Kupffer Cells

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4.1 Introduction

Kupffer cells (KC) constitute 80%–90% of the tissue macrophages present in the body. These liver macrophages are named after the pathologist C. von Kupffer, who apparently first recognized this non-parenchymal cell type [82]. KC represent about 35% of the non-parenchymal liver cells in normal adult mice [57]. They reside within the lumen of the liver sinusoids, adherent to the endothelial cells that compose the blood vessel walls. KC, found in greatest number in the periportal area, constitute the first macrophage population of the body to come in contact with bacteria, bacterial endotoxins, and microbial debris derived from the gastrointestinal tract and transported to the liver via the portal vein [23]. Consequently, KC are constantly exposed to proinflammatory factors, e.g. bacterial endotoxins, known to activate macrophages. Upon activation, KC release various products, including cytokines, prostanoids, nitric oxide, and reactive oxygen species [17]. These factors regulate the phenotype of the KC that produce them, as well as the phenotypes of neighboring cells, such as hepatocytes, stellate cells, endothelial cells and other immune cells that traffic through the liver [47]. Therefore, KC are intimately involved in the liver's response to infection, toxins, ischemia, resection and various other stresses. This chapter will summarize established basic concepts of KC function as well as their role in the pathogenesis of various liver diseases. Due to the complexity of processes mediated by KC, this review focuses on selected aspects of the pathophysiology.

4.2 Molecular Mechanisms of Kupffer Cell Activation

Kupffer cells from mammalian livers can be obtained after perfusion with proteolytic enzymes (e.g. collagenase, pronase), density-gradient centrifugation and centrifugal elutriation of the resulting liver cell suspension [17]. Isolated KC can be kept in primary culture for several days and can be used to study mechanisms of activation. Activation of KC after exposure to various stimuli is characterized by a rapid change of the KC phenotype. Phagocytosable particles and several soluble substances are able to activate macrophages via binding to specific receptors on the plasma membrane. The most important activators of KC are the complement factors C3a and C5a [63], β-glucans from bacteria and fungi [76, 17] or lipopolysaccharides (LPS), the endotoxins of gram-negative intestinal bacteria [17, 73]. As illustrated in Fig. 4.1, LPS activate KC directly via Toll-like receptor (TLR) signaling [73]. In addition, high LPS concentrations can activate KC indirectly by triggering complement activation in either the portal or the systemic circulation [38]. After complement activation, cleavage of C3 and C5 leads to the generation of the potent anaphylatoxins C3a and C5a and subsequent stimulation of their specific receptors C3aR and C5aR [20]. Thus, KC activation can be best described as a wide spectrum of gradually different alterations of the KC phenotype resulting from a complex interplay of various activators and signaling pathways.

A dominant role in signal transduction from plasma membrane-associated C3a and C5a-receptor stimulation is attributed to G proteins, which regulate phospholipase C as a major key factor of signal transduction in KC [17, 20]. The enhanced activity of this enzyme may lead to activation of protein kinase C (PKC) and to calcium mobilization from the endoplasmic reticulum and the extracellular space via opening of L-type calcium channels. Experimental data indicate that PKC is involved in the activation of NADPH oxidase, while Ca^{2+} influx is necessary for phospholipase activation and eicosanoid synthesis [19]. The resulting formation of superoxide anions by NADPH oxidase helps to destroy phagocytosed organisms but may be toxic to neighboring cells [10, 36]. The effects of the prostanoids are manifold. In the hepatocyte, prostanoids increase the

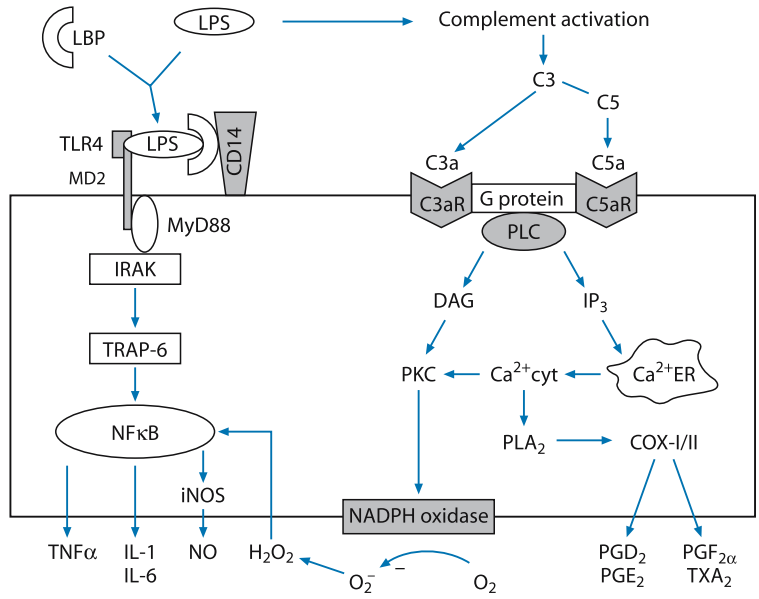

Fig. 4.1. Molecular mechanisms of Kupffer cell activation. *C3*, *C5* complement factor 3 and 5, *C3a*, *C5a* activated complement factor 3 and 5, *CD14* CD14 receptor, *COX-I/II* cyclo-oxygenase-I/II, *DAG* diacylglycerol, H_2O_2 hydrogen peroxide, *iNOS* inducible nitric oxide synthase, *IL-1* interleukin-1, *IL-6* interleukin-6, IP_3 inositol-3-phosphate, *IRAK* interleukin-1 receptor-associated kinase, *LPB* LPS-binding protein, *LPS* lipopolysaccharide, *NF-κB* nuclear factor κB, *NO* nitric oxide, PGD_2, PGE_2, $PGF_{2\alpha}$ prostaglandin D_2, prostaglandin E_2, prostaglandin $F_{2\alpha}$, *PKC* protein kinase C, PLA_2 phospholipase A_2, *PLC* phospholipase C, *TLR4* Toll-like receptor 4, *TNF-α* tumor necrosis factor α, *TRAP-6* tumor necrosis factor-activated factor 6, TXA_2 thromboxane A_2

glycogenolytic activity, thereby supplying KC with glucose for the production of NADPH via the hexose monophosphate shunt [18]. Other prostanoids such as thromboxane A_2 may induce vasoconstrictory effects [30], most likely as a result of contraction of hepatic stellate cells [43], while prostaglandin E_2 (PGE_2) plays an autoregulatory role in KC. PGE_2 inhibits the synthesis of prostaglandins and tumor necrosis factor (TNF-α) by KC [42, 56], which may explain its well-known hepatoprotective effects [6].

Increasing attention has focused on the mechanisms by which LPS activate KC. This process seems to be mediated by LPS-binding protein (LBP), CD14 and Toll-like receptor 4 (TLR4) [73]. In blood, LPS binds to LBP, a 60-kDa acute-phase protein produced predominantly by the liver and secreted into the circulation [65]. Although LBP is not required for interactions of LPS with CD14, its presence significantly decreases the concentration of LPS required for KC activation [64]. Thus, the LBP-CD14 pathway is crucial at low concentrations of LPS found under physiological conditions (see Chapter 14). Due to their location in the liver sinusoids, KC are chronically exposed to higher concentrations of LPS than circulating blood monocytes. Unlike monocytes, KC have relatively low baseline expression of CD14 [75]. However, expression of CD14 on KC can be upregulated by multiple stimuli including LPS [51]. Furthermore, CD14 expression in the liver is also increased in various liver diseases [73]. The physiological significance of these observed differences in KC CD14 expression is not entirely clear. However, it is tempting to hypothesize that changes in CD14 expression determine the sensitivity of the liver to LPS toxicity.

Since CD14 is a glycosylphosphatidylinositol (GPI)-anchored protein without a transmembrane component, downstream partners for this receptor have long been sought. Meanwhile there is substantial evidence that LPS signaling is mediated by TLR4 [73]. Signaling through TLR4 requires MD-2, a secreted protein closely associated with the extracellular domain of TLR4 [70]. Downstream of TLR4, signaling occurs via MyD88, which associates with interleukin-1 receptor-associated kinase (IRAK) and TNF-activated factor 6 (TRAF-6) [4]. TRAF-6-mediated signaling pathways activate nuclear factor-κB (NF-κB), which results in the production of proinflammatory cytokines [4].

4.3 Kupffer Cell–Neutrophil Interaction in Host Defense, Immune Tolerance and Liver Regeneration

4.3.1 Host Defense

The rapid clearance of bacteria from the blood stream has been attributed to fixed tissue macrophages, in particular to KC [46]. Recent experiments indicate that the actual mechanism is far more complicated than phagocytosis by KC alone. Rather, the rapid elimination of bacteria taken up by the liver is dependent on the complex interaction of KC and microbicidal neutrophils, which immigrate rapidly in response to infection [28, 29]. In brief, most organisms taken up in the liver are bound extracellularly by KC [28]. Experimental data suggest that binding is mediated in part by the interaction of lectins expressed by KC and carbohydrate residues expressed by the bacteria [54, 55]. In parallel, complementary adhesion molecules (i.e., CD11b/CD18 and CD54) facilitate the adherence of neutrophils to the KC [60, 79], which subsequently internalize and kill the organisms bound to the KC surface [58]. Clearance of infiltrating neutrophils from inflamed tissues is required for the resolution of inflammation. Immunohistochemical detection of KC positive for myeloperoxidase in sections of mouse and human livers supports the role of KC in neutrophil elimination [13, 68, 69]. Taken together, these findings suggest that KC play a critical role in eliminating activated neutrophils, thereby suppressing their production of toxic metabolic compounds and degradative enzymes. Furthermore, the ingestion of apoptotic neutrophils may enhance or abrogate the inflammatory response of macrophages depending on the receptors mediating uptake. Phagocytosis of apoptotic neutrophils via the $\alpha_v\beta_3$integrin/CD36 complex suppresses the production of proinflammatory cytokines such as IL-1β, TNF-α and eicosanoides [22]. Uptake of neutrophils mediated by Fc-receptors, on the other hand, induces the production of these inflammatory mediators [22].

4.3.2 Immune Tolerance

The ingestion of neutrophils by KC may also have profound implications for the development and expression of adaptive immunity in the liver. It has been suggested that the liver is actively tolerogenic and plays the key role in preventing generalized inflammation by eliminating circulating $CD8^+$ T cells specific for systemically disseminated antigens [15, 49]. Interestingly, KC recovered from chronically accepted hepatic allografts have a greater ability to induce apoptosis of alloreactive T cells, whereas the administration of these cells significantly prolongs the survival of hepatic allografts in an acute rejection model [74]. Macrophages in vitro cross-present epitopes derived from ingested apoptotic cells via the vacuolar alternate MHC class I pathway [7]. In the absence of appropriate co-stimulatory molecules, cross-presentation of antigens by macrophages is more likely to promote tolerance than to induce adaptative immunity in naïve T cells [5, 7]. Thus, apoptotic neutrophils ingested by KC may exert a significant influence on the development and expression of antigen-specific $CD4^+$ and/or $CD8^+$ T-cell-mediated immunity in the liver, where sensitized T cells are activated and naïve T cells are tolerized.

4.3.3 Liver Regeneration

The capacity to regenerate is critical for the successful outcome of liver resections and is especially important in the context of split liver and living donor liver transplantations. The unique ability of the liver to regenerate itself has been known since antiquity, but the underlying mechanisms have been explored only recently. Activation of KC is necessary for the optimal regenerative ability of the liver, possibly through the release of TNF-α [3, 50, 83] and interleukin-6 [14]. These cytokines initiate hepatocyte proliferation in vivo, at least in part, through NF-κB and STAT-3 translocation (Fig. 4.2). Interestingly, recent data suggest that these events are triggered by leukocyte–KC interaction mediated by the intracellular adhesion molecule ICAM-1 [67]. Livers from ICAM-1-deficient mice exhibited impaired regeneration after 70% hepatectomy, which was associated with a dramatic decrease in leukocyte recruitment as well as tissue TNF-α and interleukin levels. Similar impairment of liver regeneration and cytokine production in neutropenic and KC-depleted animals suggests a novel pathway in liver regeneration, where KC and leukocytes trigger a local inflammatory response leading to KC-dependent release of TNF-α and interleukin-6. KC activation could be a direct consequence of leukocyte–KC interaction. In addition, this local inflammation may induce complement activation, thereby liberating potent KC activators. This view is supported by a recent study demonstrating the essential role

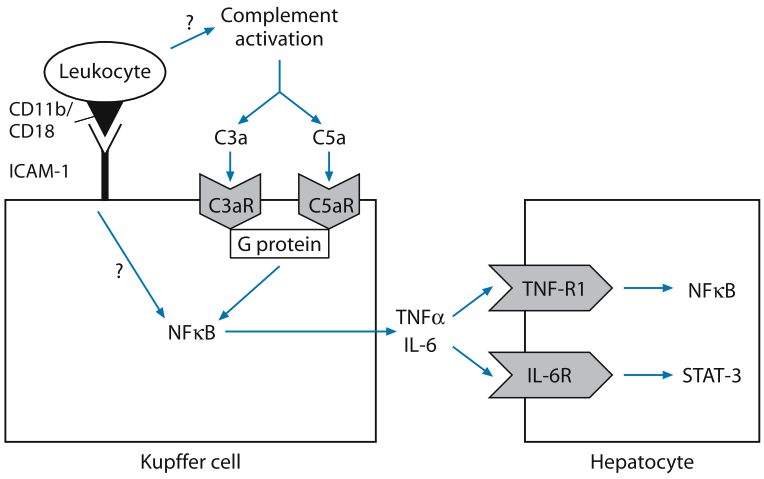

Fig. 4.2. Role of Kupffer cells in liver regeneration. *C3a*, *C5a* activated complement factor 3 and 5, *C5aR* complement receptors, *CD11b/18* C-receptor type 3, also known as MAC-1 or $\beta_2\alpha_M$-integrin, *ICAM-1* intercellular adhesion molecule 1, *IL-6R* interleukin-6 receptor, *NF-κB* nuclear factor-κB, *TNF-α* tumor necrosis factor α, *TNF-R1* tumor necrosis factor receptor 1

of complement components C3a and C5a for liver regeneration 1 [72]. C3a and C5a deficiency as well as interception of C5a receptor signaling resulted in suppression of interleukin-6/TNF-α induction and NF-κB/STAT-3 activation after hepatectomy [72]. Altogether, these results indicate that KC–leukocyte interaction together with complement activation contribute to liver regeneration (Fig. 4.2).

4.4 Role of Kupffer Cells in Liver Injury

Multiple lines of evidence indicate that KC contribute to the pathogenesis of different liver injuries, including alcoholic liver disease [78], non-alcoholic fatty liver [71], liver failure following acetaminophen intoxication [39], iron and copper toxicity [80], and ischemia-reperfusion injury during liver resection or transplantation [9, 66]. Furthermore, there is first evidence for a pathogenetic role of KC in carbon tetrachloride-induced hepatic fibrosis [59], galactosamine-induced liver injury [16], and portal hypertension [27, 86]. Several studies point to LPS as cofactor in the pathogenesis and exacerbation of liver injury [26, 73]. These findings are in line with the concept of LPS-mediated KC activation as a key mechanism in the pathogenesis of various liver diseases. However, there is evidence that other mechanisms of KC activation as well as the cytotoxic mechanisms induced by KC may play a role depending on the underlying liver disease. This aspect may be illustrated by several examples discussed below.

4.4.1 Acetaminophen

In overdose, the analgesic/antipyretic acetaminophen produces centrilobular hepatic necrosis, which can lead to acute liver failure. Depletion of intracellular glutathione and the increased generation of reactive oxygen and nitrogen species have been considered as critical pathomechanisms [39]. Recent work shows the central role of tyrosin nitration by peroxynitrite formed by the rapid reaction of nitric oxide (NO) and superoxide [32]. Surprisingly, acetaminophen toxicity and tyrosin nitration can be dramatically reduced by several KC inactivators and knockout of inducible nitric oxide synthase (iNOS) [39], while liver injury still occurs in NADPH oxidase knockout mice [40]. These findings suggest activation of KC, iNOS induction and the subsequent formation of NO, but not of KC-derived superoxide, as major determinants of peroxynitrite formation and consequently, acetaminophen toxicity. Isolated KC can be activated by acetaminophen in the absence of LPS or complement factors [25], which points to an alternative pathways of KC activation by hepatotoxins.

4.4.2 Ischemia-Reperfusion Injury

Ischemia-reperfusion injury is the major factor responsible for the morbidity associated with liver resection under vascular exclusion (Pringle maneuver) or after liver transplantation [9, 66]. The pathophysiology of hepatic ischemia-reperfusion injury includes a number of mechanisms, which contribute to various degrees to the overall injury. An excessive

inflammatory response by activated KC is clearly recognized as a key mechanism of injury during reperfusion [9, 35, 36]. Interestingly, ischemia alone induces activation of KC [61]. During reperfusion additional KC activation and cell injury may occur by accumulated LPS during the unhepatic phase of liver transplantation [85] through activation of complement factors [37, 38]. This example demonstrates the activation of KC by an uncommon still undefined pathway induced by ischemia and the subsequent activation by two common pathways. In contrast to acetaminophen toxicity, nitric oxide derived from KC or other sources may reduce ischemia-reperfusion injury due to its vasodilatory effects in line with the observation of only little peroxynitrite formation [35]. Moreover, the production of a vascular oxidant stress by the NADPH-oxidase of KC has been identified as a central pathomechanism of hepatic reperfusion injury, which enhances NF-κB and activator protein-1 (AP-1)-mediated expression of genes, such as TNF-α, chemokines and adhesion molecules [34]. Subsequent studies indicated that glutathione (GSH) released by hepatocytes via the sinusoidal GSH transporter may partially counteract the vascular oxidant stress by KC [36]. This endogenous defense mechanism is limited by the capacity of the sinusoidal GSH transporter and the rapid elimination of plasma GSH, as illustrated by the low concentration of GSH in the vascular space in contrast to 1,000-fold higher intracellular concentrations of GSH (Fig. 4.3). Accordingly, prevention of hepatic reperfusion injury can be achieved by increasing the extracellular antioxidant capacity around the KC by intravenous infusion of GSH [8, 11, 48, 62]. Interestingly, reperfusion injury by activated KC could be attenuated not only by antioxidants but also by the hormone atrial natriuretic peptide (ANP) [12, 24], which had no relevant effect on reactive oxygen formation by KC [10]. Thus, we concluded that ANP increased the resistance of hepatocytes against the oxidant stress by KC. This may be due to an inhibition of the increase in cytosolic calcium following oxidant stress in hepatocytes [81]. Additionally, ANP may exert cytoprotective effects through inhibition of TNF-α released from activated KC [44]. Recent data show the potency of ANP specifically to induce hemoxygenase-1 (HO-1) in KC independently of cGMP [45]. However, this increased expression of HO-1 does not seem to be involved in hepatoprotection conveyed by ANP because inhibition of HO-1 does not abrogate the hepatoprotective effects of ANP [45].

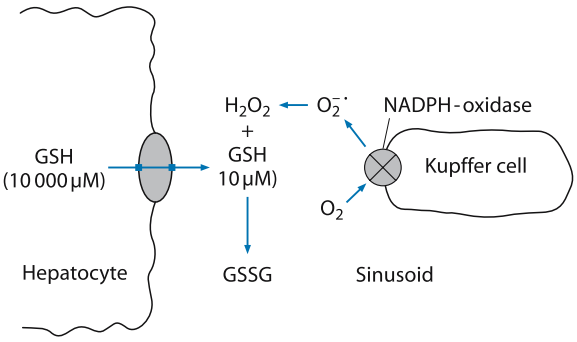

Fig. 4.3. Vascular oxidant stress by activated Kupffer cells: endogenous defense by glutathione. *GSH* reduced glutathione, *GSSG* oxidized glutathione, H_2O_2 hydrogen peroxide

4.4.3 Alcoholic Liver Disease

Hepatic macrophages play an important role in the pathogenesis of alcoholic liver disease. Early alcoholic liver injury in the intragastric ethanol infusion model is attenuated by depletion of KC with gadolinium chloride [1]. The role of KC activation by increased permeability of the gut to endotoxins [21] is also supported by studies showing hepatoprotection in ethanol-fed animals given polymyxin B and neomycin [2] or lactobacillus [53]. In fact, administration of antibodies against TNF-α attenuates alcoholic liver injury [33], and the importance of TNF-α is confirmed by the absence of alcoholic liver injury in TNF receptor-1 lock out mice [84]. Acute or chronic exposure to ethanol influences macrophage function in opposite ways: KC production of proinflammatory cytokines is inhibited by acute, but stimulated after chronic exposure to alcohol [52]. Consistent with these results, KC harvested from the livers of rats that were fed ethanol for several weeks demonstrated a time-dependent increase in TNF-α and interleukin-6 expression [41]. The studies discussed above implicate a role for LPS and intestinal bacteria. Additionally, there may be several other factors contributing to phenotypic alterations. Suppression of NF-κB and TNF-α expression by antioxidants in monocytes from alcoholic hepatitis patients suggests dysregulation of TNF-α gene transcription driven by NF-κB [31]. As shown previously, increased iron storage by KC may prime NF-κB activation in experimental alcoholic liver disease [77]. Furthermore, there is first evidence that altered methionine metabolism, in particular deficiency of S-adenosylmethionine, may also play a role in dysregulation of TNF-α gene expression [78].

4.5 Conclusions

Kupffer cells are intimately involved in the hepatic response to various toxic insults. The interaction of KC with leukocytes is important for host defense, liver regeneration after liver resection and the development of immune tolerance after liver transplantation. Furthermore, KC contribute to the pathogenesis of various liver diseases such as non-alcoholic fatty liver, alcoholic liver injury, ischemia-reperfusion injury, acetaminophen toxicity and development of liver fibrosis and portal hypertension. However, much remains to be learned about the environmental factors and genes that determine KC toxicity in various liver diseases. This knowledge will help to clarify how KC regulate the viability and function of hepatocytes and non-parenchymal cells in the liver. Consequently, a better understanding of these issues should enhance the development of treatment for liver diseases that result from activated KC.

Acknowledgments

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Selected Reading

Further information can be found as follows:

For comprehensive reviews on KC-related liver injuries, see refs. 9, 39, 66, 78, 71 below.

For Kupffer cell activation, see refs. 17, 73.

For host defense, see ref. 29.

For liver regeneration, see refs. 67, 72.

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