Liver Cancer Study Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person’s life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Liver cancer is a cancer that originates in the liver. Liver tumors are discovered on medical imaging equipment or present themselves symptomatically as an abdominal mass, abdominal pain, yellow skin, nausea or liver dysfunction. The leading causes of liver cancer is cirrhosis due to hepatitis B, hepatitis C, and alcohol. Liver cancers are different than liver metastases, which originate from elsewhere in the body and spread to the liver. Liver cancers are formed from either the liver itself or from structures within the liver, including blood vessels or the bile duct. Primary liver cancer is the sixth most frequent cancer globally and the second leading cause of cancer death. In 2012 it occurred in 782,000 people and resulted in 746,000 deaths. This article introduces recent reports as references in the related studies. [Ma H, Young M, Yang Y. Liver Cancer Study Literatures. Cancer Biology 2015;5(1):93-107]. (ISSN: 2150-1041).  http://www.cancerbio.net

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person’s life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Liver cancer is a cancer that originates in the liver. Liver tumors are discovered on medical imaging equipment or present themselves symptomatically as an abdominal mass, abdominal pain, yellow skin, nausea or liver dysfunction. The leading causes of liver cancer is cirrhosis due to hepatitis B, hepatitis C, and alcohol. Liver cancers are different than liver metastases, which originate from elsewhere in the body and spread to the liver. Liver cancers are formed from either the liver itself or from structures within the liver, including blood vessels or the bile duct. Primary liver cancer is the sixth most frequent cancer globally and the second leading cause of cancer death. In 2012 it occurred in 782,000 people and resulted in 746,000 deaths.

The following introduces recent reports as references in the related studies.


BACKGROUND: Although radiologic size criteria (Milan/University of California, San Francisco [UCSF]) have led to improved outcomes after liver transplantation (LT) for hepatocellular carcinoma (HCC), recurrence remains a significant challenge. We analyzed our 30-year experience with LT for HCC to identify predictors of recurrence. STUDY DESIGN: A novel clinicopathologic risk score and prognostic nomogram predicting post-transplant HCC recurrence was developed from a multivariate competing-risk Cox regression analysis of 865 LT recipients with HCC between 1984 and 2013. RESULTS: Overall patient and recurrence-free survivals were 83%, 68%, 60% and 79%, 63%, and 56% at 1-, 3-, and 5-years, respectively. Hepatocellular carcinoma recurred in 117 recipients, with a median time to recurrence of 15 months, involving the lungs (59%), abdomen/pelvis (38%), liver (35%), bone (28%), pleura/mediastinum (12%), and brain (5%). Multivariate predictors of recurrence included tumor grade/differentiation (G4/poor diff hazard ratio [HR] 8.86; G2-3/mod-poor diff HR 2.56), macrovascular (HR 7.82) and microvascular (HR 2.42) invasion, nondownstaged tumors outside Milan criteria (HR 3.02), nonincidental tumors with radiographic maximum diameter >/=5 cm (HR 2.71) and <5 cm (HR 1.55), and pretransplant...
neutrophil-to-lymphocyte ratio (HR 1.77 per log unit), maximum alpha fetoprotein (HR 1.21 per log unit), and total cholesterol (HR 1.14 per SD). A pretransplantation model incorporating only known radiographic and laboratory parameters had improved accuracy in predicting HCC recurrence (C statistic 0.79) compared with both Milan (C statistic 0.64) and UCSF (C statistic 0.64) criteria alone. A novel clinicopathologic prognostic nomogram included explant pathology and had an excellent ability to predict post-transplant recurrence (C statistic 0.85).

CONCLUSIONS: In the largest single-institution experience with LT for HCC, excellent long-term survival was achieved. Incorporation of routine pretransplantation biomarkers to existing radiographic size criteria significantly improves the ability to predict post-transplant recurrence, and should be considered in recipient selection. A novel clinicopathologic prognostic nomogram accurately predicts HCC recurrence after LT and may guide frequency of post-transplantation surveillance and adjuvant therapy.


Inverse associations of coffee and/or tea in relation to hepatocellular carcinoma (HCC) risk have been consistently identified in studies conducted mostly in Asia where consumption patterns of such beverages differ from Europe. In the European Prospective Investigation into Cancer and nutrition (EPIC), we identified 201 HCC cases among 486,799 men/women, after a median follow-up of 11 years. We calculated adjusted hazard ratios (HRs) for HCC incidence in relation to quintiles/categories of coffee/tea intakes. We found that increased coffee and tea intakes were consistently associated with lower HCC risk. The inverse associations were substantial, monotonic and statistically significant. Coffee consumers in the highest compared to the lowest quintile had lower HCC risk by 72% [HR: 0.28; 95% confidence interval (CI): 0.16-0.50, p-trend < 0.001]. The corresponding association of tea with HCC risk was 0.41 (95% CI: 0.22-0.78, p-trend = 0.003). There was no compelling evidence of heterogeneity of these associations across strata of important HCC risk factors, including hepatitis B or hepatitis C status (available in a nested case-control study). The inverse, monotonic associations of coffee intake with HCC were apparent for caffeinated (p-trend = 0.009), but not decaffeinated (p-trend = 0.45) coffee for which, however, data were available for a fraction of subjects. Results from this multicentre, European cohort study strengthen the existing evidence regarding the inverse association between coffee/tea and HCC risk. Given the apparent lack of heterogeneity of these associations by HCC risk factors and that coffee/tea are universal exposures, our results could have important implications for high HCC risk subjects.


INTRODUCTION: A lipiodol solution of (188)Re-4-hexadeyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol (HTDD) has been successfully developed for liver cancer therapy; however, its preparation requires a multi-step synthesis and it is characterized by a low labeling yield. METHODS: We synthesized a new compound, 4-hexadeyl-4,7-diaza-1,10-decanedithioacetate (AHDD), without gem dimethyl groups to address these issues. AHDD was formulated into a kit and was labeled with (188)Re. Biodistribution study was performed using normal BALB/c mice. RESULTS: The kit was labeled with (188)Re with a high efficiency (98.8+/−0.2%). After extraction with lipiodol, the overall yield of (188)Re-HDD/lipiodol was as high as 90.2+/−2.6%. A comparative biodistribution study of (188)Re-HTDD and (188)Re-HDD was performed in normal mice after intravenous injection. The lungs were identified as the main uptake site due to capillary-blockage. (188)Re-HDD/lipiodol showed a significantly higher lung uptake than that of (188)Re-HTDD/lipiodol (p<0.05). CONCLUSION: The newly synthesized (188)Re-HDD/lipiodol showed improved radiolabeling yield and biodistribution results compared to (188)Re-HTDD/lipiodol, and may therefore be more suitable for liver cancer therapy.


PURPOSE: To summarize the relative risks (RRs) and attributable risks (ARs) of major health outcomes associated with use of combined oral contraceptives (OCs) and menopausal hormone therapy (HT). METHODS: For OCs, measures of association are from meta-analyses of observational studies. For HT, these measures are from the Women's Health Initiative, a large randomized trial of HT for chronic disease prevention in postmenopausal women.
Membrane trafficking is known to be coordinated by small GTPases, but the identity of their regulators, the guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) that ensure balanced GTPase activation at different subcellular sites is largely elusive. Here, we show in living cells that deleted in liver cancer 3 (DLC3, also known as STARD8) is a functional Rho-specific GAP protein, the loss of which enhances perinuclear RhoA activity. DLC3 is recruited to Rab8-positive membrane tubules and is required for the integrity of the Rab8 and Golgi compartments. Depletion of DLC3 impairs the transport of internalized transferrin to the endocytic recycling compartment (ERC), which is restored by the simultaneous downregulation of RhoA and RhoB. We further demonstrate that DLC3 loss interferes with epidermal growth factor receptor (EGFR) degradation associated with prolonged receptor signaling. Taken together, these findings identify DLC3 as a novel component of the endocytic trafficking machinery, wherein it maintains organelle integrity and regulates membrane transport through the control of Rho activity.


Hepatocellular carcinoma (HCC) is still a major health problem, often diagnosed at an advanced stage. The multikinase inhibitor Sorafenib is to date the sole approved systemic therapy. Several signaling pathways are implicated in tumor development and progression. Among these pathways, the Ras/MAPK pathway is activated in 50-100% of human HCCs and is correlated with a poor prognosis. Multiple mechanisms lead to the deregulation of the Ras pathway in liver cancer. Ras and Raf genes mutations are rare events in human hepatocarcinogenesis in contrast with experimental models in rodents. Downregulation of several Ras/MAPK pathway inhibitors like GAPs, RASSF proteins, DUSP1, Sprotty and Spreed proteins is largely implicated in the aberrant activation of this pathway in the context of wild-type Ras and Raf genes. Epigenetic or posttranscriptional mechanisms lead to the downregulation of these tumor suppressor genes. Ras/MAPK pathway effectors are potential therapeutic targets. In particular after the arrival of Sorafenib, a lot of Ras/MAPK inhibitors have emerged and are still in preclinical or clinical investigation for HCC therapy. The aim of this work is to review the main intracellular mechanisms leading to aberrant Ras pathway activation in HCC and the potential therapeutic implications. This article is protected by copyright. All rights reserved.

Estimates of the worldwide incidence and mortality from 27 major cancers and for all cancers combined for 2012 are now available in the GLOBOCAN series of the International Agency for Research on Cancer. We review the sources and methods used in compiling the national cancer incidence and mortality estimates, and briefly describe the key results by cancer site and in 20 large "areas" of the world. Overall, there were 14.1 million new cases and 8.2 million deaths in 2012. The most commonly diagnosed cancers were lung (1.82 million), breast (1.67 million), and colorectal (1.36 million); the most common causes of cancer death were lung cancer (1.6 million deaths), liver cancer (745,000 deaths), and stomach cancer (723,000 deaths).


OBJECTIVE: Recent advances in the management of patients with rheumatoid arthritis (RA) increased the rates of disease remission and patient life expectancy, while malignancy has become a more common cause of death. Here, we report the incidence of malignancy in a nationwide survey of Japanese patients with RA compared to the general population, focusing on the risk of lymphoma, which often arises in patients with RA. METHODS: Data on the occurrence of malignancy were collected from patients registered in a nationwide Japanese cohort database, the National Database of Rheumatic Diseases by iNet in Japan, from 2003 to 2012. To adjust for different population composition and to compare the incidence of malignancy with the general population, standardized incidence rates (SIR) were calculated. To identify risk factors for lymphoma, individual patient data were obtained for multivariate analysis for the year before lymphoma diagnosis. RESULTS: In 10 years, the cohort composed of 66,953 patient-years yielded 559 malignancies, most frequently lung cancer, followed by gastric cancer, breast cancer, and lymphoma. The overall incidence of malignancies in patients with RA was slightly lower than in the general population (SIR 0.89, 95% CI 0.82-0.97).


Primary liver cancer encompasses both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). The Notch signaling pathway, known to be important for the proper development of liver architecture, is also a potential driver of primary liver cancer. However, with four known Notch receptors and several Notch ligands, it is not clear which Notch pathway members play the predominant role in liver cancer. To address this question, we utilized antibodies to specifically target Notch1, Notch2, Notch3, or jagged1 (Jag1) in a mouse model of primary liver cancer driven by v-akt murine thymoma viral oncogene homolog and neuroblastoma RAS viral oncogene homolog (NRas). We show that inhibition of Notch2 reduces tumor burden by eliminating highly malignant HCC- and CCA-like tumors. Inhibition of the Notch ligand, Jag1, had a similar effect, consistent with Jag1 acting in cooperation with Notch2. This effect was specific to Notch2, because Notch3 inhibition did not decrease...
tumor burden. Unexpectedly, Notch1 inhibition altered the relative proportion of tumor types, reducing HCC-like tumors but dramatically increasing CC-like tumors. Finally, we show that Notch2 and Jag1 are expressed in, and Notch2 signaling is activated in, a subset of human HCC samples. CONCLUSIONS: These findings underscore the distinct roles of different Notch receptors in the liver and suggest that inhibition of Notch2 signaling represents a novel therapeutic option in the treatment of liver cancer. (Hepatology 2015;61:942-952).


MicroRNA-31 (miR-31) is among the most frequently altered microRNAs in human cancers and altered expression of miR-31 has been detected in a large variety of tumor types, but the functional role of miR-31 still hold both tumor suppressive and oncogenic roles in different tumor types. MiR-31 expression was down-regulated in a large cohort of hepatocellular carcinoma (HCC) patients, and low expression of miR-31 was significantly associated with poor prognosis of HCC patients. Ectopic expression of miR-31 mimics suppressed HCC cell growth by transcriptional deregulation of cell cycle proteins. Additional study evidenced miR-31 directly to suppress HDAC2 and CDK2 expression by inhibiting mRNA translation in HCC cells. We also found that ectopic expression of miR-31 mimics reduced metastatic potential of HCC cells by selectively regulating epithelial-mesenchymal transition (EMT) regulatory proteins such as N-cadherin, E-cadherin, vimentin and fibronectin. HCC tissues derived from chemical-induced rat liver cancer models validated that miR-31 expression is significantly down-regulated, and that those cell cycle- and EMT-regulatory proteins are deregulated in rat liver cancer. Overall, we suggest that miR-31 functions as a tumor suppressor by selectively regulating cell cycle and EMT regulatory proteins in human hepatocarcinogenesis providing a novel target for the molecular treatment of liver malignancies.


Reduced expression of microRNA122 (miR122), a liver-specific microRNA, is frequent in hepatocellular carcinoma (HCC). However, its biological significances remain poorly understood. Because deregulated amino acid levels in cancers can affect their biological behavior, we determined the amino acid levels in miR122-silenced mouse liver tissues, in which intracellular arginine levels were significantly increased. The increased intracellular arginine levels were through upregulation of the solute carrier family 7 (SLC7A1), a transporter of arginine and a direct target of miR122. Arginine is the substrate for nitric oxide (NO) synthetase, and intracellular NO levels were increased in miR122-silenced HCC cells, with increased resistance to sorafenib, a multikinase inhibitor. Conversely, maintenance of the miR122-silenced HCC cells in arginine-depleted culture media, as well as overexpression of miR122 in miR122-low-expressing HCC cells, reversed these effects and rendered the cells more sensitive to sorafenib.


FTIR spectroscopy is a widely used technique that provides insights into disease processes at the molecular level. Due to its numerous advantages it is becoming an increasingly powerful tool for the study of biological materials and has the potential to become an excellent diagnostic method, especially considering the low cost of transfection substrates. However, questions about the usefulness of the transfection measurement mode due to the complicated nature of physical processes occurring during the measurement and in particular the Electric Field Standing Wave (EFSW) effect have been raised. In this paper we present a comparison of the two most common FT-IR measurement modes: transmission and transfection using healthy and pathologically altered tissue (histiocytic sarcoma). We found that the major differences between normal and cancerous tissue were associated with changes DNA and carbohydrate content.


Silent information regulator 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylase. In mice, mSirt1 deficiency causes the onset of fatty liver via regulation of the hepatic nutrient metabolism pathway. In this study, we demonstrate SIRT1 expression, activity and NAD+ regulation using noncancerous liver tissue specimens from hepatocellular carcinoma patients with non-B non-C (NBNC) hepatitis. SIRT1 expression levels were higher in NBNC patients than in healthy donors, while SIRT1 histone H3K9 deacetylation activity was suppressed in NBNC patients. In the liver of hepatitis patients, decreased NAD+ amounts and its
regulatory enzyme nicotinamide phosphoribosyltransferase expression levels were observed, and this led to inhibition of SIRT1 activity. SIRT1 expression was associated with HIF1 protein accumulation in both the NBNC liver and liver cancer cell lines. These results may indicate that the NBNC hepatitis liver is exposed to hypoxic conditions. In HepG2 cells, hypoxia induced inflammatory chemokines, such as CXCL10 and MCP-1.

Maass, T., J. Marquardt, et al. "Increased liver carcinogenesis and enrichment of stem cell properties in livers of Dickkopf 2 (Dkk2) deleted mice." Oncotarget. 2015 Mar 16.

Dkk2 a antagonist of the Wnt/beta-catenin-signaling pathway was shown to be silenced in diverse cancers. More recent data indicate that Dkk family members may also possess functions independent of Wnt-signaling during carcinogenesis. The detailed biological function of Dkks and its relevance for liver cancer is unknown. We analyzed the effects of a genetic deletion of Dkk2 (Dkk2/-) in a hepatocarcinogenesis model using DEN/Phenobarbital. Untreated Dkk2/- animals, showed considerable atypia with variation of hepatocytesize and chromatin density. In livers of Dkk2/- mice nodule formation was seen at 9 months of age with focal loss of trabecular architecture and atypical hepatocytes and after DEN induction Dkk2/- mice developed significantly more liver tumors compared to controls. Whole transcriptome analysis of untreated Dkk2/- livers revealed a Dkk2-dependent genetic network involving Wnt/beta-Catenin but also multiple additional oncogenic factors, such as e.g. Pdgf-b, Gdf-15 and Hnf4a. Dkk2/- tumor cells showed a significant deregulation of stemness genes associated with enhanced colony forming properties. Integration of the Dkk2/- signature into human data was strongly associated with patients survival. Dkk2 deletion results in alterations of liver morphology leading to an increased frequency of liver cancer. The associated genetic changes included factors not primarily related to Wnt/beta-Catenin-signaling and correlated with the clinical outcome of HCC-patients.


The blessed milk thistle (Silybum marianum L.), a flowering plant native to Mediterranean Europe, has been consumed and extensively used as a cure for various chronic liver ailments over several centuries. Milk thistle extract, known as silymarin, is a complex mixture of seven major flavonolignans and one flavonoid. The phytoconstituents of silymarin owe their therapeutic and hepatoprotective effects to their strong antioxidant and anti-inflammatory properties. Primary liver cancer, also known as hepatocellular carcinoma (HCC), occurs in a milieu of oxidative stress and inflammation. The etiology of HCC includes chronic infection with hepatitis B and C viruses, cirrhosis, and exposure to dietary and environmental hepatocarcinogens. Current therapeutic options for HCC, including surgical resection and liver transplantation, have limited benefits and are essentially ineffective. Chemoprevention, using phytochemicals with potent antioxidant and anti-inflammatory properties, represents a fascinating strategy, which has been a subject of intense investigation in the recent years. In this review, we explore the potential role of silymarin as a chemopreventive and therapeutic agent for HCC. The review systematically evaluates the preclinical in-vitro and in-vivo studies investigating the effects of silymarin and its constituents on HCC.


The design of highly defective herpes simplex virus (HSV) vectors for transgene expression in nonneuronal cells in the absence of toxic viral-gene activity has been elusive. Here, we report that elements of the latency locus protect a nonviral promoter against silencing in primary human cells in the absence of any viral-gene expression. We identified a CTCF motif cluster 5' to the latency promoter and a known long-term regulatory region as important elements for vigorous transgene expression from a vector that is functionally deleted for all five immediate-early genes and the 15-kb internal repeat region. We inserted a 16.5-kb expression cassette for full-length mouse dystrophin and report robust and durable expression in dystrophin-deficient muscle cells in vitro. Given the broad cell tropism of HSV, our design provides a nontoxic vector that can accommodate large transgene constructs for transduction of a wide variety of cells without vector integration, thereby filling an important void in the current arsenal of gene-therapy vectors.


A large number of biological, chemical, and dietary factors have been implicated in the development of liver cancer. These involve complex and protracted interactions between genetic,
epigenetic, and environmental factors. The survival rate for patients diagnosed with late-stage liver cancer is currently low due to the aggressive nature of the disease and resistance to therapy. An increasing body of evidence has offered support for the crucial role of non-coding microRNA (miRNA) in directing hepatic responses to environmental risk factors for liver cancer. In this review we focus on miRNA responses to environmental liver cancer risk factors and their potential biological and clinical significance.


**PURPOSE:** To evaluate the risk factors associated with short-term local recurrence of malignant liver lesions after irreversible electroporation (IRE). MATERIALS AND METHODS: Thirty-nine consecutive patients (79 malignant liver lesions) were treated with IRE, of whom 14 were excluded from the analysis (including 12 without 6 mo of follow-up and two with incomplete ablation). The remaining 25 patients (aged 59.4 y +/- 11.2) had 48 malignant liver lesions, including 22 hepatocellular carcinomas (HCCs), six cholangiocellular carcinomas, and 20 metastatic liver cancers. Multivariate analyses were used to evaluate the associations of risk factors with early recurrence. The characteristics of patients, lesions, and IRE procedures were assessed by logistic regression. RESULTS: Fourteen of the 48 treated lesions (29.2%) showed early local recurrence after 6 months. Tumor volume (< 5 cm³ vs >= 5 cm³; P = .022) and underlying disease type (HCC, cholangiocellular carcinoma, or metastatic disease; P = .023) were independently associated with early local recurrence. However, distances to the surrounding portal veins (< 0.5 cm vs >= 0.5 cm; P = .810), hepatic veins (P = .170), hepatic arteries (P = .761), and bile ducts (P = .226) were not significantly associated with local recurrence.


**ETHNOPHARMACOLOGICAL RELEVANCE:** The juice of the entire fresh herb and infusion of dried sample of Murdannia bracteata are consumed to treat liver cancer and diabetes in Malaysia. However, no scientific evidence of these bioactivities has been reported. MATERIALS AND METHODS: To verify the therapeutic potentials of sequential extracts and infusion of this plant by determining its cytotoxicity against human liver carcinoma HepG2 cells and alpha-glucosidase inhibitory activity. The cytotoxic activities of the extracts against HepG2 were determined using a methylene blue assay, and an alpha-glucosidase inhibitory assay was used to assess anti-diabetic activity. The molecular basis of the anti-hepatocellular carcinoma activity of the most active extract was determined using RT-PCR. Chemical profiling of the most active extract was performed using GC-MS and UPLC analyses. RESULTS: The results obtained from the cytotoxic screening revealed the dose-dependent growth inhibition of the HepG2 cells by only the hexane extract, with an EC50 value of 37.17 +/- 1.00μg/ml. The HepG2 cell death was found to be apoptotic in nature and based on the significant biphasic induction of caspase-3, suggesting that the extract inhibited cell growth through a caspase-3-dependent pathway. The hexane extract also displayed alpha-glucosidase inhibitory activity, with an EC50 of 117.04 +/- 2.34μg/ml. GC-MS analysis revealed that alpha-tocopherol was the major volatile compound in the hexane extract, and two phenolics (apigenin and caffeic acid derivatives) were detected using UPLC.


In the treatment of chronic hepatitis B (CHB), the ultimate goal is preventing hepatitis B virus (HBV)-associated liver disease, including hepatocellular carcinoma (HCC). Recently published studies show that in CHB patients treated with the currently recommended first-line nucleos(t)ide analogs (NAs) entecavir or tenofovir, annual HCC incidences range from 0.01% to 1.4% in non-cirrhotic patients, and from 0.9% to 5.4% in those with cirrhosis. In Asian studies including matched untreated controls, current NA therapy consistently resulted in a significantly lower HCC incidence in patients with cirrhosis, amounting to an overall HCC risk reduction of approximately 30%; in non-cirrhotic patients, HCC risk reduction was overall approximately 80%, but this was only observed in some studies. For patients of Caucasian origin, no appropriate comparative studies are available to date to evaluate the impact of NA treatment on HCC. Achievement of a virologic response under current NA therapy was associated with a lower HCC risk in Asian, but not Caucasian studies. Studies comparing entecavir or tenofovir with
older NAs generally found no difference in HCC risk reduction between agents, except for one study which used no rescue therapy in patients developing lamivudine resistance.


BACKGROUND & AIMS: gp96, or grp94, is an endoplasmic reticulum (ER)-localized heat shock protein 90 paralog that acts as a protein chaperone and plays an important role for example in ER homeostasis, ER stress, Wnt and integrin signaling, and calcium homeostasis, which are vital processes in oncogenesis. However, the cancer-intrinsic function of gp96 remains controversial. METHODS: We studied the roles of gp96 in liver biology in mice via an Albumin promoter-driven Cre recombinase-mediated disruption of gp96 gene, hsp90b1. The impact of gp96 status on hepatic carcinogenesis in response to diethyl-nitrosoamine (DENA) was probed. The roles of gp96 on human hepatocellular carcinoma cells (HCC) were also examined pharmacologically with a targeted gp96 inhibitor. RESULTS: We demonstrated that gp96 maintains liver development and hepatocyte function in vivo, and its loss genetically promotes adaptive accumulation of long chain ceramides, accompanied by steatotic regeneration of residual gp96+ hepatocytes. The need for compensatory expansion of gp96+ cells in the gp96- background predisposes mice to develop carcinogen-induced hepatic hyperplasia and cancer from gp96+ but not gp96- hepatocytes. We also found that genetic and pharmacological inhibition of gp96 in human HCCs perturbed multiple growth signals, and attenuated proliferation and expansion. CONCLUSIONS: gp96 is a pro-oncogenic chaperone and an attractive therapeutic target for HCC.


Iron oxide nanoparticles were gaining significant importance in a variety of applications due to its paramagnetic properties and biocompatibility. Various chemical methods were employed for hematite nanoparticle synthesis which require special equipment or a complex production process. In this study, protein capped crystalline hexagonal hematite (alpha-Fe2O3) nanoparticles were synthesized by green approach using culture supernatant of a newly isolated bacterium, Bacillus cereus SVK1 at ambient conditions. The synthesized nanoparticles were characterized by electron microscopy, X-ray diffraction, UV-visible spectroscopy and Fourier transform infrared spectroscopic analysis. Nanoparticles were evaluated for its possible anticancer activity against HepG2 liver cancer cells by MTT assay. Hematite nanoparticles with an average diameter of 30.2nm, exhibited a significant cytotoxicity toward HepG2 cells in a concentration-dependent manner (CTC50=704ng/ml).


A series of fifteen chiral 1,2,3,4-tetrahydroisoquinoline (THIQ) derivatives have been synthesized and their antiproliferative properties have been studied. The in vitro screening was performed against five cancer cell lines; MCF-7 (breast cancer), A549 (lung cancer), DU-145 (prostate cancer), Hela (cervical cancer) and HepG2 (liver cancer). Most of the compounds showed promising activity with IC50 Values ranging from 0.72 to 92.6 mM. Among them, compounds 9a and 9b have shown significant activity against human prostate cancer cell line, i.e., DU-145 with IC50 value 0.72 and 1.23 mM respectively. To investigate the mechanism of action, detailed biological studies of compounds 9a and 9b were carried out on the human prostate cancer cell line, DU-145. Flow cytometric analysis revealed that these compounds induced cell cycle arrest at G2/M phase. Tubulin polymerization assay and immunofluorescence analysis results suggested that these compounds effectively inhibit microtubule assembly formation in DU-145. The apoptosis inducing properties were evaluated by DNA fragmentation analysis, Caspase-3 activity assay, Annexin V-FITC assay and Western blot analysis of proapoptotic protein, Bax and antiapoptotic protein Bcl-2.


INTRODUCTION: Liver cancer is one of the most common cancers. Hepatocellular carcinoma (HCC) represents > 90% of primary liver cancers and is a major global health problem today. Chronic hepatitis B virus (HBV) infection is associated with more than half of HCCs. AREAS COVERED: Long-term therapy with nucleos(t)ide analogues (NUCs) improves outcomes in HBV-infected patients by slowing the progression of liver disease. It is associated with improvements in histological and...
clinical outcomes, improved patient survival, reduced need for liver transplantation and improved liver function in patients with decompensated liver disease. This review highlights the results of previous studies conducted on HCC prevention with long-term NUC therapy. Studies include the use of all available drugs in different clinical scenarios, and the comparison between treated and untreated patients. EXPERT OPINION: NUCs have been studied extensively in HCC prevention. A comprehensive review of the literature has shown that they can be safely and effectively used for this purpose. Despite some discrepancies between studies, most of the evidence favors using NUC therapy for HCC prevention.


CD47 is a signaling receptor for the matricellular protein thrombospondin-1 and a counter-receptor for signal regulatory protein-alpha (SIRPalpha) on macrophages. Following its initial discovery in 1992 as a cell surface protein that is over-expressed by ovarian carcinoma, elevated CD47 expression has emerged as a negative prognostic factor for a variety of cancers. CD47 is also a potential therapeutic target based on the ability of CD47 blockade to cause regression of tumors in mice, and a humanized CD47 antibody has recently entered phase I clinical trials. CD47 blockade may control tumor growth by inhibiting thrombospondin-1 signaling or by preventing inhibitory SIRPalpha signaling in tumor-associated macrophages. A recent publication by Lee et al. (Hepatology 60:179-191, 2014) provides evidence that blocking CD47 signaling specifically depletes tumor-initiating stem cells in hepatocellular carcinoma and implicates cathepsin-S/protease-activated receptor-2 signaling in mediating this therapeutic response.


Variegate porphyria (VP) and acute intermittent porphyria (AIP), the two most common types of acute porphyrias (AHPs), result from a partial deficiency of protoporphyrinogen oxidase (PPOX) and hydroxymethylbilane synthase (HMBS), respectively. A rare but serious complication in the AHPs is hepatocellular carcinoma (HCC). However, the underlying pathomechanisms are yet unknown. We performed DNA sequence analysis in cancerous and non-cancerous liver tissue of a VP and an AIP patient, both with HCC. In samples of both cancerous and non-cancerous liver tissues from the patients, we identified the underlying PPOX and HMBS germline mutations, c.1082dupC and p.G111R, respectively. Additionally, we detected a second somatic mutation, only in the cancer tissue i.e., p.L416X in the PPOX gene of the VP patient and p.L220X in the HMBS gene of the AIP patient, both located in trans to the respective germline mutations. Both somatic mutations were not detected in 10 non-porphyria-associated HCCs. Our data demonstrate that in the hepatic cancer tissue of AHP patients, somatic second-hit mutations result in nearly complete inactivation of the enzymes catalyzing major steps in the heme biosynthetic pathway. Both PPOX and HMBS, which might act as tumor suppressors, play a crucial role in the development of HCC in these individuals.


Genomic analyses promise to improve tumor characterization to optimize personalized treatment for patients with hepatocellular carcinoma (HCC). Exome sequencing analysis of 243 liver tumors identified mutational signatures associated with specific risk factors, mainly combined alcohol and tobacco consumption and exposure to aflatoxin B1. We identified 161 putative driver genes associated with 11 recurrently altered pathways. Associations of mutations defined 3 groups of genes related to risk factors and centered on CTNNB1 (alcohol), TP53 (hepatitis B virus, HBV) and AXIN1. Analyses according to tumor stage progression identified TERT promoter mutation as an early event, whereas FGFI3, FGFI4, FGFI9 or CCND1 amplification and TP53 and CDKN2A alterations appeared at more advanced stages in aggressive tumors. In 28% of the tumors, we identified genetic alterations potentially targetable by US Food and Drug Administration (FDA)-approved drugs. In conclusion, we identified risk factor-specific mutational signatures and defined the extensive landscape of altered genes and pathways in HCC, which will be useful to design clinical trials for targeted therapy.


Hepatocellular carcinoma (HCC), which is a common malignancy worldwide, usually develops in a cirrhotic liver due to hepatitis virus infection. Metabolic syndrome, which is frequently complicated by obesity and diabetes mellitus, is also a critical risk
factor for liver carcinogenesis. Green tea catechins (GTCs) may possess potent anticancer and chemopreventive properties for a number of different malignancies, including liver cancer. Antioxidant and anti-inflammatory activities are key mechanisms through which GTCs prevent the development of neoplasms, and they also exert cancer chemopreventive effects by modulating several signaling transduction and metabolic pathways. Furthermore, GTCs are considered to be useful for the prevention of obesity- and metabolic syndrome-related carcinogenesis by improving metabolic disorders. Several interventional trials in humans have shown that GTCs may ameliorate metabolic abnormalities and prevent the development of precancerous lesions. The purpose of this article is to review the key mechanisms by which GTCs exert chemopreventive effects in liver carcinogenesis, focusing especially on their ability to inhibit receptor tyrosine kinases and improve metabolic abnormalities. We also review the evidence for GTCs acting to prevent metabolic syndrome-associated liver carcinogenesis.


Primary pancreatic hepatoid carcinoma (PHC) is extremely rare, resembling hepatocellular carcinoma (HCC) in terms of morphology and immunohistochemical features. Hepatoid carcinoma can present in other organs, most noticeably in the stomach. PHC is present in two forms either a pure form like HCC or admixed with other histologic tumor components characteristic of the underlying primary site (endocrine tumors, ductal, or acinar adenocarcinomas). Here, we report a 69-year-old male patient with distal pancreatic mass incidentally found during a CT scan workup for a pulmonary nodule suspicious for metastatic prostate adenocarcinoma. We described the clinical, cytological, and histological finding and conducted a literature review.


BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) associated macrophages accelerate tumor progression by growth factor release. Therefore, tumor-associated macrophages (TAM) and their initiated signaling cascades are potential therapeutic targets. Aiming at understanding anticancer effects of systemic HCC therapy, we investigated the impact of sorafenib on macrophage function, focusing on macrophage-related growth factor secretion.

METHODS: Macrophage markers, cytokine and growth factor release were investigated in CSF-1 (M1) or GMCSF (M2) matured monocyte-derived macrophages. Macrophages were treated with sorafenib (1.2-5.0µg/ml) and culture supernatants were transferred to hepatoma cell cultures to assess growth propagation. Insulin-like growth factor (IGF) signaling was blocked with NVP-AEW541 to confirm the role of IGF-1 in macrophage-driven hepatoma cell propagation. Macrophage activation was followed by ELISA of serum soluble mCD163 in sorafenib-treated patients with HCC. RESULTS: Alternative macrophages (M2), which showed higher IGF-1 (p=0.022) and CD163 mRNA (p=0.032) expression compared to classical macrophages (M1), increased hepatoma growth. This effect was mediated by M2-conditioned culture media. In turn, sorafenib lowered mCD163 and IGF-1 release by M2 macrophages, which decelerated M2 macrophage driven HuH7 and HepG2 proliferation by 47% and 64%, respectively. IGF-receptor blockage with NVP-AEW541 reduced growth induction by M2-conditioned culture media in a dose dependent manner. A transient mCD163 reduction during sorafenib treatment indicated a coherent M2 macrophage inhibition in patients with HCC. CONCLUSIONS: Sorafenib alters macrophage polarization, reduces IGF-1-driven cancer growth in vitro and partially inhibits macrophage activation in vivo. Thus macrophage modulation might contribute to the anti-cancer activity of sorafenib. However, more efficient macrophage-directed therapies are required.


Some have suggested that the current fee-for-service healthcare payment system in the United States stifles innovation. However, there are few published examples supporting this concept. We implemented an innovative temporary balloon occlusion technique for yttrium 90 radioembolization of nonresectable liver cancer. Although our balloon occlusion technique was associated with similar patient outcomes, lower cost, and faster procedure times compared with the standard-of-care coil embolization technique, our technique failed to gain widespread acceptance. Financial analysis revealed that because the balloon occlusion technique avoided a procedural step associated with a lucrative Current Procedural Terminology billing code, this new technique resulted in a significant decrease in hospital and physician revenue in the current fee-for-service payment system, even though the new technique
would provide a revenue enhancement through cost savings in a bundled payment system. Our analysis illustrates how in a fee-for-service payment system, financial disincentives can stifle innovation and advancement of health care delivery.


PURPOSE: To assess the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in patients with unresectable intermediate- or advanced-stage hepatocellular carcinoma (HCC) treated with yttrium-90 radioembolization (RE). MATERIALS AND METHODS: Retrospective chart review was performed for 176 patients with intermediate- or advanced-stage HCC treated with RE between August 2000 and November 2012. The appropriate NLR cutoff was determined by receiver operating characteristic curves. Demographic, clinical, radiographic, and pathologic parameters were compared between patients with a normal NLR (< 5) and those with an elevated NLR (≥ 5) before RE. Barcelona Clinic Liver Cancer (BCLC) stage-stratified univariate and multivariate analyses were conducted to determine variables associated with overall survival. RESULTS: Under univariate analyses, patients with a normal NLR were found to have longer survival than individuals with a high NLR in intermediate/advanced-disease and advanced-disease cohorts. A multivariate Cox proportional-hazards model in the advanced-disease group confirmed that elevated NLR, high alpha-fetoprotein level, and low albumin level were independent predictors of worse survival. CONCLUSIONS: This study provides stage-dependent evidence for the prognostic role of NLR in the radioembolized HCC cohort. Patients with BCLC stage C disease with elevated NLR may not derive benefit from RE, and other intervening modalities should be explored in this subpopulation.


PURPOSE OF REVIEW: Recently, it has been suggested that hepatocytes can potentially convert their fate into that of cholangiocytes when the liver receives an injury. This review concisely summarizes these new findings, especially those obtained in studies using cell-lineage tracing methods.

RECENT FINDINGS: Recent advances in technologies using mutant mice with a tamoxifen-inducible Cre/loxP system have allowed heritable labeling of a particular type of cell and enabled us to follow the fate of their progeny. This is generally known as 'genetic lineage-tracing', and has been applied in various studies that require tracking of the fate of cells in living mice. Previous studies using these methods have revealed that hepatocytes themselves can give rise to cholangiocytes through Notch-mediated cell-fate conversion from hepatocytes to cholangiocytes in injured liver tissue and at the onset of liver cancer. SUMMARY: Intensive studies using in-vivo genetic lineage-tracing approaches have provided new insights into the nature of cellular identity and plasticity in the liver, which will contribute to the development of new therapeutic strategies for liver diseases.

Although the only effective drug against primary hepatocarcinoma, the multikinase inhibitor Sorafenib (SFB) usually fails to eradicate liver cancer. Since SFB targets mitochondria, cell metabolic reprogramming may underlie intrinsic tumor resistance. To characterize cancer cell metabolic response to SFB, we measured oxygen consumption, generation of reactive oxygen species (ROS) and ATP content in rat LCSC (Liver Cancer Stem Cells) -2 cells exposed to the drug. Genome wide analysis of gene expression was performed by Affymetrix technology. SFB cytotoxicity was evaluated by multiple assays in the presence or absence of metabolic inhibitors, or in cells genetically depleted of mitochondria. We found that low concentrations (2.5-5 μM) of SFB had a relatively modest effect on LCSC-2 or 293 T cell growth, but damaged mitochondria and increased intracellular ROS. Gene expression profiling of SFB-treated cells was consistent with a shift toward aerobic glycolysis and, accordingly, SFB cytotoxicity was dramatically increased by glucose withdrawal or the glycolytic inhibitor 2-DG. Under metabolic stress, activation of the AMP dependent Protein Kinase (AMPK), but not ROS blockade, protected cells from death. We conclude that mitochondrial damage and ROS drive cell killing by SFB, while glycolytic cell reprogramming may represent a resistance strategy potentially targetable by combination therapies.


This study was conducted to clarify the role of cytoglobin (Cygb), a globin expressed in hepatic stellate cells (HSCs), in the development of liver fibrosis and cancer in nonalcoholic steatohepatitis (NASH). Cygb expression was assessed in patients with NASH and hepatocellular carcinoma. Mouse NASH model was generated in Cygb-deficient (Cygb(-/-)) or wild-type (WT) mice by giving a choline-deficient amino acid-defined diet and, in some of them, macrophage depletion and N-acetyl cysteine treatment were used. Primary-cultured mouse HSCs isolated from WT (HSCs(Cygb-wild)) or Cygb(-/-) (HSCs(Cygb-null)) mice were characterized. As results, the expression of CYGB was reduced in patients with NASH and hepatocellular carcinoma. Choline-deficient amino acid treatment for 8 weeks induced prominent inflammation and fibrosis in Cygb(-/-) mice, which was inhibited by macrophage deletion. Surprisingly, at 32 weeks, despite no tumor formation in the WT mice, all Cygb(-/-) mice developed liver cancer, which was ameliorated by N-acetyl cysteine treatment. Altered expression of 31 genes involved in the metabolism of reactive oxygen species was notable in Cygb(-/-) mice. Both HSCs(Cygb-null) and Cygb siRNA-transfected-HSCs(Cygb-wild) exhibited the preactivation condition. Our findings provide important insights into the role that Cygb, expressed in HSCs during liver fibrosis, plays in cancer development with NASH.


Alcoholic liver disease (ALD) should be defined as a life-style metabolic disease. Its pathogenesis is driven by altered cell fate of both parenchymal and non-parenchymal liver cell types, contributing to different pathologic spectra. A critical turning point in progression of ALD is chronic alcoholic steatohepatitis (ASH) or alcoholic neutrophilic hepatitis (AH), which markedly predisposes patients to most devastating ALD sequela, cirrhosis and liver cancer. RESULTS: Our research identifies the pivotal roles of unique metabolic reprogramming in M1 activation of hepatic macrophages (HM) and myofibroblastic activation (MF) of hepatic stellate cells (HSC) in the genesis of inflammation and fibrosis, the two key histological features of chronic ASH and neutrophilic AH. For M1 HM activation, heightened proinflammatory iron redox signaling in endosomes or caveosomes results from altered iron metabolism and storage, promoting IKK/NF-κB activation via interactive activation of p21ras, TAK1, and PI3K. For MF cell fate regulation of HSC, activation of the morphogen Wnt pathway caused by the nuclear protein NEDDIN or the single-pass trans-membrane protein DLK1, reprograms lipid metabolism via MeCP2-mediated epigenetic repression of the key HSC quiescence gene Ppar-gamma.


Establishing a transcriptomic profile of human hepatocellular liver cancer (HCC) progression is a complex undertaking. A rat model of HCC was employed to develop a transcriptomic profile. Using three interventions, preneoplastic lesions appeared after 30 days and they progressed to HCC by 9 months. Preneplastic and cancer lesions were characterized for transcriptomic analysis, and RNA
BACKGROUND: One established model to induce hepatic preneoplasia (HP) (DEN 150) uses diethylnitrosamine (DEN) as initiator agent and 2-acetylamino-fluorene (2-AAF) as a promoter drug. In addition, both chemicals cause liver cholestasis and fibrosis. AIM: We compared DEN 150 model with another adapted by us, DEN 200 to simplify the first one and to evaluate the effectiveness of both treatments to induce HP in rats. MATERIAL AND METHODS: Male Wistar rats were divided in 3 groups: controls; DEN 150 (rats received 2 doses of DEN, 150 mg/kg body weight, 2 weeks apart, and then 2-AAF, 20 mg/kg body weight, 4 doses per week during 3 weeks); and DEN 200 (rats received a single dose of DEN 200 mg/kg body weight, and 2 weeks apart 2-AAF, 20 mg/kg body weight, 2 doses per week during 3 weeks). Four hepatic enzymes, prothrombin time percentage, the number of bile ductules, total collagen amount, the number of altered hepatic foci (AHF) per liver and the percentage of liver occupied by foci were analyzed. Results. There were no differences in the number of AHF per liver between treated groups. Rats from DEN 200 group showed a significant diminution in the volume of liver occupied by foci. DEN 200 group had no fibrosis and better hemostatic conditions than DEN 150 group. Both groups developed cholestasis.


Primary liver cancer, the majority of which are hepatocellular carcinomas, is now the second leading cause of cancer death worldwide. Hepatocellular carcinoma is a unique cancer that typically arises in the setting of chronic liver disease at a rate dependent upon the complex interplay between the host, disease and environmental factors. Infection with chronic hepatitis B or C virus is currently the dominant risk factor worldwide. However, changing lifestyle and environmental factors in western countries plus rising neonatal hepatitis B vaccination rates and decreasing exposure to dietary aflatoxins in developing countries are driving an evolution of the epidemiology of this cancer. An understanding of this change is crucial in combating the rising incidence currently being seen in western regions and will underpin the efforts to reduce the mortality rates associated with this cancer.

Purpose: To evaluate whether hepatic arterial infusion concurrent chemoradiotherapy (CCRT) could improve overall survival (OS) in patients with locally advanced hepatocellular carcinoma (LAHCC). Materials and Methods: Two databases were reviewed from Yonsei Cancer Center (YCC) and KLCSG nationwide multi-center HCC cohort. The CCRT group included 106 patients, with stage III-IV, Child-Pugh classification A, Eastern Cooperative Oncology Group performance status 0 or 1, who underwent definitive CCRT as the initial treatment at YCC. We used propensity score matching to adjust for seven clinical factors, including age, tumor size, TNM stage by the Liver Cancer Study Group of Japan, T stage, BCLC staging system, etiology of HCC, and portal vein invasion (PVI), which all differed significantly in the two databases. From the KLCSG cohort enrolled at 32 institutions, 106 patients for the non-CCRT group were defined. Results: After propensity score matching, all patient characteristics were balanced between the two groups. The CCRT group had better OS (median 11.4) than the non-CCRT group (6.6 months; p = 0.02). In multivariate analyses for all patients, CCRT (hazard ratio (HR) 1.48; 95% confidence interval (CI) 1.11-1.97; p = 0.007), tumor size (HR 1.08; 95% CI 1.04-1.12; p < 0.001), and BCLC stage (HR 0.54; 95% CI 0.36-0.8; p = 0.003) were independent prognostic factors for OS. Conclusion: CCRT showed better OS for LAHCC patients. In LAHCC patients with a good performance and normal liver function, CCRT could be a feasible treatment option. All of these findings need to be validated in prospective clinical trials.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References


