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On Leukocyte Recruitment in Cholestatic Liver Injury

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2008

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Citation for published version (APA):

Laschke, M. (2008). *On Leukocyte Recruitment in Cholestatic Liver Injury*. [Doctoral Thesis (compilation), Department of Clinical Sciences, Malmö]. Department of Clinical Sciences, Lund University.

Total number of authors:

1

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ON LEUKOCYTE RECRUITMENT IN CHOLESTATIC LIVER INJURY

Matthias W. Laschke

Academic Thesis

With permission from the Medical Faculty at Lund University
for the presentation of this PhD thesis in a public forum in the CRC,
Entrance 72, Malmö University Hospital, Malmö, on 28th November

Faculty opponent: Professor Thomas Minor, University of Bonn

Supervisor: Henrik Thorlacius, MD, PhD, Associate Professor



LUND UNIVERSITY

Faculty of Medicine

Malmö 2008

Department of Clinical Sciences, Surgery Research Unit,
Malmö University Hospital

Organization LUND UNIVERSITY Department of Surgery Malmö University Hospital SE-205 02 Malmö		Document name DOCTORAL DISSERTATION	
		Date of issue November 28th, 2008	
Author(s) Matthias Laschke		Sponsoring organization	
Title and subtitle On leukocyte recruitment in cholestatic liver injury			
Abstract <p>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 associated 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.</p>			
Key words: Cholestasis, Endothelium, Inflammation, Leukocyte and Liver			
Classification system and/or index terms (if any): Lund University, Faculty of Medicine Doctoral Dissertation Series 2008:132			
Supplementary bibliographical information:		Language English	
ISSN and key title: 1652-8220		ISBN 978-91-86059-85-9	
Recipient's notes		Number of pages 126	Price
		Security classification	

Distribution by (name and address)

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Date Oktober 2nd, 2008