

staining might be a useful additional criterion to predict likelihood of post-transplant tumor recurrence.

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ASSOCIATION BETWEEN THE PSC SUSCEPTIBILITY VARIANT IN THE *MST1* LOCUS AND CHOLANGIOCARCINOMA RISK: CASE-CONTROL ANALYSIS OF A LARGE EUROPEAN COHORT

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Background: Individuals with primary sclerosing cholangitis (PSC) are at an increased cholangiocellular carcinoma (CCA) risk. Lately, the single nucleotide variant (SNV) rs3197999 in the gene encoding macrophage stimulating 1 (*MST1*), a potent tumor suppressor [1], has been linked to PSC [2]. Here we aim to test this *MST1* polymorphism as genetic determinant of CCA in a large cohort of European patients.

Patients and Methods: We genotyped 226 patients with diagnosed CCA (126 males, age 28–90 years; PSC prevalence <2%) from Germany (n=170) and Romania (n=56). The control group consisted of 359 CCA-free individuals (160 males, age 22–90 years). The *MST1* SNV rs3197999 was genotyped using a PCR-based assay with 5'-nuclease and fluorescence detection. Consistency with Hardy-Weinberg equilibrium (HWE) was checked by exact tests; associations were tested in contingency tables (alleles: χ^2 tests; genotypes: Armitage's trend test) and regression analyses.

Results: The cases ($P=0.04$), but not controls ($P>0.05$) deviated from HWE, providing a hint for a possible association between the SNV and CCA. A trend for a higher frequency of the [G] allele in cases (31% vs. 26%, $P=0.09$) was detected. Carriers of the [GG] genotype were at higher CCA risk as compared to [AA] individuals (OR=1.95, 95% CI 1.08–3.52, $P=0.02$). In the whole cohort, gender (OR=1.53, 95% CI 1.10–2.14, $P=0.12$) and age ($P=0.03$) were associated with CCA development. In a multivariate model, including solely carriers of the genotypes [GG] and [AA], gender (OR=1.59, 95% CI 1.04–2.45, $P=0.03$) and the [GG] genotype (OR=1.95, 95% CI 1.07–3.56, $P=0.03$) proved to be independent risk factors for CCA.

Conclusions: The previously identified PSC risk variant of the *MST1* tumor suppressor gene involved in the Hippo signalling cascade increases the odds of developing CCA. This variant may increase the CCA risk irrespective of PSC status.

Reference(s)

- [1] Avruch J, et al. Br J Cancer 2010.
[2] Melum E, et al. Nat Genet 2011.

05. LIVER IMMUNOLOGY INCLUDING VIRAL HEPATITIS

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DO THE INITIAL SERUM LEVEL CHANGES OF SCD26 HAVE ABILITY TO PREDICT SUCCESSFUL TREATMENT WITH IFN-ALPHA AMONG NAIVE CHRONIC HEPATITIS B PATIENTS?

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Introduction: Hepatitis B is a major health problem with serious consequences. In hepatitis B treatment host cellular immune responses have a determinant role and T helper cells are the main active members of immune system against virological infection. The aims of this study are to investigate response rate of patients to INF-Alpha therapy and evaluation of sCD26 and sCD30 roles as presenters of T cells activities in predicting the outcome of therapy in chronic hepatitis B patients.

Methods and Materials: Fifty three chronic hepatitis B patients received IFN-9 MU S.C three times weekly for 24 weeks, and were followed up for 24 weeks. Serum levels of sCD26 and sCD30, before, 1 and 3 months after treatment commencement were evaluated in 53 chronic hepatitis B patients and 30 healthy individuals as control group.

Results: Normal level of ALT was seen in 64.1% (34/53) of patients and undetectable DNA was observed in 39.6% (21 out of 53) of them. Finally, 33.9% (18/53) of patients obtained sustain virological response. CD26 levels changes was correlated with response to treatment and significantly ($p<0.001$) increased during first 3 months of treatment among patients with successful response to therapy.

Conclusion: Interferon is an effective and safe treatment for chronic hepatitis B patients and sCD26 serum level changes might be useful in predicting the outcome of therapy in naïve chronic hepatitis B patients undergoing treatment with IFN-, as it can help clinicians for withdrawing non-responder patients for prevention of adverse events and economical burden.

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DIFFERENCES IN IP-10 LEVELS BETWEEN PATIENTS WITH CHRONIC HBV AND HCV INFECTION

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Introduction: The level of IP-10 in patients with chronic HCV infection was shown as predictor of viral response. It wasn't known about patients with chronic HBV infection. There were data for connection between of IP-10 levels with liver disease and HCV RNA levels but it was little known about IP-10 levels and chronic HBV infection.

Aim: Of the study was to compare IP-10 levels in patients with chronic HBV and HCV infection and their connection with viral replication, liver disease and viral response on treatment.

Material and Methods: 17 patients with chronic HCV infection and 14 with chronic HBV infection were involved in the study. In all patients liver biopsies, measuring of viral load and IP-10 were done. The HCV genotype 1 was proved in all patients with hepatitis C. HBeAg was positive in 5 patients with hepatitis B. Treatment with PEG-IFN α and Ribavirin was initiated in patients with chronic HCV infection and Tenofovir in patients with chronic HBV infection.

ELISA test Quantikine® was used for quantification of IP-10. HBV DNA and HCV RNA were measured by real-time PCR.

Results: The levels of IP-10 were significantly lower in patients with HBV infection than in HCV infected patients (p 0.044). It was found correlation between base IP-10 levels and HBV DNA (r 0.635; p 0.015). There was connection between IP-10 and HCV RNA only in patients without viral response (r 0.925; p 0.024). The levels of IP-10 did not correlate with sex, age, ALT, histology activity and liver fibrosis in both groups of patients. There was connection between basal IP-10 levels and virological response – rapid and early (r -0.611; p 0.009), in patients with chronic HCV infection, but not in HBV infected patients.

Conclusion: The patients with chronic HBV infection had lower plasma levels of IP-10 than those with HCV infection. The IP-10 levels correlated with HBV replication and with HCV RNA in special group of patients. IP-10 could predict virological response in patients with chronic HCV infection on treatment with PEG-IFN α and Ribavirin but not in HBV infected patients on nucleotide analogs therapy.

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IMPAIRED T-CELL GLUCOSE METABOLISM DURING CHRONIC HEPATITIS C VIRUS INFECTION

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Background and Aims: A powerful and sustained T-cell immune response is dependent on glucose metabolism within the T-cell itself, essential for the provision of energy to sustain and maintain T-cell function, so called, *fuel for energy*. In chronic hepatitis C (CHC) infection, the immune response is a key determinant to outcome to antiviral therapy. The aims of this study are to determine alterations in glucose metabolism in T-cells in HCV infected patients and its effect on the immune response.

Methods: Longitudinal peripheral blood mononuclear cells (PBMCs) from patients with CHC were examined at baseline – prior to antiviral therapy ($n=25$), at week 12 during treatment ($n=10$) and 6 months post end-treatment ($n=10$). As a control group, PBMCs from 8 healthy controls and 6 subjects with non-alcoholic fatty liver disease (NAFLD) were also examined. PBMCs from subjects are stimulated with CD3/CD28 Dyanbeads for 24 hrs. Flow cytometry was used to measure specific metabolic markers such as pAKT (a key molecule in glucose transport and metabolism) and glucose uptake (2-NBDG) in T-cells (CD4/CD8), while CD8 cytolytic function was assessed by examining granzyme B.

Results: Compared to healthy subjects and NAFLD, CD8 T-cells from patients with CHC had significantly reduced expression of pAKT ($p=0.0001$ and $p=0.02$ respectively) and exhibited less glucose uptake ($p=0.0001$ and $p=0.007$ respectively). At baseline, compared to healthy controls there was reduced CD8 T-cell cytolytic function ($p=0.04$) and this correlated with reduced glucose uptake ($p=0.02$). After viral clearance with antiviral therapy, pAKT and glucose uptake recovered to levels comparable to those of healthy subjects.

Conclusion: In patients with CHC, there is impaired T-cell glucose metabolism as assessed by pAKT and glucose uptake. Reduction in glucose uptake in particular correlated with reduced CD8 cytolytic function. Clearance of HCV with antiviral therapy restores pAKT and glucose uptake to normal levels, indicating a viral mediated impairment of T-cell glucose metabolism.

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THE HCV NS3/4A-MEDIATED IMPAIRMENT OF THE HEPATIC ANTIVIRAL IMMUNE RESPONSE IS REVERSED BY PROTEASE INHIBITION OR RIBAVIRIN IN VIVO

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Background: Hepatitis C virus (HCV) has evolved mechanisms to evade elimination by both innate and adaptive immunity resulting in HCV persistence. The HCV NS3/4A protease/helicase is known to modulate signaling pathways in the infected hepatocyte by cleaving MAVS, TC-PTP and TRIF. However, the global effects exerted by NS3/4A *in vivo* still remain unclear. This is currently of a particular interest since new antiviral therapies are being introduced based on inhibitors blocking the NS3/4A protease. Thus, these therapies may exert effects beyond the viral replication.

Objectives: We aimed to understand how NS3/4A affects intercellular signaling and immune cell function *in vivo* and to study the effects of ribavirin or NS3/4A protease inhibition on the NS3/4A-mediated modulation of the host's immune system.

Methods: The intrahepatic immune response of naive and lipopolysaccharide (LPS)/D-galactosamine (D-galN) treated NS3/4A-transgenic (Tg) mice was determined by western blot, ELISA, Real Time PCR, Flow cytometry, ALT levels, and survival. Ribavirin pretreatment or NS3/4A protease inhibition was performed to analyze the influence of antivirals on the NS3/4A-mediated effects.

Results: Hepatic IL10 expression is enhanced in NS3/4A-Tg mice both basally and after LPS/D-galN treatment, while IFN γ secretion is impaired. Furthermore, the chemokine profile (CCL2, CCL17, CXCL9) is altered towards an anti-inflammatory state. As result, the intrahepatic number of Th1 cells as well as IFN γ -positive CD4+ and CD8+ T cells in NS3/4A-Tg mice is decreased, while the amount of Th2 cells is increased. Interestingly, the NS3/4A-mediated effects could be reversed by both ribavirin treatment and inhibition of the NS3/4A protease. This is of particular importance since recent clinical trials suggest that ribavirin is essential for a functional therapy with only directly acting antiviral (DAAs) compounds.

Conclusions: NS3/4A induces a shift of the intrahepatic immune response towards a non-antiviral Th2-dominated immunity. This may impair the host response to the infection and promote viral persistence. Importantly, both ribavirin treatment and the inhibition of the NS3/4A protease can block the effects mediated by NS3/4A.

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TLR3-DEPENDENT IMMUNOLOGICAL PROPERTIES OF LIVER CELLS ARE CONTROLLED BY ANTI-INFLAMMATORY CYTOKINES THROUGH MODULATION OF MIR-155 EXPRESSION

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Background and Aims: The hepatitis C virus (HCV) can establish a persistent infection despite a strong activation of the innate immune system through TLR3 and other sensors, the so-called “IFN-paradox”. We analyzed regulatory mechanisms of TLR3-mediated immune responses in human liver and in murine non-parenchymal liver cells (NPC).

Methods: Hepatic expression of Interleukin 10 (IL-10) and transforming growth factor beta (TGF- β) in biopsies of HCV patients