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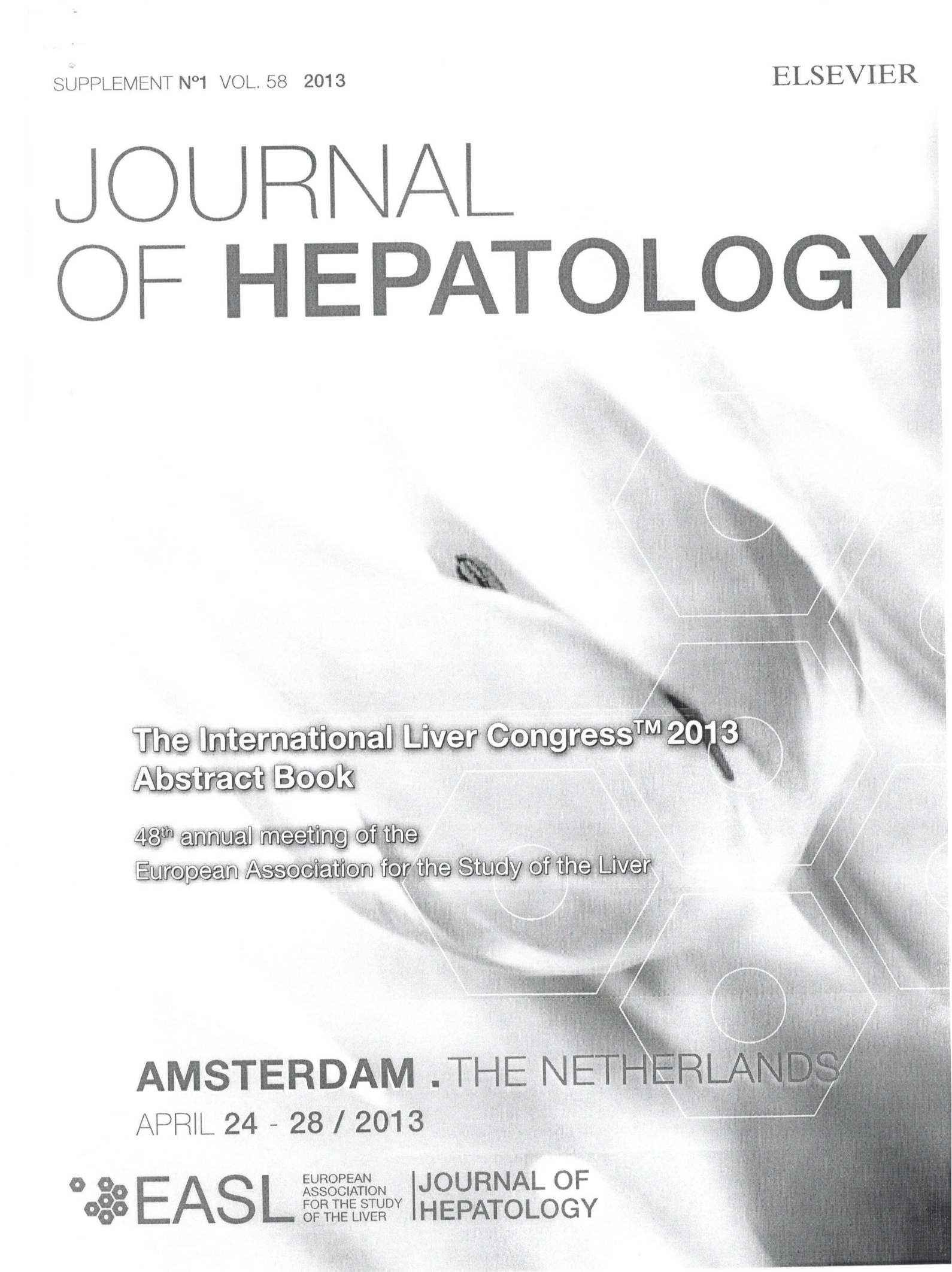

The International Liver Congress™ 2013 Abstract Book

48th annual meeting of the
European Association for the Study of the Liver

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Poster Session – Friday, April 26, 2013

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Registration of Clinical Trials
The *Journal of Hepatology* **endorses the policy of the WHO and the International Committee of Medical Journal Editors (ICMJE) on the registration of clinical trials. Therefore, any trial that starts recruiting on or after July 1, 2005 should be registered in a publicly owned, publicly accessible registry and should satisfy a minimal standard dataset. Trials that started recruiting before that date will be considered for publication if registered before September 13, 2005.**
More detailed information regarding clinical trials and registration can be found in New Engl J Med 2004; 351:1250–1251 and New Engl J Med 2005; 352:2437–2438.

Methods: TA-specific CD8+ T-cell lines were generated by peptide-specific stimulation of lymphocytes from HCC patients in the presence or absence of CD25+ cells. Epitopes derived from the TAs NY-ESO-1 and MAGE-A1 were used for the analysis of T-cell frequency (tetramer) and functionality (production of IFN-γ) by flow cytometry. Additionally, the presence of T_{reg} ($CD4^+CD25^+FoxP3^+$ cells) was analyzed in blood, liver and tumor tissue of HCC patients as well as in blood and liver of HCC-negative controls.
Results: As expected, we were unable to detect TA-specific production of IFN-γ after specific expansion of patient-derived CD8+ T-cells. Strikingly, however, despite the lack of IFN-γ producing TA-specific CD8+ T-cells, TA-tetramer binding cells were readily detectable in 20 of 37 patients (54%). In contrast, virus-specific tetramer-positive CD8+ T-cell lines were capable of producing IFN-γ. Depletion of T_{reg} prior to culture increased the proliferation of TA-specific CD8+ T-cells. Importantly, however, it did not restore functionality of TA-specific CD8+ T-cells suggesting that T_{reg} inhibit proliferation but not cytokine production of TA-specific CD8+ T cells. The biological role of T_{reg} in this setting is supported by their intratumoral enrichment in patients with HCC ($p < 0.0001$ by 1-way-ANOVA).
Conclusions: TA-specific CD8+ T-cells obtained from patients with HCC are severely impaired in functionality although still capable of proliferation. The depletion of T_{reg} enhanced the proliferation of these cells, but did not allow TA-specific CD8+ T-cells to regain effector functions. This suggests that additional mechanisms beside T_{reg} contribute to CD8+ T-cell failure in patients with HCC.

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CD4+ T CELL HELP IS ESSENTIAL FOR CD8+ MEDIATED CLEARANCE OF ACUTE VIRAL LIVER INFECTION

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The role of CD4+ T cells in acute viral hepatitis is not clear. To evaluate their function, the kinetic of Lymphocytic Choriomeningitis Virus (LCMV)-WE infection in CD4+ deprived mice was assessed.
Class II Transactivator knock-out (CIITA−/−) mice – that have only low levels of MHC class II molecules and CD4+ T cells – were infected with 10^6 Focus Forming Units LCMV-WE i.v. Viral titres, serum transaminases, IFNγ levels, degranulation capacity and numbers of virusspecific CD8+ T cells were determined. For verification, C57BL/6 wt mice were treated with CD4+ T cell depleting antibody before the infection.
At day 9 after infection with LCMV-WE these mice had clearly elevated viral titres in the liver, as compared to C57BL/6 wt mice (280×10^5 FFU vs. 40×10^5 in the controls – $p = 0.0020$). Whereas the infection in C57BL/6 wt was cleared at day 15, the virus persisted in CIITA−/− mice at least until d30 after infection (0.5×10^5 FFU per liver). Accordingly, after CD4+ T cell depletion, viral titres in C57BL/6 wt mice were 0.04×10^5 FFU per liver at day 18, while in non-depleted control mice the titre was below the detection level. Moreover, mice with impaired CD4+ T cell help also had elevated serum transaminases (600 U/L vs. 250 U/L at day 15 and 300 vs. 100 U/L at day 18 after infection in CIITA−/− mice compared to wt controls).
Even though the overall cell numbers of CD8+ T cells in the liver were not diminished, CIITA−/− mice showed considerably lower numbers of LCMV specific CD8+ T cells (3% vs. 13% in liver-lymphocytes of the controls). Moreover, after virus specific restimulation, IFNγ levels of hepatic CD8+ T cells were significantly lower in CIITA−/− mice compared to controls (1% vs. 6% of CD8+ T cells – $p = 0.0159$). The levels of the degranulation marker CD107 were also significantly lower in CIITA−/− mice compared to controls (5% vs. 17% – $p = 0.0043$).
Therefore, CD4+ T cells seem to be essential for establishing an efficient virus specific CD8+ T cell response and for clearance of acute LCMV-infection in the liver.

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THE PRO-INFLAMMATORY ROLE OF GALECTIN-3 IN ACUTE LIVER INJURY

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Background and Aims: We used Concanavalin A (Con A) and α-galactosylceramide (αGalCer) induced liver injury, well established murine models of T/NKT cell mediated hepatitis, to study the role of Galectin 3 (Gal-3) in acute liver pathology.
Methods: We tested susceptibility to Con A and αGalCer-induced hepatitis in galectin-3-deficient (Gal-3(−/−)) mice and wild-type (WT) C57BL/6 mice, as evaluated by liver enzyme test, histology, cytokine production, intracellular staining of immune cells and percentage of apoptotic mononuclear cell (MNC) in the liver.
Results: Gal-3(−/−) mice were less sensitive to both Con A and αGalCer-induced hepatitis. The level of tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin (IL)-17 and -4 in the sera and the number of TNFα-, IFNγ-, IL-17- and -4-producing CD4(+) cells as well as IL-12-producing CD11c(+) DCs were lower, whereas the number of IL-10-producing CD4(+) T cells and F4/80(+) macrophages were significantly higher in livers of Con A treated Gal-3(−/−) mice compared to WT mice. Significantly higher percentages of late apoptotic Annexin V(+) propidium-iodide(+) liver-infiltrating MNCs and splenocytes were observed in Con A treated Gal-3(−/−) mice, compared to WT mice.
The injection of αGalCer induced significantly higher expression of Gal-3 on CD3(+)NK1.1(+)NKT cells, DCs and NK1.1(+)CD11c(+) NKDCs in the liver of WT mice. Significantly lower number of CXCR3(+) NKT and DCs was noticed in livers of αGalCer-treated Gal-3(−/−) mice, compared to WT mice. The level of IL-10 in the sera and percentage of IL-10-producing CD3(+)NK1.1(+) and CD4(+)NK1.1(−)CD1d(+) cells were significantly higher in αGalCer-treated Gal-3(−/−) mice. Percentage of liver infiltrating DCs, CD1d(+) DCs and TNFα-, IFNγ-, and IL-12-producing DCs was significantly lower in αGalCer-treated Gal-3(−/−) mice. *In vitro*, αGalCer-loaded DCs, isolated from livers of untreated Gal-3(−/−) mice, produced significantly higher amounts of IL-10 and IL-4 and significantly lower amounts of IFNγ compared to DCs from WT mice.
Conclusions: Gal-3 plays an important pro-inflammatory role in acute hepatitis by promoting the activation and migration of T lymphocytes, NKT cells and DCs, secretion of proinflammatory cytokines and apoptosis of MNCs in the liver.
Supported by grants 175069 and 175103 from the Serbian Ministry of Education and Science.

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MODULATION OF LIVER FIBROSIS BY REGULATING ALTERNATIVELY ACTIVATED MACROPHAGE SIGNALING THROUGH IL-4Ralpha

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Background and Aims: Liver fibrosis progression and regression are modulated by cells of the innate immune system, especially macrophages. Macrophages can be divided roughly into classically activated and alternatively activated macrophages (CAM and AAM, resp.). While AAM have been implicated in fibrogenesis, the role of CAM and AAM as modulators of liver fibrosis is largely unexplored.

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