On Leukocyte Recruitment in Cholestatic Liver Injury

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ON LEUKOCYTE RECRUITMENT IN CHOLESTATIC LIVER INJURY

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Academic Thesis

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Abstract

Cholestasis is a frequent clinical syndrome, which is caused by a dysfunction in bile formation of the hepatocyte or from obstruction of the biliary tract. This is associated with inflammation of the liver tissue, resulting in severe liver injury. In this inflammatory process, leukocyte recruitment has emerged as a key feature. Therefore, the aim of this thesis was to analyze the detailed mechanisms behind intrahepatic leukocyte accumulation and its regulation in the pathophysiology of sepsis-associated or obstructive cholestasis and their impact on hepatocellular function and damage. For this purpose, cholestatic conditions were induced in C57BL/6 mice in the well established experimental models of LPS sepsis and obstructive cholestasis following bile duct ligation. Analyses included intravital fluorescence microscopy, histology, ELISA, RT-PCR, flow cytometry, determination of bilirubin and liver enzyme levels as well as measurement of bile flow and secretion. In doing so, it was found that P-selectin-mediated recruitment of leukocytes, but not the local production of pro-inflammatory mediators, is the primary cause of sepsis-associated cholestasis. Moreover, obstructive cholestasis is as-sociated with P-selectin-mediated intrahepatic platelet accumulation, which crucially contributes to leukocyte recruitment and liver injury. Besides, LFA-1 mediates firm leukocyte adhesion in the liver microcirculation during obstructive cholestasis. Finally, inhibition of rhokinase attenuates cholestasis-induced CXC chemokine formation, leukocyte recruitment and hepatocellular damage in the liver. Thus, the results of this thesis clearly demonstrate that leukocyte recruitment in the liver plays a key role in the pathophysiology of cholestasis. Accordingly, it may be concluded that targeting leukocyte recruitment may be an effective strategy to preserve bile flow under septic conditions and to reduce cholestasis-induced liver injury.

Key words: Cholestasis, Endothelium, Inflammation, Leukocyte and Liver

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