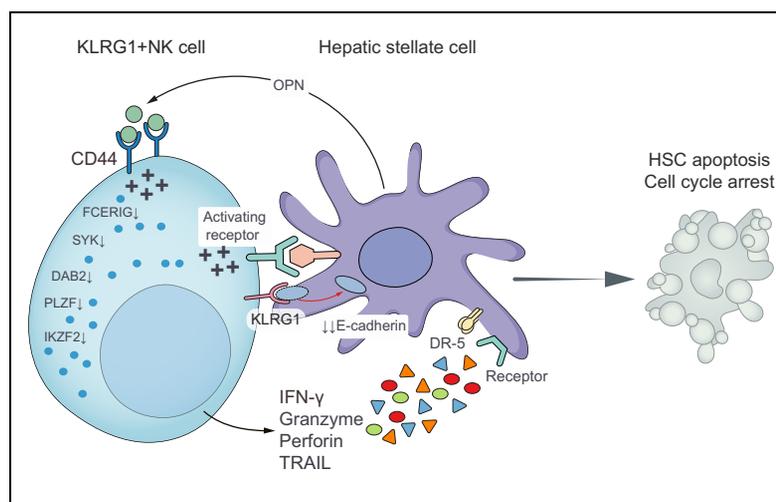


KLRG1⁺ natural killer cells exert a novel antifibrotic function in chronic hepatitis B

Graphical abstract



Highlights

- Patients with chronic HBV possess increased circulating and hepatic KLRG1⁺ NK cells.
- KLRG1⁺ NK cells possess a mature phenotype expressing elevated CD57 and DNAM-1, and reduced NKp46 and NKG2A.
- KLRG1⁺ NK cells are associated with reduced fibrosis stage in patients with chronic HBV.
- KLRG1⁺ NK cells induce hepatic stellate cell apoptosis in a TRAIL and CD44-osteopontin dependent manner.

Authors

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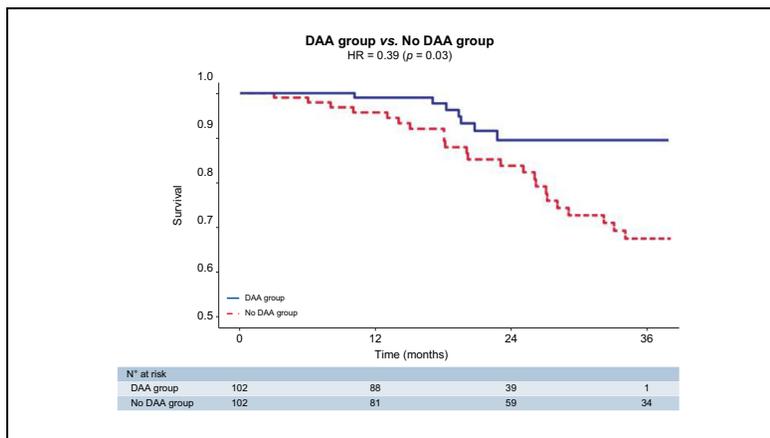
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Lay summary

Individuals that are chronically infected with hepatitis B virus (HBV) possess an increased number of immune cells, called natural killer (NK) cells expressing the surface marker KLRG1 in the blood and liver. Here, we demonstrate that these specific NK cells are able to kill activated stellate cells in the liver. Because activated stellate cells contribute to liver scarring, *i.e.* fibrosis, and subsequent liver dysfunction in individuals with chronic HBV infection, KLRG1⁺ NK cells are a novel immune cell type that can limit liver scarring.

Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients

Graphical abstract



Highlights

- DAAs improve survival in patients with HCV-related early HCC that has been successfully treated.
- The improvement in survival seems to be caused by a reduction in hepatic decompensation.
- DAAs did not impact on HCC recurrence.

Authors

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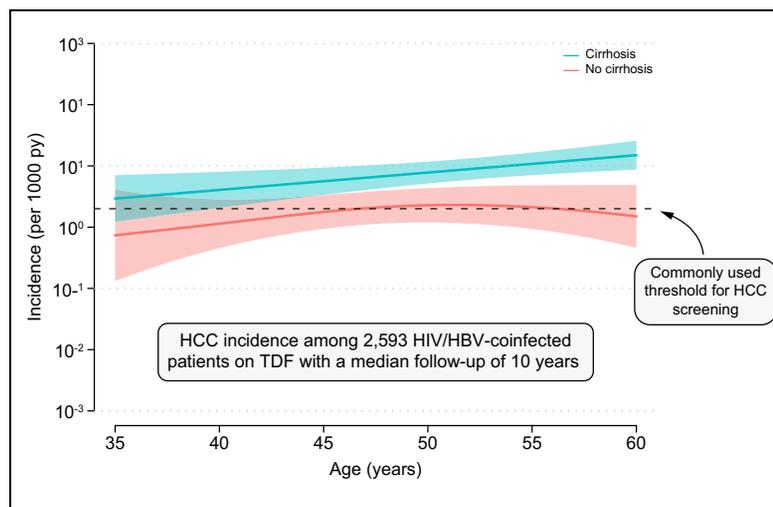
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Lay summary

We aimed to determine whether direct-acting antivirals (DAAs) significantly improve overall survival in patients with hepatitis C virus-related compensated cirrhosis and a first diagnosis of hepatocellular carcinoma (HCC) which has been successfully treated with curative resection or ablation. Using propensity-score matched patients, we found that DAAs improved overall survival and reduced the risk of hepatic decompensation. However, the risk of HCC recurrence was not significantly reduced.

Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies

Graphical abstract



Highlights

- Over 32,673 patient-years of follow-up, 60 (1.7%) HIV/HBV-coinfected individuals developed HCC.
- In cirrhotic patients on TDF-containing antiretroviral therapy, the incidence of HCC was 5.90 per 1,000 patient-years.
- In non-cirrhotic patients on TDF-containing antiretroviral therapy, the incidence was 1.17 per 1,000 patient-years.
- HCC incidence stayed below the recognized screening threshold in non-cirrhotics who started TDF when <46 years old.

Authors

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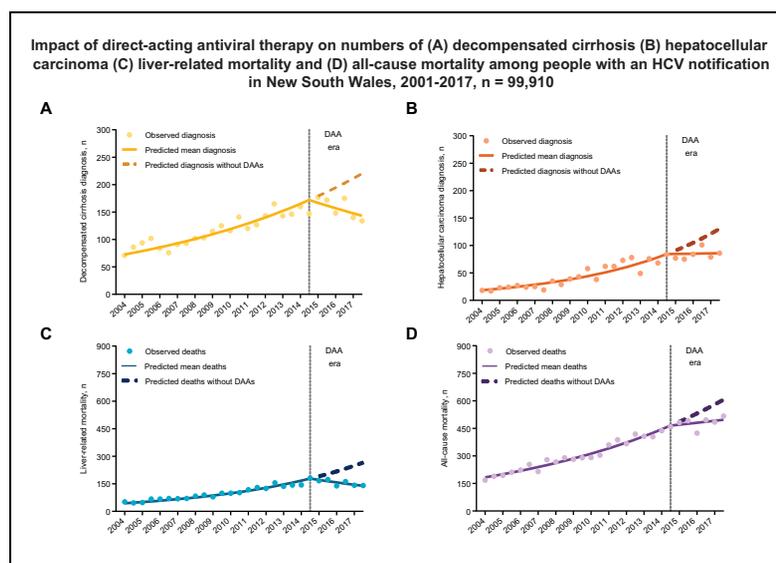
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Lay summary

We investigated the incidence of hepatocellular carcinoma in HIV/hepatitis B virus-coinfected individuals from a large multi-cohort study in Europe. Over 32,673 patient-years, 60 individuals (1.7%) developed hepatocellular carcinoma. The incidence of hepatocellular carcinoma remained low in patients without cirrhosis, who started on tenofovir disoproxil fumarate when aged <46 years old.

Declining hepatitis C virus-related liver disease burden in the direct-acting antiviral therapy era in New South Wales, Australia

Graphical abstract



Highlights

- Prior to the introduction of DAA therapy, the disease burden of HCV was rising in New South Wales.
- DAA scale-up has had a major population-level impact on HCV morbidity and mortality.
- The World Health Organization has set a 65% HCV mortality reduction target by 2030.
- To achieve this target, enhanced efforts are required to continue DAA scale-up.
- In the DAA era, the impact of heavy alcohol use on liver disease should be monitored.

Authors

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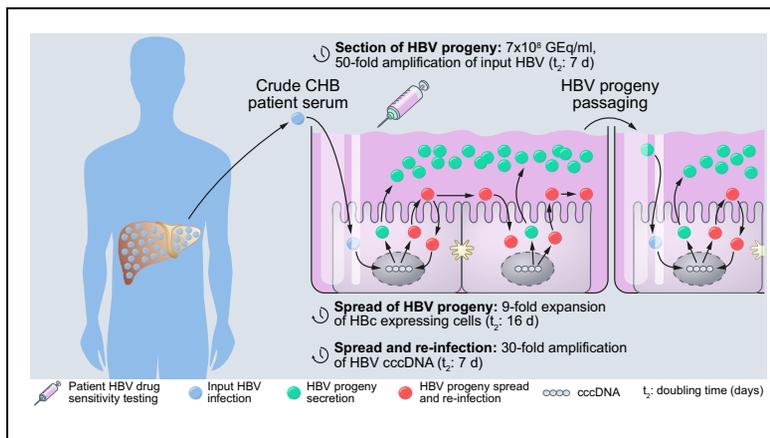
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Lay summary

Rising hepatitis C-related morbidity and mortality is a major public health issue. However, development of highly effective medicines against hepatitis C (called direct-acting antivirals or DAAs) means hepatitis C could be eliminated as a public health threat by 2030. This study shows a sharp decline in liver disease morbidity and mortality since the introduction of DAAs in New South Wales, Australia. Despite this, heavy alcohol use remains an important risk factor for liver disease among people with hepatitis C. To ensure that the benefits of new antiviral treatments are not compromised, management of major comorbidities, including heavy alcohol use must improve among people with hepatitis C.

Efficient long-term amplification of hepatitis B virus isolates after infection of slow proliferating HepG2-NTCP cells

Graphical abstract



Highlights

- Cell culture system that mimicks complete HBV life cycle from entry to egress.
- Efficient *in vitro* infection with crude HBV patient sera.
- Up to 50- and 1,300-fold net amplification of patient- and cell culture-derived input HBV in the supernatant.
- Polyethylene glycol-independent HBV spread to adjacent cells, forming infected cell clusters.
- Evaluation of patient- and cell culture-derived HBV amplification w/wo antivirals over 8 weeks.

Authors

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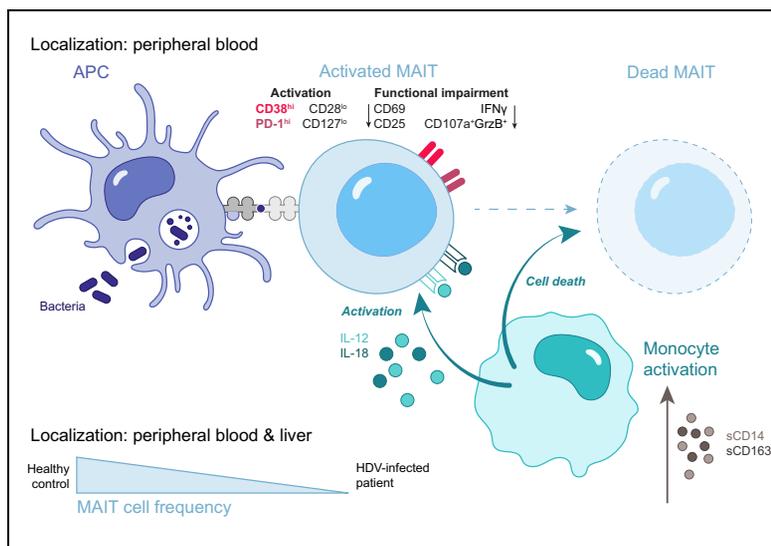
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Lay summary

Currently available laboratory systems are unable to reproduce the dynamics of hepatitis B virus (HBV) spread through the infected liver and release into the blood. We developed a slowly dividing liver-derived cell line which multiplies infectious viral particles upon inoculation with patient- or cell culture-derived HBV. This new infection model can improve therapy by measuring, in advance, the sensitivity of a patient's HBV strain to specific antiviral drugs.

Chronic hepatitis delta virus infection leads to functional impairment and severe loss of MAIT cells

Graphical abstract



Authors

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Lay summary

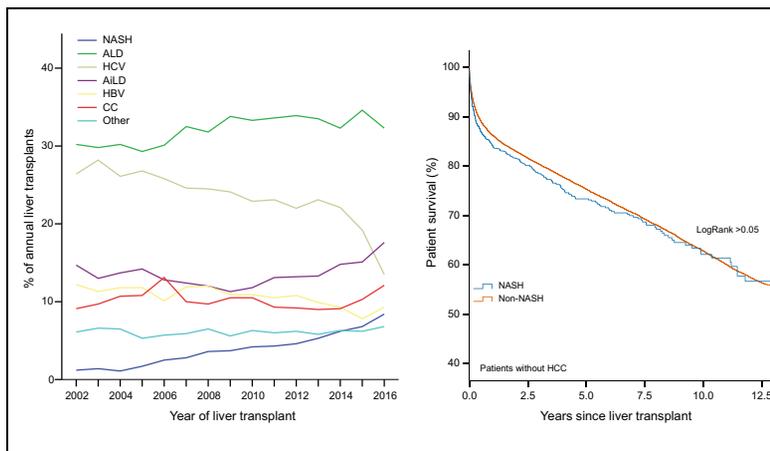
Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis. We found that in patients with HDV, a subset of innate-like T cells called mucosa-associated invariant T cells (or MAIT cells), which are normally abundant in peripheral blood and the liver, are activated, functionally impaired and severely depleted.

Highlights

- Mucosa-associated invariant T (MAIT) cells are severely depleted in peripheral blood of HDV-infected patients.
- Residual MAIT cells display a distinct CD38^{hi}PD-1^{hi}CD28^{lo}CD127^{lo} compound phenotype.
- Residual MAIT cells are functionally impaired in response to bacteria.
- Patients with HDV exhibit signs of microbial translocation and increased IL-12 and IL-18.
- IL-12 and IL-18 induce an activated MAIT cell phenotype and promote apoptosis.

Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study

Graphical abstract



Highlights

- An increasing proportion of patients are being transplanted for non-alcoholic steatohepatitis (NASH) in Europe.
- Hepatocellular carcinoma was more common in patients transplanted with NASH.
- Survival in recipients with NASH is comparable to that of other disease indications.
- Age, BMI, and advanced liver disease predicted poorer outcomes in NASH recipients.

Authors

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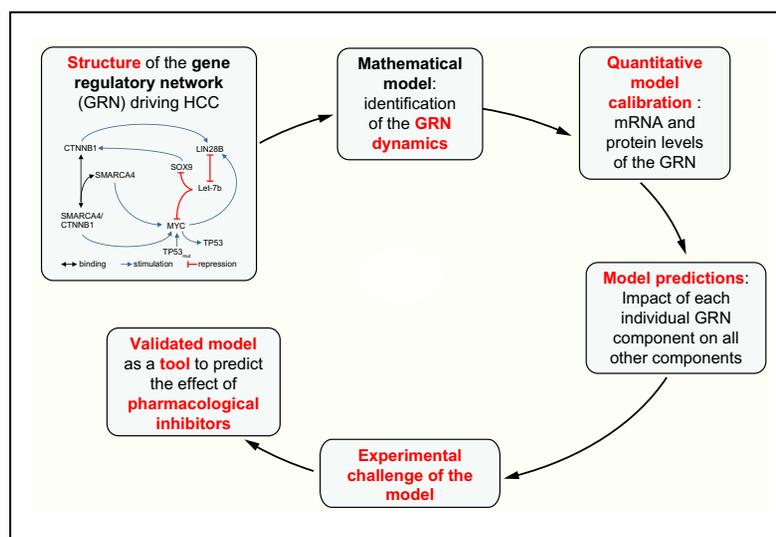
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Lay summary

The prevalence of non-alcoholic fatty liver disease has increased dramatically in parallel with the worldwide increase in obesity and diabetes. Its progressive form, non-alcoholic steatohepatitis, is a growing indication for liver transplantation in Europe, with good overall outcomes reported. However, careful risk factor assessment is required to maintain favourable post-transplant outcomes in patients with non-alcoholic steatohepatitis.

Dynamics and predicted drug response of a gene network linking dedifferentiation with beta-catenin dysfunction in hepatocellular carcinoma

Graphical abstract



Authors

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Lay summary

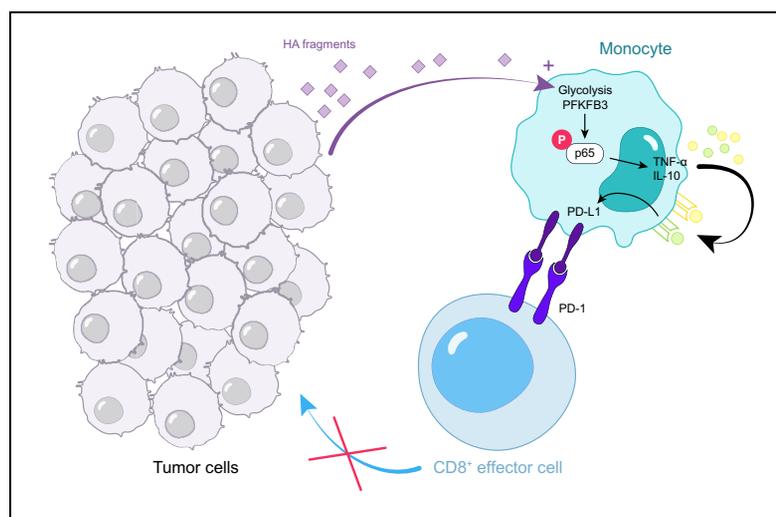
Hepatocellular carcinoma (HCC) is a heterogeneous disease driven by the concomitant deregulation of several genes functionally organized as networks. Here, we identified a gene regulatory network involved in a subset of HCCs. This subset is characterized by increased proliferation and poor prognosis. We developed a mathematical model which uncovers the dynamics of the network and allows us to predict the impact of a therapeutic agent, not only on its specific target but on all the genes belonging to the network.

Highlights

- We identified a gene regulatory network (GRN) involved in a subset of hepatocellular carcinomas.
- Expression of GRN members and targets correlates with proliferation and prognosis.
- A quantitative mathematical model of the GRN revealed the network dynamics.
- This model is a potential tool to assess the impact of pharmacological inhibitors.

Glycolytic activation of peritumoral monocytes fosters immune privilege via the PFKFB3-PD-L1 axis in human hepatocellular carcinoma

Graphical abstract



Highlights

- Peritumoral monocytes in human HCC preferentially upregulate aerobic glycolysis.
- Aerobic glycolysis induces PD-L1 expression via the PFKFB3-NF-κB pathway.
- Tumor derived hyaluronan fragments induce glycolytic activation in monocytes.
- Levels of PFKFB3⁺CD68⁺ cell infiltration predict disease progression of human HCC.

Authors

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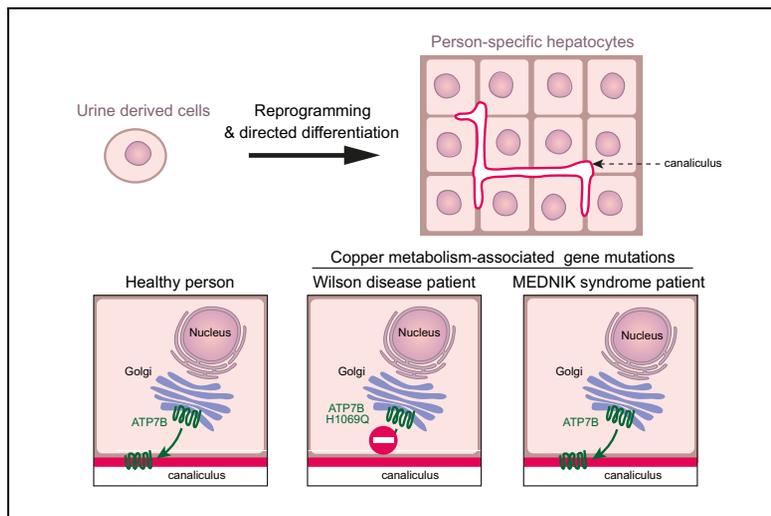
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Lay summary

Programmed cell death 1 ligand 1 (PD-L1) expressed on antigen-presenting cells, rather than tumor cells, has been reported to play an essential role in checkpoint blockade therapy. A fundamental understanding of mechanisms that regulate the expression of PD-L1 on tumor-infiltrating monocytes/macrophages will undoubtedly lead to the possibility of developing novel PD-L1 blockade strategies with high specificity and efficiency. The current study unveils a novel mechanism by which metabolic switching links immune activation responses to immune tolerance in the tumor milieu, identifying potential targets for future immune-based anti-cancer therapies.

Pluripotent stem cell-derived bile canaliculi-forming hepatocytes to study genetic liver diseases involving hepatocyte polarity

Graphical abstract



Highlights

- Functional cell polarity can be achieved in patient pluripotent stem cell-derived hepatocytes.
- This will enable the study of autologous mutant proteins in biliary processes.
- The Wilson disease-causing ATP7B-H1069Q mutation prevents its copper-induced polarized redistribution.
- MEDNIK syndrome-causing *AP1S1* mutations do not cause the expected defect in copper-stimulated redistribution of ATP7B.

Authors

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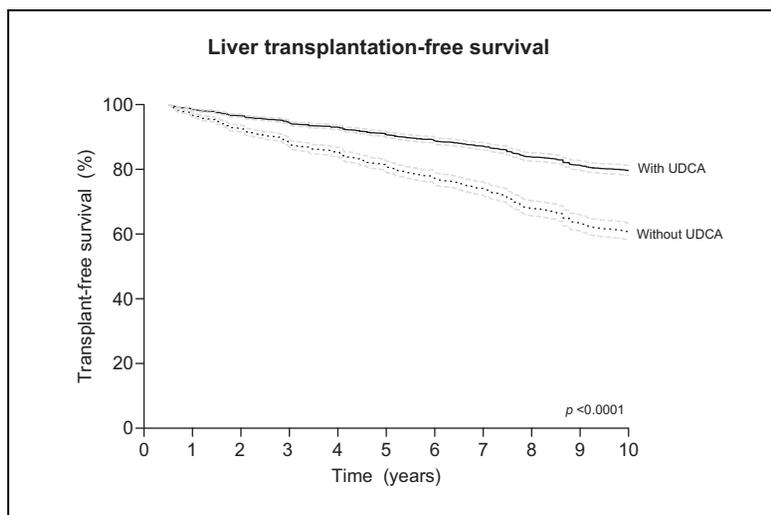
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Lay summary

This study demonstrates that cells that are isolated from urine can be reprogrammed in a dish towards hepatocytes that display architectural characteristics similar to those seen in the intact liver. The application of this methodology to cells from patients diagnosed with inherited copper metabolism-related liver diseases (that is, Wilson disease and MEDNIK syndrome) revealed unexpected and novel insights into patient mutation-specific disease mechanisms and drug responses.

Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis

Graphical abstract



Highlights

- Ursodeoxycholic acid is associated with prolonged survival in primary biliary cholangitis.
- This positive association is significant irrespective of age, sex, or disease stage.
- The association remains significant in cases where the established criteria for therapeutic response are not met.

Authors

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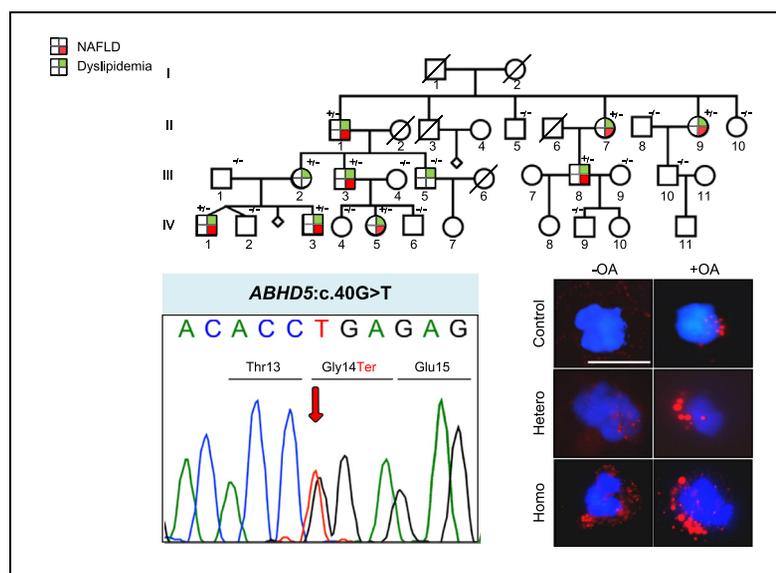
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Lay summary

In this international multicenter study of 3,902 patients with primary biliary cholangitis, we found that treatment with ursodeoxycholic acid is associated with prolonged liver transplant-free survival. This association was significant, irrespective of sex, age, or disease stage. The survival benefit remained statistically significant in patients with an incomplete biochemical response to ursodeoxycholic acid therapy.

Inherited non-alcoholic fatty liver disease and dyslipidemia due to monoallelic *ABHD5* mutations

Graphical abstract



Authors

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Lay summary

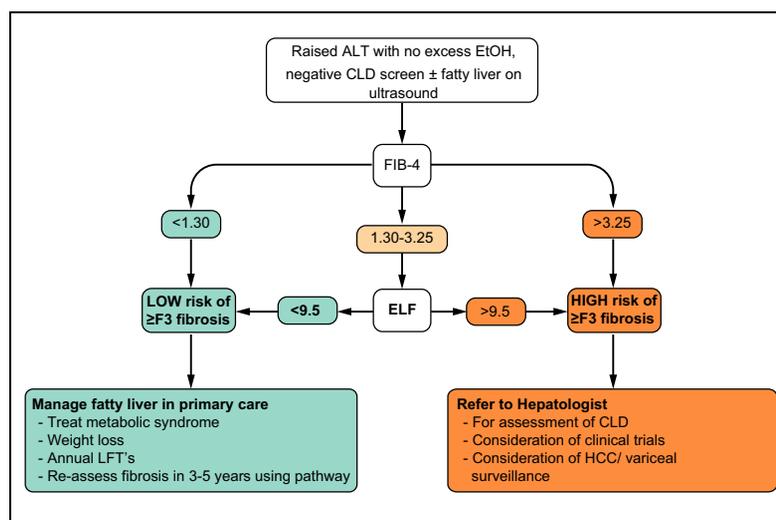
Non-alcoholic fatty liver disease (NAFLD) is a common multifactorial disorder with a strong genetic component. Inherited forms of NAFLD have been suspected but, their molecular pathogenesis has not been disclosed. Here we report a heritable form of NAFLD with clinical expression after 40 years of age, associated with monoallelic *ABHD5* mutations.

Highlights

- Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world.
- We identified monoallelic *ABHD5* mutations in 7 families with NAFLD.
- *ABHD5* is involved in neutral lipid metabolism, highlighting the role of lipid disorders in NAFLD.

Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease

Graphical abstract



Highlights

- Established blood tests can be used in primary care to stratify patients with fatty liver disease.
- A 2-step pathway (FIB-4 followed by ELF™ if required) reduced unnecessary referrals by 80%.
- This pathway also improved the detection of cases of advanced fibrosis 5-fold and cirrhosis 3-fold.
- This pathway can be used in primary care to identify patients who might benefit from referral to liver specialists.
- This should reduce unnecessary referrals while at the same time improving the detection of cirrhosis.

Authors

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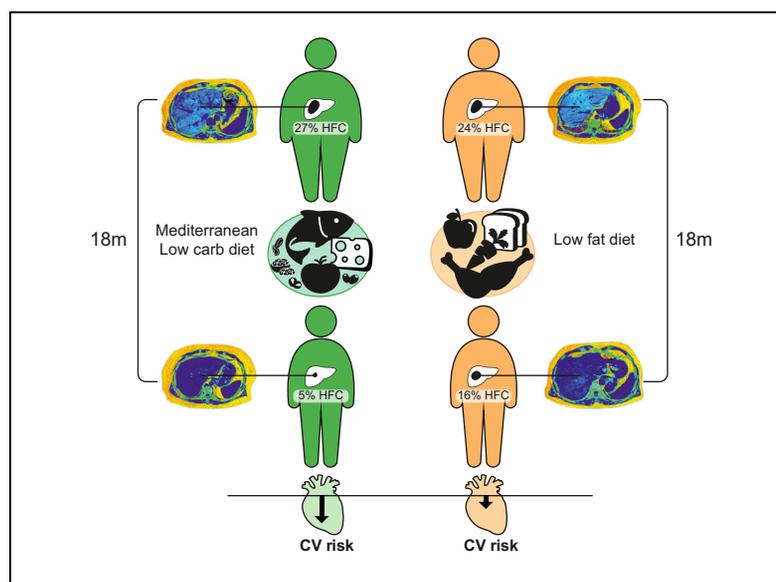
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Lay summary

Non-alcoholic fatty liver disease affects up to 30% of the population but only a minority of cases develop liver disease. Our study has shown that established blood tests can be used in primary care to stratify patients with fatty liver disease, leading to a reduction in unnecessary referrals by 80% and greatly improving the detection of cases of advanced fibrosis and cirrhosis.

The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content

Graphical abstract



Authors

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Lay summary

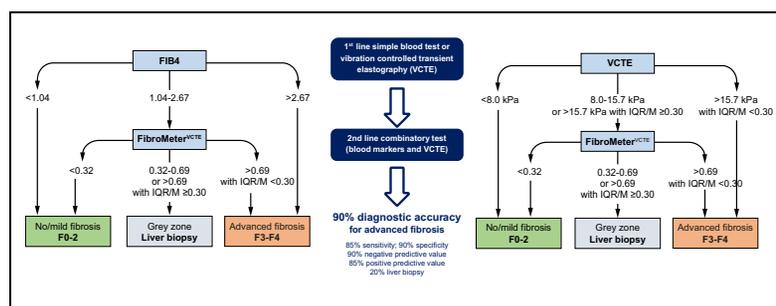
High hepatic fat content is associated with metabolic syndrome, type 2 diabetes mellitus, and coronary heart disease. In the CENTRAL 18-month intervention trial, a Mediterranean/low-carbohydrate diet induced a greater decrease in hepatic fat content than a low-fat diet, conferring beneficial health effects that were beyond the favorable effects of visceral fat loss.

Highlights

- A Mediterranean and low carbohydrate diet decreases hepatic fat more than a low-fat diet, beyond visceral fat changes.
- Decreases in hepatic fat are independently associated with specific improved parameters.
- The beneficial effect of a Mediterranean diet over a low-fat diet is mainly mediated by decreases in hepatic fat.

New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD

Graphical abstract



Highlights

- Liver-related prognosis in non-alcoholic fatty liver disease (NAFLD) is impaired in patients with advanced fibrosis.
- FibroMeter^{VCTE} is a new test combining blood markers and elastography.
- FibroMeter^{VCTE} outperforms other fibrosis tests for the diagnosis of advanced fibrosis in NAFLD.
- Algorithms using FibroMeter^{VCTE} as a second-line test provide 90% diagnostic accuracy.

Authors

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Lay summary

The evaluation of liver fibrosis is mandatory in non-alcoholic fatty liver disease (NAFLD), as advanced fibrosis identifies the subgroup of patients with impaired prognosis. FibroMeter^{VCTE} is a new fibrosis test combining blood markers and the result of vibration controlled transient elastography (VCTE) into a single diagnostic test. Our results show that FibroMeter^{VCTE} outperforms other blood fibrosis tests and VCTE alone for the diagnosis of advanced fibrosis in a large multi-centric cohort of 938 patients with biopsy-proven NAFLD. Sequential algorithms using a simple blood test or VCTE as a first-line procedure, then FibroMeter^{VCTE} as a second-line test accurately classified 90% of patients.