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TOPIC HIGHLIGHT

2016 Liver Transplantation: Global view

Role of NK, NKT cells and macrophages in liver transplantation

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Abstract

Liver transplantation has become the treatment of choice for acute or chronic liver disease. Because the liver acts as an innate immunity-dominant organ, there are immunological differences between the liver and other organs. The specific features of hepatic natural killer (NK), NKT and Kupffer cells and their role in the mechanism of liver transplant rejection, tolerance and hepatic ischemia-reperfusion injury are discussed in this review.

Key words: Liver transplantation; Natural killer cells; Kupffer cells; Graft rejection; Ischemia-reperfusion injury

Core tip: Liver transplantation has become the treatment of choice for acute or chronic liver disease. There are immunological differences between the liver and other organs. The specific features of selected hepatic immune cells, such as natural killer (NK), NKT and Kupffer cells, and their role in the mechanism of liver transplant rejection, tolerance and hepatic ischemia-reperfusion injury are discussed in this review.

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INTRODUCTION

Previous studies have intensively investigated immunological processes after liver transplantation. Ischemia-reperfusion injury and graft rejection are two major causes for poor outcomes following liver transplantation. Both processes are triggered and maintained by

immune cells. The specific features of hepatic natural killer (NK), NKT and Kupffer cells and their role in the mechanism of liver transplant rejection and hepatic ischemia-reperfusion injury based on the current literature are discussed in this review.

LIVER TRANSPLANTATION AND IMMUNOLOGICAL PROCESSES

During the last 50 years liver transplantation has become the treatment of choice for acute or chronic liver disease[1]. The main indications for liver transplantations are primary liver tumors, chronic viral hepatitis, alcohol-related cirrhosis, chronic cholestatic liver disease, autoimmune hepatitis, vascular and metabolic disorders[2,3]. With an overall 5-year survival of approximately 70%, the life expectancy of liver transplant recipients is lower than the general population[4,5]. In addition to de novo malignancies, infections, cardiovascular or renal disease, ischemia-reperfusion-injury of the liver graft and graft rejection are important immunological processes responsible for long-term graft and patient survival after liver transplantation.

The liver acts as an innate immunity-dominant organ, therefore, hepatic immune cells provide the first line of defense against pathogens, infections or tumors[6]. In addition to NK cells, macrophages (Kupffer cells), NKT cells and γδT cells, there are a large number of innate immune cells within the liver[7,8]. In humans, NK cells are the most abundant lymphocyte population in the liver[9].

Two specific and immunologically important processes occur after liver transplantation: (1) donor liver-resident cells enter the blood flow of the recipient; and (2) recipient immune cells invade the donor graft. This phenomenon occurs early after transplantation[10-12]. It has been shown, that after liver transplantation, donor specific liver NK cells are detectable in the recipients' circulation up to two weeks after liver transplantation[1,12]. The liver has been described as an immunotolerant organ[6,13]. This immunotolerance is believed to be responsible for the lower levels of immunosuppressive drugs needed and the lower rate of allograft rejection after liver transplantation compared to other solid organ transplantations[1,14]. This is reflected by the withdrawal of immunosuppression, in some cases, after liver transplantation, and the aim to wean patients from immunosuppressive drugs as soon as possible[1,15]. In addition, it has been shown that hepatic grafts might facilitate the acceptance or reverse the rejection of other transplanted grafts, *e.g.*, heart or kidney after liver transplantation[16].

MECHANISM OF GRAFT REJECTION

Acute graft rejection is a combined response of the adaptive (cellular immunity) and humoral immune system (secreted antibodies by activated B cells) in combination with the innate immune system (phagocytosis). Furthermore, early organ rejection can be distinguished from late organ rejection. Wiesner *et al*[17] suggested the following risk factors: lower recipient age, cold ischemia duration longer than 15 h, donor age and fewer human leukocyte antigen (HLA)-DR matches. T cells were believed to be solely responsible for graft rejection. However, there is increasing evidence that other cells of the adaptive immune system, such as NK cells, are also responsible and interact with T cells during graft rejection[1,18,19]. In contrast to other solid organ transplantations, HLA cross-matching is not routinely performed prior to liver transplantation despite recent studies suggesting HLA markers, such as killer cell immunoglobulin-like receptors, influence the outcome of liver grafts[20-22]. To date, clinical experience, analysis of immunosuppressive drug levels, serum liver enzymes and histological assessment have been used as markers to diagnose graft rejection[23]. During acute graft rejection, mononuclear cells infiltrate the portal tract and the accumulation of activated lymphocytes leads to the secretion of chemokines and cytokines and subsequently, liver tissue injury[24]. Furthermore, bile duct injuries and venous endotheliitis are histological features for the diagnosis of graft rejection[25]. Although the exact chemotactic triggers are still under investigation, it is postulated that for NK cells, CCL3 leads to NK cell migration to the site of liver injury[26-28].

MECHANISMS OF HEPATIC ISCHEMIA-REPERFUSION INJURY

During organ donation and transplantation, the liver undergoes trauma due to cold and non-perfused storage, warm ischemia and finally, engraftment. During ischemia-reperfusion liver injury, one important issue is organ preservation, which is initially triggered by endothelial cell injury and causes an acute inflammatory response that involves Kupffer cells, hepatocytes and hepatic stellate cells[29]. Furthermore, cell death is caused by oxidative stress, which leads to increased microcirculatory disturbances, cell dysfunction and inflammation[30,31]. To avoid organ damage due to organ preservation, several modifications have been investigated, such as perfusion solutions[32-34], use of antioxidants[35], vasodilators[36,37], hydrogen gas[38], or *ex-vivo* liver perfusion systems[39-41]. Ischemia-reperfusion injury is crucial for initial and long-term organ function[42]. Hepatic ischemia-reperfusion injury is associated with an inflammatory response, which leads to liver tissue injury, the release of reactive oxygen species (ROS), the induction of adhesion molecules, the secretion of cytokines and the activation of leukocytes[43]. In addition, several immune cells, such as T cells, B cells, NK cells, NKT cells, and Kupffer cells,

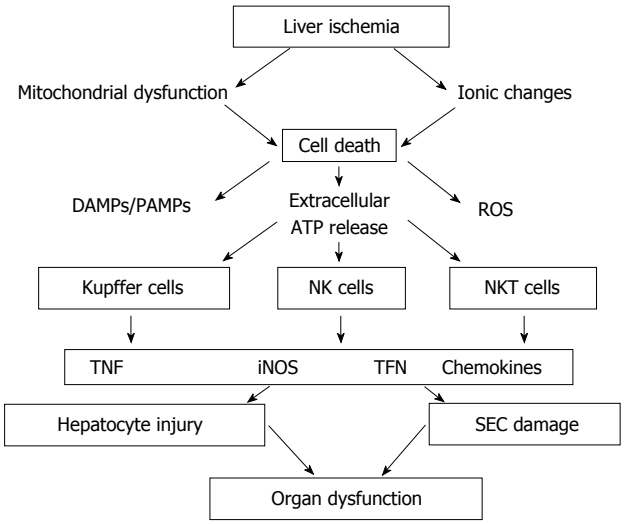

Figure 1 Simplified overview of the role of Kupffer cells, natural killer and natural killer T cells, including the humoral and cellular factors, involved in hepatocyte dysfunction and injury during hepatic ischemia-reperfusion injury. DAMPs: Damage associated molecular pattern; PAMPs: Pathogen-associated molecular pattern; ROS: Reactive oxygen species; TNF: Tumor necrosis factor; IFN: Interferon; iNOS: Inducible nitric oxide synthase; SEC: Sinusoidal endothelial cells.

are involved in hepatic ischemia-reperfusion injury[44-51], which affect liver-specific cells, such as sinusoidal endothelial cells and hepatocytes[52]. During cell injury and necrosis, danger-associated molecular patterns (DAMP) and, subsequently, pathogen-associated molecular patterns (PAMP) are released and trigger an immune response[53,54]. Tissue ischemia leads to mitochondrial dysfunction, ATP depletion, and ionic changes within the cells, which promotes further cell damage and organ dysfunction (Figure 1)[52].

HEPATIC NK CELLS

There is growing evidence that peripheral NK cells differ from hepatic NK cells with regard to function and differentiation; however, the exact mechanism of NK cell differentiation and maturation in the liver is not completely understood.

NK cells are the major lymphocyte population in the human liver and make up to 50% of the lymphocyte population. During liver disease, the number of NK cells in the liver changes possibly due to increased recruitment of NK cells to the liver[9,55]. A diverse range of receptors expressed on the surface of NK cells allows them to recognize and rapidly respond to damaged or stressed cells. Furthermore, NK cells coordinate early events in the innate immune response to injury by rapidly producing cytokines and controlling cytotoxic activity.

Human NK cells in the blood can be distinguished from other T cells by the absence of CD3 and the presence of CD56[56,57]. Furthermore, NK cells in the blood can be further differentiated into two major subsets: $CD3^{-}CD56^{dim}CD16^{+}CD27^{-}$ (cytotoxic activity) and $CD3^{-}CD56^{bright}CD16^{-}CD27^{+}$ (cytokine producing)[6]. Bone marrow-derived NK precursor cells undergo a complex maturation process, which determines their function and the expression of chemokine receptors and adhesion molecules[6,58-60]. This determination is organ specific[6,61]. Because NK cells recirculate between different organs, the maturation process is dynamic and not stationary[58]. Adoptively transferred splenic NK cells change their phenotypic and functional markers after migrating to the liver, which suggests a modification of NK cells due to the hepatic microenvironment[62]. In contrast to peripheral NK cells, hepatic NK cells lack CD16[63,64], express higher numbers of granules, and express higher levels of TRAIL, perforin, and granzyme B[65].

NK cells can potentially lyse dividing hepatocytes and/or other immune cells within the liver that contribute to the cytokine and chemokine microenvironment during regeneration and liver injury[66,67]. NK cells actively eliminate susceptible targets through multiple, non-redundant mechanisms and recruit and amplify the inflammatory response[68]. Because NK cells are closely linked to other immune cells, they are associated with Kupffer cells in the liver sinusoids, which suggests a complex interaction between these two cell types that involves cytokine and chemokine secretion[69,70].

HEPATIC NATURAL KILLER T CELLS

Natural killer T (NKT) cells are a subset of regulatory T lymphocytes[71]. In contrast to NK cells, NKT cells are found less frequently in the liver[60], and their ultrastructure contains a low nuclear:cytoplasmic ratio and dense granules compared to NK cells[72]. Therefore, NKT cells are less mature and have only a few organelles and mitochondria and short profiles of the rough endoplasmic reticulum[72]. Compared to NK cells, the granules of NKT contain perforin, but are smaller in size and less frequently observed using electron microscopy[73,74]. Interestingly, NKT cells have comparable functions with T cells, and NK cells and are able to secrete large amounts of cytokines[72]. Similar to other immune cells, NKT cells are located within the liver sinusoids and are responsible for killing tumor cells, secretion of cytokines and elimination of toxins and pathogens[60,75]. In addition, activated NKT cells are important for inducing liver injury[76-78]. In contrast to NK cells, the number of NKT cells decreases during various experimental models, such as in leptin-deficient mice[79], bacterial liver injury[80], hepatotoxic liver injury[81,82], liver steatosis[83,84], and Concanavalin A-induced liver injury[85]. However, following liver transplantation[24], hepatic ischemia-reperfusion injury[43,44], liver resection[86-89] or stress[90], the number of hepatic NKT cells increase. This change in cell number has been postulated to be due to activation-induced cell death, loss of specific NKT cell surface markers[26,76,91,92], apoptosis[93] or sympathetic activation[89]. Flow cytometry analysis

of hepatic NKT cells shows that they are mostly $CD4^-$ $CD8^-$ or $CD4^+CD8^-$[94] and express the NK cell receptor-CD161 and the invariant TCR-alpha chain[95]. NKT cells express IL-12 receptors and secret and produce perforin and interferon (IFN)[96] after stimulation, which are key mediators of cytotoxicity, inhibition of tumor angiogenesis and immune cell activation[97,98]. Furthermore, NKT cells produce anti-inflammatory and anti-tumorigenic cytokines such as IL-13 and IL-4[99-101].

KUPFFER CELLS

In 1876, von Kupffer first identified liver resident macrophages[102]. These macrophages are colocalized with sinusoidal endothelial cells, Ito cells, and pit cells in the hepatic sinusoids[103]. Kupffer cells are abundant in the liver and make up more than 50% of all resident macrophages in the human body and 15% of all hepatic cells[104,105]. Depending on their location within the liver, the function, morphology and number of Kupffer cells changes[103,106,107]. Interestingly, the intensity of immunohistochemical markers for Kupffer cells is heterogeneous. In general, the intensity of these markers decreases as the size of Kupffer cells decreases, which reflects a more immature phenotype that involves more scavenging and less inflammatory functions[103,107]. The main function of hepatic macrophages is to clear the portal circulation from foreign materials and pathogens using phagocytosis[103,108]. During this process, Kupffer cells release pro-inflammatory cytokines such as IL-1, IL-6, IL-12, IL-18, TNF and IFN[109].

SPECIFIC FUNCTION OF IMMUNE CELLS IN HEPATIC ISCHEMIA-REPERFUSION

Ischemia-reperfusion injury (IRI) significantly contributes to graft dysfunction after liver transplantation[110]. Ischemia during the early phase of IRI leads to cell necrosis, which is associated with a release of danger signals that activate innate immune cells through signaling of TLR4, RAGE and TLR9 on Kupffer cells and through signaling of the CD154-CD40 pathway on neutrophils and CD4 Th1 effector T cells[42]. This immune activation is further increased through the release of IFN from T cells, NKT and NK cells, which are stimulated by CD1d and CD39. Pro- and anti-inflammatory mediators further activate and recruit immune cells, which promotes or inhibits local inflammation[42].

NK cells express tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which is a potent inducer of hepatocyte cell death. In an experimental study, the effect of TRAIL expression on NK cells during hepatic IRI was investigated and showed that mice lacking TRAIL exhibited significantly higher liver injury, signs of necrosis, and neutrophil infiltration[47]. The adoptive transfer of NK cells into immunodeficient RAG2/common gamma null mice (lacking T, B and NK cells) revealed the specific role of NK cells during IRI and showed that the expression of TRAIL on NK cells is protective in a murine model of hepatic IRI[47]. In another study, the effect of CD39, an ectonucleotidase hydrolyzing extracellular nucleotides, on NK cells was investigated and revealed that NK cells have an important influence on the extent of hepatic IRI. This effect was based on the modulation in IFN secretion, which was regulated by pericellular ATP levels and purinergic responses[48]. Furthermore, it is postulated that liver resident NK cells are responsible for the innate immune response in the early phase of IRI through self/non-self-recognition[49].

There are two types of NKT cells that have opposing roles during IRI to promote or protect against liver injury[50]. During the early phase of IRI, NKT cells are promptly activated and release IFN[50]. This activation is mediated by the interaction of CD1d antigen-presenting molecules, which are expressed on antigen-presenting cells in the liver and on hepatocytes containing self or foreign glycolipid antigens[43,111]. NKT cells are then able to damage hepatocytes directly or through the secretion of IFN, which in turn activates Kupffer cells, neutrophils and hepatocytes[43,111]. Knockout models with reduced NKT activity result in significantly reduced IRI[43,44,111]. In addition, the recruitment of NK cells into the liver during IRI is dependent on the presence and activation of NKT cells[50].

Hepatic hypoxia electron microscopy analysis revealed morphological changes in Kupffer cells that reflected cell activation[112] and a release of cytokines and inflammatory mediators to attract neutrophils and produce reactive oxygen species[113,114]. This activation is triggered by endogenous damage-associated and/or pathogen-associated molecular pattern (DAMP/PAMP) molecules, which are generated during cellular stress or cellular injury[42]. During IRI, TLR4 on Kupffer cells is activated, which leads to hepatic injury[115]. Activation of TLR4 enhances TNF secretion probably through an antigen independent pathway[115,116] and is further associated with hepatocyte apoptosis[117,118], $CD4^+$ T cell recruitment to the liver[119], and the release of endothelin-1, which results in circulatory disturbance and increased liver injury[120,121]. Activation of the complement system is present during IRI[122] and responsible for Kupffer cell-induced oxidant stress, the formation of reactive oxygen species and continuous neutrophil recruitment to the ischemic liver[123]. Furthermore, inducible nitric oxide synthase (iNOS), which is produced by Kupffer cells and neutrophils early during hepatic IRI, leads to reduced capillary perfusion, increased liver injury and mortality[124,125]. Activated Kupffer cells enhance alterations in hepatic microcirculation during IRI through the activation and production of oxygen free radicals[126], TNF, MIP-2 and keratinocyte chemoattractant chemokine, which leads to increased liver injury[127,128].

NK CELLS, NKT CELLS AND KUPFFER CELLS DURING GRAFT REJECTION AND TOLERANCE INDUCTION

It is postulated that the rejection of solid organ grafts is mainly mediated by allospecific T lymphocytes. These T lymphocytes recognize foreign MHC molecules that are located on donor tissue cells[18,19]. However, it has been shown, that the depletion of $CD8^+$ T cells does not prevent graft rejection and an alternative pathway of organ rejection has been postulated[129,130]. Several studies using different experimental transplantation models have investigated the role of NK cells during graft rejection and demonstrated NK cell graft infiltration[131-135]. Additionally, it has been shown that recipient-derived NK cells are located in the liver graft and produce IFN after liver transplantation[24]. The depletion of NK cells or the decrease in IFN production leads to increased graft survival, therefore, NK cells are for graft rejection and survival[24]. IFN, an immunoregulatory cytokine that is one of the main cytokines secreted of NK cells, has been shown to be important during both allograft rejection[136-138] and tolerance induction[139]. Studies investigating immunosuppression withdrawal demonstrated that NK cells play a role in tolerance induction[140]. In addition, 13 genes that are highly expressed in NK cells, were found to be present in liver transplant recipients with graft tolerance, which further confirms that NK cells are involved in tolerance induction[141]. Although this conflicting role of NK cells is still not fully understood, it might explain why donor NK cells are responsible for tolerance and recipient NK cells are responsible for rejection[1]. In addition to cytokines, chemokines, such as CCL2, CCL3, CX3CL1 or CXCL10, attract and activate NK cells. Some of these chemokines are already present in the transplanted graft before NK cell infiltration is detectable[142]. Specific analysis of NK cells in the rejected liver graft revealed that these NK cells produce high amounts of cytokines, granzyme B and highly express FasL[135].

NKT cells are believed to be responsible for tolerance induction[71]. Because activated NKT cells release pro- and anti-inflammatory cytokines, they have different functions in immune response[143-145]. It has been further shown, that specific Vα14 NKT cells are responsible for the development of tolerance towards transplanted antigens[145].

As stated above, the main function of Kupffer cells is to kill and engulf microorganisms and pathogens, secrete cytokines and effect antigen presentation[146,147]. Additionally, it has been shown, that Kupffer cells are able to induce T cell apoptosis and therefore play an important role during graft tolerance[148]. After liver transplantation Kupffer cells act as antigen-presenting cells by increasing the expression of MHC class II[149,150] and identifying and interacting with recipient T cells migrating to the liver, which leads to T cell apoptosis through the Fas/FasL pathway[109]. In a study in rats, pretreatment of the recipients with Kupffer cells before liver transplantation lead to decreased liver injury, reduced cytokine levels and reduced apoptosis. The authors concluded that this lead to increased immune tolerance and improved graft survival[148]. As mentioned above, Kupffer cells secret varying amounts of cytokines, such as TNF, which in high levels can lead to hepatocyte apoptosis but in physiological levels is associated with a resistance of hepatocytes to apoptosis[151]. Therefore, further studies are necessary to elucidate the contrasting roles of Kupffer cells in the induction of immune tolerance following liver transplantation.

CONCLUSION

Several specific immune reactions that involve NK, NKT and Kupffer cells are responsible for the short- and long-term outcomes of liver transplantation. This review demonstrates that many immune cells and mediators as well as molecular signaling cascades participate in the process of liver transplantation tolerance. Despite intense research within the field of ischemia-reperfusion injury, there are still many pathophysiological and immunological mechanisms involved in tolerance induction and graft rejection that still need to be elucidated.

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