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Kupffer cell activation and portal hypertension

Christian J Steib

Kupffer cells (KC), the resident liver macrophages, constitute the liver sinusoids together with other cells such as sinusoidal endothelial cells, hepatic stellate cells, liver-specific natural killer cells and dendritic cells. KC account for approximately 10–15% of the total liver cell population and represent 80–90% of tissue macrophages in the reticuloendothelial system. KC represent an important component of innate immunity.^{1–2} One characteristic of innate immunity is the rapid response to potentially dangerous stimuli. This suggests a central role of the liver in systemic and regional immune response, because KC come in contact with all the microbiological debris from the gastrointestinal tract reaching the liver via the portal vein.³

KC express the scavenger receptor CD163; CD163 is involved in the clearance and endocytosis of the haemoglobin–haptoglobin complex.⁴ Once erythrocytes or the haemoglobin–haptoglobin complex has been taken up by KC, the heme delivered from haemoglobin is degraded by heme oxygenases. The isoform heme oxygenase-1 is only observed in KC and its

expression and the consecutive bilirubin production increases immediately after exposure to damaged erythrocytes. Heme oxygenase-1 and CD163 expression increase after exposure to inflammatory stimuli. The interplay of KC, CD163 and heme oxygenase-1 has thus been identified as an important system that is upregulated in inflammatory conditions in order to enhance haemoglobin clearance and heme degradation.⁵

The interesting study of Holland-Fischer and colleagues⁶ published in *Gut* (see page 1389) demonstrates evidence in humans that KC are activated in cirrhosis. In their study, soluble CD163 was determined by a commercially available ELISA kit. Soluble CD163 was measured as a marker of macrophage activation. The authors found that the concentration of soluble CD163 was more than threefold higher in patients with liver cirrhosis than in controls, and that soluble CD163 was linearly related to the portal venous pressure gradient. These results are of major interest, because it is one of the first studies describing macrophage activation in portal hypertension in humans. Macrophage activation in human cirrhosis has only been addressed in one previous study.⁷ In the previous study neopterin was measured as an indicator of interferon- γ -stimulated monocytes and macrophages. Later on animal studies have shown that KC activation induces oxidative stress⁸ and leads to a significant

amount of vasoconstrictors such as leukotrienes and thromboxane A₂. These vasoconstrictors increase the portal pressure in cirrhosis.^{9–10} They act on cells with contractile elements such as hepatic stellate cells and myofibroblasts. These cells increase the intrahepatic resistance, for example, by Rho kinase.^{11–12} In the study by Holland-Fischer *et al*⁶ elevated peripheral venous soluble CD163 concentrations did not change systematically after TIPS insertion although the portal pressure decreased. In contrast, the lipopolysaccharide binding protein as an indirect marker of the lipopolysaccharide concentration in peripheral blood was 70% higher in cirrhosis patients than in controls, but decreased to near-normal concentrations 4 weeks after TIPS insertion. There are various interpretations of these data: KC activation is probably not only dependent on lipopolysaccharides. Grampositive bacteria, fungal infections and perhaps even bacterial DNA could also play a role for KC activation in liver cirrhosis. Furthermore, once KC are activated they can stay in an activated status,¹³ and it can be hypothesised that the mechanical intervention of TIPS insertion does not change this activation status. In addition, KC activation in cirrhosis might be not only dependent on increased levels of bacterial products; also phagocytosis of apoptotic or necrotic cells in the cirrhotic liver could be a mechanism of KC activation.

The importance of soluble CD163 has been investigated in earlier studies. In patients with viral hepatitis and fulminant hepatic failure high levels of soluble CD163 have been detected.¹⁴ In another study, the high levels of soluble CD163 in hepatic failure were correlated with outcome. The authors concluded that

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soluble CD163 might be used in combination with other parameters to determine prognosis.¹⁵

Measurements of circulating soluble CD163 comprise both an increased expression and an increased subsequent shedding of the cell surface CD163 receptor. The phenomenon of CD163 shedding is also related to high endotoxin levels. Therefore endotoxaemia in cirrhosis, for example by bacterial translocation, could enhance the CD163 expression on KC surface and shedding of CD163.¹⁶ In the study of Holland-Fischer and colleagues⁶ the soluble CD163 concentration was measured in a subset of patients in the portal and the hepatic vein during the TIPS procedure. The concentration in the hepatic vein was higher than in the portal vein. Therefore, the authors supported the results of earlier investigations that there is a significant production of soluble CD163 in the liver by tissue-specific macrophages,¹⁴ but it has to be considered that soluble CD163 is also produced by monocytes.^{17, 18} Therefore an unknown amount of soluble CD163 could also be related to monocytes migrated to and activated in the liver. It is known that monocyte-derived hepatic macrophages are involved either in the development or in the resolution of hepatic fibrosis.¹⁹ These relations become even more interesting because different macrophage subpopulations in liver fibrosis are suspected. So-called M1 macrophages are the classically activated macrophages, they react with microbial products and release type 1 inflammatory cytokines. Alternatively activated macrophages are the M2 macrophages, which, for example, reduce inflammatory processes by anti-inflammatory factors such as interleukin 10 and transforming growth factor beta. These new findings are of major interest to develop targeted therapies. For example, the activation of macrophage subpopulations, which are responsible for phagocytosis of bacterial products, is welcome in situations of sepsis to eliminate bacterial

products; on the other hand, subsets of macrophages could be important to resolve fibrotic material. In contrast, intense reactions of macrophages are undesired; for example, in the situation of variceal bleeding when they produce high amounts of vasoconstrictors.

In summary, increased concentrations of soluble CD163 correlated with elevated portal pressure. This is a very important finding for supporting the role of macrophages in the pathophysiology of liver cirrhosis and its complications in humans. These processes are quite complex, but the further clarification on a molecular basis is of major importance for the future development of targeted therapies. In parallel, clinical studies with measurements of soluble CD163 could be very elegant. The determination of soluble CD163 might be used to estimate portal pressure; one of many conceivable clinical applications might therefore be to determine the time point for control endoscopy in patients with oesophageal or gastric varices.

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