Urinary titin N-terminal fragment concentration is an indicator of preoperative sarcopenia and nutritional status in patients with gastrointestinal tract and hepatobiliary pancreatic malignancies.

Related Articles

**Urinary titin N-terminal fragment concentration is an indicator of preoperative sarcopenia and nutritional status in patients with gastrointestinal tract and hepatobiliary pancreatic malignancies.**

Nutrition. 2020 Jul 31;79-80:110957

Authors: Miyoshi K, Shimoda M, Udo R, Oshiro Y, Suzuki S

Abstract

OBJECTIVES: Recent reports indicate that preoperative patients with gastrointestinal malignancies often have sarcopenia. The diagnosis of sarcopenia is generally done by evaluation of walking speed, grip strength, and skeletal muscle volume of the limbs on computed tomography (CT). However, these parameters are objective indices, and new indicators for diagnosis, such as molecular biomarkers, have been anticipated. The aim of this study was to investigate whether titin, a muscular contractile protein present in sarcomeres, is an indicator of sarcopenia.

METHODS: We analyzed 39 patients with gastrointestinal tract and hepatobiliary pancreatic malignancies who underwent surgery. We compared urinary titin n-terminal fragment concentration (UTF) with clinical factors, subcutaneous fat volume, and skeletal muscle volume index, and also compared UTF levels between patients with and without sarcopenia.

RESULTS: The patients comprised 24 men and 15 women, with a mean age of 72 y (range: 35-85 y). Cancer locations were the pancreas (n = 17), liver (n = 9), stomach (n = 5), colorectum (n = 5), and esophagus (n = 3). UTF was significantly higher in patients with sarcopenia (P = 0.04), and showed statistically significant negative correlations with albumin (r = -2.61, P = 0.001), pre-albumin (r = -2.14, P = 0.02), body mass index (r = -0.49, P = 0.007), cholinesterase (r = -0.02, P = 0.01), skeletal muscle volume index (r = -0.16, P = 0.04), and subcutaneous fat volume (r = -0.03, P = 0.007).

CONCLUSION: UTF may be a new index for preoperative nutritional assessment in patients with gastrointestinal malignancies.

PMID: 32866763 [PubMed — as supplied by publisher]

Potential diagnostic and therapeutic roles of exosomes in pancreatic cancer.

Related Articles

**Potential diagnostic and therapeutic roles of exosomes in pancreatic cancer.**

Biochim Biophys Acta Rev Cancer. 2020 Aug 29;:188414

Authors: Zhao X, Ren Y, Lu Z

Abstract

Pancreatic cancer (PaCa) is considered an aggressive but still asymptomatic malignancy. Due to the lack of effective diagnostic markers, PaCa is often diagnosed during late metastatic stages. Besides surgical resection, no other treatment appears to be effective during earlier stages of the disease. Exosomes are related to a class of nanovesicles coated by a bilayer lipid membrane and enriched in protein, nucleic acid, and lipid contents. They are widely present in human body fluids, including blood, saliva, and pancreatic duct fluid, with functions in signal transduction and material transport. A large number of studies have suggested for a crucial role for exosomes in PaCa, which may be utilized to improve its future diagnosis and treatment, but the underlying molecular mechanisms as well as their potential clinical applications are largely unknown. By collecting and analyzing the most up-to-date literature, here we summarize the current progress of the clinical applications related to exosomes in PaCa. Therefore, we presently provide some rationale for the potential value of exosomes in PaCa, thereby promoting putative applications in targeted PaCa treatment.

PMID: 32866530 [PubMed — as supplied by publisher]
Transcriptional and immunohistological assessment of immune infiltration in pancreatic cancer.

Related Articles

Transcriptional and immunohistological assessment of immune infiltration in pancreatic cancer.


Abstract

Pancreatic adenocarcinoma is characterized by a complex tumor environment with a wide diversity of infiltrating stromal and immune cell types that impact the tumor response to conventional treatments. However, even in this poorly responsive tumor the extent of T cell infiltration as determined by quantitative immunohistology is a candidate prognostic factor for patient outcome. As such, even more comprehensive immunophenotyping of the tumor environment, such as immune cell type deconvolution via inference models based on gene expression profiling, holds significant promise. We hypothesized that RNA-Seq can provide a comprehensive alternative to quantitative immunohistology for immunophenotyping pancreatic cancer. We performed RNA-Seq on a prospective cohort of pancreatic tumor specimens and compared multiple approaches for gene expression-based immunophenotyping analysis compared to quantitative immunohistology. Our analyses demonstrated that while gene expression analyses provide additional information on the complexity of the tumor immune environment, they are limited in sensitivity by the low overall immune infiltrate in pancreatic cancer. As an alternative approach, we identified a set of genes that were enriched in highly T cell infiltrated pancreatic tumors, and demonstrate that these can identify patients with improved outcome in a reference population. These data demonstrate that the poor immune infiltrate in pancreatic cancer can present problems for analyses that use gene expression-based tools; however, there remains enormous potential in using these approaches to understand the relationships between diverse patterns of infiltrating cells and their impact on patient treatment outcomes.

PMID: 32866185 [PubMed — as supplied by publisher]

Comparative Study on Bioactivities from Lingzhi or Reishi Medicinal Mushroom, Ganoderma lucidum (Agaricomycetes), Gives an Insight into the Fermentation Broth Showing Greater Antioxidative Activities.

Related Articles

Comparative Study on Bioactivities from Lingzhi or Reishi Medicinal Mushroom, Ganoderma lucidum (Agaricomycetes), Gives an Insight into the Fermentation Broth Showing Greater Antioxidative Activities.


Abstract

Ganoderma lucidum is one of the most famous mushrooms in traditional Chinese medicine. At present, the fully utilized parts of G. lucidum are mainly fruiting body and spore powder. The wild and artificially cultivated G. lucidum fruiting body is costly and rare. Therefore, how to improve the utilization of G. lucidum by means of fermentation is worth investigating. The present study was to perform submerged fermentation of G. lucidum and compare the bioactivities of G. lucidum submerged fermentation broth and fruiting body extract. After the extraction and submerged fermentation methods were optimized, the optimum conditions for extraction were determined as ethanol extraction at 80°C with a solid-to-liquid ratio of 1:30, and those for submerged fermentation were cultivation on malt extract medium for 6 days at 30°C. Under the optimum conditions, the antioxidative activity and tyrosinase inhibition rate of the fermentation broth were 1.2−4.1 fold higher than those of the ethanol extract. Cytotoxicity analysis showed that the ethanol and water extracts and the fermentation broth effectively inhibited pancreatic cancer cells and prostate cancer cells, with much smaller effect on nontumor human embryonic kidney (HEK293T). These results demonstrate that the submerged fermentation could improve the utilization value of G. lucidum and the fermentation broth can be used as an antioxidant additive applied in food, drugs, and cosmetics.

PMID: 32865920 [PubMed — as supplied by publisher]
Gamma-delta T cells stimulate IL-6 production by pancreatic stellate cells in pancreatic ductal adenocarcinoma.

J Cancer Res Clin Oncol. 2020 Aug 31;:
Abstract
INTRODUCTION: The immunosuppressive tumor microenvironment promotes progression of pancreatic ductal adenocarcinoma (PDAC). γδ T cells infiltrate the pancreatic tumor stroma and support tumorigenesis through αβ T cell inhibition. Pancreatic stellate cell (PSC) activation contributes to pancreatic fibrosis in PDAC, limiting the delivery and efficacy of therapeutic agents. Whether γδ T cells have direct effects on PSC activation is unknown.
METHODS: In this study, we analyzed tumor tissue from 68 patients with PDAC and determined the frequency and location of γδ T cells using immunohistochemistry and immunofluorescence. PDAC samples from the TCGA database with low and high TRGC2 expression were correlated with the expression of extracellular matrix genes. Further, PSCs were isolated from pancreatic tumor tissue and co-cultured with γδ T cells for 48 hours and cytokine production was measured using a cytometric bead array.
RESULTS: γδ T cells infiltrated the pancreatic tumor stroma and were located in proximity to PSCs. A high infiltration of γδ T cells was associated with increased expression of several extracellular matrix genes in human PDAC. In vitro, γδ T cells stimulated IL-6 production by PDAC-derived PSCs.
CONCLUSION: γδ T cells activated PSCs and modulation of this interaction may enhance the efficacy of combinational therapies in human PDAC.
PMID: 32865330 [PubMed — as supplied by publisher]

A triterpene lactone from Callistemon citrinus inhibits the PANC-1 human pancreatic cancer cells viability via suppression of unfolded protein response.

Chem Biodivers. 2020 Aug 31;:
Authors: Awale S, Tawila A, Sun S, Kim MJ, Omar A, Dibwe DF, Kim MJ
Abstract
Human pancreatic tumor cells such as PANC-1 are known for their ability to tolerate nutrient starvation and thrive under the hypovascular tumor microenvironment, a phenomenon termed as ‘austerity’. A search of agents that preferentially inhibit the cancer cell viability under the starvation condition without toxicity in the nutrient-rich condition is a promising approach in anticancer drug discovery. In this study, a triterpene lactone, 3β-Hydroxy-13,28-epoxyurs-11-en-28-one (ursenolide), isolated from a Callistemon citrinus extract has shown strong preferential cytotoxicity against PANC-1 cells under nutrient starvation with PC50 value of 0.4 µM. Ursenolide induced rounding of PANC-1 cell morphology followed by rupture of the cell membrane leading to cell death. In a real-time cell migration study, ursenolide was found to inhibit PANC-1 cell migration significantly. Mechanistically, it inhibited GRP78 and GRP94 under the starvation condition suggesting inhibition of unfolded protein response (UPR), an adaptive process of cell survival during starvation. It also inhibited the phosphorylation of the key survival protein Akt and mTOR. Overall results suggested that ursenolide is a potential anticancer agent against pancreatic cancer.
PMID: 32865330 [PubMed — as supplied by publisher]

Fc Receptor is Involved in Nk Cell Functional Anergy Induced by Miapaca2 Tumor Cell Line.

Immunol Invest. 2020 Aug 30;:
Authors: Ostapchuk YO, Perfilyeva YV, Kali A, Tleulieva R, Yurikova OY, Stanbekova GE, Karalnik BV, Belyaev NN
Abstract
Impaired NK cytotoxicity has been linked to poor cancer prognosis, but its mechanisms are not clearly established. Increasing data demonstrate that NK cells lose cytotoxicity after interaction with NK cell-sensitive tumor cells. In this paper, we provide evidence that the human adenocarcinoma cell line MiaPaCa2 and TNFa and TGFβ-treated MiaPaCa2 cultures (MiaPaCa2-TT) induced functional anergy of NK cells via FGL2 protein. MiaPaCa2-TT cultures decreased expression of IFNγ, CD107a, DNAM-1, and stimulated expression of PD1 by NK cells, as well as inhibited their cytotoxic activity in a greater manner compared to the parental culture. More importantly, we found that co-cultivation with anergized NK cells decreased expression of IFNγ and CD107a by naïve NK cells, which supports the hypothesis of NK cell functional anergy transmission. The obtained results suggest a mechanism by which tumor cells may inhibit cytotoxic functions of tumor-infiltrating and circulating NK cells in
Comparison of Image-Guided Iodine-125 Seed Interstitial Brachytherapy and Local Chemotherapy Perfusion in Treatment of Advanced Pancreatic Cancer.

Related Articles

Comparison of Image-Guided Iodine-125 Seed Interstitial Brachytherapy and Local Chemotherapy Perfusion in Treatment of Advanced Pancreatic Cancer.

J Invest Surg. 2020 Aug 30;1–6
Authors: Zhou L, Yang H, Xie L, Sun J, Qian J, Zhu L

Abstract

OBJECTIVE: To compare the efficacy and safety of iodine-125 seed interstitial brachytherapy and local chemotherapy perfusion in treatment of advanced pancreatic cancer.

METHODS: The present open prospective randomized control study included a total of 165 cases of advanced pancreatic cancer patients who were admitted in our hospital during December 2016 to April 2019. All patients were randomized into two groups with 84 cases in iodine-125 group and 81 cases in chemotherapy perfusion group. Basic clinical characteristics and demographic data were collected. The main outcome was the tumor efficiency. The pain condition was measured by visual analogue scale (VAS) and the Karnofsky score was also measured at different time points, before the treatment, 1 d, 7 d, 14 d, 1 mon, 2 mon and 3 mon after treatment. Serum levels of CEA, CA19-9 and CA50 were measured by immunochemiluminescence. The overall survival was analyzed by K-M curve.

RESULTS: The ratio of partial remission patients was significantly higher, and the ratio of stable disease (SD)+progressive disease patients was also remarkably lower in iodine-125 group than the chemotherapy perfusion group. The mean VAS scores decreased markedly after treatment and were significantly lower and the mean Karnofsky scores were remarkably higher in iodine-125 group than the chemotherapy perfusion group. The levels of CA19-9 and CA50 were measured by immunochemiluminescence. The overall survival was analyzed by K-M curve. No infection, pancreatic fistula, biliary fistula, intestinal fistula, gastrointestinal obstruction or radiation enteritis was found in both groups.

CONCLUSION: Iodine-125 seed interstitial brachytherapy could achieve better efficacy with no increased side complications than chemotherapy perfusion in advanced pancreatic cancer.
secretion, our current data indicate that the loss of SIRT4 specifically in pancreatic beta-cells, both in vivo and in vitro, does not have a significant impact on nutrient-stimulated insulin secretion. These data suggest that SIRT4 controls nutrient-stimulated insulin secretion during aging by acting on tissues external to the beta-cell, which warrants further study.

PMID: 32865009 [PubMed — as supplied by publisher]

kB-Ras and Ral GTPases regulate acinar to ductal metaplasia during pancreatic adenocarcinoma development and pancreatitis.

Related Articles
kB-Ras and Ral GTPases regulate acinar to ductal metaplasia during pancreatic adenocarcinoma development and pancreatitis.

Nat Commun. 2020 07 08;11(1):3409

Abstract
Pancreatic ductal adenocarcinoma (PDAC) is associated with high mortality and therapy resistance. Here, we show that low expression of kB-Ras GTPases is frequently detected in PDAC and correlates with higher histologic grade. In a model of KRasG12D-driven PDAC, loss of kB-Ras accelerates tumour development and shortens median survival. kB-Ras deficiency promotes acinar-to-ductal metaplasia (ADM) during tumour initiation as well as tumour progression through intrinsic effects on proliferation and invasion. kB-Ras proteins are also required for acinar regeneration after pancreatitis, demonstrating a general role in control of plasticity. Molecularly, upregulation of Ral GTpase activity and Sox9 expression underlies the observed phenotypes, identifying a previously unrecognized function of Ral signalling in ADM. Our results provide evidence for a tumour suppressive role of kB-Ras proteins and highlight low kB-Ras levels and consequent loss of Ral control as risk factors, thus emphasizing the necessity for therapeutic options that allow interference with Ral-driven signalling.

PMID: 32620742 [PubMed — indexed for MEDLINE]


Related Articles

World Neurosurg. 2020 06;138:672–679
Authors: Mu L, Zhou Q, Sun D, Wang M, Chai X, Wang M

Abstract
OBJECTIVE: In this study, we considered the treatment of cognitive characteristics of Parkinson’s subtypes under resting magnetic resonance imaging scans, and used magnetic resonance imaging to analyze brain activity characteristics of patients with
Management of the pancreatic transection plane after left (distal) pancreatectomy: Expert consensus guidelines by the International Study Group of Pancreatic Surgery (ISGPS).

Related Articles

Management of the pancreatic transection plane after left (distal) pancreatectomy: Expert consensus guidelines by the International Study Group of Pancreatic Surgery (ISGPS).

Surgery. 2020 07;168(1):72–84


Abstract

BACKGROUND: The aim was to evaluate the various operative techniques and outcomes used to manage the pancreatic transection plane (or stump) during a left (distal) pancreatectomy and to develop expert consensus guidelines.

METHODS: Evidence-based, clinically relevant questions were discussed and then were circulated among members of the International Study Group of Pancreatic Surgery. After agreement on the questions and statements, voting in a 9-point Likert scale was used to gauge the level of objective support for each.

RESULTS: Studies using the International Study Group of Pancreatic Surgery definition of postoperative pancreatic fistula including 16 randomized trials were reviewed to generate a series of statements set into 14 domains. There was strong consensus in the following statements: there was no difference in the

Related Articles

Extent of liver resection is associated with incomplete liver restoration and splenomegaly a long period after liver resection.

Surgery. 2020 07;168(1):40–48


Abstract

BACKGROUND: Little is known about the clinical significance and risk factors for incomplete liver restoration after partial hepatectomy, which is defined by a liver volume restoration of less than 100% of the original volume.

METHODS: We retrospectively analyzed patients who underwent hepatic resection for liver tumors at the Kyoto University Hospital between January 2011 and October 2015 and survived without recurrence for more than 3 years. The preoperative and postoperative data, as well as liver and splenic volume after 3 postoperative years, were assessed.

RESULTS: The percentage of resected liver was higher in the incomplete liver restoration group (n = 52, 41.6%) than in the complete liver restoration group (n = 73, 58.4%) (28 [3–78]% vs 14.5 [2–63]%, P = .0226). The percentage of resected liver was also higher in the splenomegaly group (defined by spleen volume increases of more than 35% of the original volume) than in the nonsplenomegaly group (40 [4–63]% vs 16.5 [2–78]%, P = .0002).
postoperative pancreatic fistula rate after left pancreatectomy between the handsewn and stapler techniques; a stapling technique could not be used in all cases of left pancreatectomy; the use of an energy-based tissue sealant or a chemical sealant device or combinations of these did not impact the postoperative pancreatic fistula rate; there was no difference in the postoperative pancreatic fistula rate between the open, laparoscopic, or robotic approaches; and there are 1 or more clinically important, patient-related risk factors associated with the postoperative pancreatic fistula rate. There was weak or conditional agreement on the use of prophylactic somatostatin analogs, stents, stump closure, stump anastomosis, and the role of abdominal drains.

CONCLUSION: Areas of strong consensus suggests a change in clinical practice and priority setting. Eight domains with lower agreement will require novel approaches and large multicenter studies to determine future key areas of practice.

PMID: 32249092 [PubMed — indexed for MEDLINE]

Spleen volumetry and liver transient elastography: Predictors of persistent posthepatectomy decompensation in patients with hepatocellular carcinoma.

Related Articles

Spleen volumetry and liver transient elastography: Predictors of persistent posthepatectomy decompensation in patients with hepatocellular carcinoma.

Surgery. 2020 07;168(1):17-24


Abstract

BACKGROUND: Posthepatectomy decompensation remains a frequent and poor outcome after hepatectomy, but its prediction is still inaccurate. Liver stiffness measurement can predict posthepatectomy decompensation, but there is a so-called "gray zone" that requires another predictor. Because splenomegaly is an objective sign of portal hypertension, we hypothesized that spleen volumetry could improve the identification of patients at risk.

METHODS: Patients with hepatocellular carcinoma who underwent hepatectomy in our tertiary center between August 2014 and December 2017 were reviewed. The primary endpoint was to determine if the spleen volumetry and liver stiffness measurement were independent predictors of posthepatectomy decompensation, and secondarily, to determine if they were synergistic through a theoretic predictive model.

RESULTS: One hundred and seven patients were included. The median follow-up time was 3 months (3−5). Postoperative 90-day mortality was 4.7%. By multivariate analysis, liver stiffness measurement and spleen volumetry predicted posthepatectomy decompensation. The liver stiffness measurement had a cutoff point of 11.6 kPa (area under receiver operating curve = 0.71 confidence interval 95% 0.71−0.88, sensitivity: 89%, specificity: 47%). The spleen volumetry cutoff point was 381.1 cm³ (area under receiver operating curve = 0.78, 95% confidence interval 0.77−0.93, sensitivity: 55%, specificity: 91%). The spleen volumetry improved prediction of posthepatectomy decompensation, because use of the spleen volumetry increased sensitivity (from 62% to 97%) and the negative predictive value (from 96% to 100%) along with a negligible decrease in specificity (from 96.7 to 93.4) and positive predictive value (from 64% to 59%) (P = .003).

CONCLUSION: Spleen volumetry (>380 cm³) and liver stiffness measurement (>12 kPa) are non-invasive, independent, and synergistic tools that appear to be able to predict posthepatectomy decompensation. The importance of this finding is that these measurements may help to anticipate posthepatectomy decompensation and may possibly be used to direct alternative treatments to resection.

PMID: 32204923 [PubMed — indexed for MEDLINE]

Standards for reporting on surgery for chronic pancreatitis: a report from the International Study Group for Pancreatic Surgery (ISGPS).

Related Articles

Standards for reporting on surgery for chronic pancreatitis: a report from the International Study Group for Pancreatic Surgery (ISGPS).

Surgery. 2020 07;168(1):101-105


Abstract

BACKGROUND: The International Study Group for Pancreatic Surgery provides globally accepted definitions for reporting of complications after pancreatic surgery. This International Study Group for Pancreatic Surgery project aims to provide a standardized framework for reporting of the results of operative treatment for chronic pancreatitis.

METHODS: An International Study Group for Pancreatic Surgery project circulation list was created with pre-existing and new members and including gastroenterologists in addition to surgeons. A computerized search of the literature was undertaken for articles reporting the operative treatment of chronic
pancreatitis. The results of the literature search were presented at the first face-to-face meeting of this International Study Group for Pancreatic Surgery project group. A document outlining proposed reporting standards was produced by discussion during an initial meeting of the International Study Group for Pancreatic Surgery. An electronic questionnaire was then sent to all current members of the International Study Group for Pancreatic Surgery. Responses were collated and further discussed at international meetings in North America, Europe, and at the International Association of Pancreatology World Congress in 2019. A final consensus document was produced by integration of multiple iterations.

RESULTS: The International Study Group for Pancreatic Surgery consensus standards for reporting of surgery in chronic pancreatitis recommends 4 core domains and the necessary variables needed for reporting of results: clinical baseline before operation; the morphology of the diseased gland; a new, standardized, operative terminology; and a minimum outcome dataset. The 4 domains combine to give a comprehensive framework for reports.

CONCLUSION: Adoption of the 4 domains of the International Study Group for Pancreatic Surgery reporting standards for surgery for chronic pancreatitis will facilitate comparison of results between centers and help to improve the care for patients with this debilitating disease.

PMID: 32183994 [PubMed — indexed for MEDLINE]

Inhibition of LONP1 protects against erastin-induced ferroptosis in Pancreatic ductal adenocarcinoma PANC1 cells.

Related Articles

**Inhibition of LONP1 protects against erastin-induced ferroptosis in Pancreatic ductal adenocarcinoma PANC1 cells.**

Biochem Biophys Res Commun. 2020 02;522(4):1063–1068


Abstract

Ferroptosis is identified as a regulated cell death mediated by iron accumulation and lipid peroxidation. The disturbances of mitochondrial morphology and function have been shown in this process. Mitochondrial Lon peptidase 1 (LONP1) is one of the main multi-function enzymes in regulating the mitochondrial function and cytological stability. To evaluate whether LONP1 take a role in ferroptosis, we applied erastin to initiate the ferroptosis in human pancreatic ductal adenocarcinoma (PDAC) cells. Here we show that erastin triggers cell death in both of oncogenic RAS mutant PANC1 cells and wild KRAS BxPC3 cells and the expression of LONP1 was up-regulated in this process. Gene inhibition of LONP1 only negatively regulates erastin-induced cell death and the alterations of molecular indicators in PANC1 cells. Furthermore, we show that inhibition of LONP1 activates the Nrf2/Keap1 signal pathway and up-regulates the expression of GPX4, a key peroxidase in regulating ferroptosis. Together, our results uncover a previously unappreciated mechanism coupling LONP1 to ferroptosis.

PMID: 31822343 [PubMed — indexed for MEDLINE]

A Membrane Permeable Prodrug of S223 for Selective Epac2 Activation in Living Cells.

Related Articles

**A Membrane Permeable Prodrug of S223 for Selective Epac2 Activation in Living Cells.**

Cells. 2019 12 06;8(12):

Authors: Xu Y, Schwede F, Wienk H, Tengholm A, Rehmann H

Abstract

Signalling by cyclic adenosine monophosphate (cAMP) occurs via various effector proteins, notably protein kinase A and the guanine nucleotide exchange factors Epac1 and Epac2. These proteins are activated by cAMP binding to conserved cyclic nucleotide binding domains. The specific roles of the effector proteins in various processes in different types of cells are still not well defined, but investigations have been facilitated by the development of cyclic nucleotide analogues with distinct selectivity profiles towards a single effector protein. A remaining challenge in the development of such analogues is the poor membrane permeability of nucleotides, which limits their applicability in intact living cells. Here, we report the synthesis and characterisation of S223-AM, a cAMP analogue designed as an acetoxymethyl ester prodrug to overcome limitations of permeability. Using total internal reflection imaging with various fluorescent reporters, we show that S223-AM selectively activates Epac2, but not Epac1 or protein kinase A, in intact insulin-secreting β-cells, and that this effect was associated with pronounced activation of the small G-protein Rap. A comparison of the effects of different cAMP analogues in pancreatic islet cells deficient in Epac1 and Epac2 demonstrates that cAMP-dependent Rap activity at the β-cell plasma membrane is exclusively dependent on Epac2. With its excellent selectivity and permeability properties, S223-AM should get broad utility in investigations of cAMP effector involvement in many different types of cells.

PMID: 31817822 [PubMed — indexed for MEDLINE]
CircRNA-5692 inhibits the progression of hepatocellular carcinoma by sponging miR-328-5p to enhance DAB2IP expression.

Related Articles

CircRNA-5692 inhibits the progression of hepatocellular carcinoma by sponging miR-328-5p to enhance DAB2IP expression.

Cell Death Dis. 2019 11 27;10(12):900

Authors: Liu Z, Yu Y, Huang Z, Kong Y, Hu X, Xiao W, Quan J, Fan X

Abstract

Circular RNAs (circRNAs), one kind of noncoding RNAs, can interact with miRNA and transcription factors to regulate gene expression. However, little is known on which circRNA is crucial for the pathogenesis of hepatocellular carcinoma (HCC). CircRNA expression profile was analyzed by a microarray. Regulatory gene targets were predicted by bioinformatics analysis and validated by luciferase assay. Their expression was determined by qRT-PCR and Western blotting. DNA methylation was determined by methylation-specific PCR. Gene knockdown and overexpression were mediated by lentivirus-mediated shRNA and transfection with plasmids for cDNA expression, respectively. MTT assay, wound-healing assay, transwell invasion assay, and flow cytometry were used to determine malignant behaviors of HCC cells. HCC xenograft mouse model was used to determine the in vivo effects of circRNA-5692. CircRNA-5692 expression was downregulated in HCC tissues, and circRNA-5692 overexpression attenuated the malignant behaviors of HCC cells. Bioinformatics predicted that circRNA-5692 interacted with miR-328-5p, which targeted the DAB2IP mRNA. Actually, miR-328-5p promoted the malignant behaviors of HCC cells, while DAB2IP had opposite effects. Moreover, circRNA-5692 overexpression inhibited the growth of xenograft HCC tumors in vivo by decreasing miR-328-5p expression to enhance DAB2IP expression. In conclusion, the circRNA-5692-miR-328-5p-DAB2IP regulatory pathway inhibits the progression of HCC. Our findings may provide potential new targets for the diagnosis and therapy of HCC.

PMID: 31776329 [PubMed — indexed for MEDLINE]


Related Articles


J Med Chem. 2020 03 12;63(5):2181–2193


Abstract

Medulloblastoma is a malignant brain tumor diagnosed in children. Chemotherapy has improved survival rates to approximately 70%; however, children are often left with long-term treatment side effects. New therapies that maintain a high cure rate while reducing off-target toxicity are required. We describe for the first time the use of a bacteriophage-peptide display library to identify heptapeptides that bind to medulloblastoma cells. Two heptapeptides that demonstrated high [E1-3 (1)] or low [E1-7 (2)] medulloblastoma cell binding affinity were synthesized. The potential of the peptides to deliver a therapeutic drug to medulloblastoma cells with specificity was investigated by conjugating E1-3 (1) or E1-7 (2) to doxorubicin (5). Both peptide-drug conjugates were cytotoxic to medulloblastoma cells. E1-3 doxorubicin (3) could permeabilize an in vitro blood-brain barrier and showed a marked reduction in cytotoxicity compared to free doxorubicin (5) in nontumor cells. This study provides proof-of-concept for developing peptide-drug conjugates to inhibit medulloblastoma cell growth while minimizing off-target toxicity.

PMID: 31347843 [PubMed — indexed for MEDLINE]

Genetic Risk Score in Diabetes Associated With Chronic Pancreatitis Versus Type 2 Diabetes Mellitus.

Related Articles

Genetic Risk Score in Diabetes Associated With Chronic Pancreatitis Versus Type 2 Diabetes Mellitus.

Clin Transl Gastroenterol. 2019 07;10(7):e00057

Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

Abstract

INTRODUCTION: Diabetes mellitus (DM) is a complication of chronic pancreatitis (CP). Whether pancreatogenic diabetes associated with CP-DM represents a discrete pathophysiologic entity from type 2 DM (T2DM) remains uncertain. Addressing this question is needed for development of specific measures to manage CP-DM. We approached this question from a unique standpoint, hypothesizing that if CP-DM and T2DM are separate disorders, they should be genetically distinct. To test this hypothesis, we sought to determine whether a genetic risk score (GRS) based on validated single nucleotide polymorphisms for T2DM could distinguish between groups with CP-DM and T2DM.

METHODS: We used 60 T2DM single nucleotide polymorphisms to construct a weighted GRS in 1,613 subjects from the North American Pancreatitis Study 2 and 2,685 subjects from the Multi-Ethnic Study of Atherosclerosis, all of European origin.

RESULTS: The mean GRS was identical between 321 subjects with CP-DM and 423 subjects with T2DM (66.53 vs 66.42, P = 0.95), and the GRS of both diabetic groups was significantly higher than that of nondiabetic controls (n = 3,554, P DISCUSSION: Recognizing that we lacked a gold standard to define CP-DM, our study suggests that CP-DM may be a subtype of T2DM, a notion that should be tested in future, large prospective studies.

PMID: 31232720 [PubMed — indexed for MEDLINE]