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The role of adhesion molecules in intrasinusoidal leukocyte accumulation during experimental endotoxemia in mice

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Introduction: Intrasinusoidal accumulation of leukocytes (ILA) in the liver is a component of the systemic inflammatory response, which can be triggered by the systemic immune dysfunction during sepsis, circulatory shock, burns and trauma. According to the current paradigm, ILA causes a microcirculatory disturbance and leads to the hepatocellular injury.

Aims: (1) Evaluation of the influence of ILA on the hepatic microvascular dysfunction and the liver function during experimental non-lethal endotoxemia. (2) Analysis of time-course and dynamics of ILA during the early and late stages of endotoxemia; (3) Evaluation of the role of specific cell adhesion molecules on the development, magnitude and dynamics of the ILA and on the ILA-mediated liver injury.

Materials and Methods: Endotoxemia was induced using the intraperitoneal application of low doses of LPS in adult males Lys- Enhanced green fluorescent protein (EGFP) mice, allowing visualization and analysis of ILA in response to endotoxemia. ILA was assessed 0, 2, 6 and 24 hours after induction of endotoxemia in wild-type and knockout-mice for specific adhesion molecules (LFA-1, Mac-1, ICAM-1 and CD44) using fluorescence microscopy. The liver injury was analyzed using determination of liver enzymes in plasma and liver tissue histology.

Results: Low-dose endotoxemia induced a time-dependent ILA. ILA was associated with induction of liver injury reflected in the increase of enzymes level. ILA had a gradual development during the early stage of endotoxemia, reaching its peak around 6 hours. Constant and stable levels of ILA between 6 and 24 hours were associated with a minimal elevation of enzyme levels. The lack of expression of CD44 was associated with the reduction in the magnitude of ILA, but had no effect on the ILA-stability. The knockout of β2 integrins and ICAM-1 did not reduce the magnitude of ILA. During the early phase (first 6 hours), high levels of ILA was largely determined by the baseline leukocytosis and was associated with a reduced AST and ALT levels. At the late stage, β2 integrins and ICAM-1 led to the reduction of ILA which was associated by a significant increase of liver enzymes and cell damage in comparison with WT and $CD44^{-/-}$ mice.

Conclusions: Endotoxemia induces a time-dependent intrasinusoidal leukocyte accumulation which has a protecting function at the initial stage, but the long duration of ILA contributes to the liver injury. At the early stage of the endotoxemia, ILA increase is dependent on CD44, but is independent on ICAM-1 and β2 integrins. ICAM-1 and β2 integrins, but not CD44 stabilize the ILA at the later stage of endotoxemia. The molecular modulation of ILA may have important therapeutic implications in sepsis, reducing liver injury and improving its immune defensive capabilities.