascades, highly selective STMs may not be the best clinical candidates. Instead, agents blocking multiple signal transduction pathways simultaneously may be required for meaningful clinical activity Dr. The lively plenary discussion on these methodological and regulatory themes at the end of the Amsterdam symposium, with Dr. Eric Rowinsky San Antonio, TX as an inspiring moderator, made it clear that more questions than answers will be around for the time being. Hopefully, some of these questions will be answered by the time of the next symposium in this series [3].

4: Defects in Signaling Pathways Can Lead to Cancer and Other Diseases - Biochemistry - NCBI Bookshe

The field of signal transduction and cancer is still progressing at a rapid pace. It is encouraging that the translation of this knowledge into the development of potential therapeutics is also continuing to take place.

The most common metabolic alteration in cancer cells is increased glucose uptake and glycolysis. At first glance, this might appear a disadvantage because glycolysis generates less ATP than oxidative phosphorylation; however, it allows cells to redirect carbon skeletons from glycolysis to anabolic reactions, such as the pentose phosphate pathway, which leads to nucleotide synthesis and regulates redox homeostasis. Cancer cells show increased glutamine uptake and glutaminolysis to support oxidative phosphorylation and biosynthesis of proteins, lipids, and nucleic acids. They also up-regulate lipid synthesis by redirecting citrate from the Krebs cycle to fatty acid synthesis. Regulation of glucose transport and hexokinase by Akt promotes glycolysis, leading to generation of nucleotides and amino acids necessary for cell growth Engelman et al. Akt2 regulates glucose transport through multiple mechanisms. Akt2 also regulates transcription, accumulation Barthel et al. Other Akt targets activated by phosphorylation are hexokinase II, whose association with mitochondria is increased Roberts et al. In addition, it induces pyruvate dehydrogenase kinase PDK , which inhibits pyruvate dehydrogenase PDH in the mitochondrion and thereby reduces flux from glycolysis into the Krebs cycle. Another direct target of Akt is ATP-citrate lyase ACL , an enzyme that converts citric acid to acetyl-CoA, which is required for fatty acid, cholesterol, and isoprenoid synthesis. Another family of Akt targets that affect cellular and organismal metabolism is FoxO transcription factors. These are negatively regulated by Akt phosphorylation, which causes their sequestration in the cytoplasm by proteins. Programs regulated by FoxO transcription factors that increase the cellular capacity for oxidative metabolism are thus shut off by active Akt. Ras-ERK signaling exerts many of its effects on metabolism via Myc. Myc regulates glucose uptake, glycolysis, and the pentose phosphate pathway Ying et al. It also induces enzymes involved in nucleotide and amino acid synthesis. The glycolytic enzyme pyruvate kinase is of particular interest in cancer cells. Although glycolysis rates are usually much higher than in noncancer cells, most cancer cells produce an alternative splice form of pyruvate kinase PKM2 that is less active than the enzyme PKM1 found in most terminally differentiated cells Vander Heiden et al. Cancer cells can thus redirect the flux of glycolytic intermediates into anabolic pathways for ribose, serine, and glycine production or production of NADPH and glutathione needed to combat oxidative stress. PKM2 can also enter the nucleus and play a role in gene expression Luo et al. However, deletion of PKM2 accelerates rather than impairs breast tumor formation, which indicates that it is the ability to turn off PKM2 activity that is most critical for tumor growth Israelsen et al. Other tumor suppressors also control cell metabolism, however. It also stimulates expression of SCO2, which is required for assembly of cytochrome c oxidase and promotes oxidative phosphorylation. Loss of p53 may therefore contribute to the glycolytic phenotype of cancer cells. Loss of p53 leads to increased levels of ROS and oxidative damage. Similarly, loss of the tumor suppressor LKB1 can lead to metabolic alterations. Activators of AMPK, such as metformin, are currently being used in diabetes and cancer therapy. Finally, mutations associated with cancer can lead to the elevation of metabolites uniquely elevated in cancer cells Kaelin and McKnight For example, mutations in IDH1 and IDH2 result in the production of 2-hydroxyglutarate 2HG , a metabolite not present at significant levels in normal cells. This leads to epigenetic dysregulation that can drive tumorigenesis. Other oncometabolites may include succinate and fumarate, whose levels can increase because of mutations in succinate dehydrogenase and fumarate hydratase. Both can inhibit the activity of prolyl hydroxylases that control HIF levels, leading to induction of PDK and the other glycolytic enzymes mentioned above. This is usually accompanied by changes in adhesion, cell polarity, cytoskeletal dynamics, and morphology. Migration is regulated by growth factors, chemokines, adhesion receptors, and other stimuli Vicente-Manzanares and Horwitz ; Devreotes and Horwitz , many of which are targets for dysregulated signaling in cancer. As with other processes regulated by oncoprotein signaling, the outcome of alterations in these pathways is highly context and isoform dependent. For example, Akt1 specifically suppresses migration in many contexts through inhibition of ERK, the transcription factor

NFAT, TSC2, or phosphopalladin-induced actin bundling, whereas Akt2 promotes migration through regulation of integrin expression and effects on the epithelialâ€”mesenchymal transition EMT see below; Chin and Toker Similarly, some isoforms of ERK target RSK to promote cell motility and invasion by altering transcription and integrin activity, whereas others impair cell motility and invasion through effects on the actin cytoskeleton Sulzmaier and Ramos Polarity proteins are critical regulators of tissue architecture. Three protein complexes play central roles in controlling polarity: Scribble, Par, and Crumbs complexes. Through multiple interactions, components of these pathways control signaling pathways that regulate cell polarity and tissue organization. Loss of Scribble enhances invasion stimulated by H-Ras Shaikh et al. Similarly, loss of the polarity protein Par3 leads to increased invasion in several tumor models Iden et al. Loss of cell polarity is often coupled to cell proliferation because the loss of cell adhesion molecules relieves contact inhibition. One example is the cytoskeletal protein merlin also known as neurofibromin 2 , a tumor suppressor that regulates the Hippo pathway and whose loss is well known to cause increased cell proliferation. Polarity signaling is also coupled to metabolism. Some subpopulations of epithelial cells in tumors, particularly those at tumor margins, undergo at least a partial EMT. EMTs are associated with various normal physiological processesâ€”for example, wound healing, gastrulation, and branching morphogenesis Birchmeier and Birchmeier Akt also phosphorylates and inactivates GSK3, which normally promotes ubiquitin-dependent degradation of Snail Doble and Woodgett ; Akt activation will therefore increase Snail stability, further promoting EMT. These include up-regulation of specific integrin heterodimers e. Dysregulation of both Ras-ERK and PI3K-Akt signaling thus has the potential to play an important role in cancer progression by promoting adoption of an invasive phenotype. Finally, it is important to note that EMT is not essential for invasion and tumor cell dissemination. Tumor cells can migrate as epithelial sheets within tissues as occurs during wound healing or invade by pushing through tissue borders e. The simplest examples of cancers with dysregulated development are perhaps hematopoietic malignancies in which a differentiation program is stalled before the cells reach their nonproliferative differentiated state. For example, in acute promyelocytic leukemia, a form of acute myelocytic leukemia, myeloblasts fail to differentiate into mature white blood cells because of a translocation that leads to synthesis of a fusion protein combining sequences from a protein called PML and the retinoic acid receptor RAR. Subsequently, additional mutations cause overproliferation of the undifferentiated myeloblasts. Inappropriate Wnt signaling has a similar effect in colon cancer. Further mutations can then drive neoplasia. Developmental signals can also drive cancer progression because they stimulate inappropriate cell proliferation see above. Mutations that activate Notch, for example, contribute to acute lymphocytic leukemia because Notch signaling Kopan can stimulate the cell cycle and also inhibits apoptosis in T cells. Importantly, Notch functions as a tumor suppressor in some other tissues. In others, the concentration of Notch dictates its growth suppressive or stimulatory effects Mazzone et al. Activation of the Hedgehog signaling pathway see Ingham by mutations in the Patched receptor occurs in basal cell carcinomas and medulloblastomas and again drives cell proliferation. Hedgehog signaling is also hyperactivated via autocrine loops in many tumors that affect tissues derived from the embryonic gut. The context is important, however; signaling by FGF has the potential to affect cell proliferation, apoptosis, and migration see above , as well as angiogenesis see below , but it can also have tumor suppressive effects, maintaining cells in a differentiated, nonproliferative state. For example, whereas FGFR2 is up-regulated in gastric cancers, its expression is reduced in bladder and prostate cancer Turner and Grose Aneuploidy and large-scale DNA rearrangements are frequently observed, and many cancers display elevated mutation rates. Ordinarily, a variety of cellular enzymes repair DNA damage, and checkpoint signaling ensures that DNA replication and cytokinesis are arrested in dividing cells until potentially damaging errors are corrected. Alternatively, checkpoint signaling can induce senescence or apoptosis so that affected cells do not pass on these errors. If the damage cannot be repaired and checkpoint signaling persists, p21 and p53 will induce cells to senesce or undergo apoptosis see above. Clearly, mutation or epigenetic silencing of these tumor suppressors or upstream kinases can inactivate checkpoint signaling, allowing DNA damage to persist and potentially fuel cancer progression. The mitotic checkpoint also known as the spindle assembly checkpoint ensures that when a cell divides each daughter receives a full complement of chromosomes. A complex containing the proteins Bub1,

Bub3, and Mad monitors attachment of chromosomes to the mitotic spindle, relaying checkpoint signals that block chromosome segregation and subsequent cytokinesis. Once paired, sister chromatids are all attached to microtubules emanating from opposite poles, the signal is switched off, and cells can move from metaphase into anaphase and, ultimately, cytokinesis can proceed Rhind and Russell Akt has been implicated in multiple aspects of DNA damage responses and genome instability Xu et al. As discussed above, dysregulation of the PI3K-Akt pathway suppresses apoptosis through many effectors, thus promoting survival of cells with DNA damage. Because Ras-ERK signaling also inhibits apoptosis, it too could promote survival of damaged cells. Hyperactivation of Ras-ERK signaling has been shown to lead to genomic instability, although the molecular mechanism is unclear Saavedra et al. Akt therefore modifies both the response to and repair of genotoxic damage in complex ways that are likely to have important consequences for the therapy of tumors showing deregulation of the PI3K-Akt pathway. Myc overexpression can induce genomic instability. In mammalian cells and Drosophila, overexpression of Myc increases the frequency of chromosomal rearrangements Prochownik and Li ; Greer et al. Multiple mechanisms have been associated with such genomic rearrangements, including ROS-induced DSBs, suppression of checkpoints that prevent replication of damaged DNA, and telomere clustering. However, cancer progression at least in solid tumors also depends on the ECM, blood vessels, immune cells, and noncancerous cells such as fibroblasts in the tumor microenvironment, all of which communicate with cancer cells by subverted signaling mechanisms Fig. Dissecting the roles of individual signaling pathways in these ecosystems is complex because it is difficult to distinguish cell-autonomous and non-cell-autonomous activities.

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Signal transduction. Signal transduction is the process by which the signal provided by the first messenger (i.e., the growth factor or other signaling molecule) is translated into an intracellular response.

Cells were treated with different concentrations of hyperforin for different periods of time. Effects of hyperforin on cell viability, apoptosis signaling, and expression of anti-apoptotic and proliferative proteins [cellular FLICE-like inhibitory protein c-FLIP , X-linked inhibitor of apoptosis protein XIAP , myeloid cell leukemia 1 MCL1 , and cyclin-D1] were investigated by 3- 4,5-dimethylthiazolyl -2,5-diphenyltetrazolium bromide assay, flow cytometry, and western blotting. Hyperforin significantly inhibited cell viability and expression of anti-apoptotic and proliferative proteins. We also found that hyperforin significantly induced accumulation of cells in sub-G1 phase, loss of mitochondrial membrane potential, and increased levels of active caspase-3, and caspase Taken together, our findings indicate that hyperforin triggers inhibition of tumor cell growth by inducing intrinsic and extrinsic apoptotic pathways in HCC SK-Hep1 cells. Castration-resistant prostate cancer CRPC -related deaths are increasing worldwide. Therefore, clarification of the mechanisms of hormone-related tumor progression and resistance to anti-androgen drugs is useful in order to develop strategies for appropriate treatment of CRPC. Galectin-3 has been shown to be correlated with tumor progression in a variety of cancer types through the regulation of tumor proliferation, angiogenesis, and apoptosis. We examined tumor cell invasion and migration using the xCELLigence system. Cells were treated for 24 h with or without dihydrotestosterone alone or combined with MDV and bicalutamide; gene profile was then analyzed by microarray analysis and mRNA expression was confirmed by quantitative real-time polymerase chain reaction qRT-PCR. We evaluated tumor growth using spheroids and xenograft tumor growth in a mouse model. Galectin-3 also enhanced anchorage-independent growth and xenograft tumor growth even after castration. Importantly, galectin-3 greatly enhanced transcriptional activity of the androgen receptor AR , especially on treatment with dihydrotestosterone. These AR-target genes were not fully suppressed by anti-androgen drugs such as bicalutamide or MDV Galectin-3 significantly inhibited the effect induced by anti-androgen drugs MDV and bicalutamide, suggesting that galectin-3 may be involved in resistance to anti-androgen drug through enhancement of transcriptional activity of AR and expression of AR-related genes. These results suggest that galectin-3 is a potential target molecule for future treatment of anti-androgen drug-resistant prostate cancer. Cholangiocarcinoma CCA is an aggressive cancer for which standard treatments are still ineffective. This study demonstrated the antiproliferative and anti-metastatic activity of metformin, an anti-diabetic drug, in CCA cells. The underlying mechanisms were identified using western blotting and immunocytofluorescence. Metformin significantly suppressed proliferation of CCA cells in a dose- and time-dependent manner, regardless of glucose present in the medium. Metformin is a potent antiproliferative and anti-metastatic agent against human CCA cells. These findings encourage the repurposing of metformin in clinical trials to improve CCA treatment.

SIGNAL TRANSDUCTION IN CANCER pdf

6: Cancer / Signal Transduction | Biochemistry & Molecular Biology

Antibodies to ErbB receptors in clinical development Therapeutic Development Considerations As described above, several factors are being considered in the development of targeted therapeutic agents for cancer. For example, some compounds in development target multiple ErbB family receptors in an attempt to circumvent the redundancies inherent to this system. However, the relative merits of irreversible binding to ErbB are unknown and may depend on the half-life of the agent. The relatively long half-lives of nonalkylating or reversible tyrosine kinase inhibitors may result in greater benefits than those of irreversible compounds with shorter half-lives. Additionally, the average receptor turnover time of 24â€”36 hours may also negate the benefits of irreversible compounds. The magnitude and quality of the downstream response to targeted therapies may be determined by a variety of factors that need to be identified in tumors. Thus, another important consideration in the development of targeted therapeutic agents is tumor markers; that is, the subcellular determinants of the ErbB inhibitory response, such as phosphorylated p -ErbB-1, p-Erk, and p-Akt. Following treatment with a particular compound, immunohistochemical staining of receptors, phosphorylated aspects of receptors, and ST elements has permitted seimiquantitation of these determinants [35]. Clearly, there are many different approaches to developing targeted therapies, and the relative merits of each of these approaches have yet to be determined. Prospective profiling of tumor types in large studies would help researchers to understand the complexities of the systems involved and to determine the links between tumor profiles and responses to treatment. However, this is a considerable enterprise that has yet to be undertaken extensively. Tumor Growth Inhibition and Regression While the predominant favorable effects of the ErbB inhibitors are tumor growth inhibitory in nature, overt tumor regression has occurred with many of these novel treatments, even in some well-developed tumors. It is likely that tumors that are principally driven by aberrations or overexpression of elements of the ErbB ST pathway will demonstrate the most vivid responses i. Additionally, encouraging response rates have been reported preliminarily following the treatment of several types of tumors, such as advanced and previously treated NSCLC and ovarian, head and neck, and brain glioblastoma multiforme carcinomas, with ErbB-targeted therapies [36 â€” 38]. Thus, ErbB-targeted therapies offer clinicians new therapeutic approaches to the treatment of tumors that can lead to tumor regression, tumor growth delay, and symptomatic improvement in some patients. However, the determinants of clinical benefit are not known, which emphasizes the need to prospectively characterize tumors. These kinases are involved in a number of critical regulatory cellular functions concerning cell cycle progression and cell cycle checkpoints that govern cellular responses to DNA damage, repair, and recombination [39]. PI3K plays a central role in cellular proliferation, cell adhesion, catabolism, and apoptosis, and is upregulated in cancer cells [42]. Activation of the PI3K pathway leads to the production of secondary messengers downstream that activate proliferative elements, for example, Akt and p70s6k [8 , 27 , 43]. In turn, these elements initiate a variety of local responses, including polymerization of actin, assembly of signaling complexes, and priming of protein kinase cascades [43]. In particular, phosphorylation of Akt stimulates its catalytic activity, leading to the phosphorylation of a number of other proteins that affect cell growth, cell cycle entry, and cell survival. Thus, inhibition of mTOR could eliminate the transduction of proliferative signals and thereby inhibit tumor growth where aberrant signals or mutations occur. Upon stimulation, mTOR phosphorylates a variety of downstream proteins that augment or activate the translation of proteins that are important in the G1-to-S phase traverse and ribosome biogenesis [8 , 45]. There are other signaling pathways that are activated downstream of PI3K, but the Akt pathway is of primary interest because of its role in inhibiting apoptosis and promoting cell proliferation by affecting the phosphorylation status of cell-survival and apoptosis-induction proteins such as BAD [46]. Upstream abnormalities can also activate mTOR and lead to proliferation. Originally identified as an antifungal agent, it was subsequently found to have potent immunosuppressant properties, leading to its approval for the prophylaxis of organ rejection in patients

receiving renal transplants. More recently, rapamycin has been found to have potent and broad antineoplastic activity as well, and is being developed as a target for mTOR [8 , 47]. Rapamycin forms a functional inhibitory unit by binding with receptor FKB This unit subsequently binds with and inhibits mTOR [8]. Together, these actions effectively inhibit phosphorylation of downstream proteins that ultimately block the translation of the G1 critical proteins necessary for the G1-to-S phase traverse and ribosome biosynthesis [8]. Some cell abnormalities and mutations have a hypersensitivity to rapamycin and its analogs [48]. In particular, aberrations in the PTEN tumor suppressor oncogene, prostate cancer xenograft, and hyperactivated Akt are hypersensitive to the rapamycin analog CCI Wyeth-Ayerst; Collegeville, PA , which is currently in broad clinical evaluations [8]. The PTEN tumor suppressor gene can be inactivated by deletions, mutations, and hypermethylation. Aberrations in PTEN are found in a wide variety of sporadic and inherited neoplasms [48]. However, the frequency of PTEN mutations is comparatively lower in endometrial, breast, bladder, and lung cancers, and in melanomas and lymphomas [48 â€” 50]. Thus, soluble ester analogs were synthesized and evaluated in an effort to overcome these pharmaceutical barriers. Rapamycin esters with improved i. Studies of CCI in vitro and in vivo have demonstrated that a number of human and mouse tumors are sensitive to this compound [8 , 48]. In tissue culture studies, several cancer cell lines, including human prostate, breast, small cell lung carcinoma, glioblastoma, melanoma, and T-cell leukemia, have shown a high sensitivity to CCI Human tumor xenografts treated with CCI also showed significant growth inhibition, although the predominance of tumor growth inhibition, rather than overt tumor regression, advocates that subsequent disease-directed trials should be specifically designed to detect this potential outcome i. Further, several intermittent CCI dosing regimens were shown to be effective in human tumor xenograft studies, which is important in that extended immunosuppression may result from both rapamycin and CCI administered using a continuous-dose schedule and because the immunosuppressive effects of rapamycin analogs have been shown to resolve within 24 hours following treatment [51]. CCI has been evaluated in two phase I studies, in which the agent was administered as a minute i. Those studies were designed to determine the maximum-tolerated dose based on classically defined dose-limiting toxicities. In those studies, the primary toxicities included dermatologic toxicity, myelosuppression, reversible increases in liver function tests, and asymptomatic hypocalcemia. However, the majority of these toxicities were mild to moderate in severity and the maximum-tolerated dose had not yet been determined for CCI administered weekly. In early phase II studies, tumor regression has been consistently observed in patients with breast and renal carcinoma, and a phase III study is under way in patients with renal cell carcinoma [54]. The fact that CCI produced tumor regression at relatively nontoxic doses in these trials suggests that the optimal therapeutic dose of this agent may be lower than the maximum-tolerated dose [53]. Previous Section Next Section Clinical Trial Design Numerous challenges are evident in the clinical development process of ST inhibitors, all of which may make the clinical trial process more difficult both to plan and to execute. These challenges include defining the optimal doses and administration schedules associated with maximal antitumor activities and minimal toxicities, determining long-term toxicity, and incorporating optimal and sound end points into clinical evaluations based on expectations determined in preclinical studies. Phase I and Feasibility Studies The toxicity of traditional, nonspecific cytotoxic agents in rapidly growing tissues is loosely related to antineoplastic activity, and so it can be used as an approximate measure of drug effect. In contrast, selecting an optimal dosage for ST inhibitors in disease-directed studies is much more difficult. Toxic effects may not appear at doses that effectively inhibit ST or may not even be related to target inhibition. While the results of pharmacologic studies may be used to evaluate the comparative activities of the therapeutic agent in patients versus animals, interspecies differences in tissue drug distribution, protein binding, clearance, and metabolism may preclude the direct extrapolation of data from animals to humans, thereby limiting the usefulness of pharmacologic comparisons. The development and validation of assays reflecting relevant drug effects in accessible tissues should smooth the progress of efforts to define optimal dosing regimens of ST inhibitors in phase I trials. Following the appropriate validation to reflect the desired target effect, such assays may aid the selection of dosages with the highest likelihood of achieving maximal target inhibition. In addition to dosage, determining optimal administration routes and schedules for ST inhibitors is of primary importance. Current data suggest

that continuous long-term treatment may be highly effective in achieving maximal and sustained efficacy. However, extended treatment durations may lead to acquired drug resistance, as well as potentially exposing patients to unique toxic effects. Both of these concerns must be addressed when defining optimal dosing schedules for these agents. Notably, any long-term toxicities associated with continuous long-term treatment with ST inhibitors may not be identified using standard preclinical toxicology studies, which primarily focus on highly proliferative tissues. For ST inhibitors, as well as any other rationally designed, target-based therapeutic agents, organs in which the target is highly expressed or tissues that play a role in the function s of those organs will require careful monitoring. Disease-Directed Screening Evaluations In addition to determining safety and pharmacokinetic profiles, one of the goals of phase II screening evaluations is to accurately gauge the potential for a given therapeutic agent to produce relevant clinical efficacy. Historically, the key end point for these studies was objective tumor regression, defined using standard criteria of clinical effect that have been generally validated for nonspecific antineoplastic agents. However, tumor regression does not equate to efficacy or clinical benefit, which can be conferred by achieving end points that reflect tumor growth delay i. Thus, although resource-intensive randomized trials are the only unequivocal method to demonstrate the activity of an agent in terms of time to progression and survival, tumor regression has been widely used as an end point in nonrandomized studies to screen nonspecific cytotoxic agents for potential clinical activity. Of note, imatinib, an RTK inhibitor, was approved by the FDA for the treatment of gastrointestinal stromal tumors GISTs based on the results of a randomized trial in which tumor regression was the primary end point [55 , 56]. However, complete follow-up and submission of mature data on response rate, response duration, and survival, as well as submission of data from subsequent phase III randomized trials were required by the FDA as a condition of the approval [56]. Clinical End Points Challenges involved in designing disease-directed studies of ST inhibitors correlate primarily with the difficulty of defining appropriate end points to evaluate the relative merits of agents that often produce limited or no tumor regression. While many ST inhibitors have been shown to induce regression of experimental tumors [31 , 57 â€” 59], the predominant effect in preclinical studies is tumor growth delay, which still may produce clinical efficacy in terms of greater time to progression and survival, particularly if the agent portends minimal toxicity. Delayed tumor growth can exhibit in at least three discrete circumstances. In the first, treatment does not completely stop tumor growth but decreases growth rate. In this setting, the degree of antiproliferative effect may not be evident to the clinician who cannot objectively measure drug-induced effects on the rate of tumor growth when obvious regression has not been demonstrated. Instead, the clinician may interpret any tumor growth as disease progression or treatment failure, although the decrease in tumor growth rate may result in increased time to tumor progression or overall survival, in addition to a global improvement in quality of life for the patient. In the second circumstance, a more significant antiproliferative effect occurs when the rates of tumor cell proliferation and cell death are equivalent, often interpreted as stable disease. In this setting, the clinician is likely to continue treatment as long as the patient does not demonstrate intolerable adverse effects. Although the results of preclinical studies suggest that these first two circumstances are likely to be the most common following treatment with ST inhibitors, the beneficial effects may not be obvious or unequivocally attributed to the agent in nonrandomized phase II screening studies. This is most likely to occur when the target is a major driver of tumor proliferation. Thus, designing phase II and III disease-directed studies to assess the relevant antitumor activities of ST inhibitors is a daunting task. Although many of these agents may be able to induce tumor regression in animals, tumor growth inhibition may not be the principal therapeutic effect in human cancers where the tumor is not driven by a single primary anomaly but by multiple causative anomalies of the specific target. Therefore, clinical situations that are sufficiently sensitive to detect a relevant magnitude of tumor growth inhibition will need to be incorporated into disease-directed clinical evaluations. Understanding the biology of the target is paramount with regard to selecting tumors that are most apt to be driven by the target in early screening studies. Tumor growth delay as the primary benefit of ST inhibitors offers a new challenge for the selection of appropriate end points for phase II and III studies, specifically because only randomized clinical trials can unequivocally demonstrate such effects on tumor growth. One way of obtaining such a lead is to compare the relative time to tumor

progression in patients receiving single-agent treatment with an ST inhibitor against that resulting from treatment with a relevant standard therapy or supportive care, measured just prior to administration of the experimental agent [60]. For example, in advanced pancreatic cancer, the percentage of patients surviving at least 1 year in exploratory nonrandomized studies may be considered a reasonable end point to gauge whether to proceed with randomized phase III trials. The randomized discontinuation trial has been proposed as a potentially highly efficient method to detect drug effects on time to progression, survival, and symptoms. In this design, all patients receive the study drug but only patients who do not demonstrate tumor progression are randomized to treatment with or without the study drug. On a similar note, the proportion of patients with progressive disease as their best response appears to inversely correlate with the ultimate utility of any specific agent in a given clinical setting, and a maximum acceptable threshold of patients with progressive disease as their best response may be a valuable predictor of the potential usefulness of the agent [61]. Such benchmarks, once validated, may be effective in screening ST inhibitors prior to initiating large, randomized, phase III trials. Finally, for agents that are capable of inducing a low level of tumor regression in preclinical evaluations, large phase II studies may be necessary to detect this low level of activity with sufficient confidence intervals. Additional surrogate end points that may be considered for efficacy in phase II trials include assessment of target inhibition, relevant changes on positron emission scanning PET that reflect decreased cell proliferation, and decrements in tumor markers. While all these potential end points remain intriguing for future trials, only changes on PET scanning have been associated with tumor regression or progression in a randomized clinical trial evaluating the efficacy of imatinib for the treatment of GISTs [55], and none of these surrogate end points have been validated in a wide range of tumor types or in a large population of patients. Thus, the challenge is to successfully integrate these proposed end points as new paradigms for evaluating these novel agents. The primary end points for phase III trials will continue to be based on those reflecting survival. However, the relatively low toxicity of ST inhibitors may allow for more emphasis on other end points related to clinical benefit, such as time to progression, performance status, disease-related symptoms, and quality of life. Further, preclinical data and early clinical results indicate that major tumor regression is unlikely to be the primary effect of ST inhibitors. Because clinical trials are often conducted in patients with advanced disease who require cytoreduction for clinical benefit, reasonable developmental strategies will likely involve evaluations of ST-targeted agents in combination with other therapeutic modalities, particularly because a number of these therapeutic agents have shown synergistic, additive, and supra-additive activities when combined with radiation and a variety of chemotherapeutic agents. Previous Section Next Section Summary Within only a few years, anticancer therapeutic development has moved from almost a standstill, with a paucity of new agents showing potential for major effect, to the rapid development of agents targeted against the inherent basis of cancer. This transition is based largely on the exponential rate of information acquisition regarding the cancer cell, particularly in terms of aberrant growth ST and the microenvironment of the cell. Because the ultimate goal of any signaling pathway is to regulate cell growth and division, much of the investigation into novel anticancer agents has focused on the development of ST inhibitors.

7: Signal Transduction in Cancer

Cell signal transduction therapy seeks to regulate the signaling pathways in cancer cells to make them easier to control or kill. One most effective way to trip up cancer is to use nutrients, phytochemicals (natural plant-derived chemicals), and drugs to suppress overactive signal transduction pathways, or boost under-active pathways, in cancer.

8: Current Signal Transduction Therapy | BenthamScience

Thematic issues are also published to cover selected areas of signal transduction therapy. Coverage of the field includes genomics, proteomics, medicinal chemistry and the relevant diseases involved in signaling e.g. cancer, neurodegenerative and inflammatory diseases.

SIGNAL TRANSDUCTION IN CANCER pdf

9: Signal Transduction Cancer Therapy | Oasis of Hope

Signal transduction is the process by which a chemical or physical signal is transmitted through a cell as a series of molecular events, most commonly protein phosphorylation catalyzed by protein kinases, which ultimately results in a cellular response.

SIGNAL TRANSDUCTION IN CANCER pdf

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