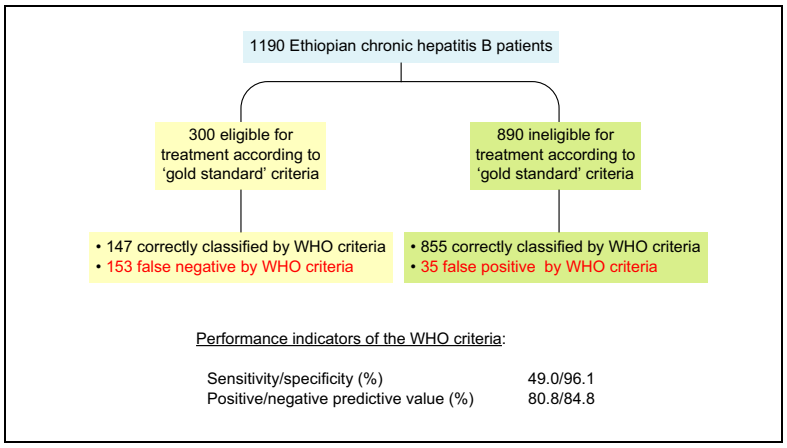
June 2019

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

The WHO guidelines for chronic hepatitis B fail to detect half of the patients in need of treatment in Ethiopia

Graphical abstract



Highlights

- In 2015, the WHO launched treatment guidelines for chronic hepatitis B.
- Little is known about the performance of the WHO guidelines in sub-Saharan Africa.
- In a large Ethiopian cohort, the WHO criteria failed to detect half of those in need of treatment.
- Most patients identified by the WHO criteria had decompensated cirrhosis.
- A revision of the WHO guidelines should take into account local data from Africa.

Authors

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Lay summary

Antiviral therapy prevents disease progression and death in patients with chronic hepatitis B (CHB), but the identification of patients in need of treatment is a challenge in low- and middle-income countries. The World Health Organization (WHO) has suggested treatment eligibility criteria for use in such settings, but in our study the WHO criteria detected less than half of those in need of therapy in a large Ethiopian cohort of 1,190 patients with CHB. Our findings suggest that the WHO criteria might be unsuitable in sub-Saharan Africa.

https://doi.org/10.1016/j.jhep.2019.01.037

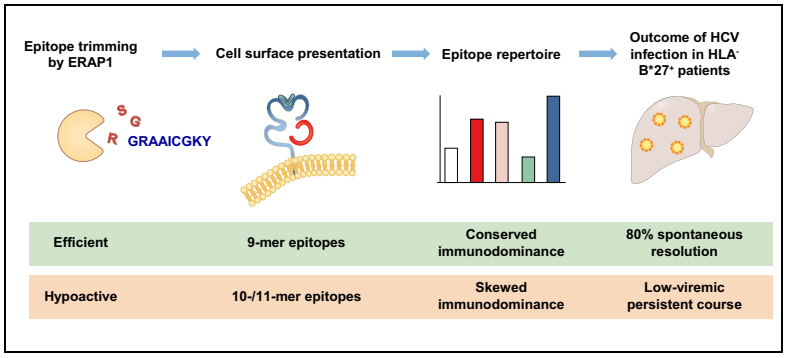
 J. Hepatol. 2019, 70, 1065–1071

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

ERAP1 allotypes shape the epitope repertoire of virus-specific CD8$^+$ T cell responses in acute hepatitis C virus infection

Graphical abstract



Highlights

- ERAP1 polymorphisms are strongly linked with HLA class I-associated autoinflammatory disorders.
- We identified 2 hypoactive ERAP1 allotypes in an HLA-B*27:05$^+$ individual with acute HCV infection.
- These ERAP1 allotypes modified the HCV-specific CD8$^+$ T cell epitope repertoire *in vivo*, leading to altered immunodominance patterns.
- Altered immunodominance patterns potentially contributed to the failure of antiviral immunity.

Authors

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Lay summary

Endoplasmic reticulum aminopeptidase 1 (ERAP1) plays a key role in antigen presentation. Genetic variants of *ERAP1* (leading to distinct allotypes) are linked with specific autoinflammatory disorders, such as ankylosing spondylitis and Behçet's disease. We found that ERAP1 allotypes modified the repertoire of virus-specific CD8$^+$ T cell epitopes in a patient with hepatitis C virus, leading to an altered pattern of immunodominance that may have contributed to the failure of antiviral immunity in this patient.

https://doi.org/10.1016/j.jhep.2019.01.034

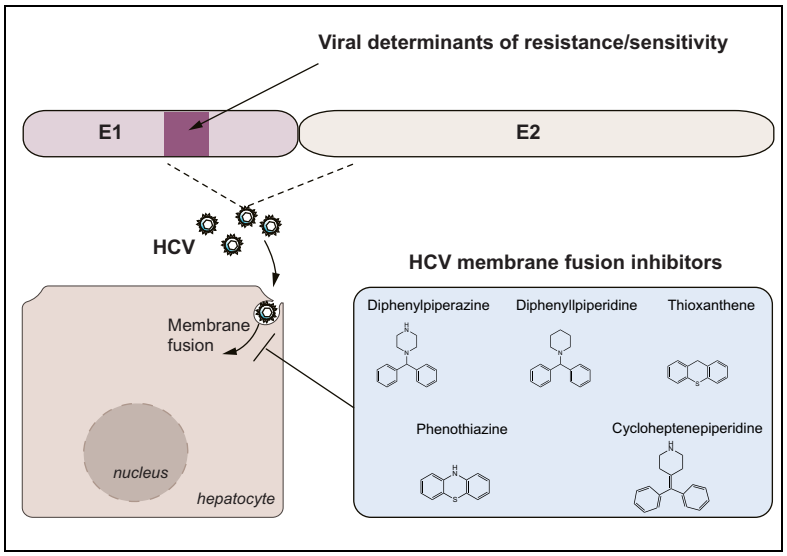
 J. Hepatol. 2019, 70, 1072–1081

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

A central hydrophobic E1 region controls the pH range of hepatitis C virus membrane fusion and susceptibility to fusion inhibitors

Graphical abstract



Highlights

- Diverse compounds from different chemotypes preferentially inhibit HCV genotype 2 membrane fusion.
- Viral determinants controlling susceptibility to these compounds map to a central hydrophobic region of E1.
- Four conserved residues within this region govern sensitivity to these compounds and pH-dependence of membrane fusion.
- The hydrophobicity of this region, proximal to the putative HCV fusion loop, predicts susceptibility to these compounds.
- Resistance to these compounds correlates with more relaxed requirements for pH-triggering of membrane fusion.

Authors

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Lay summary

This study describes diverse compounds that act as HCV membrane fusion inhibitors. It defines viral properties that determine sensitivity to these molecules and thus provides information to identify patients that may benefit from treatment with membrane fusion inhibitors.

https://doi.org/10.1016/j.jhep.2019.01.033

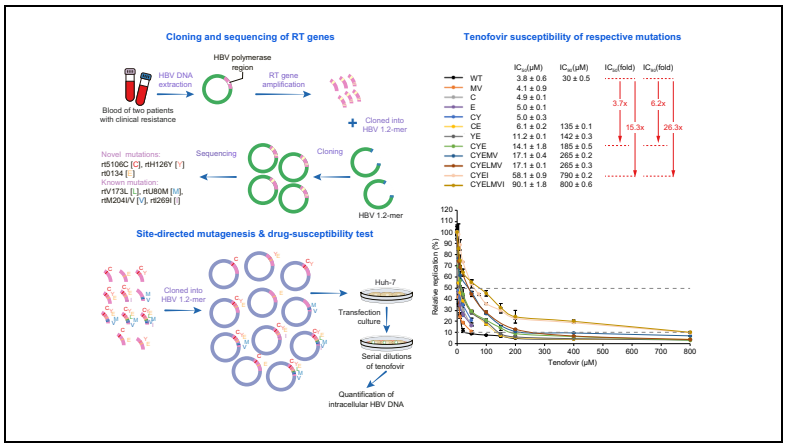
 J. Hepatol. 2019, 70, 1082–1092

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients

Graphical abstract



Highlights

- Among oral antivirals for HBV infection, only tenofovir has revealed no genotypically resistant HBV.
- However, there are patients with incomplete viral response during tenofovir-containing treatment.
- We consistently identified 7 common mutations including rtS106C (C), rtH126Y (Y), rtD134E (E), and rtL269I (I).
- The mutations C, Y, and E were novel mutations associated with drug resistance.
- The quadruple CYEI mutation increases the amount of tenofovir required to inhibit HBV by 15.3-fold in IC_{50} and 26.3-fold in IC_{90}.
- All tenofovir-resistant mutants with/without entecavir resistance were susceptible to a novel capsid assembly modulator.

Authors

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Lay summary

Tenofovir is the most potent nucleotide analogue for the treatment of chronic hepatitis B virus infection and there has been no hepatitis B virus mutation that confers >10-fold resistance to tenofovir up to 8 years. Herein, we identified, for the first time, a quadruple mutation that conferred 15.3-fold (IC_{50}) and 26.3-fold (IC_{90}) resistance to tenofovir in 2 patients who experienced viral breakthrough during tenofovir treatment.

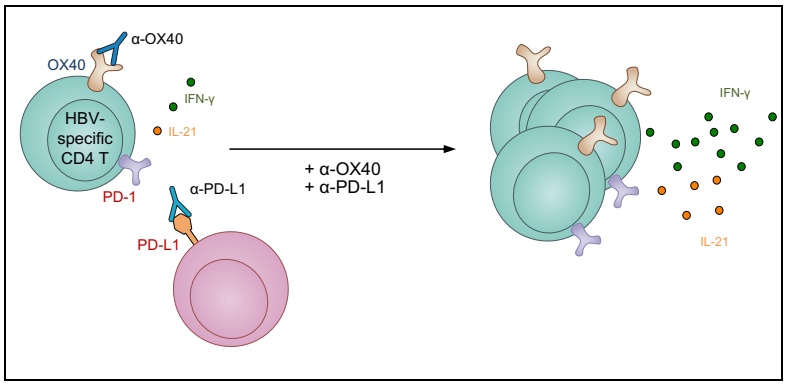
https://doi.org/10.1016/j.jhep.2019.02.006

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

OX40 stimulation and PD-L1 blockade synergistically augment HBV-specific CD4 T cells in patients with HBeAg-negative infection

Graphical abstract



Highlights

- OX40 (CD134) and PD-1 are strongly expressed on HBV-specific CD4 T cells *ex vivo.*
- The HBV-specific CD4 T cells predominantly target the polymerase and core proteins.
- Combined OX40 stimulation and PD-L1 blockade functionally augment HBV-specific CD4 T cells.

Authors

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Lay summary

CD4 T cells are important in controlling viral infections but are impaired in the context of chronic hepatitis B virus (HBV) infection. Therapeutic approaches to cure chronic HBV infection are highly likely to require an immune-stimulatory component. This study demonstrates that HBV-specific CD4 T cells can be functionally augmented by combined stimulation of the co-stimulatory molecule OX40 and blockade of the inhibitory PD-1 pathway.

https://doi.org/10.1016/j.jhep.2019.02.016

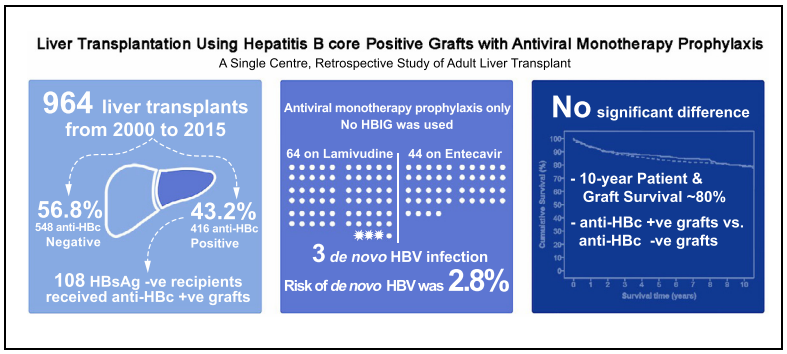
 J. Hepatol. 2019, 70, 1103–1113

Research Article
Transplantation

JOURNAL
OF HEPATOLOGY

Liver transplantation using hepatitis B core positive grafts with antiviral monotherapy prophylaxis

Graphical abstract



Highlights

- Anti-HBc positive liver grafts did not lead to inferior survival after liver transplantation.
- Donor anti-HBc status did not impact on graft and patient survival, or HCC recurrence.
- De *novo* HBV infection was extremely rare with entecavir monoprophylaxis.

Authors

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Lay summary

The risk of *de novo* hepatitis B infection after liver transplantation was rare when using hepatitis B core positive liver grafts with entecavir monotherapy prophylaxis. Hepatitis B core antibody status did not impact on perioperative and long-term outcomes after liver transplantation. This provides support for the clinical use of hepatitis B core positive liver grafts when required.

https://doi.org/10.1016/j.jhep.2019.03.003

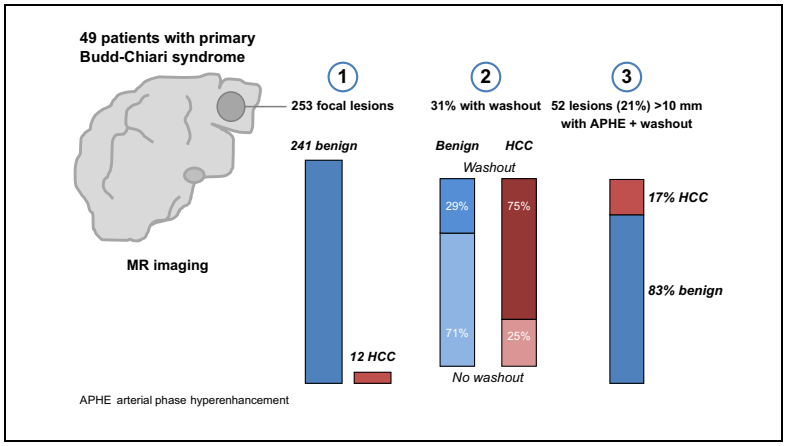
 J. Hepatol. 2019, 70, 1114–1122

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Low specificity of washout to diagnose hepatocellular carcinoma in nodules showing arterial hyperenhancement in patients with Budd-Chiari syndrome

Graphical abstract



Highlights

- Washout depicted in close to 30% of benign nodules in patients with Budd-Chiari syndrome.
- Non-invasive diagnosis of HCC cannot be applied to patients with Budd-Chiari syndrome.
- Ancillary imaging findings help differentiate benign nodules and HCC.
- Alpha-fetoprotein serum rate remains low in patients with benign nodules.

Authors

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Lay summary

Washout on MRI is depicted in a significant proportion of benign nodules in patients with Budd-Chiari syndrome (BCS), limiting its value for the differentiation between benign and malignant lesions. Criteria proposed for the non-invasive diagnosis of hepatocellular carcinoma in patients with cirrhosis cannot be extrapolated to patients with BCS. Additional imaging findings and patient characteristics, including alpha-fetoprotein serum level, can help determine the probability of a nodule being HCC in patients with BCS.

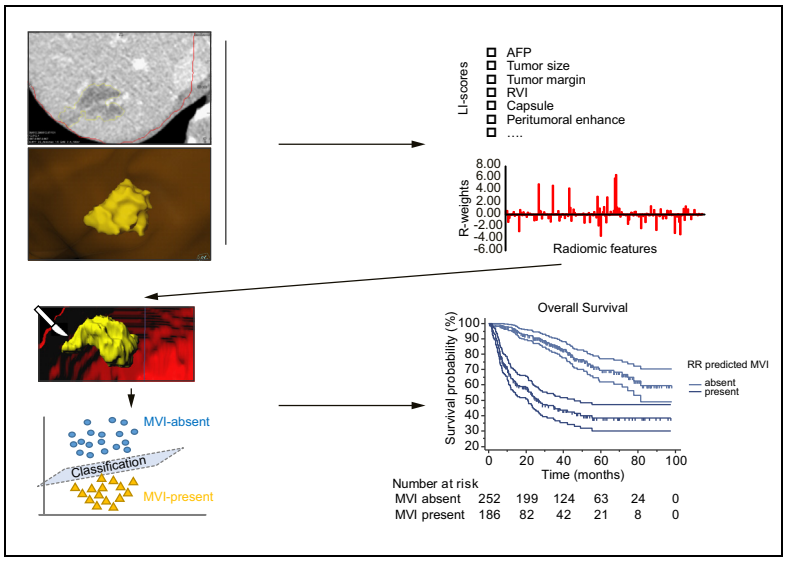
https://doi.org/10.1016/j.jhep.2019.01.009

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma

Graphical abstract



Highlights

- We identified 8 MVI preoperative risk factors in HCC, including radiomic features.
- Radiomic features do not provide significant added value to radiologist scores.
- A model integrating clinic-radiologic and radiomic features demonstrates good performance for predicting MVI.

Authors

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Lay summary

The most effective treatment for hepatocellular carcinoma (HCC) is surgical removal of the tumor but often recurrence occurs, partly due to the presence of microvascular invasion (MVI). Lacking a single highly reliable factor able to preoperatively predict MVI, we developed a computational approach to predict MVI and the long-term clinical outcome of patients with HCC. In particular, the added value of radiomics, a newly emerging form of radiography, was comprehensively investigated. This computational method can enhance the communication with the patient about the likely success of the treatment and guide clinical management, with the aim of finding drugs that reduce the risk of recurrence.

https://doi.org/10.1016/j.jhep.2019.02.023

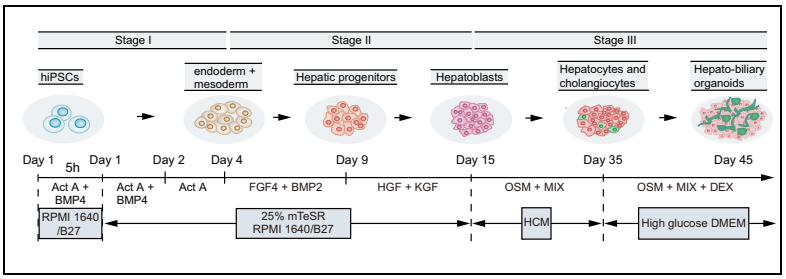
 J. Hepatol. 2019, 70, 1133–1144

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Generation of hepatobiliary organoids from human induced pluripotent stem cells

Graphical abstract



Highlights

- We established a system to generate hiPSC-derived hepatobiliary organoids *in vitro.*
- To varying degrees, this model recapitulated several key aspects of hepatobiliary organogenesis.
- The hepatobiliary organoids displayed a series of hepatic and biliary functional attributes.
- This system does not rely on any exogenous cells or genetic manipulation.

Authors

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Lay summary

Herein, we established a system to generate human induced pluripotent stem cell-derived functional hepatobiliary organoids *in vitro,* without any exogenous cells or genetic manipulation. To some extent this model was able to recapitulate several key aspects of hepatobiliary organogenesis in a parallel fashion, holding great promise for drug development and liver transplantation.

https://doi.org/10.1016/j.jhep.2018.12.028

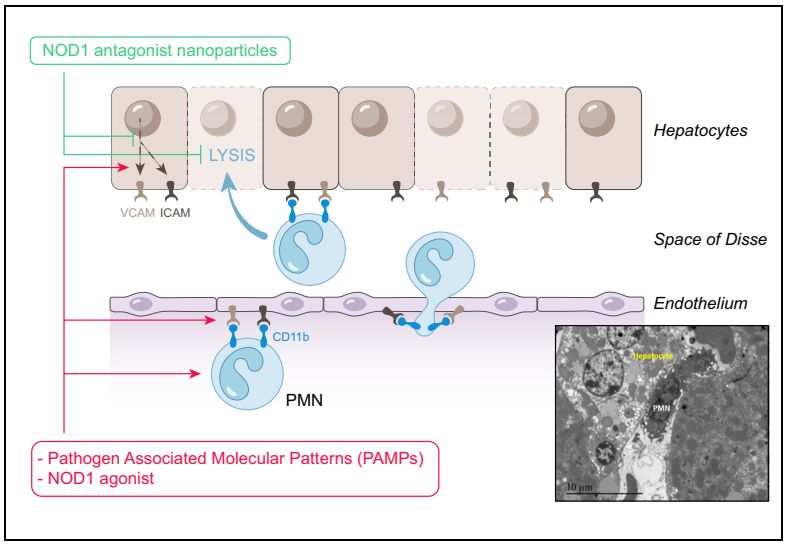
 J. Hepatol. 2019, 70, 1145–1158

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Nucleotide-binding oligomerization domain 1 (NOD1) modulates liver ischemia reperfusion through the expression adhesion molecules

Graphical abstract



Highlights

- NOD1 agonists induced expression of adhesion molecules in the normal and IR-injured livers.
- NOD1 mediates interactions between hepatocytes and polymorphonuclear neutrophils during liver IR.
- Insoluble NOD1 inhibitors were efficiently integrated into PLGA nanoparticles for use *in vivo*.
- NOD1 antagonist nanoparticles reduced ICAM-1 expression and IR-induced liver injury.
- The NOD1 pathway modulates liver IR injury by targeting polymorphonuclear neutrophil function and adhesion molecules.

Authors

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Lay summary

Nucleotide-binding oligomerization domain 1 (NOD1) is as an important modulator of polymorphonuclear neutrophil (PMN)-induced liver injury, which occurs in ischemia-reperfusion. Here, we show that the NOD1 pathway targets liver adhesion molecule expression on the endothelium and on hepatocytes through p38 and ERK signaling pathways. The early increase of adhesion molecule expression after reperfusion emphasizes the importance of adhesion molecules in liver injury. In this study we generated nanoparticles loaded with NOD1 antagonist. These nanoparticles reduced liver necrosis by reducing PMN liver infiltration and adhesion molecule expression.

https://doi.org/10.1016/j.jhep.2019.01.019

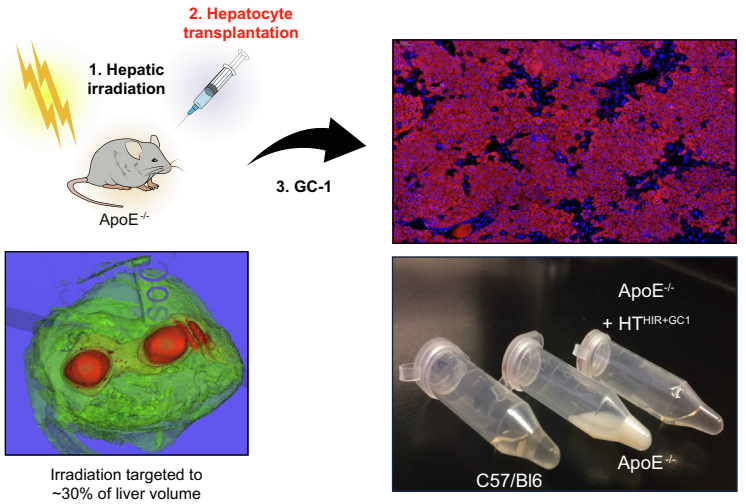
 J. Hepatol. 2019, 70, 1159–1169

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Radiation-primed hepatocyte transplantation in murine monogeneic dyslipidemia normalizes cholesterol and prevents atherosclerosis

Graphical abstract



Highlights

- Conformal hepatic irradiation (HIR) with a hepatic mitogen, GC-1 is safe.
- HIR+GC-1 enables massive liver repopulation by transplanted hepatocytes.
- HIR+HT+GC-1 leads to complete correction of inherited dyslipidemia.
- Preparative regimen of HIR+GC-1 has clinical potential.

Authors

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Lay summary

Hepatocyte transplantation is a promising alternative to liver transplantation for the treatment of liver diseases. However, it is inefficient, as restricted growth of transplanted cells in the liver limits its therapeutic benefits. Preparative treatments improve the efficiency of this procedure, but no clinically-feasible options are currently available. In this study we develop a novel well-tolerated preparative treatment to improve growth of cells in the liver and then demonstrate that this treatment completely cures an inherited lipid disorder in a mouse model.

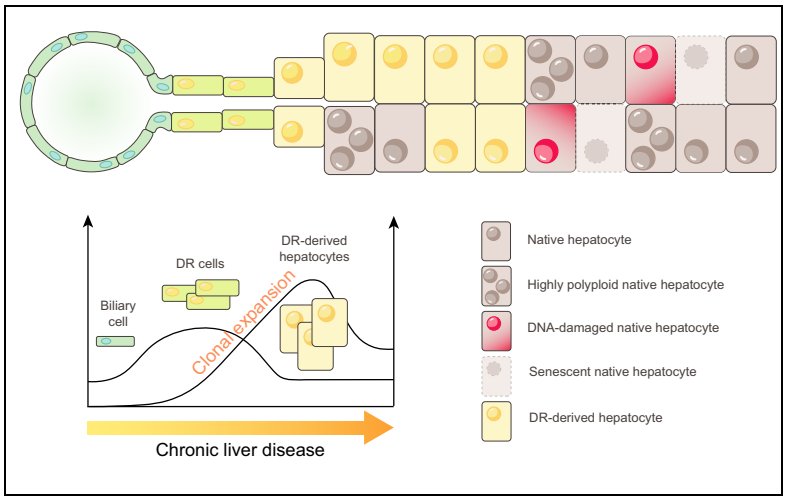
https://doi.org/10.1016/j.jhep.2019.01.010

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Reactive cholangiocytes differentiate into proliferative hepatocytes with efficient DNA repair in mice with chronic liver injury

Graphical abstract



Highlights

- During chronic injury, native hepatocytes become damaged, replicatively senescent and accumulate DNA damage.
- New hepatocytes with specific characteristics of "undamaged and young hepatocytes emerge and undergo clonal expansion.
- Our cell tracing studies suggest that these new hepatocytes derive from reactive cholangiocytes.

Authors

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Lay summary

During chronic liver disease, while native hepatocytes are exhausted and genetically unstable, a subset of cholangiocytes clonally expand to differentiate into young, functional and robust hepatocytes. This cholangiocyte cell population is a promising target for regenerative therapies in patients with chronic liver insufficiency.

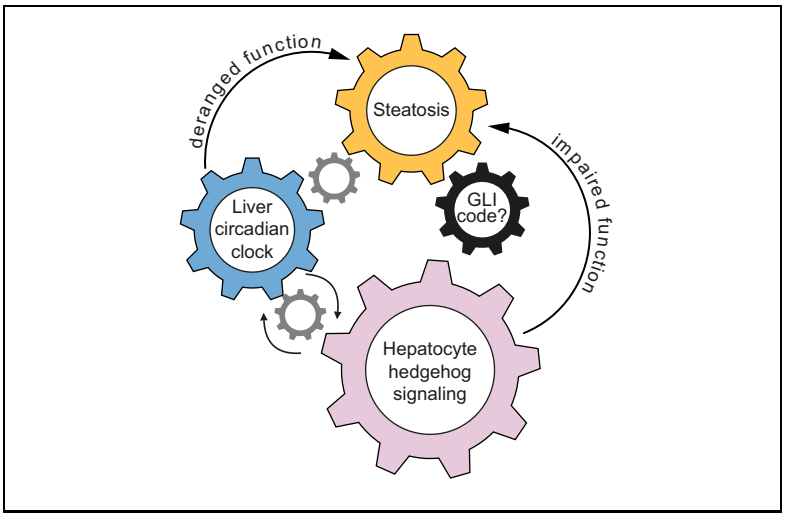
https://doi.org/10.1016/j.jhep.2019.02.003

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Tick-tock hedgehog-mutual crosstalk with liver circadian clock promotes liver steatosis

Graphical abstract



Highlights

- Hh signaling shows diurnal oscillations in liver and hepatocytes *in vitro* and *in vivo*.
- Hh signaling feeds-back on the liver clock via GLI transcription factors.
- The amplitude of the oscillations of the liver clock is decreased in hepatocytes from *Smo*-knockout mice.
- Rhythmicity of many metabolic pathways, including hepatic lipid metabolism, is affected by oscillating Hh signaling.
- Diurnal timing of starvation affects the clock-hedgehog module differently.

Authors

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Lay summary

The results of our investigation show for the first time that the Hh signaling in hepatocytes is time-of-day dependent, leading to differences not only in transcript levels but also in the amount of Hh ligands in peripheral blood. Conversely, Hh signaling is able to feed back to the circadian clock.

https://doi.org/10.1016/j.jhep.2019.01.022

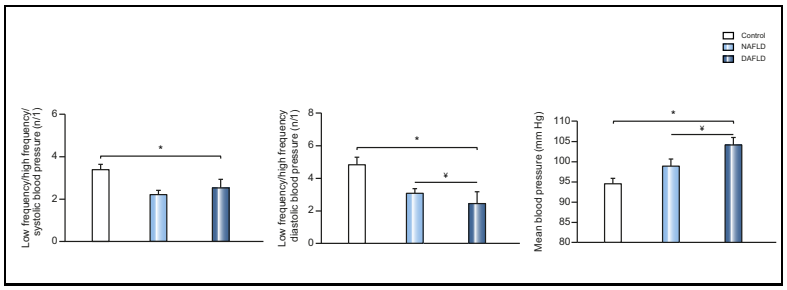
 J. Hepatol. 2019, 70, 1192–1202

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

The degree of hepatic steatosis associates with impaired cardiac and autonomic function

Graphical abstract



Highlights

- Patients with elevated liver fat and poor metabolic control have impaired cardiac and autonomic function.
- Liver fat, metabolic dysfunction, inflammation and fibrosis staging correlate with cardiac and autonomic dysfunction.
- Elevated alcohol intake enhanced the impact of liver fat on diastolic autonomic dysfunction.

Authors

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Lay summary

Increased levels of fat in the liver impair the ability of the cardiovascular system to work properly. The amount of fat in the liver, metabolic control, inflammation and alcohol are all linked to the degree that the cardiovascular system is affected.

https://doi.org/10.1016/j.jhep.2019.01.035

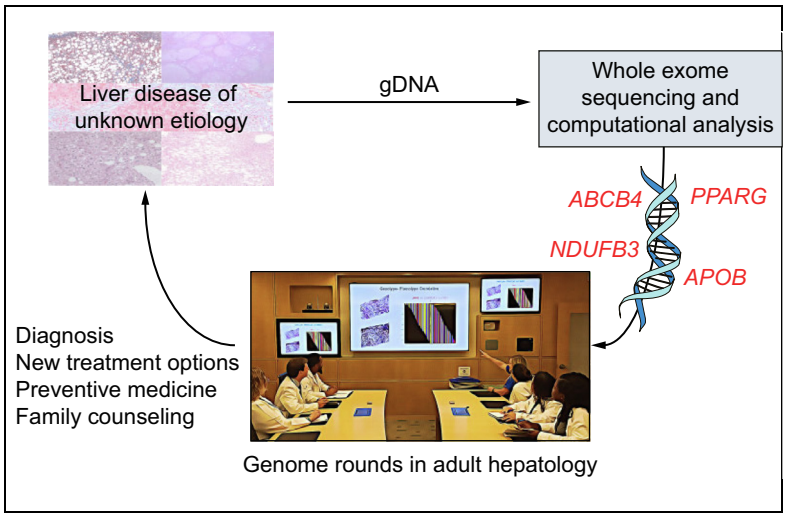
 J. Hepatol. 2019, 70, 1203–1213

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Clinical utility of genomic analysis in adults with idiopathic liver disease

Graphical abstract



Highlights

- Whole exome sequencing led to a diagnosis in 5/19 cases of unexplained liver disease.
- These 5 cases represented 4 monogenic disorders diagnosed in adulthood.
- Genomic analysis informed the treatment and management of liver disease.

Authors

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Lay summary

We performed whole-exome sequencing in 19 adult patients with unexplained liver disease after an unrevealing conventional work-up performed by a hepatologist. In 5 cases, genomic analysis led to a diagnosis and informed treatment and management of the disease. Therefore, we suggest using whole-exome sequencing in the evaluation and management of adults with unexplained liver disease.

https://doi.org/10.1016/j.jhep.2019.01.036

 J. Hepatol. 2019, 70, 1214–1221