RAS-RAF-MEK-ERK PATHWAY INHIBITORS pdf

1: Background Bread wheat (. by the B genome are the least â€“ Ras-Raf-MEK-ERK pathway

Inhibition of Ras/Raf/MEK/ERK pathway inhibitors in HCC The role played by MEK inhibitors PD, U and ERK1/2 antisense oligonucleotide in the proliferation, apoptosis, cell cycle and tumor occurrence in HCC Hep3B cells and HepG2 cells was studied by Wiesenauer et al (55).

Background[edit] Overall, the extracellular mitogen binds to the membrane receptor. It can now activate MAP3K e. MAPK can now activate a transcription factor, such as Myc. Ras activation[edit] Receptor-linked tyrosine kinases such as the epidermal growth factor receptor EGFR are activated by extracellular ligands , such as epidermal growth factor EGF. The EGFR becomes phosphorylated on tyrosine residues. Docking proteins such as GRB2 contain an SH2 domain that binds to the phosphotyrosine residues of the activated receptor. Ras can then bind GTP and become active. As discussed below, many additional targets for phosphorylation by MAPK were later found, and the protein was renamed "mitogen-activated protein kinase" MAPK. Such series of kinases provide opportunities for feedback regulation and signal amplification. Regulation of translation and transcription[edit] Three of the many proteins that are phosphorylated by MAPK are shown in the Figure. This activates RSK, which, in turn, phosphorylates ribosomal protein S6. MAPK can phosphorylate C-myc. By altering the levels and activities of transcription factors, MAPK leads to altered transcription of genes that are important for the cell cycle. The 22q11, 1q42, and 19p13 genes are associated with schizophrenia , schizoaffective , bipolar , and migraines by affecting the ERK pathway. Regulation of cell cycle entry and proliferation[edit] Role of mitogen signaling in cell cycle progression The ERK pathway plays an important role of integrating external signals from the presence of mitogens such as epidermal growth factor EGF into signaling events promoting cell growth and proliferation in many mammalian cell types. In a simplified model, the presence of mitogens and growth factors trigger the activation of canonical receptor tyrosine kinases such as EGFR leading to their dimerization and subsequent activation of the small GTPase Ras. The phosphorylation of ERK results in an activation of its kinase activity and leads to phosphorylation of its many downstream targets involved in regulation of cell proliferation. In most cells, some form of sustained ERK activity is required for cells to activate genes that induce cell cycle entry and suppress negative regulators of the cell cycle. The first is a result of mitogen stimulation though the ERK leading to the expression of the transcription factor Myc, which is a direct activator of E2F. Finally, these interactions are all reinforced by an additional positive feedback loop by E2F on itself, as its own expression leads to production of the active complex of Cyclin E and CDK2, which further serves to lock in a cells decision to enter S-phase. As a result, when serum concentration is increased in a gradual manner, most mammalian cells respond in a switch-like manner in entering S-phase. This mitogen stimulated, bistable E2F switch is exhibits hysteresis, as cells are inhibited from returning to G1 even after mitogen withdrawal post E2F activation. Furthermore, the pathway has been shown to encode the strength of signaling inputs though frequency modulated pulses of its activity. Furthermore, the dynamics of ERK activation in response to mitogens were found to be relevant for unique downstream responses including timing of S-phase entry in MCF10A cells. The levels of these regulators vary from cell to cell after mitosis and stoichiometry between them strongly influences cell cycle commitment though activation of Cdk2. Chemical perturbations using inhibitors of ERK signaling or inducers p53 signaling in mother cells suggest daughter cells with high levels of p53 protein and low levels of Cyclin D1 transcripts were shown to primarily enter G0 whereas cells with high Cyclin D1 and low levels of p53 are most likely to reenter the cell cycle. These results illustrate a form of encoded molecular memory though the history of mitogen signaling through ERK and stress response though p Protein microarray analysis can be used to detect subtle changes in protein activity in signaling pathways.

RAS-RAF-MEK-ERK PATHWAY INHIBITORS pdf

2: Ras-Raf-MEK-ERK-MAPK pathway

The RAS/RAF/MEK/ERK pathway (also known as the MAPK/ERK pathway) is one of the most important signaling pathways in cancer. It is also one of most thoroughly studied and best understood pathways (Fig. 1).

China Published online on: This is an open access article distributed under the terms of Creative Commons Attribution License. Abstract Hepatocellular carcinoma HCC is the fifth most common tumor worldwide and has a very poor prognosis. Its occurrence has been on the increase in recent years. The median survival time of unresectable or metastasizing HCC patients is only a few months. Existing systemic treatment methods are not effective for advanced HCC patients and a new method of treatment is needed for these patients. It has been established that the HCC occurs in multiple stages, however, the pathogenesis at a molecular level is not clear and many key factors are yet to be determined. Introduction Hepatocellular carcinoma HCC , is the fifth most common tumor worldwide and has a poor prognosis. The estimated incidence of new cases is approximately ,â€”1,, annually, causing , mortalities globally per year 1. Previous studies found four different MAPKs: ERK cascade reaction can be activated by various stimuli, such as receptor tyrosine kinase RTK and G protein-coupled receptors. After activation it can regulate the proliferation, differentiation and apoptosis 5. Various stimuli can activate the corresponding cell surface receptors that, in turn, activates the signal transduction pathway and produce an appropriate biological response 6. Briefly, the process involves: The effects of different subtypes in mediating different pathways are varied. The mutation frequency of different Ras subtypes in human cancers is also different. The mutation frequency of Ki-Ras is higher in most type of cancer while the mutation frequency of N-Ras is higher only in some cancers. Mutation may occur in different positions in B-Raf protein; however the majority of common mutations occur at the residue number , which replaces valine to glutamic acid VE This cascade participates in the regulation of a large variety of processes including apoptosis, cell cycle progression, cell migration, differentiation, metabolism, and proliferation. The mutant-type MEK activation eliminates the cytokine dependence of hematopoietic cells and leads NIH-3T3 to morphological changes The activated EPK can phosphorylate corresponding protein kinases in cytoplasm, cell membrane, and nucleus, thus extending and diversifying the cascade reaction of the signaling pathway. With the exception of ERK, no other kinase was capable of activating various downstream substrates. Previous findings showed that even subtle changes in ERK activation can lead to its regulatory effects By isolating the cells with adriamycin and paclitaxel resistance from the cytokine-dependent FL5. Other studies on the MEK gene-deficient cells showed that the activation of MEK can increase the resistance of cells towards adriamycin fold 9. On the other hand, the sensitivity of deficient cells to adriacin was improved. In breast cancer, activated Raf was able to lead to doxorubicin and paclitaxel resistance by expressing drug-pump Mdr-1 and Bcl-2 anti-apoptotic proteins 9. A study on cytokine dependence of FL5. Thus, ERK inhibitors do not constitute the focus of attention for investigators. To reduce cyclin D1 expression, a higher dose of MEK inhibitors was required. The results obtained from the animal experiments have promoted the clinical trial of MEK inhibitors in cancer treatment. For example, in breast, colon, non-small cell lung and pancreatic cancer, PD CI reached phase II trials, where its antitumor efficacy and safety was assessed. However, PD did not reveal effective antitumor properties in the abovementioned cancers, clinical trials had to be suspended Klein et al 28 carried out a study on the effects of PD by inoculating hepatoma carcinoma cells into nude mice. The results of that study showed that PD inhibited the tumor formation in nude mice but was not significantly effective in tumorigenic mice. When PD was applied to cells and tumor cells for the first time, MEK activation was significantly reduced. However, in the long term, MEK expression was gradually restored to normal levels, indicating that the cells that survived the first round of drug therapy adapted to MEK inhibitors and rapidly lost their high sensitivity. Those results were confirmed by several experiments on tumor cells PD, which is now in phase II clinical trials, was found to exert a strong inhibitory effect on ERK activation Raf inhibitors are in the trial phase Experiments on Raf inhibitor BAY suggested that B-Raf was active in melanoma cells and reducing B-Raf expression had an inhibitory effect on the cell cycle process and improved the cell apoptotic rate Thus, BAY has also been employed in clinical trials. Evidence suggests that tumor stem

cells are present in many tumor cells 30 and although cancer stem cells accounted for only a small part of the tumors 0. The embryonic stem cell proliferation did not require any ERK activation; by contrast, a high level of ERK expression affected the self replication of embryonic stem cells and promoted their differentiation If characteristics of tumor stem cells were similar to those of embryonic stem cells, MEK inhibitors may not be able to remove the tumor but promote tumor recurrence. Secondly, Raf kinase was overexpressed in most HCC cases In several human primary tumors and cell lines we observe active ERK. Oka et al reported that ERK expression in tumor tissues was 1. In breast cancer, ERK expression in tumor tissues was 5- to fold higher than that in para-carcinoma tissues These levels were slightly lower than the level observed in renal carcinoma and breast cancer and were different from the para-carcinoma tissues in renal carcinoma and breast cancer. Para-carcinoma tissues in HCC were accompanied with regeneration and reconstruction resulting from chronic inflammations, such as chronic hepatitis and cirrhosis. For cases with nerve damages, the joint effects of regeneration and inflammation led to increased ERK activity of HCC para-carcinoma tissues Consequently in HCC, even a low level of ERK activity was able to surpass the compensatory mechanism regulation on cell growth and transmit effective signals to downstream. ERK phosphorylation activates a variety of target molecules to promote the development of liver cancer Previous findings showed that ERK was mainly found in the HCC cell nucleus; thus, it was noteworthy to establish the existing relationship between ERK and the gene expression. It was established that ERK, after being activated, entered the nucleus 43 and activated some transcription factors via phosphorylation. The kinase-defective mutated ERK inhibited the expression and transformation of c-Fos ERK also activated c-Jun through phosphorylation Transcription activating factor-1 is able to combine with the transcription activating factor-1 binding site in the upstream promoter region and induce the transcription of multiple genes, including cell cycle protein D1 cyclin D1 Cyclin D1 is required for progression through the G1 phase of the cell cycle and is degraded as the cell enters the S phase Cyclin D1 was found to be excessively expressed in HCC In addition, cell cycle protein D1 is capable of inducing the instability and DNA amplification, resulting in the variation and transformation of cells Cyclin D1 was transcribed and activated through ERK. In the absence of ERK kinase activity, cyclin D1 expression was also inhibited These results indicated that cyclin D1 expression may be mediated by c-Fos expression induced by ERK. Additionally, transcription factor-1 induced the transcription of matrix metalloproteinases MMP. MMP in many malignant tumors either hydrolyzed components of the extracellular matrix or reconstructed extracellular matrix, thereby promoting invasion and metastasis This mechanism may also exist in HCC and result in tumor invasion and metastasis. Ito et al showed that, an increase in tumor size led to an increase in the ERK expression level Hepatocyte growth factor HGF can promote cell growth and inhibit cell proliferation. Their results showed that HepG2 cell proliferation can be inhibited by MEK blocker PD, and the inhibition was concentration-dependent. However, when the PD concentration was increased or decreased, such inhibition was not completely restored. These results showed that the promotion and inhibition of HepG2 cell proliferation required ERK regulation, and these opposite effects were determined by the activation level of ERK. The two MEK inhibitors played an efficient role against cancer by obstructing cell cycle, improving the apoptotic rate and decreasing tumor incidence. Cell growth inhibition was more pronounced compared to HepG2 cells. Results showing that the hepatitis C virus core protein can combine with H-ras and transform myofibroblastic tumors 58 , indicated that viral infection may be involved in the regulation of signal transduction and may be associated with ERK activation in HCC. The results of Sato et al suggested that the hepatitis C virus core protein and envelope glycoprotein E2 can activate ERK pathway Hepatitis C virus infection was a major cause of chronic hepatitis, liver cirrhosis and HCC. However, the exact mechanism of hepatitis C virus action in the occurrence of HCC remains to be determined. Surgical resection versus transplantation for early hepatocellular carcinoma: Involvement of the p38 mitogen-activated protein kinase cascade in hepatocellular carcinoma. Cancer Am Cancer Soc. Phosphorylated ERK is a potential predictor of sensitivity to sorafenib when treating hepatocellular carcinoma: Induction of postmitotic neuroretina cell proliferation by distinct Ras downstream signaling pathways. Rationale and importance to inhibiting these pathways in human health. Ras isoforms vary in their ability to activate Raf-1 and phosphoinositide 3-kinase. B-RAF is a human oncogene. Mutations of the BRAF gene in human cancer. Analysis of BRAF mutation in

primary and metastatic melanoma. Identification of the sites in MAP kinase kinase-1 phosphorylated by p74raf A conditionally- active form of MEK1 results in autocrine tranformation of human and mouse hematopoietic cells. ERK implication in cell cycle regulation. B-raf and insulin synergistically prevent apoptosis and induce cell cycle progression in hematopoietic cells. Blockade of the MAP kinase pathway suppresses growth of colon tumors in vivo. Multicenter phase II study of the oral MEK inhibitor, CI, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. Noninvasive imaging of cell proliferation following mitogenic extracellular kinase inhibition by PD N Engl J Med. Signalling, cell cycle and pluripotency in embryonic stem cells. Targeting RAS signalling pathways in cancer therapy. Over-expression of c-raf-1 proto-oncogene in liver cirrhosis and hepatocellular carcinoma. Constitutive activation of mitogen-activated protein MAP kinases in human renal cell carcinoma.

RAS-RAF-MEK-ERK PATHWAY INHIBITORS pdf

3: The Ras/Raf/MEK/ERK signaling pathway and its role in the occurrence and development of HCC

Ras pathway signaling plays a critical role in cell growth control and is often upregulated in human cancer. The Raf kinases selectively interact with GTP-bound Ras and are important effectors of Ras signaling, functioning as the initiating kinases in the ERK cascade.

 This article has been cited by other articles in PMC. Abstract Hepatocellular carcinoma HCC is the fifth most common tumor worldwide and has a very poor prognosis. Its occurrence has been on the increase in recent years. The median survival time of unresectable or metastasizing HCC patients is only a few months. Existing systemic treatment methods are not effective for advanced HCC patients and a new method of treatment is needed for these patients. It has been established that the HCC occurs in multiple stages, however, the pathogenesis at a molecular level is not clear and many key factors are yet to be determined. Introduction Hepatocellular carcinoma HCC , is the fifth most common tumor worldwide and has a poor prognosis. The estimated incidence of new cases is approximately ,â€”1,, annually, causing , mortalities globally per year 1. Previous studies found four different MAPKs: ERK cascade reaction can be activated by various stimuli, such as receptor tyrosine kinase RTK and G protein-coupled receptors. After activation it can regulate the proliferation, differentiation and apoptosis 5. Various stimuli can activate the corresponding cell surface receptors that, in turn, activates the signal transduction pathway and produce an appropriate biological response 6. Briefly, the process involves: The effects of different subtypes in mediating different pathways are varied. The mutation frequency of different Ras subtypes in human cancers is also different. The mutation frequency of Ki-Ras is higher in most type of cancer while the mutation frequency of N-Ras is higher only in some cancers. Mutation may occur in different positions in B-Raf protein; however the majority of common mutations occur at the residue number , which replaces valine to glutamic acid VE This cascade participates in the regulation of a large variety of processes including apoptosis, cell cycle progression, cell migration, differentiation, metabolism, and proliferation. The mutant-type MEK activation eliminates the cytokine dependence of hematopoietic cells and leads NIH-3T3 to morphological changes The activated EPK can phosphorylate corresponding protein kinases in cytoplasm, cell membrane, and nucleus, thus extending and diversifying the cascade reaction of the signaling pathway. With the exception of ERK, no other kinase was capable of activating various downstream substrates. Previous findings showed that even subtle changes in ERK activation can lead to its regulatory effects By isolating the cells with adriamycin and paclitaxel resistance from the cytokine-dependent FL5. Other studies on the MEK gene-deficient cells showed that the activation of MEK can increase the resistance of cells towards adriamycin fold 9. On the other hand, the sensitivity of deficient cells to adriacin was improved. In breast cancer, activated Raf was able to lead to doxorubicin and paclitaxel resistance by expressing drug-pump Mdr-1 and Bcl-2 anti-apoptotic proteins 9. A study on cytokine dependence of FL5. Thus, ERK inhibitors do not constitute the focus of attention for investigators. To reduce cyclin D1 expression, a higher dose of MEK inhibitors was required. The results obtained from the animal experiments have promoted the clinical trial of MEK inhibitors in cancer treatment. For example, in breast, colon, non-small cell lung and pancreatic cancer, PD CI reached phase II trials, where its antitumor efficacy and safety was assessed. However, PD did not reveal effective antitumor properties in the abovementioned cancers, clinical trials had to be suspended Klein et al 28 carried out a study on the effects of PD by inoculating hepatoma carcinoma cells into nude mice. The results of that study showed that PD inhibited the tumor formation in nude mice but was not significantly effective in tumorigenic mice. When PD was applied to cells and tumor cells for the first time, MEK activation was significantly reduced. However, in the long term, MEK expression was gradually restored to normal levels, indicating that the cells that survived the first round of drug therapy adapted to MEK inhibitors and rapidly lost their high sensitivity. Those results were confirmed by several experiments on tumor cells PD, which is now in phase II clinical

trials, was found to exert a strong inhibitory effect on ERK activation Raf inhibitors are in the trial phase Experiments on Raf inhibitor BAY suggested that B-Raf was active in melanoma cells and reducing B-Raf expression had an inhibitory effect on the cell cycle process and improved the cell apoptotic rate Thus, BAY has also been employed in clinical trials. Evidence suggests that tumor stem cells are present in many tumor cells 30 and although cancer stem cells accounted for only a small part of the tumors 0. The embryonic stem cell proliferation did not require any ERK activation; by contrast, a high level of ERK expression affected the self replication of embryonic stem cells and promoted their differentiation If characteristics of tumor stem cells were similar to those of embryonic stem cells, MEK inhibitors may not be able to remove the tumor but promote tumor recurrence. Secondly, Raf kinase was overexpressed in most HCC cases In several human primary tumors and cell lines we observe active ERK. Oka et al reported that ERK expression in tumor tissues was 1. In breast cancer, ERK expression in tumor tissues was 5- to fold higher than that in para-carcinoma tissues These levels were slightly lower than the level observed in renal carcinoma and breast cancer and were different from the para-carcinoma tissues in renal carcinoma and breast cancer. Para-carcinoma tissues in HCC were accompanied with regeneration and reconstruction resulting from chronic inflammations, such as chronic hepatitis and cirrhosis. For cases with nerve damages, the joint effects of regeneration and inflammation led to increased ERK activity of HCC para-carcinoma tissues Consequently in HCC, even a low level of ERK activity was able to surpass the compensatory mechanism regulation on cell growth and transmit effective signals to downstream. ERK phosphorylation activates a variety of target molecules to promote the development of liver cancer Previous findings showed that ERK was mainly found in the HCC cell nucleus; thus, it was noteworthy to establish the existing relationship between ERK and the gene expression. It was established that ERK, after being activated, entered the nucleus 43 and activated some transcription factors via phosphorylation. The kinase-defective mutated ERK inhibited the expression and transformation of c-Fos ERK also activated c-Jun through phosphorylation Transcription activating factor-1 is able to combine with the transcription activating factor-1 binding site in the upstream promoter region and induce the transcription of multiple genes, including cell cycle protein D1 cyclin D1 Cyclin D1 is required for progression through the G1 phase of the cell cycle and is degraded as the cell enters the S phase Cyclin D1 was found to be excessively expressed in HCC In addition, cell cycle protein D1 is capable of inducing the instability and DNA amplification, resulting in the variation and transformation of cells Cyclin D1 was transcribed and activated through ERK. In the absence of ERK kinase activity, cyclin D1 expression was also inhibited These results indicated that cyclin D1 expression may be mediated by c-Fos expression induced by ERK. Additionally, transcription factor-1 induced the transcription of matrix metalloproteinases MMP. MMP in many malignant tumors either hydrolyzed components of the extracellular matrix or reconstructed extracellular matrix, thereby promoting invasion and metastasis This mechanism may also exist in HCC and result in tumor invasion and metastasis. Ito et al showed that, an increase in tumor size led to an increase in the ERK expression level Hepatocyte growth factor HGF can promote cell growth and inhibit cell proliferation. Their results showed that HepG2 cell proliferation can be inhibited by MEK blocker PD, and the inhibition was concentration-dependent. However, when the PD concentration was increased or decreased, such inhibition was not completely restored. These results showed that the promotion and inhibition of HepG2 cell proliferation required ERK regulation, and these opposite effects were determined by the activation level of ERK. The two MEK inhibitors played an efficient role against cancer by obstructing cell cycle, improving the apoptotic rate and decreasing tumor incidence. Cell growth inhibition was more pronounced compared to HepG2 cells. Results showing that the hepatitis C virus core protein can combine with H-ras and transform myofibroblastic tumors 58 , indicated that viral infection may be involved in the regulation of signal transduction and may be associated with ERK activation in HCC. The results of Sato et al suggested that the hepatitis C virus core protein and envelope glycoprotein E2 can activate ERK pathway Hepatitis C virus infection was a major cause of chronic hepatitis, liver cirrhosis and HCC. However, the exact mechanism of hepatitis C virus action in the occurrence of HCC remains to be determined. Guthle M, Dollinger MM. Surgical resection versus transplantation for early hepatocellular carcinoma: Current and novel therapeutics for hepatocellular carcinoma. Involvement of the p38 mitogen-activated protein kinase cascade in

hepatocellular carcinoma. Cancer Am Cancer Soc. Chung E, Kondo M. Phosphorylated ERK is a potential predictor of sensitivity to sorafenib when treating hepatocellular carcinoma: Induction of postmitotic neuroretina cell proliferation by distinct Ras downstream signaling pathways. Rationale and importance to inhibiting these pathways in human health. Ras isoforms vary in their ability to activate Raf-1 and phosphoinositide 3-kinase. Garnett MJ, Marais R. B-RAF is a human oncogene. Mutations of the BRAF gene in human cancer. Analysis of BRAF mutation in primary and metastatic melanoma. Identification of the sites in MAP kinase kinase-1 phosphorylated by p74raf A conditionally- active form of MEK1 results in autocrine tranformation of human and mouse hematopoietic cells. ERK implication in cell cycle regulation. B-raf and insulin synergistically prevent apoptosis and induce cell cycle progression in hematopoietic cells. Blockade of the MAP kinase pathway suppresses growth of colon tumors in vivo. Multicenter phase II study of the oral MEK inhibitor, CI, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. Noninvasive imaging of cell proliferation following mitogenic extracellular kinase inhibition by PD N Engl J Med.

RAS-RAF-MEK-ERK PATHWAY INHIBITORS pdf

4: MAPK/ERK pathway - Wikipedia

The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway) is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell.

This pathway is conserved trough evolution and transfer information from the environment growth factors, mitogens and antigen receptors, by GPCR activation, by stress and infiammatory stimulus, by UV, FASL activation to the nucleus through a three levels pathway that involves the sequential phosphorylation of three kinases: For these reasons the activation of MAPK pathway is an indicator of a "good state" of the cell because it is involved in pro-proliferation and pro-survival response. Raf kinase signaling RAS GTPases are activated by the majority of growth factor receptors and bind and recruit Raf to the cell membrane upon activation. More than 70 nuclear and non-nuclear effector molecules of the mitogenic cascade have been identified so far. In addition, Raf kinase signaling in a cascade-independent fashion has been described. This includes the activation of the NF-kB transcription factor, the prevention of apoptosis by antagonizing proapoptotic factors such as MST2, the mammalian sterile like kinase, ASK1, the apoptosis signal-regulating kinase1, and BAD, the BCLantagonist of cell death, and finally the positive regulation of cell migration via the Rho effector kinase Rok-a. The regulation of Raf kinase activity is quite complex, far from being fully understood. The key feature involves assembly of the cascade at the membrane from preexisting modules Ras module, Raf module, KSR module. This process is paralleled by an intricate pattern of phosphorylation and dephosphorylation events leading to conformational changes of signaling molecules. The kinetics of this process depends on the presence of individual Raf isoenzymes and on the engagement of various positive and negative feedback loops. Primarily the phosphorylation status and the localization of Raf kinases determine the association with interacting partners, such as chaperones, other kinases, prolyl isomerases, phosphatases, scaffolding proteins and also lipids and vice versa. Within this signaling zoo along the mitogenic cascade, there is still more room for novel players. They are definitely more than just additional signaling proteins and contribute significantly to our understanding how Raf kinase signaling really works. Homo- and heterodimerization of Raf kinases clearly exist, and that heterodimerization can be Ras induced. In addition, it was shown that Raf heterodimerization is regulated by proteins, mitogens and the Mixed-lineage kinase 3 and is also stabilized by MEK inhibition. Role of Raf in Cancer Since its first isolation as a potential cellular oncogene, many studies involving Raf were focused on its role in cancer. These included examining both its direct role in cancer and its involvement in mediating transformation by its upstream effectors, especially Ras and growth factor receptors. Raf Regulation Most of understanding of Raf regulation comes from studies using C-Raf, though several fundamental studies using B-Raf have also provided significant input to view of this complex process. Thus, the N-terminal half of Raf is considered to be a negative regulatory domain which helps in maintaining Raf in an inactive state in the absence of stimulation. The common view is that the catalytic domain of Raf is folded and bound to the N-terminal regulatory domain. This interaction is stabilized by the binding of a dimer at two C-Raf phosphorylated sites, S and S As to the Raf activation process following the interaction with active Ras, the common thinking is that C-Raf undergoes a series of phosphorylation and dephosphorylation events that result in a stably active form. This aspect of Raf regulation turned out to be a highly challenging task to tackle and remains only partially resolved. Conclusions and Future Perspectives Many of the studies on Raf and the entire MAPK pathway have focused on experimental models using acute growth factor activation high concentrations for a short time period. These models do not reflect physiological conditions in the organism, in which acute growth factor exposures are highly rare events. Furthermore, one would expect that these functions would be largely cell type and organ specific. In this regard, even our understanding of the role of Raf and the MAPK pathway in a relatively defined biological setting of cell cycle progression is considerably limited and even less known are isoform specific Raf functions during this process. As regards to the role of Raf in cancer, though B-Raf is distinguished at present as the principal Raf isoform associated with human cancer due to the prevalence of its mutations, these cancer cases overall represent only a small fraction of human cancers in which Raf may play a key role. Thus,

in these settings it is important to define the relative contribution of the three Raf isoforms in the tumorigenic process. Thus far, many of the experimental approaches involved the use of dominant negative Raf forms that function largely by inhibiting Ras or MEK and are not informative in determining the role of Raf in these settings or distinguishing between isoform specific functions. Similarly, the existing small molecule Raf inhibitors do not differentiate between the three Raf isoforms. The main tool to address this question is the use of RNAi reagents specific for each Raf isoform. However, even this approach may not provide conclusive answers when considering the recent reports that C-Raf and B-Raf could act in concert through heterodimerization, though the physiological significance of these observations awaits further confirmation.

RAS-RAF-MEK-ERK PATHWAY INHIBITORS pdf

The Acts of Judas Thomas. Preparation of electrodes for solid polymer electrolyte fuel cells Body sculpting bible express Political dimension of the settlement phase during a revolutionary war Cyberbullying is a serious, widespread problem Mastersizer 2000 user manual Transitions to Competitive Government Types of small businesses and their operations A geography of time Stonebreakers Ridge Network security auditing Galliformes Brian H. Coles Pt. 1. Challenges facing the VA claims adjudication and appeal process A reviving middle kingdom for China: Chinese nationalism German bombers over Russia Shaw the Annual of Bernard Shaw Studies (Shaw) Histories of Art and Design Education Islamic wazaif ka encyclopedia in urdu The tale of Applebeck Orchard Getting started : Vikings prehistory and the first season The Legs of William Wordsworth Lincolns plan for reconstruction Wild foods of Great Britain I wonder why Romans wore togas and other questions about Ancient Rome Tales from the totems of the Hidery W Tetzlaff and J D Steeves Highlight on ipad app Walt Disneys Winnie the Pooh and Tigger too The kidney disease solution book Aristotles Metaphysics Book Lambda Emissary from Hamelin. Tales of the prophets = A Treatise on the Venereal Disease: By John Hunter The uglified ducky Wanting it and not wanting it A level economics textbooks A brief view of the missionary proceedings in the western country Uli/Umta Policy Forum on Joint Development of Rail Transit Facilities New essays on Daisy Miller and The turn of the screw Time-lapsed man and other stories.