P0138
Paper Poster Session
Cellular immunity as marker of viral infection

Evaluation of immune system role in the pathogenesis of chronic hepatitis C viral infection

Daniela Rios[1], Paola Casciato[2], Elena De Matteo[1], María Soledad Caldirola[3], María Isabel Gaillard[3], Liliana Bezrodnik[3], Eduardo Mullen[4], Beatriz Margarita Ameigeiras[5], Carlos Brodersen[6], Pamela Valva*[1], María Victoria Preciado[1]

[1]*Laboratory of Molecular Biology, Hospital de Niños Ricardo Gutiérrez, Pathology Division, Buenos Aires, Argentina*

[2]*Hospital Italiano de Buenos Aires, Liver Unit, Buenos Aires, Argentina*

[3]*Hospital de Niños Ricardo Gutiérrez, Department of Immunology, Buenos Aires, Argentina*

[4]*Hospital Italiano de Buenos Aires, Pathology Division, Buenos Aires, Argentina*

[5]*Hospital Ramos Mejía, Liver Unit, Buenos Aires, Argentina*

[6]*Hospital General de Agudos "Carlos G. Durand", Liver Unit, Buenos Aires, Argentina*

Background: During Chronic hepatitis C (CHC) the immune system is actively involved in liver damage generation; however, the mechanism underlying pathogenesis and the role of the different immune cells are still unknown. The aims were to explore portal/periportal infiltrate microenvironment and to compare frequency of certain immune cells both in liver and peripheral blood (PB) to elucidate the role of the immune system in the pathogenesis of CHC.

Material/methods: Liver biopsies and concomitant PB samples from 27 adult CHC patients were analysed. Liver microenvironment was explored through: 1) characterization of the portal/periportal infiltrate [total, $CD20^+$, $CD4^+$, $CD8^+$, $Foxp3^+$ and $Tbet^+$ cells] by immunohistochemistry in formalin-fixed paraffin-embedded biopsies, and 2) quantification of IFN-γ and TGF-β mRNA expression in fresh liver biopsies by qPCR. The frequency of $CD19^+$B cells, $CD8^+$T cells, total $CD4^+$ T helper (Th) cells, as well as Threg ($CD4^+/CD25^{hi}/CD127^{low}/Foxp3^+$) and Th1($CD4^+/IFN\text{-}\gamma^+$), were determined in PB by flow cytometry in HCV patients and uninfected donors. The results were integrated and also evaluated in the context of liver damage.

Results: All studied lymphocyte populations were observed in portal/periportal infiltrates, with predominance of $CD8^+$, followed by $CD20^+$, $CD4^+$, $Foxp3^+$ and $Tbet^+$ cells. INF-γ and TGF-β mRNA levels were variable among different patients, and they were associated with hepatitis severity (INF-γ p=0.02, TGF-β p=0.03). The intrahepatic INF-γ-producing cells evaluated here ($CD8^+$ and $Tbet^+$cells) didn't show correlation with INF-γ levels, and were not associated with liver injury. Regarding $Foxp3^+$cells, they were associated with hepatitis severity (p=0.03), but did not correlate with the expression of TGF-β mRNA. Furthermore, no lymphocyte frequency differences in PB were depicted

between CHC patients and donors. They were not associated with liver damage either. In addition, no correlation were observed in lymphocyte frequency between compartments.

Conclusions: CHC pathogenesis is a complex process involving several immune cell populations. Although $CD8^+$ and $Tbet^+$ cells were present in infiltrate, they didn´t prove a clear role on liver damage. Since liver IFN-γ levels did not match with the frequency of IFN-γ producing cells, the contribution of other cell types not evaluated here, such as Natural Killer, could explain its association with damage severity. Both $Foxp3^+$ cells and TGF-β were associated with hepatitis severity but not correlated, denoting that Treg cells were not only increased but also showed a greater activity reflected by TGF-β higher levels. In turn, given that intrahepatic $Foxp3^+$ cells participate in a delicate balance between protective immunity and injury mediated immunity, their augment related to severe hepatitis may reflect its role in mitigating the inflammatory process. In line with the postulation that CHC is a localized inflammatory process no immune cell frequency differences were observed between patients and donors in PB.