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Evaluation of TLR-4 in peripheral M1 monocytes and IL-6 and CXCL-8 in alcoholic liver disease

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Background and aim: Intestinal permeability increases in alcoholics allowing the passage of lipopolysaccharide (LPS) to liver, promoting TLR-4 activation in Kupffer cells and the production of pro-inflammatory cytokines. At the present, the modulation of LPS in alcoholics at systemic level, is not fully understood. Aim. To evaluate TLR-4 in M1 monocytes and the production of IL-6 and CXCL-8 in alcoholic liver disease.

Material and methods: Cross-sectional study, that include Alcoholic patients (according WHO) from the Liver clinic of the General Hospital of Mexico were included. They were classified by absence (OH) or presence (CiOH) of liver damage and patients with active alcoholic hepatitis (HOH). Control group (CT): AUDIT <8 and intake of <10gOH / day. Blood samples were taken on one occasion (10 ml) to obtain mononuclear cells by density gradient. To which cell marking was performed by flow cytometry (M1 and TLR-4) and in serum was performed the determination of cytokines (IL-6 and CXCL-8) by arrangement in multiple suspension. Mann Whitney U statistical analysis. All patients signed informed consent. Protocol approved by the General Hospital of Mexico (HG/DI/16/107/03/082) and UNAM (FMD/DI/15/2019).

Results: 24 CT, 12 OH, 10 CiOH and 10 HOH were included. The percentage of Monocytes was: CT = 8%, OH = 19%, CiOH = 22% and HOH = 35% (OHvsCT $p = 0.003$, CiOHvsCT $p = 0.05$, HOHvsCT $p < 0.0019$). The significant differences in M1 monocytes were found in CiOHvsCT $p = 0.05$, HOHvsCT $p = 0.019$, CiOHvsOH$p = 0.009$ and HOHvsOH $p = 0.01$. Interestingly, TLR4 expression showed differences in OHvsCT $p = 0.002$, CiOHvsCT $p = 0.007$ and HOHvsCT $p < 0.001$. On the other hand, the concentration of IL-6 and IL-8 (pg/mL) presented significant differences according with liver damage (CiOHvsCT $p < 0.05$, HOHvsCT $p < 0.001$, OHvs.HOH $p = 0.001$ and CiOHvsHOH $p = 0.01$).

Conclusions: Alcohol has an effect at a systemic level promoting the increase of monocytes/M1 and the expression of TLR-4, supporting the fact that the receptor is activated in the periphery, being higher in patients with active Alcoholic Hepatitis, favoring a state of continuous inflammation and promoting susceptibility to infections and mortality.

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Evaluation of IL-1RA, IL-1β IFN-γ and CXCL-10 as mediators of damage and hepatic repair in chronic hepatitis and fibrosis progresion

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Background and aim: During chronic Hepatitis C (CHC) is generates persistent inflammation that can progress to fibrosis. IL-1β is responsible for the initiation of inflammation, the action of IL-1β, its activity is regulated by IL-1RA which has also been implicated in the liver in cell proliferation. IFN-γ is the main initiating agents of the antiviral response, additionally promotes the production of CXCL-10 / IP-10 activating the chemotaxis of lymphocytes and NK cells. Objective. To evaluate the serum levels IL-1β, IL-1RA, IFN-γ and CXCL-10 in patients with CHC and its association with liver fibrosis.

Material and methods: A cross-sectional study, patients with CHC without comorbidities with grade of fibrosis for Fibroscan/Fibrotest and control group (CT) were included. Subjects CT with negative viral panel and without signs of liver disease. The quantification of IL-1β, IL-1RA, IFN-γ and CXCL-10 molecules in serum the multiple suspension method. Statistical analysis was performed using Mann-Whitney U test, $p < 0.05$ was considered significant. All patients signed informed consent. Protocol approved by the General Hospital of Mexico (HG/ DI/16/107/03/082) and UNAM (FMD/DI/15/2019).

Results: CHC (107) and CT (192) subjects were include. The concentration (pg/mL) of IL-1β was 7 ± 2 for CHC and 3 ± 0.1 for CT ($p = 0.048$), of IL-1RA was 44 ± 11 for CHC and 50 ± 13 for CT ($p = 0.734$). The serum levels of IFN-γ 9 ± 4 for CHC, and for CT 11 ± 3 ($p = 0.002$). In the case of CXCL-10, 938 ± 92 for of CHC and 361 ± 21 for the CT ($p < 0.001$). Comparing by grade of fibrosis for IL-1β, no significant difference was found. IL-1RA showed differences in F1vsF4 and F3vsF4. The IFN-γ in F1vsF4 and F2vsF4. Finally, CXCL-10, presented significance only in F1vsF4.

Conclusions: Higher levels of IL-1β and CXCL10 were found in HCc, as part of the active inflammatory response. Whereas in the comparison of fibrosis stages: IFN-γ and CXCL-10 showed participation in early stages. On the other hand, IL-1β does not display changes, however, their antagonist IL-1RA increases in F4 suggesting their participation in liver regeneration.

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