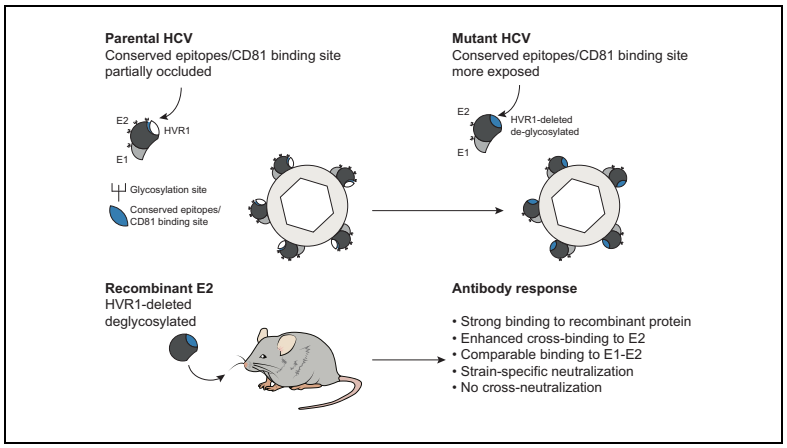
April 2019

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Functional and immunogenic characterization of diverse HCV glycoprotein E2 variants

Graphical abstract



Highlights

- High resolution mapping of HVR1 and glycosylation sites' impact on CD81 binding, antibody binding and virus neutralization.
- Viral mutants lacking HVR1 and selected glycosylation sites are functional.
- These mutants expose the viral CD81 binding site and conserved cross-neutralization epitopes.
- E2 proteins with these mutations induce cross-binding and non-interfering antibodies in mice.

Authors

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Lay summary

Conserved viral epitopes can be made considerably more accessible for binding of potently neutralizing antibodies by deletion of hypervariable region 1 and selected glycosylation sites. Recombinant E2 proteins carrying these mutations are unable to elicit cross-neutralizing antibodies suggesting that exposure of conserved epitopes is not sufficient to focus antibody responses on production of cross-neutralizing antibodies.

https://doi.org/10.1016/j.jhep.2018.11.003

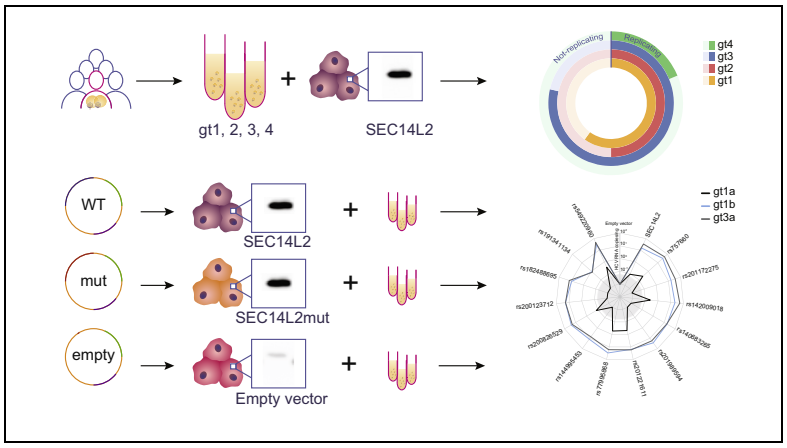
 J. Hepatol. 2019, 70, 593–602

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

SEC14L2, a lipid-binding protein, regulates HCV replication in culture with inter- and intra-genotype variations

Graphical abstract



Highlights

- SEC14L2 was shown to allow natural HCV isolates to replicate *in vitro*.
- Natural isolates from genotypes 1,2,3 and 4 replicate in cells overexpressing SEC14L2.
- Replication does not occur in 100% of the cases and varies with genotype.
- SNP rs191341134 causes lower levels of SEC14L2 in the cytosol and lower viral replication.
- SNP rs757660 recapitulates the wild-type protein phenotype *in vitro* and *in vivo*.

Authors

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Lay summary

Until the year 2015, consistent replication of patient-derived isolates of hepatitis C virus (HCV) in an *in vitro* model remained a limitation in HCV research. In 2015 a group of authors identified a protein named SEC14L2 that enabled the replication of HCV isolates in cell culture. We performed a large screen encompassing 73 isolates of 4 different HCV genotypes. Additionally, we replaced the natural SEC14L2 with 13 different mutants to test if the protein variation significantly altered its HCV replication enhancing functions. We showed that different genotypes of HCV react differently to the presence of this protein and the variants of the protein mimic the behavior of the wild-type.

https://doi.org/10.1016/j.jhep.2018.11.012

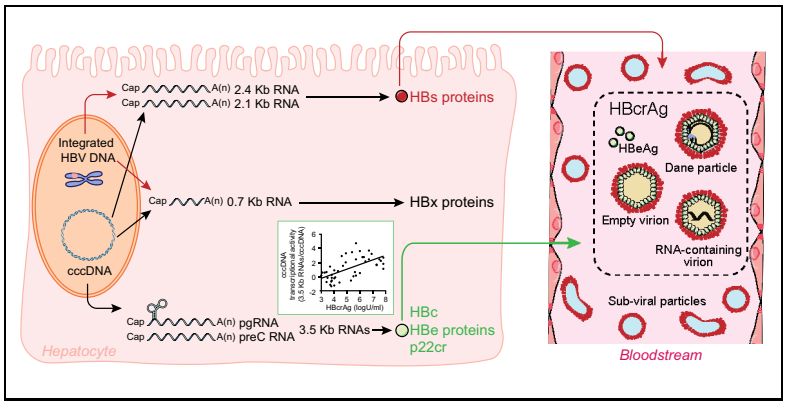
 J. Hepatol. 2019, 70, 603–614

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Serum hepatitis B core-related antigen (HBcrAg) correlates with covalently closed circular DNA transcriptional activity in chronic hepatitis B patients

Graphical abstract



Highlights

- Liver HBV cccDNA is responsible for viral persistence despite antiviral treatments.
- cccDNA activity, rather than amount, is correlated with disease progression.
- Serum HBcrAg highly correlates with intrahepatic cccDNA activity.
- Lower levels of HBcrAg are correlated with a more favorable course of the disease.

Authors

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Lay summary

Hepatitis B virus causes a chronic infection which develops into severe liver disease and liver cancer. The viral covalently closed circular DNA (cccDNA) is responsible for the persistence of the infection in hepatocytes. To better manage patient treatment and follow-up, and to develop new antiviral treatments directly targeting the intrahepatic pool of cccDNA, serum surrogate markers reflecting the viral activity in the liver are urgently needed. In this work, we demonstrate that quantification of hepatitis B core-related antigen in serum correlates with cccDNA amount and activity and could be used to monitor disease progression.

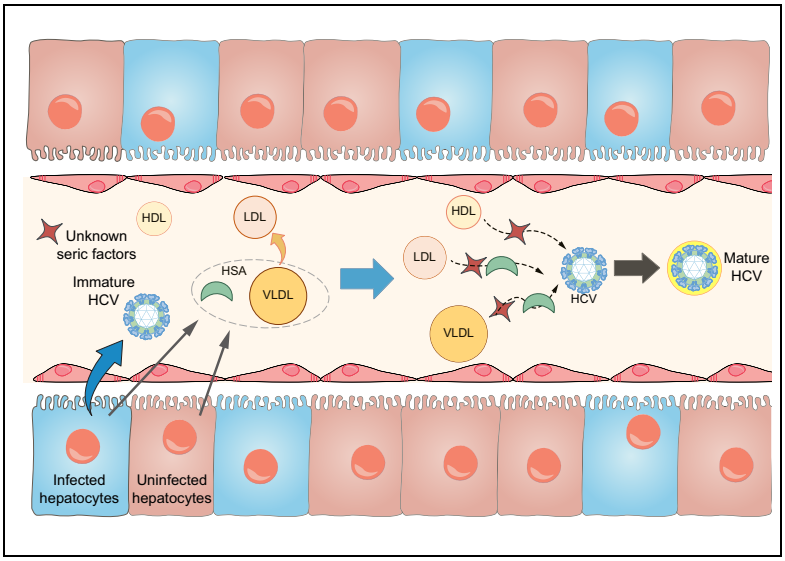
https://doi.org/10.1016/j.jhep.2018.11.030

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

A serum protein factor mediates maturation and apoB-association of HCV particles in the extracellular milieu

Graphical abstract



Highlights

- After cell egress, HCV particles may associate with apoB and acquire neutral lipids, and hence, low-buoyant density.
- The hypervariable region 1 (HVR1) is a major viral determinant of E2 that controls this process.
- Besides lipoproteins, specific serum factors including albumin promote extracellular maturation of HCV virions.
- Simple culture conditions enable production of infectious HCV particles resembling those of infected patients.

Authors

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Lay summary

Hepatitis C virus (HCV) particles may associate with apoB and acquire neutral lipids after exiting cells, giving them low-buoyant density. The hypervariable region 1 (HVR1) is a majorviral determinant of E2 that controls this process. Besides lipoproteins, specific serum factors including albumin promote extracellular maturation of HCV virions. HCV particle production *in vitro*, with media of defined serum conditions, enables production of infectious particles resembling those of chronically infected patients.

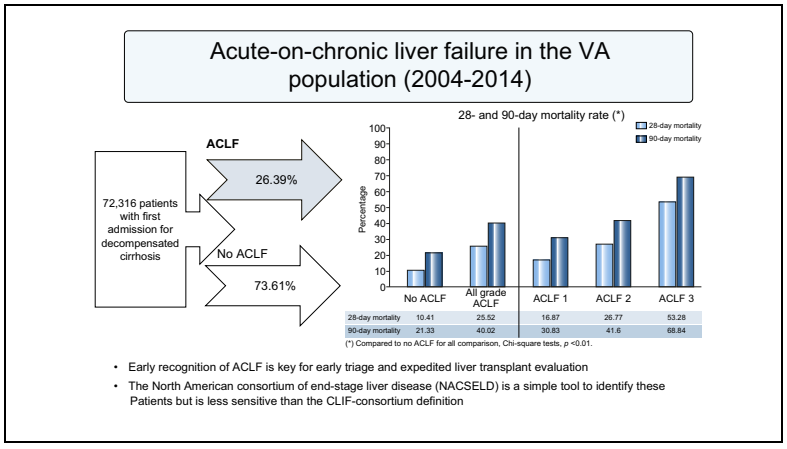
https://doi.org/10.1016/j.jhep.2018.11.033

 J. Hepatol. 2019, 70, 626–638

JOURNAL
OF HEPATOLOGY

Prevalence and short-term mortality of acute-on-chronic liver failure: A national cohort study from the USA

Graphical abstract



Highlights

- Of 72,316 ethnically diverse patients from 127 Veterans Affairs facilities in the US, 19,082 (26.39%) met ACLF criteria.
- Patients with ACLF had high 28- and 90-day mortality (25.52% and 40.02%, respectively).
- Mortality risk increased in parallel with the number of OFs, ranging from 17–53% at 28 days and 31–69% at 90 days.
- African-American race and being seen at a transplant centre were associated with a lower risk of ACLF mortality.

Authors

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Lay summary

Acute-on-chronic liver failure (ACLF) is a condition marked by multiple organ failures in patients with cirrhosis and associated with a high risk of death. In this study of US patients hospitalised with cirrhosis, 1 in 4 patients developed ACLF. In total, 25% of patients with ACLF died within 1 month and 40% died within 3 months. Thus, early recognition of ACLF is important for the initiation of aggressive management, which is required to save these patients' lives.

https://doi.org/10.1016/j.jhep.2018.12.018

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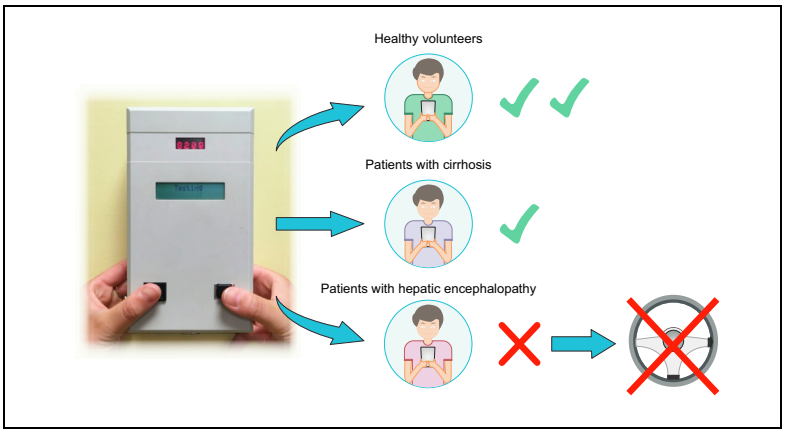
Research Article
Cirrhosis

JOURNAL
OF HEPATOLOGY

The psychomotor vigilance task: Role in the diagnosis of hepatic encephalopathy and relationship with driving ability

Graphical abstract



Highlights

- The Psychomotor Vigilance Task (PVT) is a test of vigilance and provides a series of parameters which are stable in the healthy population, regardless of sex, age and level of education.
- PVT parameters correlate well with standard measures of hepatic encephalopathy (HE).
- PVT parameters may be useful to quantify mild overt HE and identify dangerous drivers among patients with cirrhosis.

Authors

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Lay summary

Hepatic encephalopathy (HE) is a complication of advanced liver disease that can manifest as excessive sleepiness. Some patients with HE have been shown to have difficulty driving. Herein, we used a test called the Psychomotor Vigilance Task (PVT), which measures sleepiness and can also be used to assess driving competence. We showed that PVT performance is fairly stable in healthy individuals. We also showed that PVT performance parallels performance in tests which are commonly used in cirrhotic patients to measure HE. We suggest that this test is helpful in quantifying HE and identifying dangerous drivers among patients with cirrhosis.

https://doi.org/10.1016/j.jhep.2018.12.031

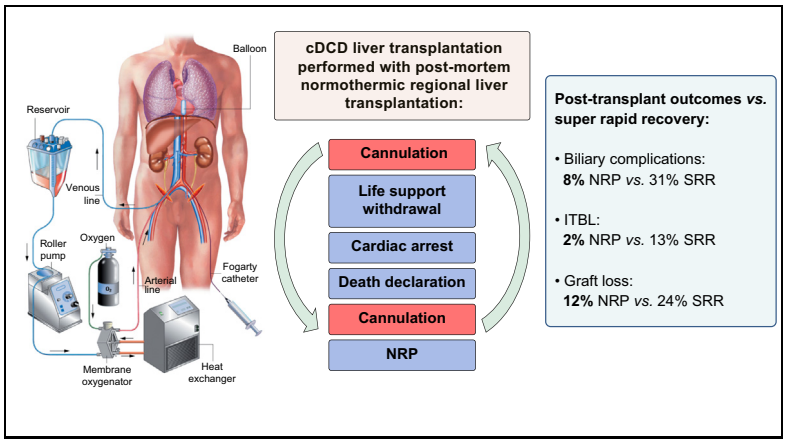
 J. Hepatol. 2019, 70, 648–657

Research Article
Transplantation

JOURNAL
OF HEPATOLOGY

Normothermic regional perfusion *vs.* super-rapid recovery in controlled donation after circulatory death liver transplantation

Graphical abstract



Highlights

- In cDCD livers, postmortem NRP reduces biliary complications, in particular ITBL.
- Postmortem NRP helps improve cDCD liver graft survival.
- Use of postmortem NRP facilitates successful transplantation of older cDCD livers.

Authors

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Lay summary

This is a propensity-matched nationwide observational cohort study performed using livers recovered from donors undergoing cardiac arrest provoked by the intentional withdrawal of life support (controlled donation after circulatory death, cDCD). Approximately half of the livers were recovered after a period of postmortem *in situ* normothermic regional perfusion, which restored warm oxygenated blood to the abdominal organs, whereas the remainder were recovered after rapid preservation with a cold solution. The study results suggest that the use of postmortem normothermic regional perfusion helps reduce rates of post-transplant biliary complications and graft loss and allows for the successful transplantation of livers from older cDCD donors.

https://doi.org/10.1016/j.jhep.2018.12.013

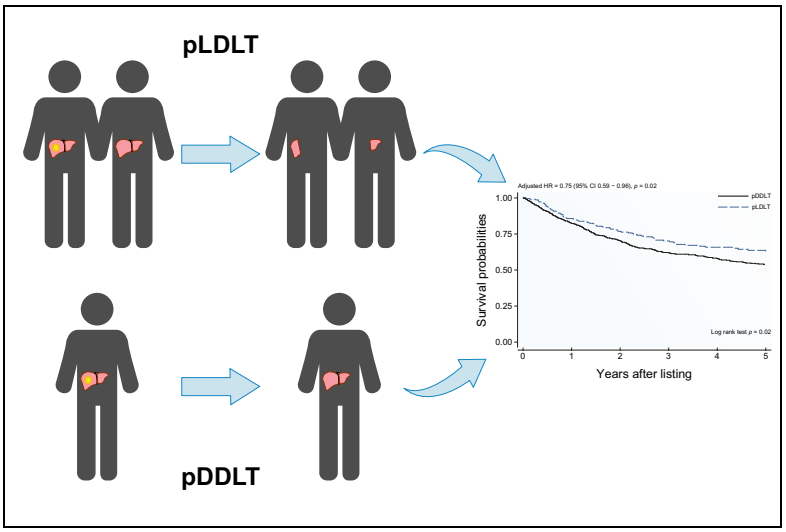
 J. Hepatol. 2019, 70, 658–665

Research Article
Transplantation

JOURNAL
OF HEPATOLOGY

Live donor liver transplantation for patients with hepatocellular carcinoma offers increased survival *vs.* deceased donation

Graphical abstract



Highlights

- The dropout rate is lower for patients listed for liver transplantation with a potential live donor.
- The waiting time is shorter for patients listed for liver transplantation with a potential live donor.
- These 2 advantages of live donation result in a survival benefit for patients with HCC listed with a potential live donor.

Authors

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Lay summary

Liver transplantation (LT) offers the best chance of survival for patients with hepatocellular carcinoma and can be performed using grafts from deceased donors or live donors. In this work, we aimed to assess the differences in survival after live donor LT when compared to deceased donor LT. We studied 219 patients listed for live donor LT and 632 patients listed for deceased donor LT. Patients who had a potential live donor at the time of listing had a higher survival rate. Therefore, being listed for a live donor LT was a protective factor against death.

https://doi.org/10.1016/j.jhep.2018.12.029

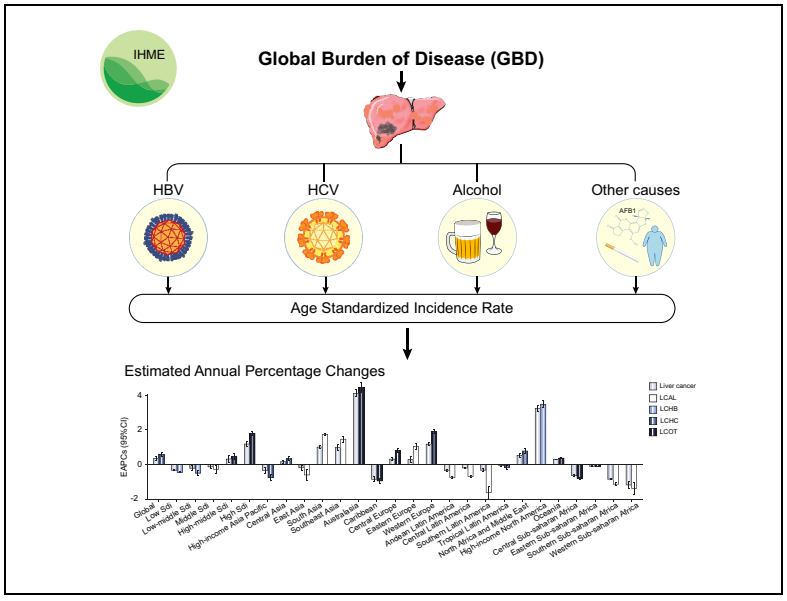
 J. Hepatol. 2019, 70, 666–673

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

The trends in incidence of primary liver cancer caused by specific etiologies: Results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention

Graphical abstract



Highlights

- Primary liver cancer incidence is still on the rise at the global level.
- Pronounced increases in liver cancer incidence were mostly observed in countries with high socio-demographic indexes.
- Liver cancer has been alleviated in some regions due to the control of HBV and HCV infections.
- HCV-related liver cancer might be an important public health issue in the near future.

Authors

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Lay summary

Liver cancer is a common malignant neoplasm worldwide. The incidence patterns of liver cancer caused by different etiologies varied considerably across the world. In this study, we aim to determine the pattern of liver cancer incidence as well as the temporal trends, thereby facilitating the establishment of more tailored prevention strategies for liver cancer.

https://doi.org/10.1016/j.jhep.2018.12.001

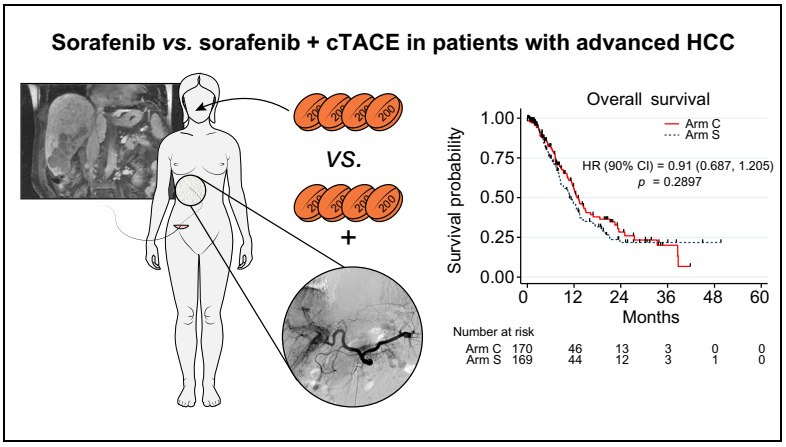
 J. Hepatol. 2019, 70, 674–683

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAH trial

Graphical abstract



Highlights

- Sorafenib combined with concurrent chemoembolization did not improve overall survival.
- Combination therapy significantly improved tumor response and secondary outcomes.
- Sorafenib alone remains first-line standard of care for advanced hepatocellular carcinoma.

Authors

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Lay summary

For patients with advanced hepatocellular carcinoma requiring sorafenib therapy, co-administration with conventional transarterial chemoembolization did not improve overall survival compared to sorafenib alone. Therefore, sorafenib alone remains the first-line standard of care for patients with advanced hepatocellular carcinoma.

https://doi.org/10.1016/j.jhep.2018.11.029

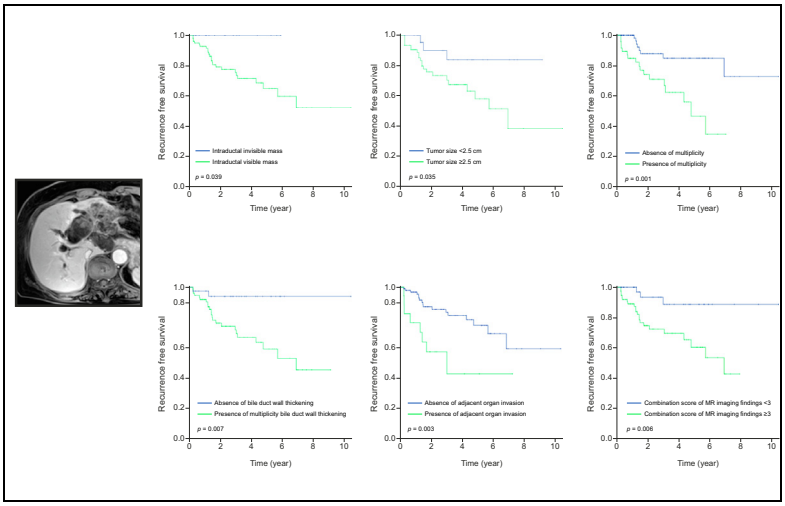
 J. Hepatol. 2019, 70, 684–691

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Intraductal papillary neoplasm of the bile duct: Assessment of invasive carcinoma and long-term outcomes using MRI

Graphical abstract



Highlights

- MRI findings were able to discriminate IPNB with an invasive carcinoma from IPNB with intraepithelial neoplasia.
- MRI findings of IPNB with an invasive carcinoma were linked to worse clinical outcome.
- Tumor multiplicity on MRI was an independent factor for RFS of IPNB after surgery.

Authors

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Lay summary

Significant magnetic resonance imaging findings that differentiated between an intraductal papillary neoplasm of the bile duct (IPNB) with an associated invasive carcinoma and an IPNB with intraepithelial neoplasia were intraductal visible mass, tumor size ≥2.5 cm, multiplicity of the tumor, bile duct wall thickening, and adjacent organ invasion. Significant magnetic resonance imaging findings of invasive IPNB have a negative impact on recurrence-free survival.

https://doi.org/10.1016/j.jhep.2018.12.005

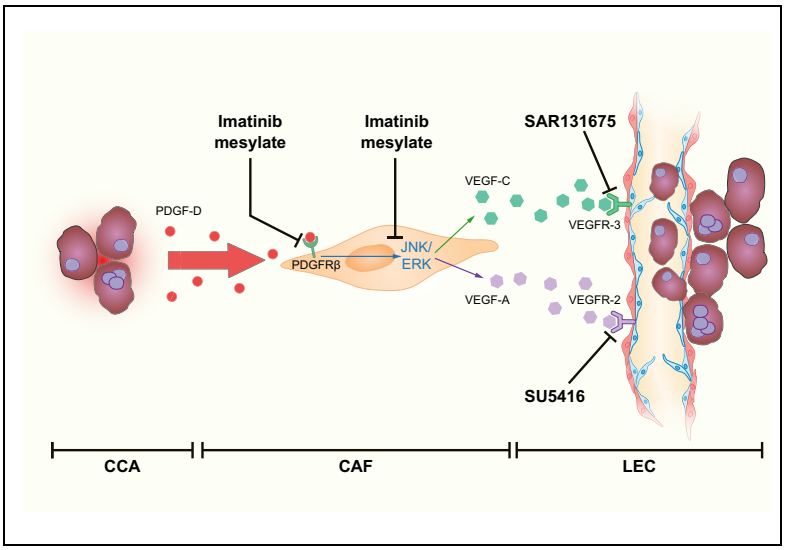
 J. Hepatol. 2019, 70, 692–699

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Platelet-derived growth factor-D enables liver myofibroblasts to promote tumor lymphangiogenesis in cholangiocarcinoma

Graphical abstract



Highlights

- Cholangiocarcinomas are rich in stroma containing cancer-associated fibroblasts and lymphatic vessels.
- PDGF-D released by tumoral ducts attracts and activates liver fibroblasts to secrete VEGF-C/VEGF-A.
- Lymphangiogenesis and lymphatic invasion are driven by VEGF-A/-C released by liver myofibroblasts.
- Targeting liver myofibroblasts *in vivo* inhibits tumor-associated lymphangiogenesis and lymph node metastases.
- These studies identify new possible molecular targets for the treatment of cholangiocarcinoma.

Authors

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Lay summary

Cholangiocarcinoma is a highly malignant cancer affecting the biliary tree, which is characterized by a rich stromal reaction involving a dense population of cancer-associated fibroblasts that promote early metastatic spread. Herein, we show that cholangiocarcinoma-derived PDGF-D stimulates fibroblasts to secrete vascular growth factors. Thus, targeting fibroblasts or PDGF-D-induced signals may represent an effective tool to block tumor-associated lymphangiogenesis and reduce the invasiveness of cholangiocarcinoma.

https://doi.org/10.1016/j.jhep.2018.12.004

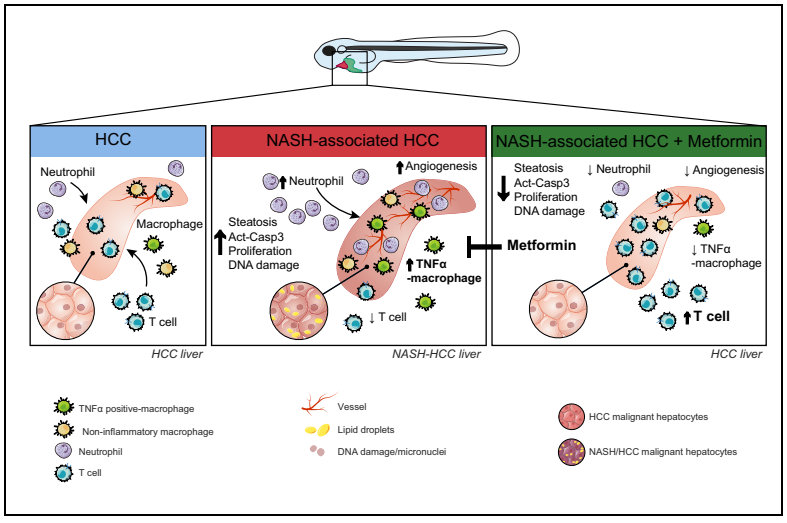
 J. Hepatol. 2019, 70, 700–709

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Metformin modulates innate immune-mediated inflammation and early progression of NAFLD-associated hepatocellular carcinoma in zebrafish

Graphical abstract



Highlights

- HFD enhances HCC progression and modulates the immune response in the liver microenvironment.
- HFD induced changes in macrophage polarization with increased numbers of TNFα-positive macrophages in the liver.
- HFD reduces T cell infiltration to liver area in NASH-associated HCC larvae.
- Ablation of macrophages reduces disease progression in NASH-associated HCC larvae, but not in HCC alone.
- Metformin specifically affects the progression induced by diet in NASH-associated HCC in zebrafish.

Authors

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Lay summary

This paper reports a new zebrafish model that can be used to study the effects of diet on liver cancer. We found that a high-fat diet promotes non-resolving inflammation in the liver and enhances cancer progression. In addition, we found that metformin, a drug used to treat diabetes, inhibits high-fat diet-induced cancer progression in this model, by reducing diet-induced non-resolving inflammation and potentially restoring tumor surveillance.

https://doi.org/10.1016/j.jhep.2018.11.034

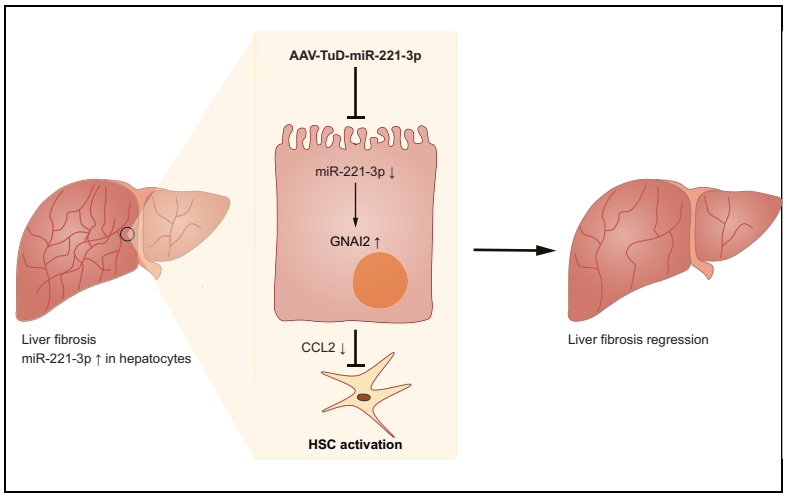
 J. Hepatol. 2019, 70, 710–721

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Hepatocyte-specific suppression of microRNA-221-3p mitigates liver fibrosis

Graphical abstract



Highlights

- Identification of microRNA-221-3p as a regulator of liver fibrosis *in vitro*.
- Inhibition of microRNA-221-3p in hepatocytes is capable of reducing liver fibrosis in mouse models.
- Treatment of primary human hepatocytes with microRNA-221 inhibitor suppresses activation of human myofibroblasts.

Authors

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Lay summary

Liver fibrosis majorly contributes to mortality resulting from various liver diseases. We discovered a small RNA known as miRNA-221-3p, whose down-regulation in hepatocytes results in reduced liver fibrosis. Thus, inhibition of miRNA-221-3p may serve as one of the therapeutic approaches for treatment of liver fibrosis.

https://doi.org/10.1016/j.jhep.2018.12.016

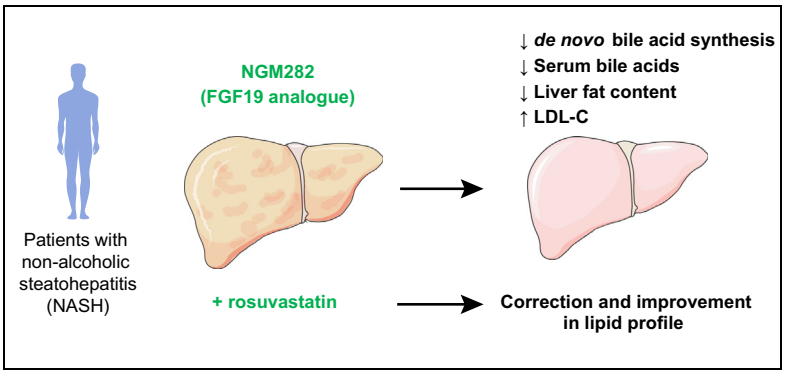
 J. Hepatol. 2019, 70, 722–734

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Rosuvastatin improves the FGF19 analogue NGM282-associated lipid changes in patients with non-alcoholic steatohepatitis

Graphical abstract



Highlights

- NGM282 is a first-in-class, engineered analogue of the gut hormone FGF19.
- NGM282 therapy is associated with an elevation of blood cholesterol in patients with NASH.
- Co-administration of rosuvastatin significantly reduces LDL-C, LDL particles, triglycerides and VLDL particles.
- Co-administration of rosuvastatin results in increases in HDL-C and HDL particles.

Authors

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Lay summary

Non-alcoholic steatohepatitis (NASH) represents a large and growing public health concern with no approved therapy. NGM282, an engineered analogue of the gut hormone FGF19, reduces liver fat, liver injury and inflammation in patients with NASH. However, NGM282 increases cholesterol levels. Here we show that co-administration of a statin can manage the cholesterol increase seen in patients with NASH receiving treatment with NGM282, producing a favorable overall lipid profile.

https://doi.org/10.1016/j.jhep.2018.11.032

 J. Hepatol. 2019, 70, 735–744