IL-17a and IL-22 cytokines like triggers of human liver fibrosis

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Background and Aims: IL-17A and IL-22 are both related to liver fibrosis. Their role is dual, depending on the type of the model that was used. IL-17A is considered to be a profibrotic cytokine while IL-22 shows anti-fibrotic properties in the mice models of acute liver diseases. Here, we analyzed IL-17A and IL-22 secretion in human liver tissue samples of different fibrotic stages, as well as their influence on fibrotic markers expression in the model of human liver slices culture. **Method:** Human fibrotic liver samples (F0-F4 fibrosis stage) were collected after liver resection. Human precision-cut liver slices of 350 µm were stimulated with different cytokines (IL-17A, IL-22, TGF-beta) for 48 hours, fibrotic markers (alpha-SMA, MMP-2, MMP-9, TIMP-1) were assessed by western blotting and Elisa. Intrahepatic liver infiltrating immune cells were extracted from post-surgery liver samples, stimulated and analyzed by flow cytometry. Thirty human liver samples after liver resection were analyzed for IL-17A, IL-22, TGF-beta expression. **Results:** Here, we report an unexpected raise of IL-17A and IL-22 cytokine concentration in human liver tissue samples (F0-F1, F2) compared to advanced fibrosis (F3-F4), as well as their significant correlation. On the other side, the TGF-beta secretion was higher in advanced fibrotic stages. Liver infiltrating CD3+CD4+ lymphocytes and MAIT cells were the principal source of IL-17A and IL-22 among lymphoid cells. We identified much stronger secretion of INF-gamma in the liver tissue compared with blood samples of the same patient. In addition, the liver tissue from mild fibrotic samples had significantly greater infiltration by the CD45+CD3+TCRValpha7.2 cells than the liver samples with advanced fibrotic stages. In the second time, we stimulated human liver slices culture by IL-17A, IL-22 or TGF-beta. We observed that IL-17A promotes IL-6 production in the liver, as well as MMP-2, MMP-9 and TIMP-1 production. However, IL-22 didn't induce MMP-9 and TIMP-1 expression during 48 h of stimulation neither alone nor in presence of TGF-beta. IL-17A and IL-22 both were capable to stimulate alpha-SMA synthesis, the principal marker of stellate cells activation contributing either to liver regeneration or to liver fibrosis. **Conclusion:** The strong expression of IL-17A and IL-22 in earliest fibrotic stages as well as the increased expression of fibrotic markers should highlight the importance of these cytokines to trigger human liver fibrosis