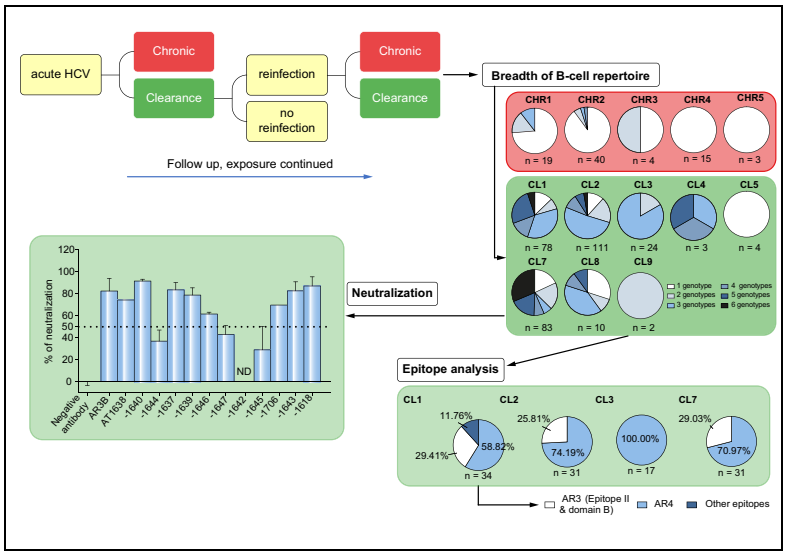
July 2019

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Cross-genotype AR3-specific neutralizing antibodies confer long-term protection in injecting drug users after HCV clearance

Graphical abstract



Highlights

- HCV clearance is associated with a high number of cross-genotype specific antibodies.
- Antigenic region 3 (AR3) is the dominant epitope recognized by the antibodies.
- AR3-specific antibodies neutralized HCV pseudoparticles and cell culture viruses.
- A large number of clearers develop antibodies targeting antigenic region 4 (AR4).
- AR4-specific antibody AT1618 also neutralized neutralization-resistant variants.

Authors

Sabrina J. Merat, Camille Bru, Dorien van de Berg, ..., Hergen Spits, Tim Beaumont, Janke Schinkel

Correspondence

tbeaumont@aimmtherapeutics.com (T. Beaumont), j.schinkel@amsterdamumc.nl (J. Schinkel)

Lay summary

Although effective treatments against hepatitis C virus (HCV) are available, 500,000 people die from liver disease caused by HCV each year and approximately 1.75 million people are newly infected. This could be prevented by a vaccine. To design a vaccine against HCV, more insight into the role of antibodies in the protection against HCV infection is needed. In a cohort of injecting drug users, we found that antibodies interfering with virus cell entry, and recognizing multiple HCV genotypes, conferred long-term protection against chronic HCV infection.

https://doi.org/10.1016/j.jhep.2019.02.013

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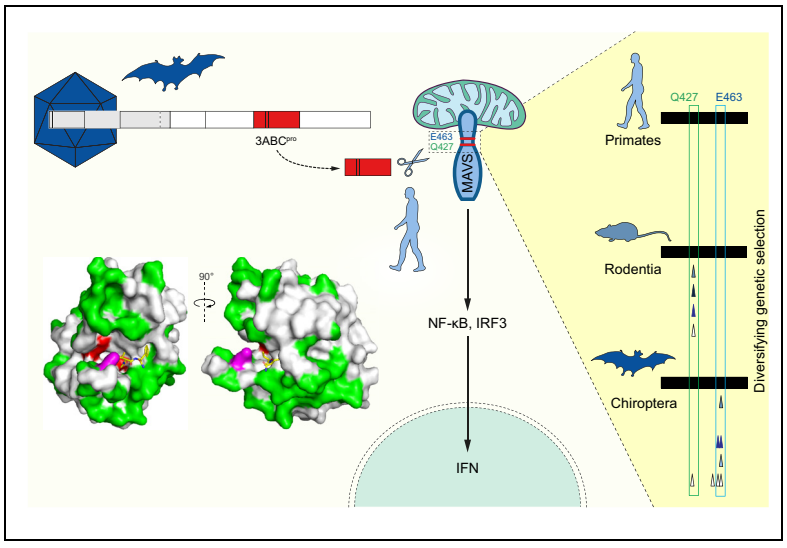
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Hepatovirus 3ABC proteases and evolution of mitochondrial antiviral signaling protein (MAVS)

Graphical abstract



Highlights

- 3ABC proteases expressed by bat hepatoviruses cleave human MAVS at Glu^{463}/Gly^{464}.
- Bat hepatovirus 3ABC proteases disrupt viral activation of interferon-β in human cells.
- MAVS orthologs from rodents and bats resist cleavage by cognate hepatovirus 3ABC proteases.
- Bat and rodent MAVS orthologs have been subject to diversifying selection at 3ABC cleavage sites.
- Cross-species disruption of MAVS signaling by 3ABC may facilitate hepatovirus host species shifts.

Authors

Hui Feng, Anna-Lena Sander, Andrés Moreira-Soto, Daisuke Yamane, Jan Felix Drexler, Stanley M. Lemon

Correspondence

smlemon@med.unc.edu
(S.M. Lemon)

Lay summary

Hepatitis A virus, a common cause of acute hepatitis globally, is likely to have evolved from a virus that jumped from a rodent species to humans within the last 10–12 thousand years. Here we show that distantly related hepatoviruses, that infect bats and rodents today, express proteases that disrupt innate antiviral responses in human cells. This conserved attribute of hepatoviruses may have contributed to that ancient host species shift.

https://doi.org/10.1016/j.jhep.2019.02.020

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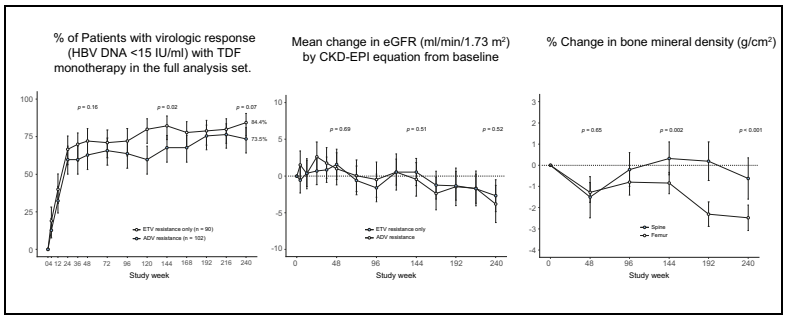
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Monotherapy with tenofovir disoproxil fumarate for adefovir-resistant *vs.* entecavir-resistant chronic hepatitis B: A 5-year clinical trial

Graphical abstract



Highlights

- 240 weeks of TDF monotherapy provided an increasing virologic response rate in patients with multidrug-resistant HBV.
- Virologic breakthrough was rare and not associated with emergence of additional resistance mutations.
- The HBeAg seroconversion rate was very low and no patient achieved HBsAg seroclearance up to week 240.
- Prolonged continuous treatment may be needed to maintain viral suppression in these patients.
- Progressive and significant decreases in renal function and bone mineral density after week 144 raise safety concerns.

Authors

Young-Suk Lim, Geum-Youn Gwak, Jonggi Choi, ..., Byung Chul Yoo, So Young Kwon, Han Chu Lee

Correspondence

limys@amc.seoul.kr (Y.-S. Lim), hch@amc.seoul.kr (H.C. Lee).

Lay summary

In patients chronically infected with hepatitis B virus resistant to multiple drugs including lamivudine, entecavir, and/or adefovir, tenofovir disoproxil fumarate (TDF) monotherapy showed non-inferior efficacy compared with the combination therapy of TDF plus entecavir. Nonetheless, short-term TDF monotherapy was associated with suboptimal virologic response, and its long-term safety was uncertain. This study displayed that 240 weeks of TDF monotherapy provided a virologic response in most of those patients, but it was associated with poor serological responses and decreasing renal function and bone mineral density.

https://doi.org/10.1016/j.jhep.2019.02.021

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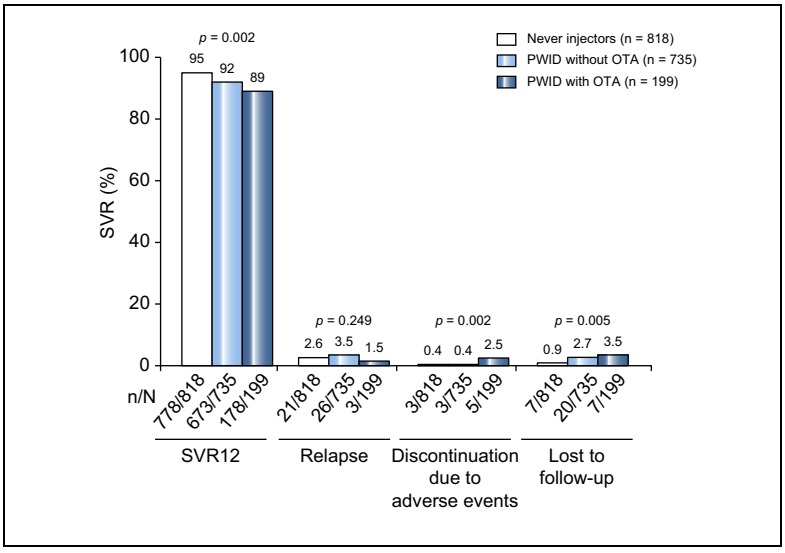
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Response to direct-acting antiviral therapy among ongoing drug users and people receiving opioid substitution therapy

Graphical abstract



Highlights

- HCV-infected PWID achieve high SVR12 rates with IFN-free antiviral regimens in clinical practice.
- PWID have lower SVR12 rates than patients who never used drugs.
- Active drug use during antiviral treatment was an independent predictor of lower response, opioid agonist therapy was not.
- The main reasons for non-response among PWID are discontinuations due to adverse events and, particularly, drop-outs.

Authors

Juan Macías, Luis E. Morano, Francisco Téllez, ..., Antonio Rivero, Federico García, Juan A. Pineda

Correspondence

juan.macias.sanchez@gmail.com
(J. Macías)

Lay summary

Patients with hepatitis C virus infection who are on opioid agonist therapy can achieve high cure rates with current treatments. The use of illicit drugs during treatment can drive drop-outs and reduce cure rates. However, hepatitis C can be cured in most of those using drugs who complete treatment and follow-up.

https://doi.org/10.1016/j.jhep.2019.02.018

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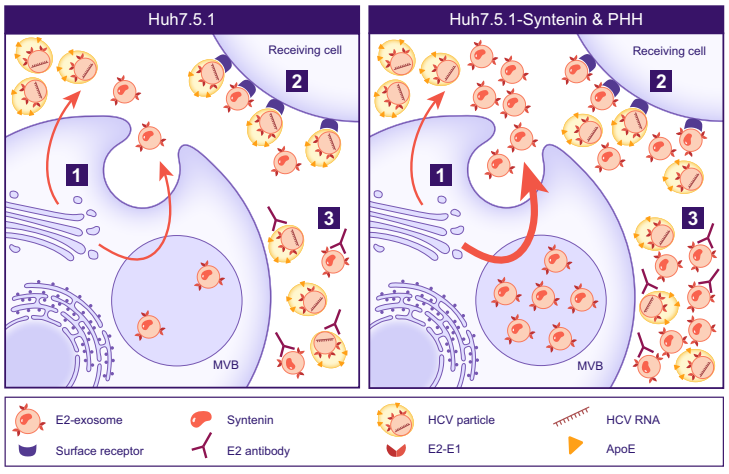
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Syntenin regulates hepatitis C virus sensitivity to neutralizing antibody by promoting E2 secretion through exosomes

Graphical abstract



Highlights

- Syntenin is a key determinant of the efficiency of E2-coated exosome production.
- E2-coated exosome biogenesis is independent of HCV infectious lipo-viral-particle production.
- Robust E2-coated exosome production assists HCV infection in the presence of neutralizing antibody.

Authors

Libin Deng, Wang Jiang, Xiaoning Wang, ..., Junqi Niu, Ralf Bartenschlager, Gang Long

Correspondence

glong@ips.ac.cn
(G. Long)

Lay summary

This study identifies a key role for syntenin in the regulation of E2 secretion via exosomes. Efficient production of E2-coated exosomes was shown to make hepatitis C virus less sensitive to antibody neutralization. These results may have implications for the development of an hepatitis C virus vaccine.

https://doi.org/10.1016/j.jhep.2019.03.006

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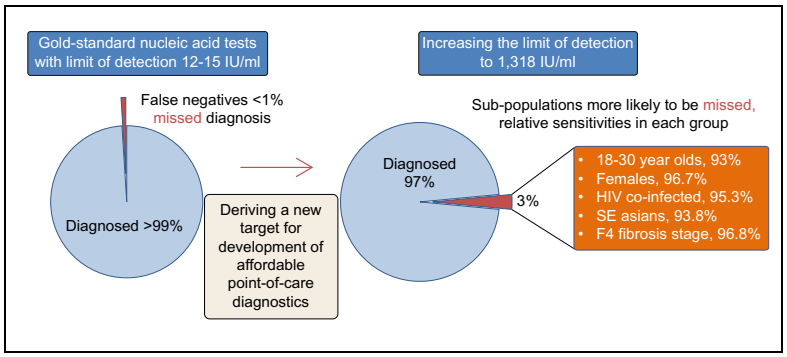
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Deriving the optimal limit of detection for an HCV point-of-care test for viraemic infection: Analysis of a global dataset

Graphical abstract



Highlights

- >97% of those with chronic hepatitis C virus have viraemia >1,318 IU/ml.
- Low-level viraemia among 66,640 individuals did not vary significantly by genotype.
- The sensitivity of HCV diagnostic tests was maintained even when increasing the detection limit by 100×.

Authors

J. Morgan Freiman, Jianing Wang, Philippa J. Easterbrook, ..., Tengiz Tsertsvadze, Claudia M. Denkinger, Benjamin Linas

Correspondence

j.morgan.freiman@bmc.org (J.M. Freiman) Benjamin.linas@bmc.org (B. Linas)

Lay summary

We created and analysed a dataset from 12 countries with 66,640 participants with chronic hepatitis C virus infection. We determined that about 97% of those with viraemic infection had 1,300 IU/ml or more of circulating virus at the time of diagnosis. While current diagnostic tests can detect as little as 12 IU/ml of virus, our findings suggest that increasing the level of detection closer to 1,300 IU/ml would maintain good test accuracy and will likely enable development of more affordable portable tests for use in low- and middle-income countries.

https://doi.org/10.1016/j.jhep.2019.02.011

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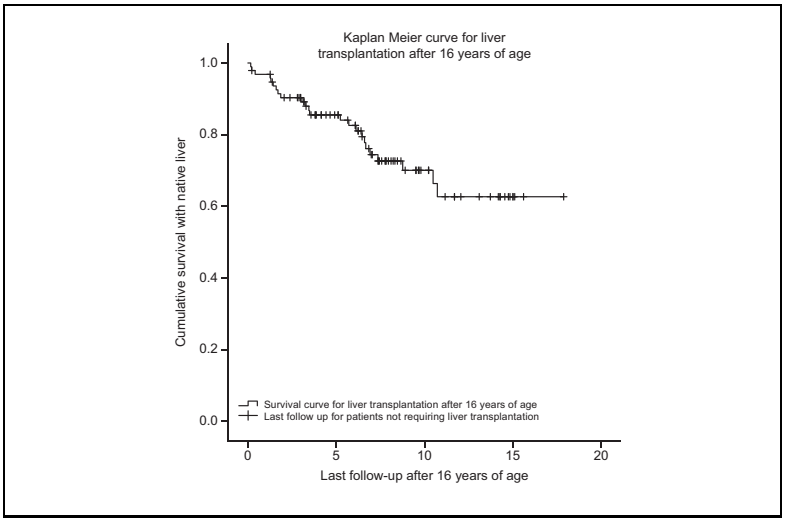
Research Article
Transplantation

JOURNAL
OF HEPATOLOGY

Prognostic markers at adolescence in patients requiring liver transplantation for biliary atresia in adulthood

Graphical abstract



Highlights

- Patients with biliary atresia are at risk of needing a liver transplant when >16 years old.
- Higher bilirubin and lower creatinine at 16 years of age are predictors of the need for liver transplant.
- Cholangitis and varices in adolescence increase the risk of needing a liver transplant when >16 years old.

Authors

Vandana Jain, Charlotte Burford, Emma C Alexander, ..., Nigel Heaton, Nedim Hadzic, Marianne Samyn

Correspondence

vjain@nhs.net (V. Jain)

Lay summary

Patients with biliary atresia commonly require liver transplantation before reaching adulthood. Those who reach adulthood with their own liver are still at risk of needing a transplant. This study aimed to identify tests that could help clinicians predict which patients with biliary atresia who reach the age of 16 without a transplant will require one in later life. The study found that the presence of bilirubin $\geq$21 μmol/L, lower creatinine levels, and a history of portal hypertension or gastro-oesophageal varices at 16 years, as well as cholangitis in adolescence, could predict the future likelihood of needing a liver transplant for young people with biliary atresia.

https://doi.org/10.1016/j.jhep.2019.03.005

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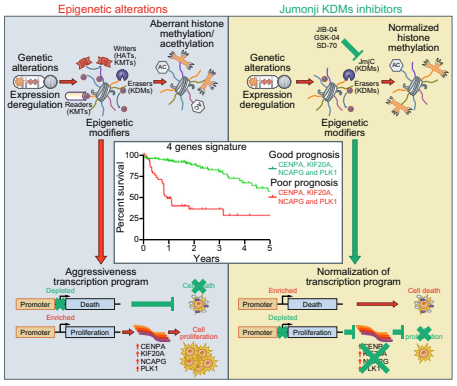
Research Article
Cancer

JOURNAL
OF HEPATOLOGY

A comprehensive study of epigenetic alterations in hepatocellular carcinoma identifies potential therapeutic targets

Graphical abstract



Highlights

- Mutations and expression alterations of epigenetic modifiers are frequent in HCC.
- Jumonji lysine demethylase inhibitors normalize aggressive transcription programs in HCC.
- *CENPA, KIF20A, NCAPG* and *PLK1* gene expression signature defines prognosis in HCC.
- Epigenetic inhibitors are a potential new therapeutic tool for HCC.

Authors

Juan Bayo, Esteban J. Fiore, Luciana M. Dominguez, ..., Josepmaria Argemi, Elisabeth D. Martinez, Guillermo D. Mazzolini

Correspondence

gmazzoli@austral.edu.ar
(G.D. Mazzolini)

Lay summary

In this study, we found that mutations and changes in expression of epigenetic modifiers are common events in human hepatocellular carcinoma, leading to an aggressive gene expression program and poor clinical prognosis. The transcriptional program can be reversed by pharmacological inhibition of Jumonji enzymes. This inhibition blocks hepatocellular carcinoma progression, providing a novel potential therapeutic strategy.

https://doi.org/10.1016/j.jhep.2019.03.007

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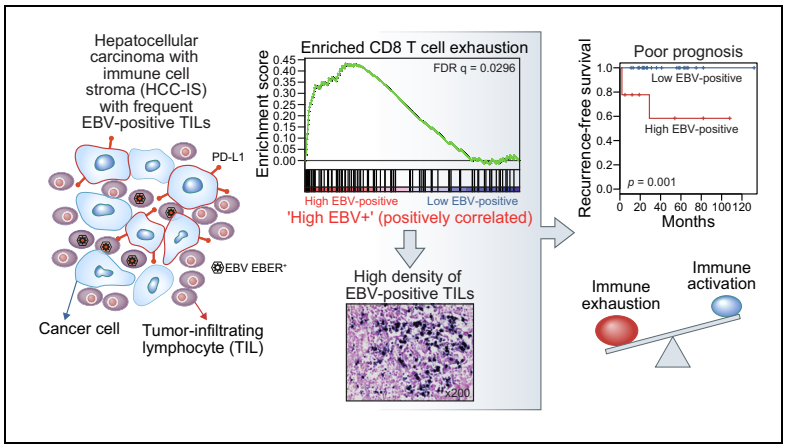
Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Immunogenomic landscape of hepatocellular carcinoma with immune cell stroma and EBV-positive tumor-infiltrating lymphocytes

Graphical abstract



Highlights

- EBV positivity in CD20-positive tumor-infiltrating lymphocytes was present in over 70% of HCC-IS.
- HCC-IS lacked *CTNNB1* mutations and exhibited increased global DNA hypermethylation.
- Both PD-1 and PD-L1 in tumor-infiltrating lymphocytes, and PD-L1 in tumor cells were overexpressed in HCC-IS.
- HCCs with high EBV positivity, paradoxically, were associated with a poor prognosis.
- HCCs with high EBV positivity exhibited increased levels of functionally exhausted CD8 T cells.

Authors

Hyo Jeong Kang, Ji-Hye Oh, Sung-Min Chun, ..., Ju Hyun Shim, Chang Ohk Sung, Eunsil Yu

Correspondence

s5854@amc.seoul.kr (J.H. Shim), co.sung@amc.seoul.kr (C.O. Sung), esyu@amc.seoul.kr (E. Yu)

Lay summary

Hepatocellular carcinomas with histologic evidence of abundant immune cell infiltration are characterized by frequent activation of Epstein-Barr virus in tumor-infiltrating lymphocytes and less aggressive clinical behavior. However, a high density of Epstein-Barr virus-positive tumor-infiltrating lymphocytes is associated with inferior prognostic outcomes, possibly as a result of immune escape due to significant CD8 T cell exhaustion.

https://doi.org/10.1016/j.jhep.2019.03.018

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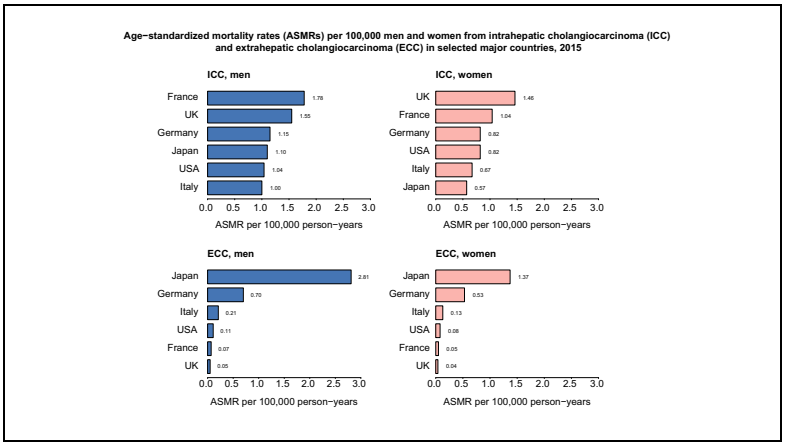
Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma

Graphical abstract



Highlights

- Mortality from intrahepatic cholangiocarcinoma (ICC) tended to rise globally.
- Mortality from extrahepatic cholangiocarcinoma (ECC) decreased in most countries.
- Mortality rates were around 1–2/100,000 for ICC and below 1/100,000 for ECC in most countries.
- The rise in ICC mortality is due to increased incidence.
- The fall in ECC mortality is due to laparoscopic cholecystectomy.

Authors

Paola Bertuccio, Matteo Malvezzi, Greta Carioli, ..., Hashem B. El-Serag, Carlo La Vecchia, Eva Negri

Correspondence

paola.bertuccio@unimi.it
(P. Bertuccio)

Lay summary

Biliary tract cancers include intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC), however there are some differences in their risk factors. Consequently, the distinction between ICC and ECC is important. Over the last few decades, mortality from ICC has tended to rise in several areas of the world, following the increased prevalence of its major risk factors. In contrast, mortality from ECC tended to decrease in most countries, following the increased use of laparoscopic cholecystectomy.

https://doi.org/10.1016/j.jhep.2019.03.013

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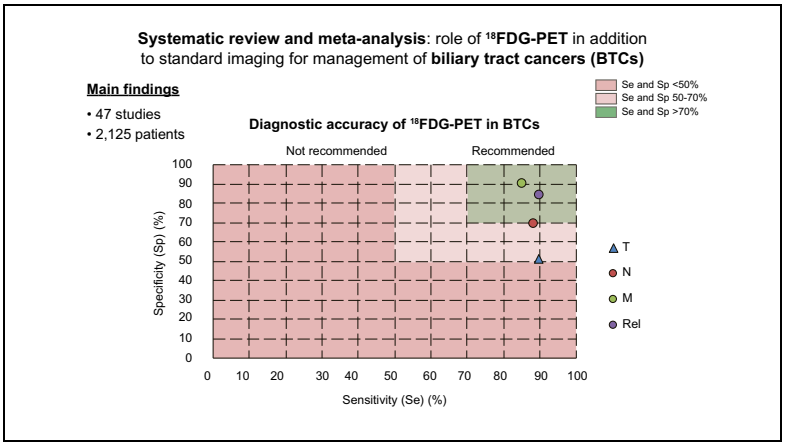
Research Article
Cancer

JOURNAL
OF HEPATOLOGY

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) for patients with biliary tract cancer: Systematic review and meta-analysis

Graphical abstract



Highlights

- Role of ^{18}FDG-PET in diagnosis (T), staging (N/M) and relapse of BTC was assessed.
- ^{18}FDG-PET is not recommended for diagnosis (T) in the absence of cytology/histology.
- ^{18}FDG-PET should be incorporated into current guidelines for staging (N/M) and relapse.
- ^{18}FDG-PET should be used for staging (N/M) if identification of occult sites of disease will alter management.
- ^{18}FDG-PET should be used to identify relapse if suspicion remains following standard imaging.

Authors

Angela Lamarca, Jorge Barriuso, Amarjot Chander, ..., Derek ÓReilly, Prakash Manoharan, Juan W Valle

Correspondence

angela.lamarca@christie.nhs.uk
(A. Lamarca) juan.valle@christie.nhs.uk
(J.W Valle)

Lay summary

A positron emission tomography (PET scan), using ^{18}F-fluorodeoxyglucose (^{18}FDG), can help doctors identify areas of cancer in the body by highlighting ‘‘hot spots’’. These hotspots may be cancerous (true positive) but may also be non-cancerous, like inflammation (false positive). We show that PET scans are useful to assess how far advanced the cancer is (by assessing spread to lymph glands and to other organs) and also to identify if the cancer has recurred (for example after surgery), thus helping doctors to make treatment decisions. However, a biopsy is still needed for the initial diagnosis of a biliary tract cancer, because of the high chance of a ‘‘false positive’’ with PET scans.

https://doi.org/10.1016/j.jhep.2019.01.038

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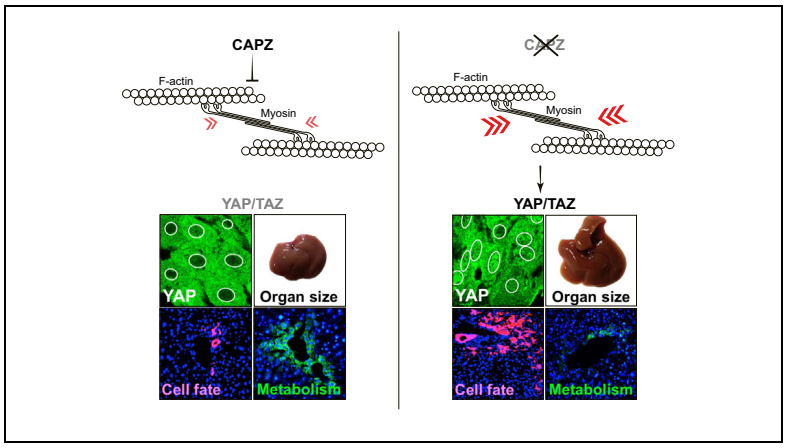
Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

F-actin dynamics regulates mammalian organ growth and cell fate maintenance

Graphical abstract



Highlights

- Absence of CAPZ leads to increased cell contractility and tissue stiffness.
- Loss of CAPZ leads to liver overgrowth, hepatocyte reprogramming and metabolic defects.
- These phenotypes are due to YAP hyperactivation, and occur in parallel to LATS1/2.
- ROCK inhibition rescues the effects of CAPZ inactivation.
- Loss of CAPZ unveils the relevance of mechanical signals for tissue homeostasis.

Authors

Arianna Pocaterra, Giulia Santinon, Patrizia Romani, ..., Nils Gauthier, Kristian Franze, Sirio Dupont

Correspondence

sirio.dupont@unipd.it
(S. Dupont)

Lay summary

The mechanical properties of cells and tissues (*i.e.* whether they are soft or stiff) are thought to be important regulators of cell behavior. Herein, we found that inactivation of the protein CAPZ alters the mechanical properties of cells and liver tissues, leading to YAP hyperactivation. In turn, this profoundly alters liver physiology, causing organ overgrowth, defects in liver cell differentiation and metabolism. These results reveal a previously uncharacterized role for mechanical signals in the maintenance of adult liver homeostasis.

https://doi.org/10.1016/j.jhep.2019.02.022

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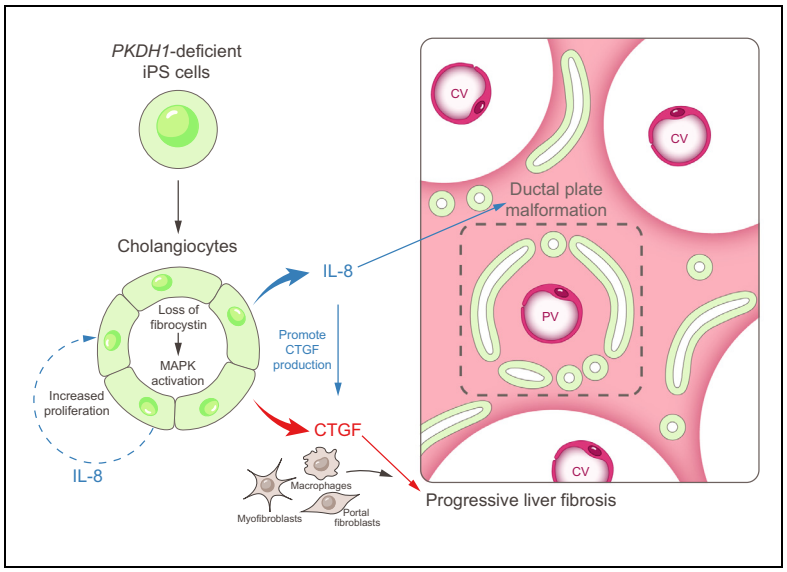
Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Loss of fibrocystin promotes interleukin-8-dependent proliferation and CTGF production of biliary epithelium

Graphical abstract



Highlights

- We established a human iPS cell-model of congenital hepatic fibrosis.
- Loss of fibrocystin increases the production of IL-8 in cholangiocytes.
- The proliferation of fibrocystin-deficient cholangiocytes and their production of CTGF are increased in an IL-8-dependent manner.
- Expression of IL-8 and CTGF is increased in the livers of patients with congenital hepatic fibrosis.

Authors

Tomoyuki Tsunoda, Sei Kakinuma, Masato Miyoshi, ..., Hiromitsu Nakauchi, Yasuhiro Asahina, Mamoru Watanabe

Correspondence

skakinuma.gast@tmd.ac.jp
(S. Kakinuma) asahina.gast@tmd.ac.jp
(Y. Asahina) mamoru.gast@tmd.ac.jp
(M. Watanabe)

Lay summary

Congenital hepatic fibrosis (CHF) is a genetic liver disease caused by mutations of the *PKHD1* gene. Dysfunction of the protein it encodes, fibrocystin, is closely associated with CHF pathogenesis. Using an *in vitro* human induced pluripotent stem cell model and patient samples, we showed that the loss of fibrocystin function promotes proliferation of cholangiocytes and the production of connective tissue growth factor (CTGF) in an interleukin 8 (IL-8)-dependent manner. These results suggest that IL-8 and CTGF are essential for the pathogenesis of CHF.

https://doi.org/10.1016/j.jhep.2019.02.024

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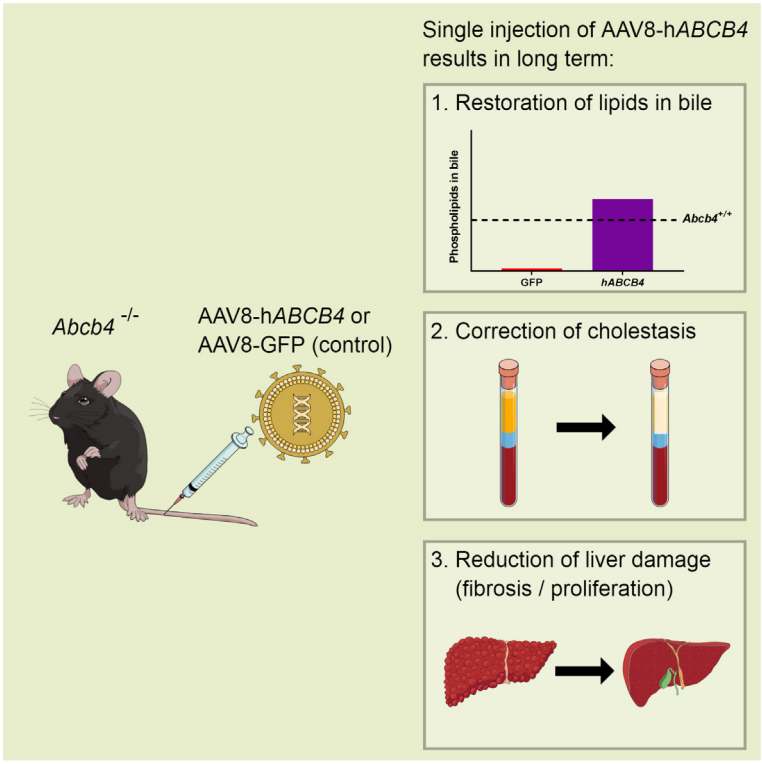
Research Article
Cholestasis and Autoimmune Diseases

JOURNAL
OF HEPATOLOGY

Liver-directed gene therapy results in long-term correction of progressive familial intrahepatic cholestasis type 3 in mice

Graphical abstract



Highlights

- Adeno-associated virus (AAV)-mediated gene therapy can correct Abcb4 deficiency (PFIC3) in mice.
- By restoring phospholipid transport to bile, cholestasis and liver damage were strongly reduced.
- Stable transgene expression resulted in long-term correction of the phenotype (26 weeks).
- Hepatic transgene persistence was achieved by sufficiently reducing hepatocyte proliferation.

Authors

Sem J. Aronson, Robert S. Bakker, Xiaoxia Shi, ..., Ulrich Beuers, Coen C. Paulusma, Piter J. Bosma

Correspondence

p.j.bosma@amc.uva.nl
(P.J. Bosma)

Lay summary

Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a severe genetic liver disease that results from impaired transport of lipids to bile, which makes the bile toxic to liver cells. Because therapeutic options are currently limited, this study aims to evaluate gene therapy to correct the underlying genetic defect in a mouse model of this disease. By introducing a functional copy of the missing gene in liver cells of mice, we were able to restore lipid transport to bile and strongly reduce damage to the liver. The proliferation of liver cells was also reduced, which contributes to long-term correction of the phenotype. Further studies are required to evaluate whether this approach can be applied to patients with PFIC3.

https://doi.org/10.1016/j.jhep.2019.03.021

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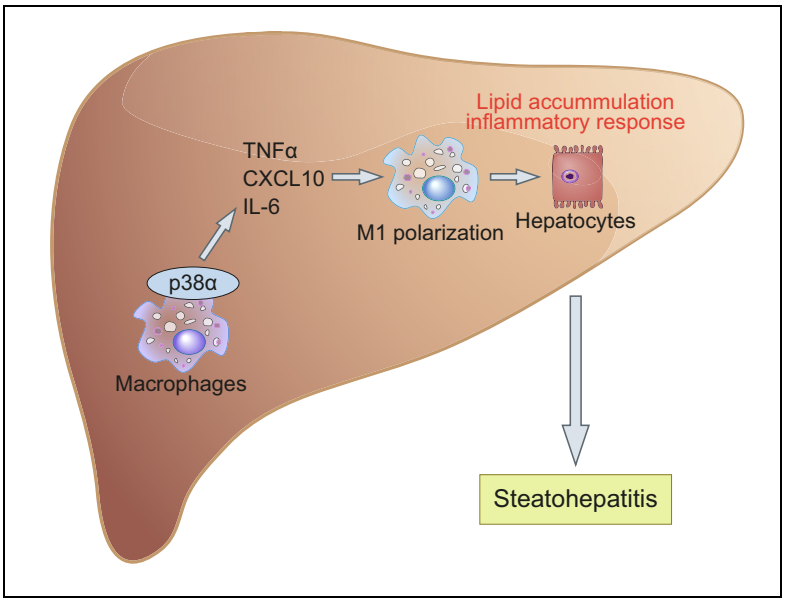
Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Macrophage p38α promotes nutritional steatohepatitis through M1 polarization

Graphical abstract



Highlights

- p38α expression is increased in livers of human patients with non-alcoholic fatty liver diseases.
- Macrophage p38α induces experimental steatohepatitis.
- Macrophage p38α causes M1 macrophage polarization.
- p38α deleted macrophages attenuate steatohepatitic changes in hepatocytes.
- Pharmacological p38 inhibitors prevent steatohepatitis in mice.

Authors

Xiang Zhang, Lina Fan, Jianfeng Wu, ..., Jiahuai Han, Jianlin Ren, Jun Yu

Correspondence

renjianl@xmu.edu.cn (J. Ren)
junyu@cuhk.edu.hk (J. Yu)

Lay summary

p38 mitogen-activated protein kinases are important inflammatory factors. In the present study, we demonstrated that p38α is upregulated in liver tissues of patients with non-alcoholic fatty liver diseases. Genetic deletion of p38α in macrophages led to ameliorated nutritional steatohepatitis in mice through decreased pro-inflammatory cytokine secretion and increased M2 macrophage polarization.

https://doi.org/10.1016/j.jhep.2019.03.014

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