Kupffer Cells Activity During Pathogenesis of Liver Diseases

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Summary

The resident liver macrophages Kupffer cells, have long been considered as mostly scavenger cells responsible for removing particulate material from the portal circulation. However, evidence derived mostly from animal models, indicates that Kupffer cells may be implicated in the pathogenesis of various liver diseases including viral hepatitis, steatohepatitis, alcoholic liver disease, intrahepatic cholestasis, activation or rejection of the liver during liver transplantation and liver fibrosis. There is accumulating evidence, reviewed in this paper, suggesting that Kupffer cells may act both as effector cells in the destruction of hepatocytes by producing harmful soluble mediators as well as antigen presenting cells during viral infections of the liver. Moreover they may represent a significant source of chemoattractant molecules for cytotoxic CD8 and regulatory T cells. Whether all these variable functions in the liver are mediated by different Kupffer cell subpopulations remains to be evaluated. In this review we propose a model that demonstrates the role of Kupffer cells in the pathogenesis of liver disease.

Abbreviations: SEC- sinusoidal endothelial cells, SC-stellate cells, LPS- lipopolysaccharide,

Key words: *Kupffer cells, Liver disease, Hepatic injury, Liver fibrosis, Hepatocellular carcinoma, Hepatitis.*

Introduction

The sinusoidal lining of the liver contains the nonparenchymal cell populations which consist of Kupffer cells (KCs), sinusoidal endothelial cells (SEC) and stellate cells (SC). All three cell-types seem to play a crucial role in liver homeostasis and in the pathogenesis of liver disease [1]. KCs constitute 80%-90% of the tissue macrophages in the reticuloendothelial system and account for approximately 15% of the total liver cell population [2]. They are mainly found in the periportal area of the lobule (43%), but KCs also exist in the midzonal (28%) and in the central area (29%) [2]. Despite the view that KCs are fixed tissue macrophages of the liver, there is evidence that they have the ability to migrate along sinusoidal walls with a mean speed of 4.6 ± 2.6 (SD) microns/min[3]. Since the description of these resident liver macrophages in 1876 by von Kupffer various theories have been proposed with regard to their origin and involvement in liver homeostasis and injury. It should be noted that almost all available evidence for the role of Kupffer cells comes from animal models. KCs are the first cells to be exposed to materials absorbed from the gastrointestinal tract. Their ability to eliminate and detoxify microorganisms, endotoxins, degenerated cells, immune complexes, and toxic agents (e.g. ethanol) is an important physiological function. Due to their key location, KCs might function as antigen-presenting cells [4] and participate in tumour surveillance [5] and the regeneration processes of the liver[6]. They also seem to play a key role in innate immune responses and host defence through the expression and secretion of soluble inflammatory mediators [7]. There is accumulating evidence that the interaction between KC and lipopolysaccharide (LPS) may be the initiating event leading to hepatotoxicity in various types of liver injury including endotoxinaemia, alcoholic liver injury and ischemia/reperfusion injury[8,9] and systemic viral infections[10].

The Role of Kupffer Cells I Hepatic Injury

Kupffer cells are involved in the pathogenesis of liver injury mediated by chemical substances, toxins and pharmacological agents such as carbontetrachloride (CCl4), endotoxin, galactosamine and acetaminophen through the release of biologically active substances that promote the pathogenic process. In liver injury and hepatocellular necrosis activated Kupffer cells are a major source of inflammatory mediators including cytokines, superoxide, nitric oxide, eicosanoids, chemokines, lysosomal and proteolytic enzymes and demonstrate increased cytotoxicity and chemotaxis.

The pivotal role of Kupffer cells in the initiation of hepatocellular damage is supported by experimental models that have demonstrated a correlation between the degree of activation of Kupffer cells and the degree of hepatocellular destruction. Administration of endotoxin to rats with activated Kupffer cells due to liver resection induced damage of endothelium, sinusoidal fibrin deposition, and lethal massive hepatic necrosis. In another rat model, activation with endotoxin enhanced CCl4-induced liver damage, while pretreatment with polymyxin B or administration of endotoxin in low doses induced immune tolerance which protected the liver from CCl4-induced damage. Other studies demonstrated that activated Kupffer cells express CD95L and could induce apoptosis in CD95+ T lymphocytes and hepatocytes. Liver fibrosis is a complex process that involves many cells of the hepatic sinusoid and is characterized by disturbance of the architecture and composition of extracellular matrix in the liver. The extracellular matrix in the subendothelial space of Disse mainly consists of collagen type IV, laminin, and proteoglycans that are progressively replaced during fibrosis by collagen type I and III. This excess deposition disrupts the normal architecture of the hepatic lobule. Ito or stellate cells are the main cellular source of extracellular matrix proteins in the liver. The initiation and maintenance of fibrogenesis in the liver is characterized by two processes. The former is characterized by the activation and transformation of Ito cells to myofibroblasts resulting in increased production of collagen types I and III. In parallel, there seems to be a disturbance of the homeostatic mechanisms involved in extracellular matrix deposition due to reduced expression of the proteolytic enzymes that degrade the extracellular matrix and increased expression of their inhibitors. Thus, maintaining fibrosis involves decreased production of matrix metalloproteinases (MMPs) and increased production of specific (tissue inhibitors of matrix metalloproteinases, TIMPs) or non specific metalloproteinase inhibitors (alpha1-antitrypsin), the another mechanism that could lead to the phenotypic change of Ito cells is the production of gelatinases by Kupffer cells. It has been demonstrated that extracellular matrix proteins play a crucial role in the maintenance of normal function of hepatocytes and Ito cells.

The Role of Kupffer Cells in Liver Infections

Kupffer cells are involved in the defence against infections of the liver. Their major role in the host defence and the prognosis of liver infection is indicated by studies in experimental models of sepsis. LPS pre-treatment has been shown to increase Kupffer cell numbers leading to a reduction of bacterial load and improvement of prognosis in a Salmonella septicemia model. Infection of mice with Listeria monocytogenes is a well studied liver infection model. In this model, the accumulation of bacillus in the liver depends on recognition of bacillus surface sugars and lectins by cognate receptors on Kupffer cells. On the other hand, production of inflammatory mediators such as IL-6, IL-12, IL-1β, TNF-α, and nitric oxide by infected Kupffer cells inhibits proliferation of the microorganism. Being the first line of defence, Kupffer cells also represent the portal of entry for viruses such as cytomegalovirus and parasites such as Plasmodium bergeiand Leishmania, which enter and proliferate in Kupffer cells and then infect the rest of the liver cells.

Kupffer Cells and Hepatocellular Carcinoma

The liver is a frequent site of hematogenous metastasis particularly for cancers of the gastrointestinal system. Isolated Kupffer cells were found to be cytotoxic against human colon adenocarcinoma cells and this cytotoxicity was increased significantly when the KC were stimulated with INF-γ and endotoxin. It has been suggested that this effect is related to TNF-α expression by Kupffer cells as it is inhibited by anti-TNF-α. Other studies have demonstrated that Kupffer cells induce Fas expression in colon cancer cells and malignant glioma cells leading to Fas-mediated apoptosis and death in the presence of tumour infiltrating lymphocytes or TNF-α. In vivo microscopy has shown that Kupffer cells are attracted to tumour cells in the hepatic circulation and have the ability to phagocytose these cells. Nitric oxide produced by Kupffer cells after stimulation with endotoxin, TNF-α and prostaglandin E2 may also be an effective weapon of the Kupffer cell machinery against tumor cells. Moreover, an indirect mechanism of defence by Kupffer cells against hepatic tumours is the induction of natural killer cell (NK-cell) cytotoxicity via the production of IL-12 and a possible anti-tumour effect of octreotide in hepatocellular carcinoma might, in part, be explained by its antiapoptotic effect on Kupffer cells.

Alcohol-Related Liver Disease and Kupffer Cells

Animal studies have shown that acute or chronic ethanol administration is associated with an increase in numbers of Kupffer cells that exhibit morphologic signs of cell activation[9], up regulation of CD14 expression and increased production of inflammatory mediators such as IL-1, TNF-α [99] and oxygen free radicals. Kupffer cell depletion with GdCl3 has been found to prevent early alcohol-induced liver inflammation and necrosis.

Kupffer Cells and Liver Transplantation

There is indirect evidence indicating that Kupffer cells may play a role in the process of graft rejection following liver transplantation mainly though their ability to act as antigen presenting cells (APC). Kupffer cells express MHC class II and have been found to be effective APC in vitro. Animal studies have shown that following liver transplantation Kupffer cells up-regulate MHC class II expression and this

has been associated with the initiation of the rejection process. In humans the rate of reconstitution of the graft with recipient-derived Kupffer cells has been found to increase during the rejection phase. Finally, graft rejection and the vanishing-bile duct syndrome occur more frequently in cases of MHC class I incompatibility accompanied by a MHC class II partial or complete match, which suggests that presentation of MHC I antigens of the biliary epithelium by donor Kupffer cells may also take place.

Kupffer Cells and Portal Hypertension

Kupffer cells have been shown to be the main source of thromboxane A2 production in the liver and this production is mediated by COX-1 and COX-2. Recently it was demonstrated that the infusion of endothelin-1 significantly increased portal pressure in animal models. This increase was mediated by the production of thromboxane A2 by the Kupffer cells, since both thromboxane synthase inhibition and thromboxane A2 receptor antagonists blocked the effect of endothelin-1 on portal pressure. Whether this is relevant to the situation in humans remains to be established.

Kupffer Cells and Intrahepatic Cholestasis

Kupffer cells have been implicated in the pathogenesis of intrahepatic cholestasis following hepatic ischaemia-reperfusion injury. Many hepatic canalicular transporters were reduced in parallel to the production of cytokines by Kupffer cells in an experimental model. Moreover, depletion of Kupffer cells abolished the reduced expression of transporters[10]. However, the role of Kupffer cells in cholestasis remains controversial. Recently, in bile duct ligated rats, selective anti-inflammatory blockade of Kupffer cells increased fibrosis and deposition of collagen I and III. More recently, in a bile duct ligated mouse model, depletion of Kupffer cells by intravenous inoculation of dichloromethylenediphosphonate resulted in high serum alanine transaminase levels and serious histologic portal inflammation and hepatocellular necrosis, indicating that Kupffer cells abrogate cholestatic liver injury in mice. Moreover it seems that the abrogation of liver injury in this model might be cytokine dependent, mostly through the production of IL-6 by Kupffer cells.

Results/conclusion:

Evidences derived mostly from animal models, indicates that Kupffer cells may be implicated in the pathogenesis of various liver diseases including viral hepatitis, steatohepatitis, alcoholic liver disease, intrahepatic cholestasis, activation or rejection of the liver during liver transplantation and liver fibrosis. There is accumulating evidence, reviewed in this paper, suggesting that Kupffer cells may act both as effector cells in the destruction of hepatocytes by producing harmful soluble mediators as well as antigen presenting cells during viral infections of the liver. Moreover they may represent a significant source of chemoattractant molecules for cytotoxic CD8 and regulatory T cells. Their role in fibrosis is well established as they are one of the main sources of TGFβ1 production, which leads to the transformation of stellate cells into myofibroblasts. Whether all these variable functions in the liver are mediated by different Kupffer cell subpopulations remains to be evaluated.

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