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Toll-like receptor-4 expression by hepatic progenitor cells and biliary epithelial cells in HCV-related chronic liver disease

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Background. Toll-like receptor-4 (TLR4) is a transmembrane pattern recognition receptor that plays a key role in innate immunity by triggering inflammatory responses to Gram negative bacteria lipopolysaccharide (LPS) (1). Since liver is the main clearance organ for LPS, which is excreted in large amounts in the bile (2), it is not surprising that TLR4 has been involved in the pathogenesis of most liver diseases (3). Numerous evidences suggest a role for TLR4 in the pathogenesis of chronic hepatitis C virus (HCV) infection (4) and hepatic fibrosis (5), but the localization and level of TLR4 expression in the liver of patients with hepatitis C have never been investigated.

Aim and methods. We aimed to evaluate, by means of immunohistochemistry (IHC) and real-time polymerase chain reaction (rt-PCR), hepatic TLR4 expression in patients with chronic HCV infection. Sixty-one patients with chronic HCV infection, and 12 controls free of liver disease, were included in the study. Each case was analyzed by IHC for TLR4, α–smooth muscle actin (αSMA) and cytokeratin-7 (CK-7), and a subgroup of patients and all controls by rt-PCR for TLR4. A score of activation of portal/septal myofibroblasts and lobular hepatic stellate cells (HSCs) was evaluated by IHC for α-SMA, whereas IHC for CK-7 was analysed in order to count hepatic progenitor cells (HPCs), interlobular bile ducts and intermediate hepatocytes.

Results. The parenchimal elements responsible for the highest TLR4 level of expression were HPCs and biliary epithelial cells (BECs) of interlobular bile ducts in the infected group. Double-labeling experiments with anti-TLR4, anti-CK7 and anti-CD133 confirmed this finding. TLR4-positive HPCs and interlobular bile ducts were significantly correlated with the stage of liver disease ($p<0.001$), the grade of inflammation ($p<0.001$), and with the activity of portal/septal myofibroblasts ($p<0.001$). Rt-PCR study confirmed an increased TLR4 expression in the 26 patients analyzed with respect to controls ($p<0.001$). TLR4 expression positively correlated with fibrosis ($p<0.05$) and inflammation ($p<0.05$).

Conclusions. The expression of TLR4 in HPCs and BECs in HCV-related liver damage significantly correlates with inflammation, activation of portal/septal myofibroblasts and fibrosis.

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