LB002

Genetic variation in TERT modifies the risk of hepatocellular carcinoma in alcohol-related cirrhosis: results form a genome-wide case-control study

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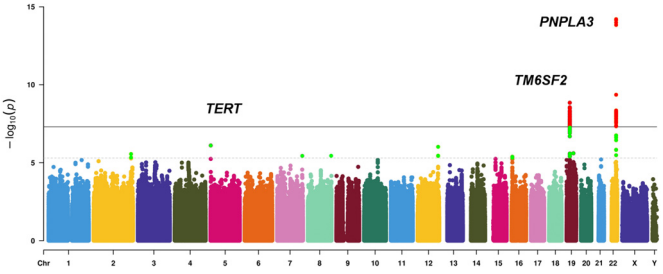
Background and aims: Hepatocellular carcinoma (HCC) often develops in patients with alcohol-related cirrhosis (ArC) at an annual risk of up to 2.9%. Some host genetic risk factors have been identified but do not account for the majority of the variance in occurrence. This study aimed to identify novel risk factors for the development of HCC in people with alcohol related cirrhosis.
Method: Patients with alcohol-related cirrhosis with HCC (cases: n = 1, 214) and without HCC (controls: n = 1, 866), recruited from Germany, Austria, Switzerland, Italy and the UK, were included in a two-stage GWAS utilizing a case-control design. A validation cohort of 1, 520 people misusing alcohol but with no evidence of liver disease was included to control for possible association effects of alcohol misuse *per se*. Genotyping was performed using the Infinium®Global Screening Array (GSA) (version 24v2, Illumina) and the OmniExpress Array (version 24v1-0a, Illumina).
Results: Associations with variants rs738409 in *PNPLA3* and rs58542926 in *TM6SF2* previously associated with HCC in patients with alcohol-related cirrhosis were confirmed at genome-wide significance. In addition, a novel locus rs2242652 in *TERT* (telomerase reverse transcriptase) attained genome-wide significant association in the combined meta-analysis with alcohol-related HCC at ($p = 6.41 \times 10^{-9}$, odds ratio (OR) = 0.61 (95%CI, 0.52–0.72). This protective association remained significant after correction for sex, age, BMI, type 2 diabetes, and ancestry. The minor alleles of variants rs2242652 ($p = 2.12 \times 10^{-44}$) and rs10069690 ($p = 4.08 \times 10^{-84}$) in *TERT* were associated with increased leukocyte telomere length.



Conclusion: This study identifies rs2242652 in *TERT* as a novel protective factor for HCC in patients with alcohol-related cirrhosis.

LB003

Reprogramming necroptosis limits immune responses and prevents liver cancer development

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Background and aims: Necroptosis is a novel form of programmed cell death controlled through the molecules RIPK3 and MLKL. Recent studies showed that necroptosis and not apoptosis represents the dominant cell death pathway activated in non-alcoholic fatty liver disease (NAFLD). However, it is unknown how necroptosis and immune reactions are functionally related in the liver, if sublethal forms of necroptosis exist in vivo and how these molecular processes control the transition from chronic liver disease to hepatocellular carcinoma (HCC).
Method: We generated conditional genetic mouse models to activate necroptosis in hepatocytes and performed genetic sub-crossings for functional pathway dissection. We characterized liver inflammation through immunohistochemistry, biliary architecture through 3-D-Reconstruction of multi-slice immuno-fluorescence and HCC development through array-CGH-analysis. Immune-signatures ('Necroptome') were characterized by scRNA sequencing. Moreover, we developed a novel 2-photon-approach for live-imaging of necroptosis and the spatial and dynamic relation to immune cells in vivo. Mechanistic findings in mice were correlated with data from human NAFLD and HCC.
Results: We show for the first time that two alternative forms of necroptosis exist in the liver triggering distinct immunological response-programs licensed through the activation status of NF-kB. As such, pre-activation of NF-kB transforms hepatocytes into a sublethal state. In this "undead" state, the necroptosis machinery induces leakiness of cell membranes, allowing the release of NF-kB-dependent cytokines including CCL-20, IL-6 and MCP1. These functional alarmins promote activation of necroptosis-specific monocyte/macrophage subsets that in turn show a pro-carcinogenic and pro-fibrotic profile on single-cell level, ultimately promoting HCC development. In contrast, inhibition of distinct members of the NF-kB pathway (IKK-beta, NEMO, RelA) converts necroptosis into a rapidly lethal form of cell death. These rapidly dying hepatocytes do not release cytokines/alarmins upon their death, thus failing to trigger a reactive immune and stellate cell signature. Consequently, reprogramming towards this "hypo-reactive" necroptosis form prevents HCC development. In line, we identified areas of co-activation of NF-kB and the necroptosis machinery in human NAFLD biopsies and additionally could show that human patients with HCC featuring a transcriptional profile matching the newly discovered NF-kB/Necroptosis/Signature in mice had a specifically fatal clinical outcome.
Conclusion: Necroptosis can occur in two functionally distinct forms in the liver. Pharmacological reprogramming between these two alternative forms might represent a novel strategy to prevent the transition from chronic liver disease towards HCC development in high-risk NAFLD patients.

LB004A

Efficacy and safety of bepirovirsen in patients with chronic hepatitis B virus infection not on stable nucleos (t)ide analogue therapy: interim results from the randomised phase 2b B-Clear study

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Background and aims: Bepirovirsen (BPV; GSK3228836) is an antisense oligonucleotide shown to induce a reduction in hepatitis B surface antigen (HBsAg), and in some cases transient HBsAg seroclearance, following 4 weeks (wks) treatment with a favourable safety profile in a phase 2a study in patients (pts) with chronic hepatitis B (CHB) infection. B-Clear is a phase 2b trial (NCT04449029) assessing the efficacy and safety of 12 or 24 wks BPV treatment in pts with CHB on-stable nucleos (t)ide analogue (NA) treatment or not on-NA therapy at study start. The study is ongoing; here we present interim results through the end of BPV treatment (EoT) for pts not on NA therapy.
Method: Multicentre, randomised, partial-blind (investigator unblinded), parallel-cohort study in pts with CHB. Pts required HBsAg >100 IU/ml, HBV DNA >2000 IU/ml and alanine aminotransferase <3× upper limit of normal. Pts were randomised (3:3:3:1) to 1 of 4 treatment arms, with treatment administered weekly with (w/) or without (w/o) loading doses (LD) on Days 4 and 11: 1. BPV 300 mg w/LD for 24 wks; 2. BPV 300 mg w/LD for 12 wks then 150 mg for 12 wks; 3. BPV 300 mg w/LD for 12 wks then placebo (PBO) for 12 wks; 4. PBO for 12 wks then BPV 300 mg w/o LD for 12 wks. Pts were stratified by baseline hepatitis B e antigen (HBeAg; positive/negative) and HBsAg level (≤3 or >3 log10 IU/ml). Primary end point: proportion of pts achieving HBsAg <lower limit of quantification (LLOQ) and HBV DNA <LLOQ sustained for 24 wks without rescue medication after planned BPV EoT. Secondary end points reported here: proportion of pts achieving HBsAg <LLOQ and HBV DNA <LLOQ by BPV EoT. Safety was assessed via adverse event (AE) monitoring.
Results: 230 pts (54% male, 57% Asian, 74% HBeAg negative, 19% HBsAg ≤3 log10 IU/ml) were included in the intent-to-treat