Liver Cancer Literature Update

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Genotoxic activities of wastewater after ozonation and activated carbon filtration: Different effects in liver-derived cells and bacterial indicators.

Related Articles

Genotoxic activities of wastewater after ozonation and activated carbon filtration: Different effects in liver-derived cells and bacterial indicators.

Water Res. 2020 Aug 21;186:116328
Authors: Mišík M, Ferk F, Schaar H, Yamada M, Jaeger W, Knasmueller S, Kreuzinger N

Abstract

Aim of this study was to investigate the impact of advanced wastewater treatment techniques (combining ozonation with activated carbon filtration) on acute and genotoxic activities of tertiary treated wastewater. Concentrated samples were tested in Salmonella/microsome assays. Furthermore, induction of DNA damage was measured in liver-derived cells (human hepatoma and primary rat hepatocytes) in single cell gel electrophoresis experiments, which are based on the measurement of DNA migration in an electric field. These cell types possess phase I and phase II enzymes, which catalyze the activation/detoxification of mutagens. Acute toxicity was determined with the trypan blue exclusion technique. We found no evidence for mutagenic effects of non-ozonated samples in several bacterial tester strains (TA98, TA100, YG7108, YG7104, YG7112 and YG7113) but clear induction of His+ mutants after O3 treatment in two strains with defective genes encoding for DNA repair, which are highly sensitive towards alkylating agents (YG7108 and YG7104). These effects were reduced after activated carbon filtration. Furthermore, we detected a slight increase of mutagenic activity in strain YG1024 with increased acetyltransferase activity, which is sensitive towards aromatic amines and nitro compounds in untreated water, which was not reduced by O3 treatment. A completely different pattern of mutagenic activity was seen in liver-derived cells; non ozonated samples caused in both cell types pronounced DNA damage, which was reduced (by ca. 25%) after ozonation. Activated carbon treatment did not cause a substantial further reduction of DNA damage. Additional experiments with liver homogenate indicate that the compounds which cause the effects in the human cells are promutagens which require enzymatic activation. None of the waters caused acute toxicity in the liver-derived cells and in the bacterial indicators. Assuming that hepatic mammalian cells reflect the genotoxic properties of the waters in vertebrates (including humans) more adequately as genetically modified bacterial indicators, we conclude that ozonation has beneficial effects in regard to the reduction of genotoxic properties of treated wastewaters.

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

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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 =
UTF was significantly higher in patients with sarcopenia (P = 0.04), and showed statistically significant negative correlations with albumin (r = -2.14, P = 0.02), 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.

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Related Articles

Superior outcomes of nodal metastases compared to visceral sites in oligometastatic colorectal cancer treated with stereotactic ablative radiotherapy.

Radiother Oncol. 2020 Aug 28;:

Abstract
BACKGROUND: Stereotactic ablative radiotherapy (SBRT) is a radical option for oligometastatic colorectal cancer (CRC) patients, but most data relate to visceral metastases.

METHODS: A prospective, multi-centre database of CRC patients treated with SBRT was interrogated. Inclusion criteria were ECOG PS 0–2, ≤ 3 sites of disease, a disease free interval of > 6 months unless synchronous liver metastases. Primary endpoints were local control (LC), progression free survival (PFS) and overall survival (OS).

RESULTS: 163 patients (172 metastases) were analysed. The median FU was 16 months (IQR 12.2 — 22.83). The LC at 1 year was 83.8% (CI 76.4% — 91.9%) with a PFS of 55% (CI 47% — 64.7%) respectively. LC at 1 year was 90% (CI 83% — 99%) for nodal metastases (NM), 75% (63% — 90%) for visceral metastases (VM). NM had improved median PFS (9 vs 19 months) [HR 0.6, CI 0.38 — 0.94, p = 0.032] and median OS (32 months vs not reached) [HR 0.28, CI 0.18 — 0.7, p = 0.0062] than VM, regardless of whether the NM were located inside or outside the pelvis. On multivariate analysis, NM and ECOG PS 0 were significant good prognostic factors. An exploratory analysis suggests KRAS WT is also a good prognostic factor.

CONCLUSION: Nodal site is an important prognostic determinant of SBRT that should incorporated into patient selection. We hypothesise this may have an immunoediting basis.

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Matrine promotes hepatic oval cells differentiation into hepatocytes and alleviates liver injury by suppression of Notch signalling pathway.

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Matrine promotes hepatic oval cells differentiation into hepatocytes and alleviates liver injury by suppression of Notch signalling pathway.

Life Sci. 2020 Aug 28;118354
Authors: Shi J, Han G, Wang J, Han X, Zhao M, Duan X, Mi L, Li N, Yin X, Shi H, Li C, Xu J, Yin F

Abstract
AIMS: Recent studies have shown that the hyperactive Notch pathway is involved in cirrhosis and hepatocellular carcinoma (HCC) development by regulating differentiation of hepatic oval cells (HOCs) into cancer cells. The aim of this study was to investigate whether matrine can alleviate liver injury and promote HOC differentiation into hepatocytes by suppression of Notch pathway.

MAIN METHODS: We evaluated the expression of Notch-1, Jagged-1, and Hes-1 in HCC tissue by immunohistochemistry. Stem cell characteristics of HOCs were evaluated by CCK-8, cell cycle, and apoptosis. The expression of Notch pathway, HOC markers and albumin (ALB) was detected by immunohistochemistry, QRT-PCR and western blotting. The effects of matrine in protecting liver in vivo were investigated in a rat Solt-Farber precancerous model.

KEY FINDINGS: We found an abnormal activated Notch pathway in HCC tissue, and the hyperactive Notch pathway was strongly associated with poor liver function in patients with cirrhosis with HCC. Using siNotch-1 to inhibit Notch pathway confirmed that Notch pathway could maintain stem cell characteristics of HOCs. Matrine inhibited stem cell characteristics of HOCs, the expression of Notch pathway and HOC markers but upregulated ALB. Matrine in combined with siNotch-1 RNA decreased the more potently inhibited HOC markers and Notch pathway. In rat Solt-Farber precancerous model, prophylactic application of matrine alleviated liver injury, downregulated Notch pathway and HOC markers, and upregulated ALB in a dose-dependent manner.

SIGNIFICANCE: Matrine could promote the differentiation of HOCs into hepatocytes by inhibiting the Notch signalling pathway and alleviate liver injury.

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Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study.

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Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study.

Lancet Gastroenterol Hepatol. 2020 Aug 28;:

Abstract
BACKGROUND: Despite concerns that patients with liver transplants might be at increased risk of adverse outcomes from COVID-19 because of coexisting comorbidities and use of immunosuppressants, the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on this patient group remains unclear. We aimed to assess the clinical outcomes in these patients.

METHODS: In this multicentre cohort study, we collected data on patients with laboratory-confirmed SARS-CoV-2 infection, who were older than 18 years, who had previously received a liver transplant, and for whom data had been submitted by clinicians to one of two international registries (COVID-Hep and SECURE-Cirrhosis) at the end of the patient’s disease course. Patients without a known hospitalisation status or mortality outcome were excluded. For comparison, data from a contemporaneous cohort of consecutive patients with SARS-CoV-2 infection who had not received a liver transplant were collected from the electronic patient records of the Oxford University Hospitals National Health Service Foundation Trust. We compared the cohorts with regard to several outcomes (including death, hospitalisation, intensive care unit [ICU] admission, requirement for intensive care, and need for invasive ventilation). A propensity score-matched analysis was done to test for an association between liver transplant and death.

FINDINGS: Between March 25 and June 26, 2020, data were collected for 151 adult liver transplant recipients from 18 countries (median age 60 years [IQR 47–66], 102 [68%] men, 49 [32%] women) and 627 patients who had not undergone liver transplantation (median age 73 years [44–84], 329 [52%] men, 298 [48%] women). The groups did not differ with regard to the proportion of patients hospitalised (124 [82%] patients in the liver transplant cohort vs 474 [76%] in the comparison cohort, p=0.106), or who required intensive care (47 [31%] vs 185 [30%], p=0.837). However, ICU admission (43 [28%] vs 52 [8%], p=0.038). The combination of galunisertib and sorafenib showed acceptable safety and a prolonged OS outcome.

PMID: 31295152 [PubMed — indexed for MEDLINE]
Variable Features of Juvenile Polyposis Syndrome With Gastric Involvement Among Patients With a Large Genomic Deletion of BMPR1A.

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Variable Features of Juvenile Polyposis Syndrome With Gastric Involvement Among Patients With a Large Genomic Deletion of BMPR1A.

Clin Transl Gastroenterol. 2019 07;10(7):e00054


Abstract

OBJECTIVES: Loss-of-function mutations of BMPR1A cause juvenile polyposis syndrome (JPS), but large genomic deletions in BMPR1A are rare, reported in few families only, and data regarding the associated phenotype are limited.

METHODS: We investigated clinical features and genomic data of 7 extended seemingly unrelated families with a genomic deletion of the entire coding region of BMPR1A. We defined mutation size, mutation prevalence, and tumor pathogenesis using whole-genome sequencing, targeted genotyping, and haplotype analysis.

RESULTS: Patients with JPS from 7 families of Bukharin Jewish ancestry carried a deletion of 429 kb, encompassing the BMPR1A coding sequence and 8 downstream genes. Haplotype analysis and testing controls identified this as a common founder mutation occurring in 1/124 individuals of Bukharin origin. Tumor testing did not demonstrate loss of heterozygosity. Among carriers, JPS was almost fully penetrant, but clinical features varied widely, ranging from mild to very severe, including pan-enteric polyps, gastritis, and colorectal, esophageal, and testicular cancer, and carriers with phenotypes, which would not have raised suspicion of JPS.

DISCUSSION: The phenotype in this large cohort was extremely variable, although all carriers shared the same variant and the same genetic background. New observations include a preponderance of adenomatous rather than juvenile polyps, possible association with testicular cancer, and unexpected upper gastrointestinal involvement.

PMID: 31259752 [PubMed — indexed for MEDLINE]

MicroRNA-301b-3p contributes to tumour growth of human hepatocellular carcinoma by repressing vestigial like family member 4.

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MicroRNA-301b-3p contributes to tumour growth of human hepatocellular carcinoma by repressing vestigial like family member 4.


Abstract

MicroRNAs (miRNAs) are key regulators in the tumour growth and metastasis of human hepatocellular carcinoma (HCC). Increasing evidence suggests that miR-301b-3p functions as a driver in various types of human cancer. However, the expression pattern of miR-301b-3p and its functional role as well as underlying molecular mechanism in HCC remain poorly known. Our study found that miR-301b-3p expression was significantly up-regulated in HCC tissues compared to adjacent non-tumour tissues. Clinical association analysis revealed that the high level of miR-301b-3p closely correlated with large tumour size and advanced tumour-node-metastasis stages. Importantly, the high miR-301b-3p level predicted a prominent poorer overall survival of HCC patients. Knockdown of miR-301b-3p suppressed cell proliferation, led to cell cycle arrest at G2/M phase and induced apoptosis of Huh7 and Hep3B cells. Furthermore, miR-301b-3p knockdown suppressed tumour growth of HCC in mice. Mechanistically, miR-301b-3p directly bond to 3'UTR of vestigial like family member 4 (VGLL4) and negatively regulated its expression. The expression of VGLL4 mRNA was down-regulated and inversely correlated with miR-301b-3p level in HCC tissues. Notably, VGLL4 knockdown markedly repressed cell proliferation, resulted in G2/M phase arrest and promoted apoptosis of HCC cells. Accordingly, VGLL4 silencing rescued miR-301b-3p knockdown attenuated HCC cell proliferation, cell cycle progression and apoptosis resistance. Collectively, our results suggest that miR-301b-3p is highly expressed in HCC. miR-301b-3p facilitates cell proliferation, promotes cell cycle progression and inhibits apoptosis of HCC cells by repressing VGLL4.

PMID: 31207037 [PubMed — indexed for MEDLINE]
Extracellular vesicles-derived OncomiRs mediate communication between cancer cells and cancer-associated hepatic stellate cells in hepatocellular carcinoma microenvironment.

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Carcinogenesis. 2020 04 22;41(2):223–234


Abstract

Tumor microenvironment (TME) is a critical determinant for hepatocellular carcinoma (HCC). Hepatic stellate cells (HSCs) are main interstitial cells in TME and play a vital role in early intrahepatic invasion and metastasis of HCC. The potential mechanism on the interactions between HSCs and HCC cells remains unclear. In this study, the effects of extracellular vesicles (EVs)-derived OncomiRs that mediate communication between HCC cells and cancer-associated hepatic stellate cells (caHSCs) and remodel TME were investigated. The results found that the HCC cells-released EVs contained more various OncomiRs, which could activate HSCs (LX2 cells) and transform them to caHSCs, the caHSCs in turn exerted promotion effects on HCC cells through HSCs-released EVs. To further simulate the effects of OncomiRs in EVs on construction of pro-metastatic TME, a group of OncomiRs, miR-21, miR-221 and miR-151 was transfected into HCC cells and LX2 cells. These microRNAs in the EVs from OncomiRs-enhanced cells were demonstrated to have oncogenic effects on HCC cells by upregulating the activities of protein kinase B (AKT)/extracellular signal-regulated kinase (ERK) signal pathways. Equivalent results were also found in HCC xenografted tumor models. The findings suggested that the OncomiR secretion and transference by cancer cells-released EVs can mediate the communication between HCC cells and HSCs. HCC cells and caHSCs, as well as their secreted EVs, jointly construct a pro-metastatic TME suitable for invasion and metastasis of cancer cells, all these TME components form a positive feedback loop to promote HCC progression and metastasis.

PMID: 31140556 [PubMed — indexed for MEDLINE]