Conclusion HCV $core_{35–44}$ inhibits NK cell activity via two distinct mechanisms, directly via KIR2DL2/3, and synergistically via the CD94:NKG2A receptor. This synergistic interaction at CD94:NKG2A represents a novel mechanism for inhibiting NK cells. It demonstrates the sensitivity of NK cells to small changes in the peptide content of HLA class I, and is thus potentially a sensitive mechanism for viral escape from the host innate immune response.

P92 CD161+ γ-δ T CELLS: DEFINING THEIR ROLE IN PATIENTS WITH AND WITHOUT CHRONIC HEPATITIS C

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Introduction γ-δ T cells have been found in blood/liver of patients infected with hepatitis C (HCV). CD161+ is a C-type lectin found on the surface of T cells in humans. HCV specific T-cells have been found to express CD161 with enrichment within the liver. The role & function of CD161+ γ-δ cells has not been established in HCV.
Aim To explore the phenotype and function of CD161+ γ-δ T cells in humans, and to assess the impact on these cells of HCV infection.
Method Whole blood/Peripheral Blood Mononuclear cell (PBMC) antibody staining with subsequent flow cytometry was performed to assess phenotype. Function was examined by Intracellular Cytokine staining (ICS). Intrahepatic lymhocytes (IHLs) were isolated from patients having liver biopsies for clinical indications with paired blood samples. Cord blood samples were used after ethical approval gained and consent from mothers.
Results In healthy controls, the CD161 subset encompassed a mean of 82.1 (±12.8)% of γ-δ cells. The CD161 subset expressed more CXCR3/CCR6/IL-18R (p=0.03/0.01 and 0.03 respectively) than the CD161- subset. The CD161+ cells expressed significantly more If-y/TNF-α (p=0.001 respectively) than the negative subset, and more Granzyme A, B and K and perforin in keeping with a Th1 profile. 20% of γ-δ cells from cord blood samples expressed CD161, suggesting it is an innate feature but expanded throughout life. Whole blood γ-δ populations were significantly reduced in HCV compared to healthy donors (70% v 40%, p=0.0031), with the proportion of CD161+ γ-δ T-cells reduced in chronic HCV (82.1% vs 39%, p=0.006). The γ-δ cells in HCV expressed significantly more activation markers (CD38/CD69) and CXCR6 than in healthy controls irrespective of CD161 status. Of the CD161+ γ-δ cells, the predominant subset were Vδ2 in healthy controls blood however in HCV this was significantly reduced (p=0.0173) with the Vδ1 subset dominating. On isolation of IHLs (n=17: 8 HCV, 3 HBV and rest NAFLD/NASH), there was an enrichment of CD3+ γ-δ T-cells in liver tissue compared to blood irrespective of CD161 status. On sub-analysis there were no statistical differences between CD161 status of the γ-δ cell T-cells when comparing viral v non-viral aetiologies.
Conclusion Our data suggests that HCV infection does directly reduce the γ-δ T-cell population in peripheral blood: mainly the CD161 subset. The virus also causes a reversal in the CD161 γ-δ T-cell population from Vδ2 to Vδ1 in the periphery, however it appears the enrichment of γ-δ T cells to the liver is not specific to CD161+ cells or to HCV infection. The CD161 phenotype present at birth but expanded throughout life. The CD161 subset appears to display a more Th1 profile and unlike their CD8 CD161++ α-β counterparts, CD161 expression by γ-δ T-cells is not tightly linked to a Type-17 differentiation pathway.

P93 NFκB ACTIVATION BY TLR AGONISTS IS DEFICIENT IN MACROPHAGES LACKING STAT2

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Introduction Engagement of Toll-like receptors (TLRs) is an important initiator of the innate immune response in inflammatory liver diseases and leads to release of a range of inflammatory cytokines. TLRs signal through divergent signal transduction pathways but the majority lead to activation of members of the NFκB family. STAT2 is an essential component of canonical signalling through the type I and type III interferon (IFN) receptor but, unlike other members of the Stat family, is not believed to be involved in other signal transduction pathways.
Aim We examined the role of STAT2 on inflammatory signalling.
Results Loss of STAT2 markedly reduced immortalised macrophages' response to a range of TLR agonists (lipopolysaccharide (LPS), poly I:C and IL-1)—production of TNFα and RANTES proteins and a range of inflammatory mRNAs were decreased. The reduction in inflammatory cytokine production could be reversed by reconstitution with STAT2 but blockade of type I IFN signalling did not reproduce the phenotype. Restoration of the normal response to LPS could be achieved with tyrosine phosphorylation defective STAT2 indicating that STAT2 interacts with these signalling pathways without phosphorylation on Tyr690. The multiplicity of STAT2's effect suggests a common defect to these signalling pathways. There were no abnormalities in the activation of early signalling components in the absence of STAT2, however, levels of phosphorylated IκB, although not total IκB, were reduced in $STAT2^{-/-}$ cells. Phosphorylation of this inhibitor of NFκB leads to its degradation and release of NFκB proteins into the nucleus. We found that translocation of the NFκB protein p65 into the nucleus and its subsequent binding to DNA was impaired in STAT2 deficient cells.
Conclusion These data suggest that STAT2 is a critical component of the TLR signalling response to early inflammatory stimuli, in particular through maintaining the normal phosphorylation of IκB.

P94 RAPAMYCIN HELPS MAINTAIN THE REGULATORY PHENOTYPE OF CYTOCHROME P450IID6-SPECIFIC TREG EXPANDED FROM PATIENTS WITH AUTOIMMUNE HEPATITIS TYPE 2 BY REDUCING THE NUMBER OF $IFN\gamma^+$ CELLS

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Introduction Control of T cell reactivity to cytochrome P450IID6 (CYP2D6) is key to immune-tolerance restoration in autoimmune hepatitis type 2 (AIH-2). $CD4^+CD25^+$ regulatory T cells (Treg), central to autoreactive T cell regulation, are impaired in AIH-2. Cell therapy based on CYP2D6-specific Treg (CYP-Treg) could provide specific control over effectors of liver damage in AIH-2. We have generated CYP-Treg from AIH-2 patients and demonstrated that these cells exert greater suppression than polyclonal Treg. Whether CYP-Treg can undergo expansion maintaining their functional phenotype is untested.
Aim To assess CYP-Treg functional phenotype over 2-week expansion in AIH-2 patients.